II. Cell Membrane-Associated Antigens

Transplantation of tissues and organs is a widely used technique. It can be performed on the same organism (autotransplantation), between organisms of the same inbred strain (syngeneic graft), between members of a normal population (allogeneic graft) or between individuals of different species (hetero- or xenograft). In the beginning, all grafts look the same. Within a few days, however, a dramatic difference becomes apparent. Only the auto- and syngeneic grafts remain normal and of healthy appearance. The allo- and xenografts become inflamed: inflammation caused by the xenograft is usually more pronounced and appears sooner. Eventually both grafts form a hard crust and are rejected. The speed of the reaction is related to the relationship between the donor and the recipient. The farther the subjects are apart phylogenetically, the faster and stronger is the reaction.

Such reactions were observed at the end of the last century, not only with normal tissues but with malignant tumors as well. Eventually it was learned that this reaction is immunological in nature and that it is caused by differences in so-called transplantation antigens found in normal and malignant tissues.

Within a given population there are no two individuals so antigenically identical that they will retain skin grafts permanently. Monozygotic twins, however, are an exception to this rule. A second exception is inbred strains of animals, i.e., animals bred for many generations by brother-sister mating and selected for antigenic homogeneity. These syngeneic strains are primarily mice and rats, but guinea pigs, rabbits, hamsters, dogs, ducks and fish are also available. The uniqueness of a given individual in any randomly bred population, such as the human population is supposed to be, is guaranteed not by the existence of an unlimited number of individually specific transplantation antigens but rather by endless variation of a limited number of these antigens. This situation can be graphically illustrated by a simple schema (Fig. 1) of hypothetical population containing only five different antigens — A, B, C, D, E. In fact, each species must have more than a hundred such antigens. On this imaginary population individuum 1 will reject tissues from individuals 2 and 3 by reacting against antigen E. Individuum 3 will react against antigen A etc. In a situation with only five antigens and their possible combinations, individual specificity can be provided for 625 individuals; in the case of 100 such antigens, individual specificity can be provided for $100^{90}$ individuals, which is more than enough to assure individual specificity throughout the population, even for some generations at this rate of reproduction.

The transplantation antigens are expressed on the cell surface and in some form even on the endoplasmic reticulum (MANSON et al., 1968). Only the antigens associated with the cell membrane, however, can be responsible for the transplantation reaction. Transplantation antigens are genetically controlled characteristics of the organism,
and basically all cells of the same organism — both normal and malignant cells — contain the same set of such antigens. The inheritance of these antigens is controlled by Mendelian genetics (Tyzzer and Little, 1916, 1924). Snell (1953) later formulated four main conditions which determine the fate of grafts:

1. Tumor isotransplants1, i.e. tumors transplanted within the strain of origin grow progressively and kill all hosts.
2. Tumor homotransplants2, i.e. tumor transplanted within the species but outside the strain of origin, fail to grow, or grow temporarily and then regress;
3. F1 hybrids produced by crossing two inbred strain will grow tumor indigenous to either parent strain3;
4. Only a fraction of mice of an F2 generation, or of a backcross produced by mating to the resistant parent, will grow tumors from the inbred lines involved.

Fig. 1. Immunological reaction expressed in the form of a reflex arc. Initial the antigenic stimulus (A) (skin graft) is recognized as foreign and information about it is carried by afferent way (B) (macrophages?) to immunological centrum (C) (spleen, lymph nodes). Here are produced antibodies and immune cells and carried efferently (D) to the target (foreign skin graft). Finally, the graft destroyed by immune cells (E) (small lymphocytes)

The transplantation antigens can be divided according to their “strength”, i.e. the speed and strength of the transplantation reaction they are able to elicit. This phenomenon has been studied most extensively in mice. The “strong” antigens elicit skin-graft rejection within 10—12 days and the “weak” antigens cause a reaction within 14 or more days. In some strain combinations, the reaction takes up to several months. In every species, several genetic loci occur on the chromosomes on which

1 Current terminology: syngeneic.
2 Current terminology: allogenic.
3 Animals of both parent strains will reject tumors derived from F1 hybrids.