Xenotransplantation-A Closer Look

David K.C. Cooper

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"The secret of being a bore is to say everything."

—Voltaire

When invited to edit these two special issues of *Graft* devoted to xenotransplantation, i.e., the current and the next issues, my initial response was to wonder how I could possibly review the field in a way that had not been done previously. The medical literature is replete with long articles reviewing one or more aspects of this intriguing subject. I came up with the format you see in this issue and which will be continued in the next issue. A large number of scientists, physicians and others with an interest in xenotransplantation have provided brief updates in their fields of study. Together, these short papers provide an overview of where we currently stand in our efforts to develop experimental xenotransplantation to the point where we can begin clinical trials of organ xenotransplantation.

The question I asked the contributors to answer was, "In the pig-to-primate, what progress have we made in . . . (the topic you have been requested to review)?" By designating the pig-to-primate, I clearly neglected many important studies continuing in in vitro models, in rodent concordant and discordant models, and in nonhuman primate concordant models. Although these models continue to provide data of relevance to achieving our goal of the introduction of clinical xenotransplantation, it is the pig-to-nonhuman primate model where therapeutic options are fully tested. Success in this model is most likely to indicate that we can consider proceeding to the clinical venue.

The reviews included in these two issues, therefore, provide an up-to-date statement of our state of development in the highly-relevant preclinical pig-to-nonhuman primate model. Several reviews, however, relate directly to trials in humans that have been or are being undertaken at the present time, particularly with regard to cell transplantation. Furthermore, many of the topics covered in these issues, including ethical, regulatory, legal, and financial aspects of xenotransplantation, are of direct relevance to clinical xenotransplantation.

Believing brevity to be a virtue and believing that most of us have little enough time to devote to reading scientific articles, I suggested a response limited to 1500 words, although a few contributors have provided slightly lengthier articles. My guidelines also restricted the number of references and figures that could be included, though again I readily agreed if an author felt unable to comply. I hoped that these guidelines would lead to the contributions being short and to the point, thus providing the information the reader requires with a minimum of "padding". I believe the authors have largely achieved the intended goal.

One aspect of xenotransplantation that requires some attention is that of terminology and definitions. The science is still young enough that definitions are evolving, different terms being suggested by various workers in the field. For example, if hyperacute rejection is successfully prevented, the rejection that develops within days or weeks has been variously termed delayed xenograft rejection, acute vascular rejection and, most recently, acute humoral xenograft rejection. Various contributors to these issues used different terms for this phenomenon and, as there is as yet no single universally-accepted term for this form of rejection, I have not tried to limit the authors' preference. One author goes so far as to differentiate between delayed xenograft rejection and acute vascular rejection, believing the two to be different, whereas most authors use these terms interchangeably.

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Cell xenotransplantation has already entered the realms of clinical trials, with clinical neuronal cell transplantation still continuing on a limited basis and liver support devices containing porcine hepatocytes currently being tested.

transplantation still continuing on a limited basis and liver support devices containing porcine hepatocytes currently being tested. Organ xenotransplantation remains at the preclinical stage of development. These clinical forays and preclinical advances have stimulated considerable activity by microbiologists (to determine the potential risk of infection), ethicists, lawyers, and those involved with regulatory controls in medicine. I have been fortunate in persuading several authorities in these fields to contribute to these issues. Rarely have the implications of a major potential development in medicine been discussed so extensively before its introduction. That was certainly not the case with allotransplantation, where regulation (e.g., regarding the concept of brain death) tended to follow clinical innovations rather than precede them. We therefore have a great opportunity of planning the cautious introduction of xenotransplantation as a clinical therapy. I thank all of the contributors to these issues, and join with them in hoping that you, the reader, enjoy the brief updates that follow.