CYTOTOXIC ANTIBODIES IN RENAL TRANSPLANTATION

THESIS

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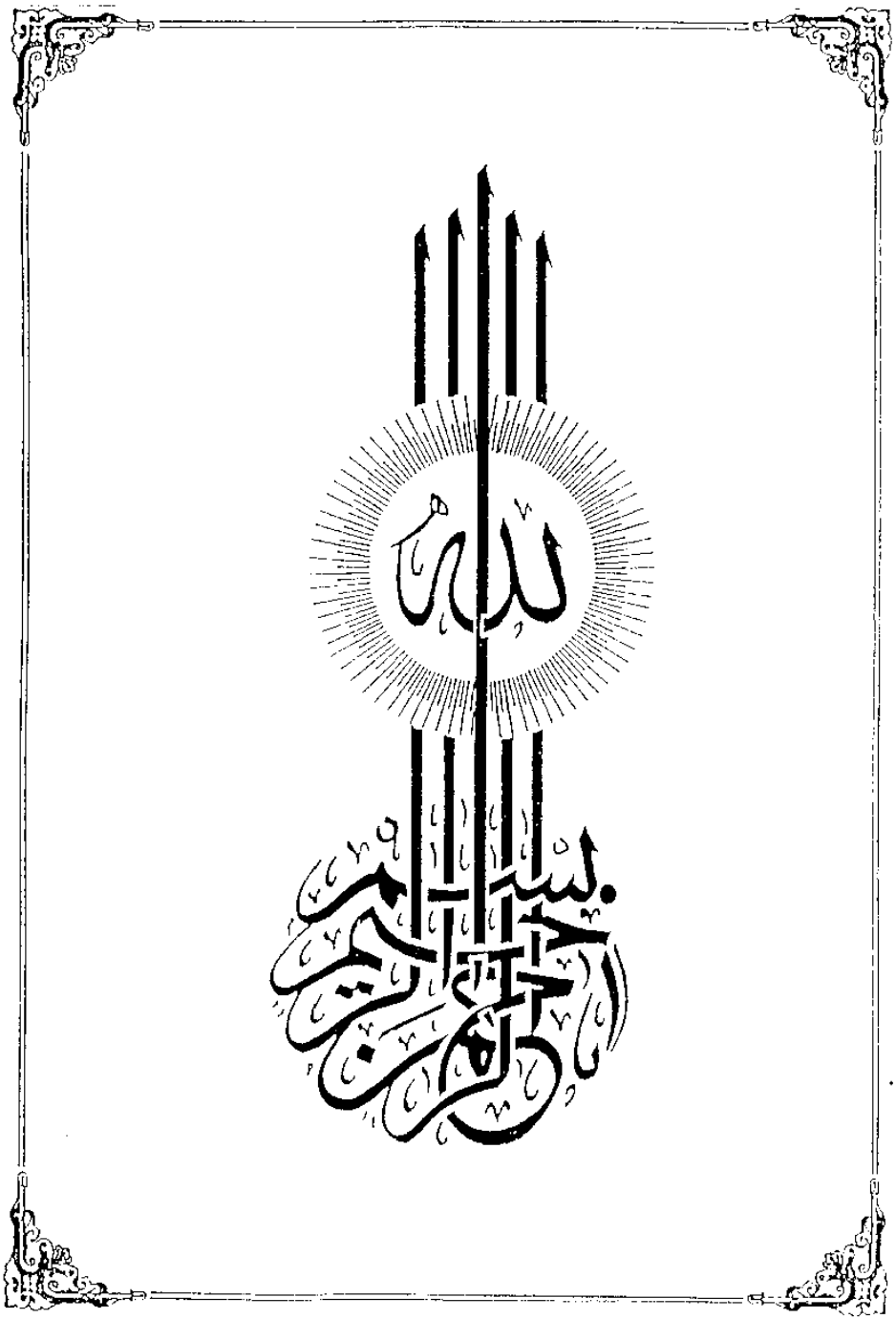

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INTRODUCTION

It has been established that the presence of activated T lymphocytes is an absolute requirement for acute cellular allograft rejection (Hall and Dorsch 1984).

So, it is not surprising that most centers continue to evaluate the relationship of positive or negative cytotoxic crossmatches to either graft survival or rejection. (Kolbec et al., 1984).

Although the role of anti class I antibodies to mediate hyperacute rejection have been established, their pathogenic role in acute rejection remain ill defined, (Karuppan et al.,1990).

AIM OF STUDY

The aim of this study is to detect the presence of cytotoxic antibodies in renal transplant recipients and to correlate their presence with the graft survival and function.

REVIEW OF LITERATURE

RENAL TRANSPLANTATION

Clinical transplantation became a reality in 1954 with the first successful transplantation between identical twins at the peter Bent Brigham hospital. (Tilney, N.L. 1986).

The evolution of organ transplantation, however, dates back to the early 1900's with the use of autografts, allografts, and xenografts in animals and humans (Hume,et al., 1955). During this period, the notion of foreign tissue rejection due to the host immunologic response lay the ground work for investigation in the field of histocompatibility, or transplantation antigens, as well as research in manipulating the host's immune system to allow successful alloengraftment. Although sublethal total body x-irradiation was shown to be effective in prolonging graft survival (Murray,et al.,1960), the discovery of the antimetabolite 6 mercaptopurine (6-MP) in 1959 by Schwartz and Damashek was a major milestone in the allogenic organ transplantation. These investigators demonestrated that 6-MP produced immunologic tolerance in rabbits. 6-MP was later shown to prolong graft survival in dogs (Calene, et al., 1962;Zuhoski et al.,1961).

