IMMUNOSUPPRESSION AND IMMUNOPOTENTIATION

THESIS

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BY

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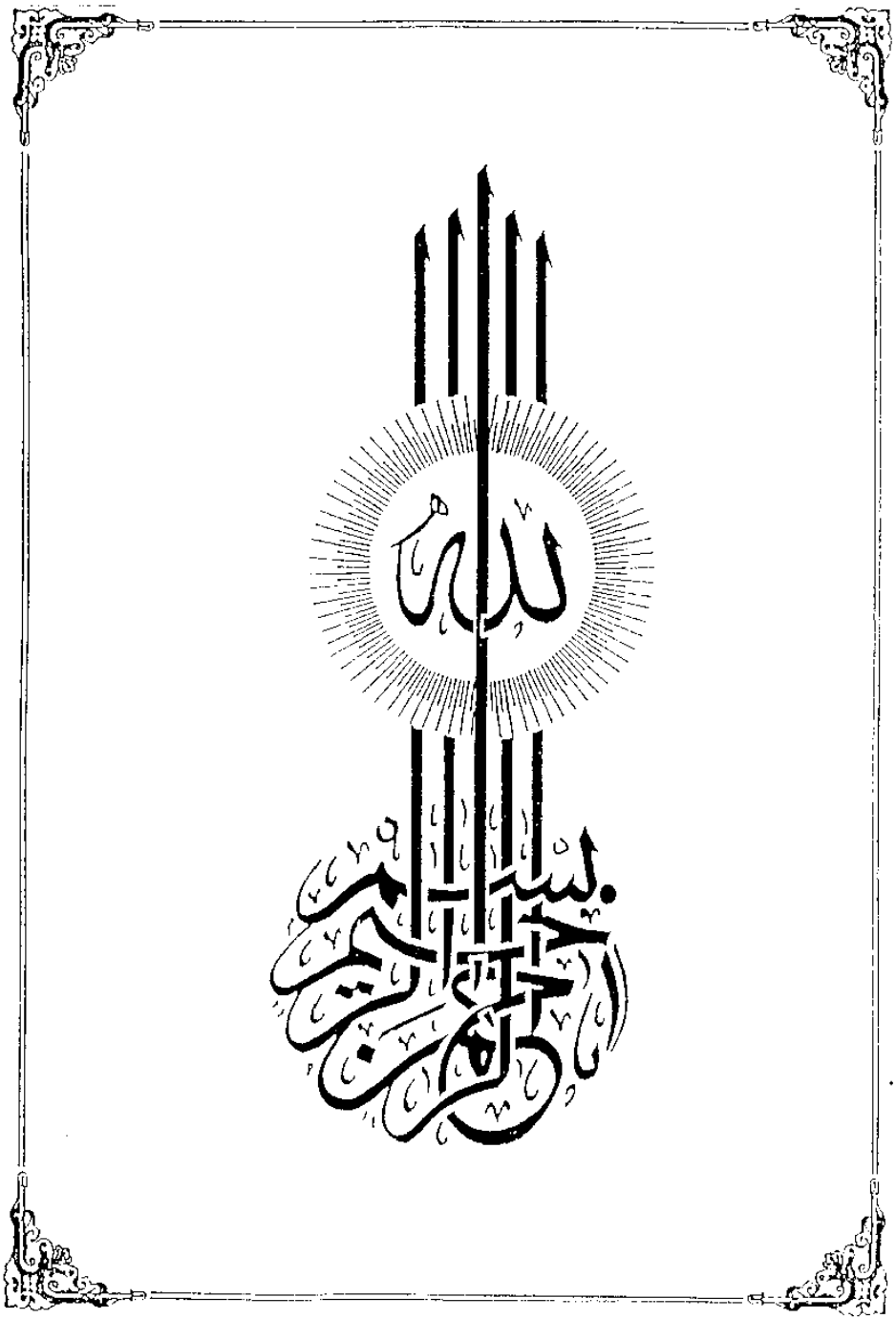

ABBREVIATIONS

Antibody - dependent cellular cytotoxicity	ADCC
Antiglomerular basement membrane	Anti-GBM
Antilymphocyte globulin	ALG
Antilymphocyte serum	ALS
Bacille-Calmette Guérin	BCG
Corticosteroids	CS
Corynebacterium parvum	CP
Human leukocyte antigen	HLA
Interferon	IFN
Interleukin	IL
Major histocompatibility complex	MHC
Messenger RNA	m-RNA
Methanol extraction residue of BCG	MER
Migration inhibitory factor	MIF
Mixed lymphocyte reaction	MLR
Molecular weight	MW
Natural killer	NK
Prostaglandins	PGs
Rhesus	Rh
Thoracic duct drainage	TDD
Total lymphoid irradiation	TLI
Transfer factor	TF

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INTRODUCTION

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Immunosuppression can be defined as an acquired or artificially induced form of unresponsiveness, in which the host is rendered incapable of responding immunologically. All forms of immunosuppression are not restrictive and lead to a diminution of responsiveness directed not only to the specific antigen, but also to a wide variety of unrelated antigens, with the exception of specific antibody, which leads to a specific suppression of antibody synthesis. These agents may be used in conjunction with specific antigens to induce specific tolerance (Bellanti, 1971).

