STUDY IN

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THESIS

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By

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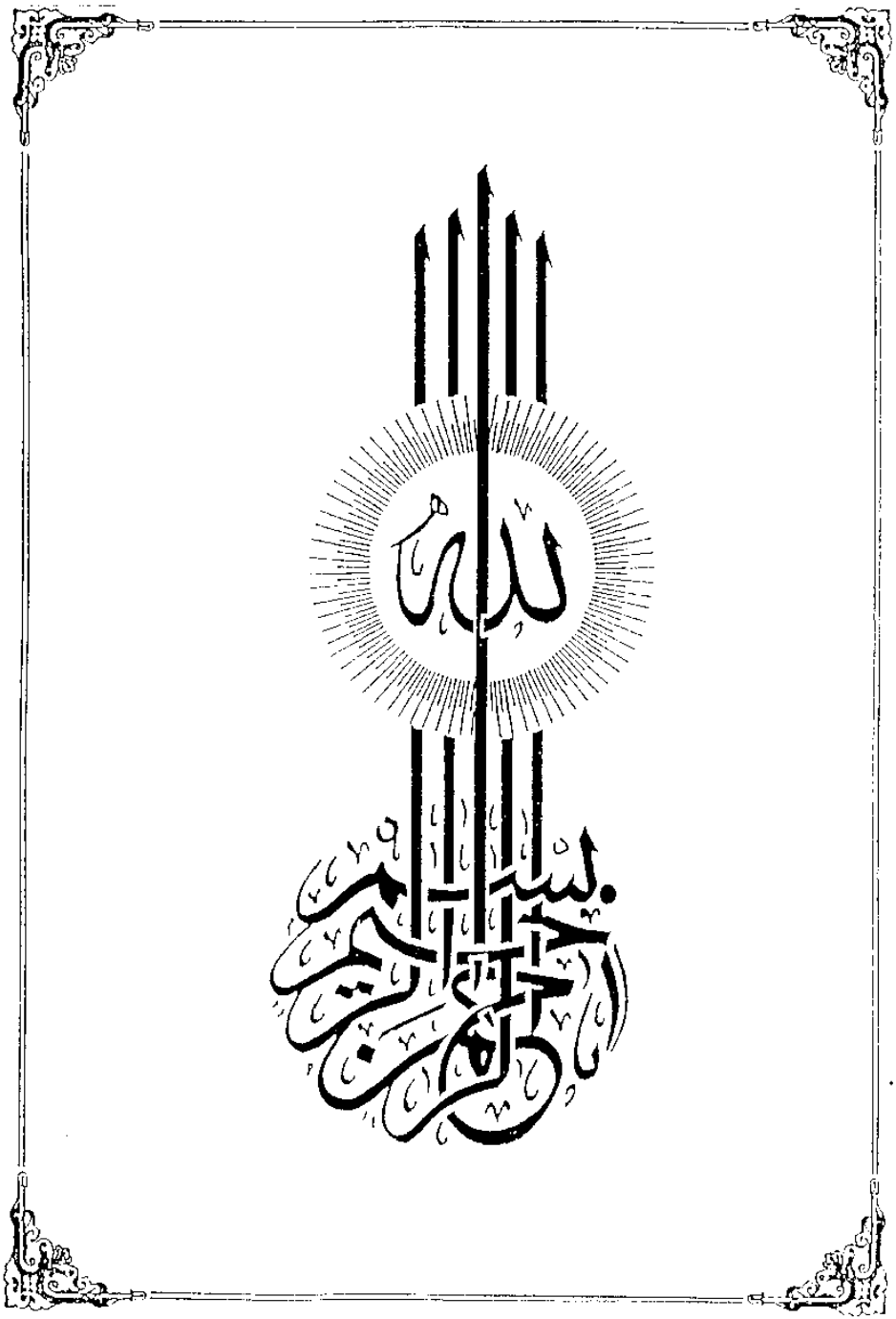

C O N T E N T S

INTRODUCTION AND HISTORY

Immunotherapy is the treatment of disease by active or passive immunization or by the use of agents designed to potentiate, suppress or modify the actions of immune cells.

Classically, immunotherapy referred to passive immunisation through the use of serum of gamma globulin that confers temporary protection by transferring to one host antibodies actively produced in another. A specialized application of immunotherapy is its use in immunosuppression and prevention of isoimmunization.

The meaning of immunotherapy has been broadened to include the use of immunopotentiators, agents used in treatment of cancer and in hyposensitization therapy of allergy.

The complexity of the term has been increased by the extension of its meaning to include the replacement not only of antibody, but also of immunocompetent lymphoid tissues, e.g., bone marrow and thymus, or their products, e.g., thymosin and transfer factor.