Its imidazole derivative, azathioprine, now used clinically, set a precedent for the use of chemical immunosuppression. Since then, the immunosuppressive armamentarium has grown to include corticosteroids, cyclosporin A, polyclonal antilymphocyte or antithymocyte globulins, pan-T-cell monoclonal antibodies (MAbs), and MAbs against cell surface proteins involved in the immuneresponse. When successful, kidney transplantation has allowed remarkable rehabilitation of patients with end stage renal disease (ESRD) and is an established mode of treatment for this disordes. The observed 3-year patient survival was reported to be better with transplantation (living related donor, 91 percent; cadaveric donor, 78 percent). than with dialysis (56 percent) in an analysis of 76.000 patients with end stage renal disease between 1977 and 1980 (Krakauer, et al., 1983). This analysis however, which showed an apparent superior patient survival rate with transplantation contains some selection because younger and healthier patients undergo transplantation. This comparison therfore does not take into considration important variables such as age and comorbid conditions (e.g diabtes, cardiac disease) that have an independent influence on

survival.

Multivariate analysis to adjust for the effect of these independent co- variants on observed patient survival has shown that, where as living related transplant rec ipients have superior results (90 percent at 5 years), difference in 5 years), There was no difference in 5 years surival between cadaveric donor transplant receipients and patients treated with dialysis. (Hutchinson,et al., 1984). Among transplanted patients, however, 1- year patient survival has improved over the past decade from about 85 to 93 percent (Bethesda 1989). This improvement in mortality is explained in part by optimization of receipient health before transplantation, advanced surgical technique, and a change in the philosophy of transplant teams to limit cumulative exposure to immunesuppressive drugs. One year graft survival has increased from 86 percent in 1982 to 89 percent in 1987 for living related transplant, and from 65 percent in 1982 to 77 percent in 1987 for cadaver transplants (Bethesda 1989). This may be related to the use of cyclosporin A. Certain patient subgroups tend to have poorer graft outcomes - the elderly, blacks and diabetic patients.

Finally, despite the recent improved first year graft survival rates with the newer immunosupperssive modalities, all grafts (with the exception of identical twins and two haplotype, HLA matched, living related donor transplant) are subject to relentless decline in function. This decline is thought to be due to the combined effects of chronic rejection, hyperfilteration injury secondary to reduction in nephron mass, and chronic systemic hypertenstion.

MAJOR HISTOCOMPATIBILITY COMPLEX

The antigenic stimulus for initiation and progression of the rejection response to grafted tissue is provoked by cell surface molecules that are polymorphic i.e. They vary in structure from individual to another individual, and these differences are treated as foreign intruders to be recognized and destroyed. Transplantation antigens are classified according to their relative potencies in eliciting rejection as either major or m inor.

The major antigens in all mammalian species studied are encoded by a closely linked series of genes called the major histo compatibility complex (MHC). The MHC was first defined in mice by Grorer and Snell, (Grorer 1937 ; Snell, 1948) as responsible for rapid rejection of tumor transplants between inbred strains of mice. This antigen system was called H-2 and was found to function in rejection of normal tissues as well.

Rejection elecits serum antibodies that are used for typing of H-2 antigens. It was subsequently shown that cytotoxic T cells also arise in response to H-2 differences,

and that the H-2 genes are all clustered in a single region on chromosome 17 (Klein 1977.Shreffler 1975).

Except for some details of the ordering of genes, the human lymphocytic antigen (HLA) and rat (RT1) MHC regions are homologous. HLA is located on the short arm of chromosome 6 (Dausset J. 1958 ; Lamm,et al.,1974). The species chromosome number are different only because they have not been numbered in a manner reflecting the location of actual genes.

Transplants compatible for the MHC antigens can still be rejected because of minor antigen incompatibilities but not with the same intensity as with MHC-incompatible grafts. Modification of rejection by drugs or other means is more readily accomplished when the donor and receipient MHC antigens are matched. Extensive work in the mouse skin graft model with a large number of differing major (H-2) and minor incompatibilities has shown (Graff et al.,1966).in general that the sum total of multiple non H-2 (minor) incompatilities, once the receipients has become immunized to such antigens, can be equal to the strength of the H-2 barrier alone in the unimmunized, or first set, rejection

response. For MHC or non MHC barriers, when a second graft is placed from the same donor, it is rejected at an accelerated pace (second set rejection).

Discernment of first versus second set rejection phenomenon in humans was first made by Holman in 1924, with skin grafts in burn patients. During second world war, the problem of extensive burn injuries prompted the initiation of fundamental studies in skin grafting by Medawar in 1924 . Together with the emerging concept of a major transplantation antigen system (Gorer,P.A. 1937;Snell G.D.1948). These studies laid the ground work for the developement of clinical transplantation in the second half of the 20^{th} century.

Although the initial discovery and definition of the MHC came from studies in transplantation, its central role in the initiation and expression of the immune response in general has become increasingly evident. The ability to produce an efficient immune response to many antigens is inherited in a mendelian autosomal dominant fashion and the controlling genes, called Ir for immune response,are of the MHC. In fact, the failure to mount a response to a peptide antigen may be attributed to a genetically determined inability to bind the