PANEL V: MECHANISMS OF GRAFT REJECTION

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CHAIRMAN: Dr. Clement L. Markert — Department of Biology, Yale University, New Haven

PANELIST: Dr. Oliver Smithies — Professor of Genetics, University of Wisconsin, Madison

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The format followed was that the panel members discussed one category each under the main topic.

Dr. Billingham presented a brief outline of the current knowledge on mechanisms of graft rejection in which he stressed the following:

(1) The primary response to a homograph (a transplant from the same species) seems to take place in the regional lymph nodes draining the area containing the homograph.

(2) Certain lymphocytes which have a long lifespan are important in the response to the homograph. These lymphocytes can transfer a sensitivity to the homograph to another animal when injected into that animal.

(3) All attempts to transfer this sensitivity to the homograph by serum have failed.

(4) Sir Peter Medawar showed that the primary response to a homograph may also take place in the cellular components of the blood. This was proved by attaching a homograft to its host only by blood supply and noting the appearance of sensitivity to the homograph.

(5) The graft versus host reaction occurs when the homologous graft contains immunologically capable cells and the host has a non-active immunological system. This reaction leads to runting and deaths of the host.

Dr. Wilson discussed various systems and methods by which immunological reactions can be studied in Vitro. One system proposed, included taking lymphocytes from the thoracic duct of an animal with a homograph and placing these cells in a tissue culture of renal cells from the homograph donor. The destruction of donor cells is studied qualitatively and quantitatively. During the experiment it was found that certain lymphocytes, when added, immediately cluster around the donor cells. Within 10-22 hours many of the donor cells have become pyknotic and have stopped increasing in DNA. Immunosuppressive drugs or a reduction in temperature would stop the death of the donor cells but not the agglutination of the lymphocytes around the donor cells. Certain extracts from the lymphocytes destroyed the donor cells but the exact mechanism of destruction is unknown. Quantitatively this study showed that the lymphocytes have the greatest capacity to destroy the donor cells six days after their host has been sensitized. Apparently only 3% of the lymphocytes used actually took part in clustering around donor cells.

A second culture system using peritoneal cells helped in the separation of a MACROPHAGE INHIBITING FACTOR from lymphocytes of TB sensitive animals. This factor may be the unknown destruction factor in the first experiment.

A third culture system using humanleukocytes from two separate donors showed an increase in the total DNA of the cells which varied according to how different the two donors were. The more genotypically different the two sets of cells were the greater was the increase in DNA. Immunologically tolerant cells did not proliferate and showed no increase in DNA.

Dr. Sherwood Lawrence discussed homograft rejection in man. Lymphocytes can

transfer by injection sensitivity to the TB organism from a TB positive person to a TB negative person. The reaction which occurs in TB sensitive people on contact with TB organism is called a delayed sensitivity reaction. The lymphocytes which can transfer sensitivity to TB have been broken down into a "transfer factor" which does the same thing. This "transfer factor" is from the mitochondrial and endoplasmic reticulum part of the lymphocyte. "Transfer factor" is thought to act by inducing host lymphocytes to react against TB carrying macroplages. The reaction above can occur in the form "transfer factor" against homografts. In fact the reaction of delayed TB sensitivity is very similar to homograft sensitivity.

Dr. Dixon talked about antibody mediated antigraft reaction as compared to the other panelists who discussed the lymphocyte antigraft reaction. Dr. Dixon admitted that lymphocytes play the major role in graft rejection but that antibodies have a role in the pathology of glomerulonephritis which is very important in kidney transplants. Also antibodies have a major role in transplants between different species. Antibodies are used to protect an RH woman who carries an Rh+ fetus. The antibodies, which are injected into the mother, combine with the dangerous RH+ antigens of the fetus thus preventing the production of a large numbers of RH+ antibodies by the mother which might lead to the death of the fetus.

Glomerulonephritis has two possible causes. One is the catching of antibody-antigen complement complexes in the glomerulor basement membrane leading to destruction of the basement membrane. Another cause is the production by the body of antibodies against the glomerular basement membrane. Patients suffering from glomerulonephritis of the first causation do reasonably well with Kidney transplants. However, patients producing antibodies against their basement membranes do poorly with Kidney transplants which usually develop glomerulonephritis. To combat this immuno-suppressive drugs are started one month before transplant and appear to help. In fact these drugs are used in patients suffering from glomerulonephritis caused by their own antibodies when their Kidneys are in fair shape. This allows patients to go for years without needing a transplant.