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Immunologic Modification: A Basic Survival Mechanism

Cellular adaptation contributes to tumor growth, allograft survival, and mammalian embryogenesis.

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Changes in phenotypic expression of immunogenicity often contribute to survival of cells or tissues that otherwise would be eliminated by an immune reaction. Such cellular adaptation has been demonstrated extensively in a variety of experimental systems, the diversity of which suggests that this is a basic biological mechanism. Examples of these adaptations induced in vitro and in vivo are (i) altered potential for immune activity in response to undefined physiologic changes resulting from tissue passage in vitro, (ii) modulation of antigen expression induced by exposure to specific antibodies, (iii) alteration of the antigen recognition mechanism by exposure to specific antigens, and (iv) changes induced by exposure of allografts to immunologically unresponsive recipients. Although in the latter case it is initially the response that is modified, there is ample evidence that the tissue against which the response is directed also is affected. Cellular antigens and the responding organism interact in a dynamic way, and, although it is sometimes difficult to define the primary change, both participate in affecting the end result, be it survival or death of grafted cells. Examples with implications for evolutionary significance are drawn from various species, and we did not attempt an exhaustive review of the literature. In particular, we have called attention to changes in immunologic function occurring in cell and tissue culture after exposure to antibodies in vitro and in vivo, after exposure to antigenic material and ribonucleic acid (RNA) preparations, and in the fetal-maternal interrelationship. Such changes in expression of immunogenicity and responsiveness are recorded for hematopoietic and fixed tissues, both normal and neoplastic.

Phenotypic Alteration of Cell Surface Antigens

Since Schlesinger (*1*) has reviewed the work on phenotypic expression of cells in vitro, we present here only a few examples of reversible change in antigenic specificity in order to complete the correlation with other systems.

After an initial adaptation to the environment in vitro, tissue culture cell lines may maintain their differentiated phenotypes for many years (*2*). Although the expression of some traits such as pigment and cartilage formation (*3*) and antigen expression (*4*) may appear lost, they may be recovered either spontaneously or by changing the culture conditions, indicating modification of phenotype rather than selection of genetic variants (*5*).

A greater reduction in immunogenicity induced by organ culture explantation as compared to that induced by cell culture may be associated with a more favorable physiological environment usually obtainable when disassociated cells are used. However, since specificity of cultured cells has not been tested routinely by allotransplantation [terminology defined in (*6*)], modified immunogenicity may have been overlooked when unaltered antigenicity was present. While cellular antigens may be demonstrable by in vitro reactivity with serum or lymphoid cells and by their ability to respond to cellular or humoral reactions in sensitized recipients, these same antigens do not invariably evoke an effective primary immune response (*7*).

The expression of cellular antigens and serum proteins is influenced by the stage of differentiation of the organism and the presence or absence of neoplasia. The time of expression and the quantity of alloantigens on cells of different tissues also varies (*8*). A "thymus specific" antigen detectable only on brain and thymic cells has been identified in several species (*9*). Likewise, antigens present during fetal life may be greatly reduced or absent in adults only to reappear with the development of neoplasia; for example, the carcinoembryonic antigen de-

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scribed by Gold and Freedman normally is present in human digestive tissue only during the first two trimesters of fetal development, but is again demonstrable in adenocarcinomas of the adult digestive system (*10*). Alpha fetoprotein is another fetal antigen found in serum from human, mouse, and rat fetuses, and it is either absent or greatly reduced in adults of these species except in individuals bearing induced or spontaneous hepatomas (*11*). Hepatoma cell monolayers may cease to produce alpha fetoprotein with prolonged culturing in vitro; however, production of this antigen is resumed on return of the tumor to an animal of its strain of origin (*12*). Gamma fetoprotein, another fetal antigen, is associated with a large percentage of diverse human tumors (*13*). Whether fetal antigen production associated with neoplasia results from an altered pattern of gene regulation accompanying neoplastic transformation, changes in cellular metabolism, or other factors remains to be determined.