Immunosuppression differs from immunologic tolerance. Immunologic tolerance can be defined as the inability to respond to a specific antigen, due to immature or incompetent immunologic system, the genetic constitution of the host (Dresser, 1976). Tolerance may occur as a natural or as an acquired event, it causes highly restrictive unresponsiveness directed only towards the antigen which initiated it. The duration of tolerance may be permanent (Thomson, 1976).

Suppression or destruction of lymphoid cells had been observed as early as 1899 by Metchnikoff (Bellanti, 1971). Shortly thereafter Smith , (1909), demonstrated that passively administered specific antibody given concomitantly with antigen would lead to a suppression of the immune response. At the same time, Metchnikoff and Besredka, (1902) prepared antileucocyte antisera and observed that such antisera possessed cytotoxic activity against leukocytes. Immunologic tolerance also called immunologic unresponsiveness was observed by Felton, (1942). Medawar and his collaborators (1935) performed careful experiments on mammals, their studies on transplantation formed the basis for subsequent research on acquired immunologic tolerance and are of fundamental importance for the problem of tissue grafting (Grabar, 1982).

Immunosuppressive agents may be used either in the prevention of an immune response (as in the prevention of Rh sensitization) or in therapy (as in the treatment of systemic lupus erythematosus). Immunosuppressive agents have been used extensively and effectively over

the past two decades. Except for the small proportion of transplants performed between identical twins, all of the many hundreds of successful kidney transplants carried out each year depend absolutely on the effectiveness of these agents. In addition, much of the marked improvement in the prognosis of many diseases as the nephrotic syndrome is due to their use (Gabrielson and Good, 1967).

However, patients given immunosuppressive agents are rendered immunologically incompetent and are exposed to infection from a wide variety of opportunistic agents, including viruses, parasites, fungi and bacteria (Bellanti, 1971). More fundamentally disturbing are reports of the development of malignancy as a sequelae of immunosuppressive therapy (Kabat, 1968). Therefore, in using them, it is essential to know what is established about their beneficial and bad effects and to understand their mode of action as present knowledge permits (Grabielson and Good, 1967).

Immunopotentiation, on the other hand, means the enhancement of the immune response, an increase in the

rate at which the immune response develops, an increase in the intensity or level of the response, a prolongation of the response, or the development of an immune response to an otherwise non-immunogenic substance (Allison, 1979). The interest in immunopotentiation developed when Jenner in 1798 discovered that inoculation with cowpox crust protected against small pox (Weir, 1977).

The proposal of the germ theory of infectious diseases by Louis Pasteur in 1847 and the confirmation that many important life-threatening diseases are caused by microorganims soon led to a search for the factors that might protect individuals from the consequences of infection. Several workers tried to develop a nontoxic but still immunogenic preparation by treating bacterial toxins with various chemicals such as formol which was used by Eisler and Lovenstein (1915) for tetanus toxoid and by Glenny, (1921) for diphtheria toxin (Grabar, 1982).

Clinical observations made by physicians in the last part of the nineteenth century led to initial studies on immunopotentiation as an attempt to control cancer in man. Several patients with inoperable or incompletely removed malignant neoplasms were noted to

have regression of tumour following an attack of erysipelas. Hence, the beginning of treating cancer patients with a variety of bacterial toxins e.g.: Streptococcus and Serratia marcescens (Thomson, 1976).

Early studies on antibody production also led to the realization that certain combination of antigens could increase the antibody response. Furthermore, it was discovered that guinae pigs injected with tuberculosis produced more antibody to certain antigens than did non-injected animals (Bast et al., 1974). This phenomenon of enhancing antibody response became known as an adjuvant action (White, 1976).

Moreover BCG exerts a favourable effect against a variety of oncogenic viruses. The successful treatment of cancer with immuno-adjuvants is well demonstrated both experimentally and clinically (Bast et al., 1974).

As suggested earlier, everything - including vaccination - which involves a stimulation of a previously non immune state could be termed potentiation. But now, immunopotentiation is considered to be limited to those

states in which there is an increase in the immune response above that which can be achieved by injection of antigen alone.

Preliminary observations suggest that immunopotentiation is capable of modifying resistance to a variety of diseases including cancer, immune deficiency disorders, and chronic infections. However considerable progress in basic knowledge regarding these agents is crucial to their successful application, and this will lead to new approaches in immunopotentiation.

Aim of the Essay:

The prevention or reversal of established immune responses as well as its enhancement has become increasingly important in many clinical conditions.

Also the use of agents which enhance or suppress immune responses in experimental research and the understanding of their action at cellular and molecular levels provides a mean for analyzing the different steps involved in the normal immune response.

So the aim of this review is to discuss in details immunosuppressive and immunopotentiating agents, their mode of action, their major potential use in different clinical situations and the main complications encountered during their use.

REVIEW OF LITERATURE