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EDITORIAL

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IMMUNOPOTENTIATION

Immunopotentiation modalities of treatment are often used by the dermatologist of today. Recent interest in these methods of treatment have helped to define the mechanism by which the immune system works. 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 and protect animals and man from disease.

Immunopotentiation or enhancement of the immune response may mean an increase in the rate at which the immune response develops, an increase in the intensity of response, a prolongation of response or development of a response to an otherwise non-immunogenic substance. Agents or adjuvants which enhance immune response are of two categories (i) general potentiation — refers to substances which enhance both cellular and humoral immune responses to a wide variety of antigens, (ii) specific potentiation – refers to a specific class of molecules which enhance specific responses to certain antigens.

Generally vaccination which involves stimulation of a previously non-immune state could be termed potentiation. Besides immunopotentiation may 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.

General potentiation : Adjuvants in this group are of several categories (i) Water and oil emulsions (Freunds adjuvant) (ii) synthetic polynucleotides (iii) hormones, drugs and cyclic nucleotides (iv) endotoxins and (v) allogenic effect.

(1) Water and oil emulsions and inorganic compounds (Freunds Adjuvant)

A mixture of mineral oil, lanolin and killed mycobacteria–this adjuvant mixed with aqueous antigen was popular experimentally, its mechanism of action was poorly understood. The slow release of antigen to the target cells and the components of mycobacteria – cell wall lipids, mucopolysaccharides and RNA may be the potent adjuvants.

Inorganic compounds like alum (potassium aluminium sulphate), aluminium hydroxide and calcium phosphate have been used as adjuvants. Alum precipitated antigen preparations are employed in desensitization of allergic individuals, they induce high titres of circulating antibodies and results in anti-body mediated suppression of the allergic response.

The slow release of antigen by these compounds and their ability to cause inflammation accounts for their activity.

(2) Synthetic Polynucleotides

Braun showed these compounds to be potent stimulators of all aspects of immunoresponsiveness. Synthetic polynucleotide—Poly AV with antigen stimulates helper T cell function, delayed hypersensitivity and cell mediated cytotoxicity. Besides it acts directly on B cells to increase production of anti-body. The mechanism of action appears at the level of the cell membrane and related in some way to changes in cyclic nucleotide metabolism. These compounds are still under study and it remains to be seen if they will prove clinically useful.

(3) Hormones, Drugs and Cyclic Nucleotides

Biogenic amines, cholinergic agents and prostaglandins appear to be linked to changes in cyclic nucleotide metabolism of lymphocytes. Agents that raise intracellular cAMP levels will block or delay antigen or mitogen stimulated lymphocyte blast transformation and induce immature T lymphocytes to develop into more mature cells. Alterations in cAMP levels appear to block several efferent functions of immuno-competent cells such as anti-body secretion, cell mediated cytotoxicity and one stage of IgE mediated histamine release. These drugs which raise cyclic nucleotide levels can enhance or suppress various aspects of the immune response. Such drugs are used in the treatment of allergic asthma, general allergic responses, immune deficiency disease, cancer and benign proliferative diseases like psoriasis. The future of such compounds looks quite promising.

(4) Endotoxins

Bacterial endotoxins — cell wall components e. g. Ecoli, shigella, salmonella — non specifically stimulate B-cells. However, their limitation is that they are immunogenic and pyrogenic and hence of no therapeutic value.

(5) Allogeneic Effect

Recently it has been reported that T lymphocytes stimulated in an allogeneic system or supernatants from T cells stimulated by alloantigens-cause enhancement of immune responses both specifically and non-specifically. How this system will be useful to define aspects of immunoresponsiveness remains to be seen.

Specific Immunopotentiation

(1) Dialyzable Transfer Factor (TFd) – is a dialyzable extract of immune leukocytes, it is capable of transferring cellular immunity from a skin test positive donor to a skin test negative recipient. The recipient upon retesting with antigen to which he was previously insensitive will exhibit a specific delayed skin reaction to this antigen. Transfer factor acts on the stem cell, which may have specificity for an antigen or a group of antigens and assist in recruiting specific antigen sensitive cells; besides it may also have a non specific effect and act as an adjuvant by enhancing the reactivity of lymphocytes. Chemically its Mol. Wt. is 5,000 — 10,000; it is a small nucleopeptide and a non-antigenic substance. It can be lyophilized and stored without loss of potency and appears to have no serious side effects. Recent reports indicate its effectiveness in immunodeficiencies e.g. Wiskott Aldrich syndrome — infectious disease — viral, fungal and bacterial; In lepromatous leprosy skin test conversion has been reported. Clinical trials are under current study.

(2) Immune Ribonucleic Acid – possibly related to transfer factor. RNA has been reported to 'transfer' the ability to respond to an antigen to a recipient animal in the absence of antigen. A portion of the RNA might be coupled to small amounts of antigen yielding what is called a "super-antigen". Their potential usefulness remains to be determined.

Experimentally many adjuvants and drugs with either specific or non-specific effects are now under intensive clinical investigation.

1. **Bacillus Calmette-Guerin (BCG)**– acts mainly by stimulating the reticulo-endothelial system. It is not clear whether this is a primary effect or secondary one mediated by T cell activation. It may be that macrophages activated by BCG are more active killer cells, are more efficient in clearing antigens or antigen-antibody complexes, or are capable of inducing active participation of other cells of the immune system. In malignant melanoma, BCG intralesionally has shown dramatic effects – 50% of cases the local lesion regress and disappear and 20% remote lesions disappear.

2. Dinitrochlorobenzene (DNCB) — applied to primary or metastatic skin tumors as a chemical sensitizer in challenging doses caused intense reactions in the cutaneous neoplasms and induced complete regression.

3. **Corynebacterium parvum** — used as a heat-killed or formaldehyde suspension given orally or parenterally. It acts both non-specifically by activating macrophages and also specifically on T cells. Preliminary reports in patients with melanoma receiving intralesionally C parvum have been encouraging.

4. **Levamisole** — restores and increases delayed skin hyper-sensitivity to various antigens in man. It has been given with claimed clinical improvement in aphthous stomatitis, herpes labialis and genitalis, warts & chronic staphylococcal infections. A dose of 2.5 mg/kg/day for three days, repeated every other week. Daily administration may even produce immunosuppression.

5. **Thymus Factors** — These factors act as hormones and play a role in regulation and differentiation of T cells. Multiple factors with thymic activity have been isolated (thymosin, thymus factor, thymopoietins). These factors will be valuable where a congenital or acquired T cell defect is suspected.

It is clear that much remains to be done before the varied facets of immunopotentiation are understood. The present day use of agents which enhance specific immune responses is increasingly important in our attempts at dissecting and defining the mechanisms by which the immune system works; one is reminded of the words of Somerset Maugham who said "the present is all we can be sure of; it is only common sense to extract its utmost value from it; the future will one day be the present, and will seem as important as the present does now". The future possible utility of potentiation may lie in its role as therapy for patients with suppressed responses, as in some forms of cancer.

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