Modulation of antigen expression also may be induced. The classic example of this phenomenon is described by Boyse and co-workers (*14*). The thymus leukemia (TL) antigen usually present only on thymic cells of certain TL(+) strains of mice is detectable on leukemic cells of TL(−) mice. The TL(+) antigens on leukemic cells and normal thymocytes disappear in cells exposed in vitro or in vivo to antibody to TL, but they reappear in an antibody-free environment. It was proposed (*14*) that the gene controlling expression of thymic leukemia antigen (Tla) fails to undergo derepression during thymocyte differentiation in TL(+) mice but is repressed in TL(−) strains. During leukemogenesis derepression occurs and TL(−) thymocytes become TL(+) neoplastic cells. Examples of antibody-induced suppression of antigens also exist in other systems (*15*).

Similarities exist between antigenic changes in mammalian cells and those occurring in the ciliary antigens of paramecium. Paramecia are immobilized by dilute antiserum from rabbits immunized against specific ciliary antigens (*16*). Clones of paramecia inherit an array of characteristic antigenic types. These antigens are controlled by nuclear genes while the expressed serotypes are under cytoplasmic control. Exposure to antibody or to changes in culture conditions may result in cytoplasmic modifications which in turn induce changes in expression of serotype. However, each clone has a characteristic variability (*17*). An extensive analogy between this phenomenon in paramecia and nongenic alterations of mammalian cells which might favor tumor induction was made by Sonneborn (*18*), while an analogy between the transformation of serotypes in paramecium and modulation of the TL antigen was drawn by Boyse *et al.* (*14*). Other examples of antibody induced changes in antigenicity of mammalian cell phenotypes and their analogy to serotype expression in paramecia were compiled by Schultz (*19*). In premammalian species cytoplasmic modifications brought about by selective gene action made available a mechanism whereby adaptation to the environment occurred more quickly and with less permanence than would have occurred by natural selection of genetic mutants. The availability of such an adaptive mechanism to a mammalian female bearing an antigenically unrelated conceptus may have had an important evolutionary impact. However, cytoplasmic control of gene expression in mammalian cells has not been conclusively demonstrated.

Modification of Immunogenicity by Manipulation of Donor Tissue

Sufficient experimental success in increasing the transplantability of tissue by graft alteration has been achieved to warrant further exploitation of this area. The obvious advantage to be gained by reducing the immunogenicity of grafts is a decrease in the need for prolonged immunosuppression of the recipient.

Control of the graft-versus-host reaction was achieved by transplanting modified bone marrow cells from donors treated with either cellular or subcellular tissue antigens or by treatment of the marrow cells with these antigens in vitro (*20*). The in vitro experiments were designed to evaluate the effect that exposure of marrow cells to antigens might have on the ability of the graft to function. Both unresponsiveness and increased responsiveness could be affected, the results depending on the relative strength of the antigen used for the treatment (*21*). While this approach is potentially useful, its practicability depends on the technical problem of detecting the specific immunogenicity of the antigen used for conditioning the marrow. The ease with which the function of the hematopoietic tissue graft is modified indicated that secondary alterations in the hosts' immunologic function probably contribute to survival of allografts of other tissues much as the developing fetus modifies the subsequent responsiveness of its mother long after parturition (*22*).

Incubation in vitro with antigenic material may alter immunogenicity and responsiveness to other tissues. Helmann and Duke (*23*) induced rejection of syngeneic transplants that had been incubated with allogeneic skin. However, prolonged allograft survival was not achieved by preliminary incubation of the graft with skin from the recipient strain. Similarly, bone marrow cells incubated with erythrocytes from mice of the prospective recipient strain may lead to better survival when transplanted into the lethally irradiated allogeneic as compared to syngeneic recipients (*21*). The result obtained depends on the genetic relationship between the two strains.

Prior treatment of donors in vivo (*24*) or donor tissue in vitro (*25*) with various antiserums has extended allograft survival. Likewise, nucleic acid preparations have been used to produce altered cell functions. By manipulation of the culture medium, Amos *et al.* (*26*) were able to induce chicken fibroblast cells incubated with either *Escherichia coli* RNA or mouse myeloma RNA to produce proteins antigenically similar to that coded for by the corresponding bacterial or mouse protein. Similarly, Guttmann *et al.* (*27*) caused rejection of syngeneic mouse skin grafts by their exposure to allogeneic RNA in vitro. Conversely, Lemperle (*28*) prolonged mouse skin allograft survival across both histocompatibility barriers H-1 and H-2 by incubating donor tissue with RNA or deoxyribonucleic acid (DNA) from the recipient strain. Prolonged survival of canine kidney also was induced by incubation of donor tissue or organ in various RNA preparations (*29*). Specificity of the RNA source did not appear to be required for graft prolongation, indicating that the mechanism does not involve induction of a genetic change.

