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# Xenografting from Pigs, a Solved Problem Needing Urgent Application

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## Abstract

The histocompatibility system is responsible for the rejection of allograft. The system exists to counter the explosive speed of viral replication. It does this by directing the defensive immune attack by cytotoxic T cells on to histocompatibility antigens on the infected cell's surface. This enables destruction of the virus factories that the infected cells become, before the cytotoxic T cells are swamped by the myriad numbers of new virions, a thousand coming from each infected cell every 10 hours. The immunity system mistakes alloantigens for virus infected host cells that need swift destruction. For transplantation, Sykes has improved Kaplan's technique by adding recipient bone marrow cells to the donor ones injected for reconstitution of the recipient after immune ablation. This protocol should enable xenografting from untreated pigs, offering instant and unlimited supply of grafts for man.

**Keywords:** Histocompatibility system; Xenograft in pigs; Acceptance-rejection in piglets

## Rejection of Tissue Grafts

Oncologists, wishing to study tumours by transplanting them from their source to another laboratory animal, found that the tumours were rejected. Haldane [1] realised that this was based not on tumour antigens but on tissue antigens that differ from animal to animal, analogous to the blood group antigens, but on all nucleated cells. Medawar [2] observed that the rejection of foreign skin grafts on a woman was accelerated on the second occasion, concluding that an immunological process was involved in the rejection.

To emulate identical twins for acceptance of foreign grafts, oncologists used brother-sister mating of rodents to produce inbred strains. This led to discovery of the histocompatibility (tissue compatibility) system, governed by a major genetic complex, named the Major Histocompatibility Complex (MHC). These genes code for surface antigens on all nucleated cells. The MHC is present in all species of vertebrates, including man. Why does it exist?

## Functions of the MHC

The MHC does not exist to frustrate Transplant Surgeons. It is essential for survival of virus infections, as shown in the tables 1 and 2, and protects, imperfectly, against autoimmune disease [3]. In a famous experiment Zinkernagel and Doherty found that a cell infected by a virus extrudes a viral peptide on to its surface histocompatibility antigens, where it can be attacked by a complementary cytotoxic T cell clone, if one exists [4].

| The contestants | Replication time | Progeny |
|---|---|---|
| Influenza virus | 10 hours | 1,000 virions |
| Cytotoxic T cell | 18 hours | 2 T cells |

**Table 1:** The race between virus and cytotoxic T cell.

| The race | Virions | T cells | Virion/T cell ratio |
|---|---|---|---|
| Day 0 | 1 | $10^6$ | $1/10^6$ |
| Day 1 | $1\times1{,}000^{2.4}$ | $10^6\times2^{1.3}$ | 6/1 |
| Day 2 | $2.5\times10^{14}$ | $6.3\times10^6$ | $10^7/1$ |
| Day 3 | $4\times10^{21}$ | $16\times10^6$ | $10^{14}/1$ |

The result: the virus wins, the patient dies.
Adams DD, Lancet 1987; ii: 245.
Hence, cytotoxic T cell clones need to be
1. Large, preformed (no time for expansion).
2. Specific for conjoint virus-MHC antigenic target, so as not to be muffled by the myriad numbers of free virions.
This explains
1. The strength of allograft rejection (Simonsen phenomenon)
2. The need for Zinkernagel and Dohery's MHC restriction phenomenon [4], the presentation of viral antigens to cytotoxic T cells on host histocompatibility antigens, so that the anti-viral immune attack is directed at the virus-infected cells, the virus factories, not muffled by the myriad number of free virions.

**Table 2:** Consequences of the explosive speed of viral replication.

## Mechanism of Immune Tolerance

Parents can react to each other's histocompatibility antigens. They impart to their offspring all the genes necessary for this. Therefore, some mechanism must prevent reaction with self histocompatibility antigens. It was proposed that immunocytes in the foetus are deleted by contact with complementary antigen supported by graft survival after in-utero injection of foetuses with cells from the future donor.

Nossal and Pike, with superb technology, showed that the switch from deletion to reactivity is not a stage in the life of an animal, but a stage in the life of every developing lymphocyte. This explains the continuing influence of histocompatibility antigens on the immune repertoire [5].

## Solution of Transplantation

Henry Kaplan, radiotherapist and researcher, who revolutionised treatment of Hodgkin's disease, found that animals can be made hematological chimeras by total lymphoid irradiation followed by inoculation with allogeneic bone marrow, after which they will accept allogeneic skin and organ grafts from the donor of the bone marrow [6].

## Further Progress

Megan Sykes describes Kaplan's procedure as induction of Full Chimerism. For successful transplantation in rodents, she found it inferior to induction of Mixed Chimerism, in which immunoablation of the recipient is followed by reconstitution with bone marrow cells from the graft recipient (autologous) as well as from the graft donor (allogeneic) [7].

Duncan Adams points out that application of this protocol to

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xenografting from untreated pigs would be a monumental achievement, offering instant and unlimited supply of grafts without rejection problems [8]. Currently popular attempts to modify pigs are based on defective theory and are a waste of time.

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