It has long been known that numerous infectious diseases develop only once in a given individual, but only at the begining of the eighteenth century was the first vaccination achieved. Vaccination from man to man was

introduced in 1721 in England. However, the method was too direct and included risks of severe reactions and transmission of infections, such as leprosy and syphilis. The method was rationalized by Jenner, who in 1796 proposed vaccination by cow-produced vaccine. Vaccination, in the broader sense, was then rapidly developed against diseases other than measles and small-pox. Great progress was achieved under the aegis of Pasteur, who prepared the first antibacterial vaccine by attenuating cholera bacilli after prolonged in vitro culture.

The first uses of antitoxin in the therapy of infectious diseases such as diphtheria and tetanus, were seen during the early part of this century. The early dramatic successes obscured the preferable clinical situation of prevention of infectious diseases by active immunization through the use of vaccines. Today, the use of antitoxin in these same diseases would mean a failure of community of private medical practice, which has the alternative of active immunization during childhood and later life. Nevertheless, passive immunization is still needed for protection against those diseases for which vaccines are not available, e.g., botulism, and in the treatment of individuals incompletely immunized. Newer

applications of immunotherapy include the prevention of Rho sensitization and immunosuppression during tissue transplantation. The realization that the major barrier to allograft transplantation was immunologic in nature greatly stimulated the development of methods of immunosuppression. For several years after the features of allograft rejection were defined, it was assumed that this process was one of nature's most powerful weapons for preserving the body's integrity. It was suggested that exposure of the fetus to donor tissue might similarly confer protection persisting after birth to subsequent grafts from the same donor but not to those from other donors.

The interest in immunopotentiation developed first with the work of Jenner. A more systematic approach resulted from the work of Pasteur and Koch in their attempts to "Vaccinate" or otherwise protect both humans and animals from disease. In this sense, any inoculation may be regarded as immunopotentiation. Immunosuppression and immunopotentiation were recongnized as immunologic phenomena long before elucidating their underlying mechanisms.

In some situations, such as severe burns, the patients may have a limited period of acquired immune deficiency that requires immunotherapy to prevent serious and sometimes life threatening infection.

Replacement of immunological capacity is the rationale behind all forms of treatment of primary immunodeficiency states. Passive transfer of normal immunoglobulin has been the most widely used and most successful of the replacement therapies. More recently the transfer of adoptive immunity by bone marrow grafts. Boosting of the immune capacity has also been attempted as transfer factor (HITZIG et al, 1974; LAWRENCE, 1974) or thymic hormone administration, or by the use of the drug levamisole (EDITORIAL, 1975).

A fundamental understanding of the principles underlying immunotherapy is, therefore necessary so that passive immunization can be properly used, and evaluate applications that will inevitably appear in the future.

Immunotherapy is in its infancy; progress is slow. So far, the provided sophisticated tests do not suggest a specific therapeutic approach.

The success in immunotherapy is due to its inherent attractiveness, it has risen to prominence only because of the pressure of medical necessity. Diseases or disabilities due to immunologic failure, insufficiency or malfunction of the immunologic response need one or other form of immunotherapy to achieve immunologic balance.

It is still openended, and because of this it is vulnerable.

IMMUNIZATION.

VACCINATIONS AND SEROTHERAPY.

Infectious diseases cause a favourable host response, i.e. acquired immunization. The study of these active immunizations has permitted recognition of relevant humoral and cellular factors and has provided insight into the bases of prophylactic, and even curative, immunization if administered prior to or at the time of contact with the infectious agent.

Induced immunization may be active; the so called vaccination or may be passive; this is called serotherapy. It also includes treatment by transfer factors.

Active immunization:

Actively induced immunization confers immunity specific for the vaccinial infectious antigen. It is linked to the appearance in the vaccinated subject of one or more factors of specific resistance. Considerable effort has been devoted to ensure optimal conditions for the best effective and durable immunity.

Evaluation of the protection induced by the vaccine is made possible by controlling the immune responses of the vaccinated subjects to the vaccinal antigen by evaluating

the vaccine's effect at the onset of infection by epidemiologic studies, or most, rarely, by controlled infectious trials.

The duration of protection afforded by a vaccine relates to the quality of the vaccine and to the amount administered. Inactivated and living vaccines are distinguished.

Dead or inactivated vaccines consist of destroyed microbial elements as diphtheria and tetanus anatoxins.

Living vaccines are live microbial elements, either attenuated or innocuous in certain hosts, that confer cross-immunity to the virulent infectious agent. However, living vaccines are always more dangerous than killed vaccines, at least theoretically. In fact, only living vaccines are effective in infections in which specific defense mechanisms are cell mediated. e.g. tuberculosis, measles or poliomyelitis. Attenuated living vaccines must be evaluated in terms of standardized viable units, maintenance of attenuation, and risks of possible contamination.