Immunogenicity of tumors also was decreased by a single intermediate overnight passage in allogeneic mice of the prospective recipient strain (*30*). This short-term passage in vivo

produced a modified transplantation behavior similar to that described below for tumors modified by passage in organ culture.

Organ culture has been used to precondition normal endocrine tissues for improved growth in allogeneic hosts. In these early studies, survival of the grafts was not conclusive or the grafts were placed into immunologically privileged sites (*31*). However, more recently, Swaen reported improved growth of rat hepatoma allografts by explantation in organ culture for 2 weeks prior to subcutaneous transplantation to immunologically immature animals (*32*).

Short-term (24 hours to 4 weeks) organ culture explantation of a variety of mouse and rat tumors conditioned them to grow as allografts (*33*). The production of this modification was independent of the media or temperature and occurred with or without antibiotics or fetal calf serum. However, results vary since some tumors were maintained for up to 8 years, some were lost after one to three passages in allogeneic strains, while others were not modified. A testicular interstitial (Leydig) cell tumor which had been carried for over 10 years in castrate syngeneic males without losing its strain specificity, hormone production, or hormone dependency was conditioned to grow in H-2 histoincompatible mice. This conditioning was strain specific and reversible by a single passage in the strain of origin. The modified tumor was rejected by specifically sensitized allogeneic recipients, indicating that the change did not result from antigen deletion (*33, 34*).

Modification of the allogeneic recipients of these altered tumors is indicated by their decreased response to the nonmodified tumor counterpart and to skin allografts syngeneic with the tumor strain (*34*). In some recipients the growth of modified tumor allografts was prevented when unmodified tumor tissue was injected 1 week later. However, when the altered tumor did grow, the unaltered line was accepted in about half of these recipients. In addition, a significantly prolonged acceptance of skin allografts syngeneic with the tumor occurred even when the tumor was rejected. Other examples of host conditioning with tumor tissue (*35*) and normal tissue (*36*) exist. Thus, conditioning of a host to accept nontreated tissue by prior exposure to tissue of the same specificity may be a generally occurring phenomenon that indicates host modifications subsequent to allograft exposure also contribute to graft survival.

Tumor lines modified by in vitro passage do not elicit detectable levels of serum hemagglutinins against the donor strain, and the ability to accept allografts is not passively transferred with serum or cells from allograft hosts (*34*). However, spleen cells give an unaltered graft-versus-host reaction in hybrid mice produced by reciprocal crosses (*37*). This unaltered reaction is similar to that observed in rats receiving successful kidney allografts (*38*). These observations are not consistent with the classical concepts of tolerance or enhancement.

Prolonged survival of ovarian allografts also was conditioned by passage in vitro prior to implantation into H-2 incompatible (*39*) or into outbred (*40*) recipients. Allograft survival across H-2 barriers in mice and HL-A barriers in humans after donor skin culture recently was reported by Summerlin *et al.* (*41*). However, attempts to confirm Summerlin's observations on the transplantation of cultured skin have not been successful (*42*).

Graft Adaptations Induced by Exposure to a Modified Host

Graft modification may be induced by passage through an unresponsive host (*43–45*). Barrett and co-workers found that a single passage of a tumor through an F_1 hybrid between the tumor's strain of origin and an allogeneic strain altered the frequency of takes when the tumor was passaged into backcross progeny of these two strains (*43*). By enclosing tumors in cell-impermeable chambers, Klein *et al.* (*44*) showed that direct contact with host cells was not needed to induce these changes and they also found no evidence for immunoselection of cells from a heterogeneous population. Since the modified and nonmodified cells behaved similarly when transplanted to preimmunized F_2 hosts, the phenomenon involves a change in ability to elicit a response rather than in the hosts' ability to respond. Another type of reversible F_1 adaptation was observed by Huemer (*46*). Passage of a tumor through an F_1 hybrid abrogated the tumor's susceptibility to the hybrid resistance phenomenon (*47*). Adaptation was reversed upon passage of the tumor through hybrids other than those in which the modification was induced.

