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Discussion

Dr. Francis D. Moore (Boston): I believe that this recent work by Dr. Murray and the group marks a milestone in our thinking that is difficult to absorb in a quick ten-minute presentation. It is a milestone in relation to the choice of preferable methods for immune suppression in homotransplantation. Although irradiation, antimetabolites and chelating agents may involve a final common pathway in their cellular action on protein replication and antibody production, their clinical usefulness in the surgery of transplants presents many important contrasts.

Irradiation given in one or two doses has to do its whole job in one sledge-hammer blow. Each cell is hit hard—how hard, we never know—and recovery is slow or may never occur.

In sharp contrast, the antimetabolites can be used gently and with sequential discrimination, altering the dosage required by the sharply opposing needs of the graft (for immune suppression) on the one hand and the host (for survival) on the other.

The essence of this *balance of survival* is shown in several of Dr. Murray's dogs. The animal is holding the new kidney but at the same time he has such an intact immune system that he remains in good health in a normal environment and can reject a skin graft.

Essential to this concept and to its clinical use is the demonstration that the tissue-destroying rejection-sequence is, up to a point, reversible. This makes it possible to adjust the drug dose at a low level without fear that a beginning rejection will be fatal. The dose of the drug is then increased, if required, to abate the rejection response. This is *tough medicine* with whole body irradiation but it is gentle, feasible and practical with these drugs, as Dr. Murray and his group have so nicely shown.

Dr. Joseph E. Murray (closing): I concur with Dr. Moore's analysis. I would just like to reemphasize the nature of the abrupt shutdown that we have seen in these human beings who have been irradiated. It is so rapid that we believed it must be mediated by some humoral, that is, a noncellular antibody, a thesis at odds with the classical thinking of transplantation immunity.

We have been able to duplicate this rapid noncellular cessation of function in the laboratory by sensitizing the recipients with spleen cells, skin grafts, kidney grafts from specific as well as nonspecific, i.e., indifferent, donors.

Although the *humoral* rejection is a different type of reaction microscopically and temporally, it is still lethal to the transplant, and therefore should be thoroughly worked out in the laboratory before again being tried in the human.