Doses of antigen used in inactivated vaccines are always higher than those used in living vaccines. In the later case, viral proliferation in vivo induces stimulation

of specific resistance factors which eliminates only pathogens when the dose of antigen produced is sufficient; with inactivated vaccine, it is necessary to administer the optimal quantity of antigen to induce a sufficient immune response. Several injections are usually necessary either to augment the intensity of the response or to increase the avidity of the antibodies produced. Only antigenic boosters ensure maintenance of a sufficient antibody level for 100 % protection. In some cases, especially in certain antiviral vaccines in endemic countries, the immunity is subsequently reinforced by natural reinfections without detectable clinical signs. Boosters are not then necessary.

The administration simultaneously of several vaccinal antigens may increase the effectiveness of vaccinal antigens as compared to separate administration. Potentialization seems to be due to the adjuvant action of some vaccinal preparations. In certain cases, the addition of inert adjuvants like calcium phosphate or aluminum hydroxide improves the immune response, especially antibody formation.

Table -1- Show the principal vaccines in common use.

Disease	*Antigen preparation*	*Indications*	*Immunization route*	*Result*
Diphtheria	Formaldehyde-treated toxin	Children	Intramuscular	Satisfactory
Tetanus	Formaldehyde-treated toxin	Children	Intramuscular	Satisfactory
Botulism	Formaldehyde-treated toxin	On exposure	Intramuscular	Needs improvement
Whooping cough	Killed bacteria	Children	Intramuscular	Satisfactory
Typhoid	Killed bacteria	Endemia	Subcutaneous	Satisfactory
Cholera	Phenol-treated bacteria	Endemia	Subcutaneous	Needs improvement
Plague	Formalin-killed bacteria	On exposure	Subcutaneous	Needs improvement
Pneumonia	Bacterial extracts	Endemia	Subcutaneous	Needs improvement
Meningitis	Bacterial extracts	Endemia	Subcutaneous	Needs improvement
Tuberculosis	Attenuated organisms Bacille Calmette-Guérin (BCG)	Children	Intradermal	Needs improvement
Poliomyelitis	Attenuated or inactivated virus	Children	Oral	Satisfactory
Measles	Attenuated virus	Children	Subcutaneous	Satisfactory
Mumps	Attenuated virus	Children	Subcutaneous	Satisfactory
Yellow fever	Attenuated virus	Endemia	Subcutaneous	Needs improvement
Smallpox	Attenuated virus	Children	Subcutaneous or intradermal	Satisfactory
Rubella	Attenuated virus	Children	Subcutaneous	Satisfactory
Influenza	Inactivated virus	High-risk group	Subcutaneous	Needs improvement
Rabies	Inactivated virus	On exposure	Subcutaneous	Needs improvement
Typhus	Killed rickettsies	On exposure	Subcutaneous	Satisfactory

Table -1- principal vaccines in common use.

Some vaccines are perfectly innocuous and never are associated with side effects, namely antitetanus and anti-diphtheria vaccines. Other vaccines, however, predispose to severe complications, such as encephalitis relating to anti-variolia or antirabies vaccinations.

So, the possible side effects and the alternate risks of infection must be taken into account.

Certain antirubella vaccines (living attenuated vaccines) may cause placental lesions and fetal malformations.

Certain oral attenuated living vaccines may induce dissemination of the vaccinal strain in the environment, with predictable effects on immunodeficient subjects who are unable to mount a normal response to the living organism.

Vaccination may lead to a hypersensitivity state with IgE production or delayed hypersensitivity. A subsequent infectious contact may then induce clinical hypersensitivity, sometimes more significant than the normal clinical infection.

When vaccination is very effective both in individual and whole populations, a decrease occurs in disease morbidity, this result may be followed by a tendency of large numbers

of people to refuse vaccination. Collective susceptibility to infection increases, which may be harmful because certain infections are more severe in the adult than in children. (e.g. poliomyelitis, measles).

Some bacterial or viral vaccinations alter collective immunity and may lead to the selection or appearance of genetic variants that are insensitive to acquired resistance factors (e.g. certain myxoviruses).

Passive immunization :

Induced passive immunization of a virginal or immunodeficient recipient consists of transfer of serum from a normal or immune donor (man or animal). Most passively induced immunizations involve injection of Ig in the form of antibodies specific for a given antigen. This type of immunization is called seroprophylaxis or serotherapy.

Serotherapy has important applications when the anticipated incubation period is so short that active protection by vaccine cannot be achieved and curative therapy is unavailable; when the antigen is not borne by an infectious agent, as is the case with new born hemolytic disease; when there is