Enhancement represents another mechanism contributing to host adaptation, producing an indefinite prolongation in survival or delayed regression of an allograft as a consequence of specific antigraft antibody in the host. At least two elements are involved: (i) interference with the hosts' immune response by enhancing antibody and (ii) alterations in the graft. Although the mechanism remains unclear, the peripheral action of blocking antibodies cannot account for all of the existing observations (*48*). Graft adaptation coupled with host adaptation probably has not been adequately considered as a factor affecting survival of the graft. However, it has been suggested that physiological alteration of the graft may contribute to its survival (*49*). Amos and co-workers (*50*) demonstrated histochemical changes in enzyme concentrations following enhancement of ascites tumors; but similar changes were not demonstrable in the strain A sarcoma 1, growing in C57BL/Ks mice as an enhanced solid tumor (*51*).

Although allotransplantability of enhanced tumors occurs, it may be lost spontaneously after several transplant generations (*30*) or upon passage through the strain of origin (*52, 53*). The acquired allotransplantability of these tumors and the observation that an animal bearing an enhanced tumor may reject a second tumor from the same source (*49*) is further evidence that tumor adaptation contributes to their survival. Variations in serial transplantability, in the reversibility, and in the specificity of the alteration are present in enhanced grafts as well as in those modified by other procedures and probably reflect inherent differences in a particular graft-host combination.

There are numerous examples of reversible graft adaptations occurring during growth in nonspecifically and specifically immunoincompetent recipients. Parks and Jacobs, working with the same tumor-host combination employed in the organ culture system discussed above, demonstrated adaptation of the BALB/c tumor in DBA/1 mice after the tumor was passaged through recipients that were either neonatally thymectomized, or treated with either rabbit antiserum to mouse brain, or treated with a mitomycin C inactivated BALB/c tumor (*54*). However, differences did occur between

modified lines in the percentage of takes and ability to grow in specifically sensitized recipients. Yaffe and Feldman (*55*) demonstrated that grafts of a C57BL tumor were accepted by irradiated C3H mice protected with C3H fetal liver cells. This tumor line then acquired the ability to grow in untreated C3H mice. Reversion to strain specificity was reestablished by one passage in C57BL or (C57BL × C3H)F_1 recipients. Reversible tumor allotransplantability after fetal passage (*56*) and altered strain specificity after passage in either newborn or irradiated adult mice (*53*) have been reported. Although the mechanism accounting for these reversible changes in transplantability is unknown, immunoselection cannot account for the initial adaptation. However, selection of antigenically simplified cell populations may subsequently occur leading to an irreversible loss of specificity (*57*).

Allografts also may be conditioned by residence in immunologically privileged sites such as the anterior chamber of the eye. Survival of thyroid grafts in random-bred guinea pigs occurred when the grafts were conditioned by residence in the anterior chamber of the eye prior to transfer to a subcutaneous site in the same animal (*58*). However, Warden *et al.* (*59*) using histoincompatible rats found that transfer from the anterior chamber to a subcutaneous site of a *different* animal caused rejection of the conditioned thyroid graft. They attributed adaptation to the host rather than to the graft. An alternative explanation is that both the graft and host adaptations contribute to survival in the initial host.

Lymphoma allografts were conditioned to grow by partially enclosing them in Lucite cylinders (*60*). These grafts became serially allotransplantable for up to 11 passages but regained specificity after a single syngeneic passage. Saal *et al.* (*60*) present evidence suggesting that tumors implanted in this artificially constructed privileged site in hosts with lowered immune resistance (the Lucite cylinders have a nonspecific immunosuppressive effect) induce protection by blocking antibody comparable with that proposed by Hellström *et al.* (*61*). It is assumed that, in the absence of adaptation in immunologically privileged sites, the failure to expose the graft to either the efferent or afferent arc of the immunologic reaction would result in allograft survival. The adaptation of tumors placed in Lucite cylinders may have resulted from a combination of lowered response both on the efferent and afferent level, even though some exposure to reacting host cells and antibody occurred.

The successful maternal-fetal relationship has been attributed to the placenta being a privileged site. However, the reduced responsiveness of females toward paternal antigens of their hybrid progeny was demonstrated by Breyere and Barrett (*62*). It has been shown that both the mother and her progeny were affected by their interrelationship (*22, 63*). A successful pregnancy may require a qualitative change and reduction in phenotypic expression of antigenicity of the fetus. The reduced immunogenicity of the fetus in turn induces a reduction in responsiveness of the mother to the specific alloantigens of her fetus. The resulting threshold effect represents an equilibrium between antigenicity and responsiveness and requires mutual contact. The tenuous nature of this equilibrium is illustrated by experiments in which multiparous female mice have a reduced response to alloantigens of their female progeny but exhibit an accelerated response to male progeny (*63*). The time of expression of the Y antigens of male progeny or the way these antigens are expressed may have contributed to the production of an appropriate antigenic stimulus, disrupting the equilibrium required for unresponsiveness and resulting in sensitization.

There is an obvious survival advantage of an adaptive mechanism lowering the immunogenicity of the fetus while reducing the responsiveness of the mother. This fundamental mechanism could be responsible for all tissue adaptation, whether embryonic, normal, or neoplastic. However, reduced responsiveness is maintained regardless of the role of host—that is, the mother of a developing fetus, the recipient of an organ graft, or the victim of both primary and metastatic neoplasia. In each case growth or survival occurs in the presence of demonstrable antigenic differences. One of the challenges to current biomedical research is to learn how to take advantage of this fundamental mechanism in order to control allograft survival and thus reduce or eliminate the necessity for prolonged immunosuppressive therapy. The feasibility of this approach already has been demonstrated in various types of marrow transplantation experiments in which the severity of the graft-versus-host reaction was controlled by marrow donor selection or by modification of the bone marrow in vitro before inoculation into lethally irradiated recipients (*20, 64*). Similarly, marrow transplantation experiments were used to determine the extent of the maternal influence on the immune response. By selecting the appropriate inbred strains of mice, it was found that tissue immunogenicity and responsiveness to specific tissue antigens could be either decreased or increased depending upon the genotype of the maternal ancestors (*65*).

Immunotherapy of tumors could be potentiated by manipulating this same mechanism in the direction of increased, rather than decreased, responsiveness. Such therapy, for primary and metastatic cancer, should utilize methods which would both increase the immunogenicity of the target cells and increase the ability of the host to recognize these cells. Such an approach has been successful in an experimental system consisting of combined treatment with BCG (*Mycobacterium bovis*, strain BCG) and neuraminidase-treated tumor cells to cause regression of established tumors (*66*).

The successful experimental manipulation inducing functional changes in bone marrow transplants results from the exposure of undifferentiated, immunologically immature cells to an environment containing the conditioning antigen (*67*). Similar modifications occur as a result of the maternal-fetal relationship. Although the mechanism by which these influences are transmitted through the maternal line has not been determined, all available evidence indicates that it represents a cell surface change induced by contact with antigenic substances and probably is a modification of the antigen recognition system (*63*). The similarity between the ova transfer technique (*68*) as a "culturing" of homozygous fertilized ova in the uterus of an allogeneic foster mother, and the organ culture methods described by Jacobs and Huseby (*33*) becomes apparent when the types of adaptation occurring in both experimental systems are compared.

Organ transplants may persist when immunosuppressive therapy is discontinued or reduced (*69*). Survival has been attributed to (i) acquired immunologic tolerance, (ii) immunologic enhancement, (iii) replacement

of stromal tissue of graft genotype with that of recipient genotype, or (iv) induced graft adaptation. These mechanisms are not mutually exclusive and could act together in perpetuating the graft. Under experimental conditions graft adaptation may be demonstrated in several ways: (i) rejection of a second transplant from the donor of a well-established allograft while the first graft survives, (ii) acceptance of an established allograft when it is transferred to an untreated recipient syngeneic with the first, or (iii) functional changes in the allograft. However, such apparently unequivocal evidence for antigenic or immunogenic modification can be questioned if one assumes that survival is associated with replacement of donor passenger leukocytes by those of the host. Guttmann *et al.* (*70*) reported that a hybrid kidney allograft from a parental strain host treated with antilymphocyte serum could be successfully transferred to an untreated recipient. They proposed that survival was due to loss of leukocytes from the renal interstitium. Steinmuller (*71*) attributed skin graft survival to replacement of passenger lymphocytes by those of the host. However, in testing this hypothesis, it was found that varying the genetic relationship between donor and recipient produced opposite results in the same experimental system (*72*). Therefore, it can no longer be assumed arbitrarily that replacement of passenger lymphocytes accounts for all cases of allograft adaptation. Current knowledge does not allow one to localize the site of adaptation beyond that of the graft as a whole.

Conclusion

The obvious survival advantage of mutual adaptation in the maternal-fetal relationship may account for the evolutionary development of this adaptive process. Although the mechanism responsible for adaptive changes in tissue immunogenicity is unknown, adaptation does occur in numerous situations and is indistinguishable from that demonstrated in the maternal-fetal test system. Recent advances in technology for elucidating the molecular structure of the cell membrane should make research into the mechanism of these changes a feasible goal. Such studies would enable comparison of these changes in a variety of systems and might indicate whether adaptations observed in widely different situations are, in fact, brought about by a single basic mechanism. The existence of these adaptations has important implications in developmental embryology as well as in a variety of experimental and clinical fields. Certainly in the case of tissue and organ transplantation any decrease in immunogenicity is desirable; however, such changes also would contribute to the survival of undesirable tissue in the case of the cancer host. Control of this system may be achieved by purposeful induction of phenotypic changes leading to increased or decreased immunogenicity to produce the desired result, for example, rejection or acceptance of antigenic cells, tissues, or organs. Additional studies with induction of tissue adaptation as an adjunct to immunotherapy are necessary. Investigations to determine the mechanism by which adaptive changes are induced would aid in specifically directing them toward the desired end.

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Immigration Composition and Population Policy

Recent changes in immigration policy and composition have implications for proposals to alter immigration.

Charles B. Keely

The reports of the Commission on Population Growth and the American Future increased public awareness of the impact of immigration on the United States. The commission reported that about 20 percent of current population growth in the United States is due to immigration (*1*). This is about half the amount that contributed to population growth in the peak immigration years before World War I, but greater than the contribution during the period of the baby boom following World War II. The increased importance of immigration in U.S. population growth, therefore, reflects the effects of changing birth rates as well as the amount of immigration. But the point was driven home by the population commission. Immigration is not just a marginal phenomenon whose importance for American society ceased with the restrictive legislation of the 1920's.

Since the final report of the population commission was made, debate on immigration policy has been increasing, centering primarily on the size of net alien immigration, including the separate problem of illegal entrants. The roles of immigration policy in drawing foreign-trained professionals to the United States, in the retention of foreign students, and in the American labor market in general have also been argued, but these concerns are clearly subordinate to the growth issue. Public discussion is beginning to mirror the hotly contested debate of the population commission (*2*).

The lines seem to be clearly drawn between two value positions. The encounter centers on whether the population effects of immigration will overshadow the economic, social, and humanitarian values which have only recently emerged as the major influences in immigration policy. Those interested in achieving a stationary population for the United States are among the leading proponents of the view that immigration, legal and illegal, is a growth factor and, therefore, to be negatively valued. In effect, they argue that the population question is of such magnitude that population effects ought to be the paramount criteria in developing immigration policy. In this perspective, other criteria ought to play a part, but they should be subordinate to a policy of achieving a stationary population.

The opposition argues that it is yet to be demonstrated that immigration is a major contributor to whatever population problem the United States has. They maintain that the rates and percentages quoted by the no-growth advocates in advancing their argument that immigration is a major cause of population problems are, to a not insignificant extent, statistical artifacts (*3*). Citing one of the papers prepared for the population commission, this view maintains that there is no indication that drastically reducing legal immigration will appreciably affect the speed with which the United States achieves zero population growth (*4*, pp. 589–603). Illegal immigration is a different issue, they maintain, and legally admitted aliens ought not to be made the scapegoats of law enforcement failures due to understaffing of the Immigration and Naturalization Service.

In exploring these issues and evaluating these contentions, I shall review the current policy and the results of that policy on demographic and economic characteristics of recent immigrants. I shall also analyze and evaluate the quality of data on immigration.

Current Immigration Policy

The Immigration Act of 1965 ended a 44-year policy of using national origin as one of the major criteria for admitting immigrants. The development of the restrictive policy in the United States has a long and involved history dating back to the Chinese Exclusion Acts of the 1880's at the beginnings of federal immigration policy. Over the years, many devices have been used to limit the amount of immigration, including the quota system, numerical ceilings, and outright racial exclusion. In addition, mechanisms for

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