HOMOEOPATHY AND IMMUNOLAGY

BY

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ABSTRACT

The thrust of this thesis, is an attempt to understand in depth the function of the Immune System from a homoeopathic perspective. Today a wealth of information is available on the various functions of the immune system, and daily even more is being discovered. A serious attempt has been made to correlate relevant information with homoeopathic principles and therapeutics.

Section 1 deals mainly with all relevant information from a homoeoapthic point of view, gained from various authorities with a major contribution form Ivan Roitt's 'Essential Immunology'. These include an understanding of the basic functioning of the Immune system and its anatomy, as well as signs of immune system breakdown. These signs finally are manifested as Hypersensitivity Reactions and Autoimmune Diseases.

Section2 explores the scope of homoeopathic remedies in various functions of the immune system as well as their application in several autoimmune diseases. There has been an attempt to suggest possible mechanisms of action of the Similimum in a given disease condition. Suggestions are also made for documenting the modifying action of homoeopathic drugs. These are indicative rather than definitive, and aim at giving an insight into further scope for research in homoeopathy.

PHYSIOLOGICAL AND PATHOLOGICAL CONSIDERATIONS IN IMMUNOLOGY

PART 1 (A) : BASIC INNATE IMMUNITY

INTRODUCTION : - To have a proper understanding of how homoeopathy could be improving the immune system, we need to first understand the functioning and varied aspects that make up the body's immune mechanisms.

Many components could be probably altered by homoeopathic medication, but only proper research would ultimately prove itself.

An in-depth understanding of the immunological processes in the body is essential before further hypotheses can be made.

Part 1 (A) deals with innate immune responses of the human body. It is an attempt to understand how basic immunological processes work, and the various responses and counter-responses to microbial stimuli.

I BARRIERS AGAINST INFECTION:-
SKIN:- Bacteria fail to survive on the skin for long because of the direct inhibitory effects of lactic acid and fatty acids in sweat and sebaceous cysts and the low pH which the generate.

Mucous secreted by membranes lining the inner surfaces of the body act as a protective barrier to block the adherence of bacteria to epithelial cells. These are then further removed by mechanical actions such as ciliary movement , coughing, sneezing, etc. These also include the washing acion of tears, saliva and urine. Bactericidal components are present in most body secretions such as acid in gastric juice, spermin and zinc in semen, lactoperoxidase in milk, lysozyme in tears, nasal secretions and saliva.

Another mechanism is that of microbiobial antagonism associated with normal bacterial flora of the body. This suppresses the growth of potentially pathogenic bacteria and fungi at superficial sites, by competition for essential nutrients or by production of inhibitory substances, e.g. :

1. Pathogen invasion in the vaginal area is limited by lactic acid produced by commensal bacteria which metabolise the glycogen secreted by vaginal epithelium.
2. When protective commensals aredisturbed by antibiotics, susceptibility to opportunistic infections like Candida or Clostridium Difficile is increased.
3. Gut commensals produce colicins, a class of bactericidins which bind to the bacterial surface causing it to become hydrophobic , and form a voltagedependent channel that kills by destroying the cell's energy potential.

If microorganisms do penetrate the body, two main defensive operations come into play:

1. Destructive effect of bacterial enzymes
2. Phagocytosis

PHAGOCYTES and PHAGOCYTOSIS

1. Polymorphonuclear neutrophil :- (P.m.n.)
This is a non-dividing, short-lived cell, with a multilobed nucleus, containing granules of 2 types:

(i) Azurophil granules
These contain myeloperoxidase, non-oxidative antimicrobial effectors like defensins, bactericidal/permeability-increasing factor and cathepsin G.

(ii) Secondary specific granules:-
These contain lactoferrin, much of the lysozyme, alkaline phophatase and membrane-bound cytochrome 6558. Abundant glycgen stores enable these cells to function under anaerobic conditions as well.

2. Macrophage:-
The macrophage originates from the bone marrow monocytes, which mature into blood marrow monocytes, which mature into blood monocytes. These enter tissues to develop into tissue-mature macrowhich form part of the mononuclear phagocyte system. These modified cells present in connective tissue: Basement membrane of small blood vessels

Lung - alveolar macrophages
Liver - kupfer cells
Spleen sinusoids and lymph-node medullary sinuses where they filter off foreign material.
Mesangial cells of the kidney glomeruli
Brain microgha
Osteoclasts of the bone marrow.

These cells basically combat that group of bacteria, viruses and protozoa which are capable of **living within** the cells of the host.

Bacterial enzymes effectively kill a group of invading organisms by the following mechanisms:

A) Reactive OXYGEN intermediates:-

NADPH oxidase initiates the formation of reactive oxygen intermediates.

NADPH + O2 ---------- NADP+ + O2 (superoxide anion)
Which undergoes conversion to hydrogen peroxide and finally to hydroxyl radicals. Therefore peroxide, myeloperoxidase and halide ions are a potent halogenationg system, capable of killing both bacterial and viruses.

B) Reactive NITROGEN intermediates:-

Nitric oxide formation within macrophages and pmn's have a powerful antimicrobial system through degradation of Fe - S prosthetic groups of electron transport enzymes.

C) Catonic proteins and peptides function in the high pH of pmn's.

These ' defensins ' are rich in arginine. They are disinfectant against a wide range of gram +ve and gram -ve fungi and enveloped viruses. Low pH, lysozyme, lactoferrine are bactericidal and bacteriostatic factors which are oxygen independent and function under anaerobic conditions. Hydrolytic enzymes finally digest the enymes already killed.

COMPLEMENT SYSTEM
The complement systems facilitate phagocytosis by producing a rapid, highly amplified response to trigger stimulus, mediated by a cascade phenomenon, where the product of one reaction is the enzymatic catalyst of the next.

COMPLEMENT-MEDIATED Acute Inflammatory Reaction
The process in steps:

The enzyme convertase C3bBb on the surface of the microbe cleaves large amounts of C3,
C3a is released.
C3b binds to microbe.
C5a is generated.
Membrane attack complex of
C3a + C5a ± mediators triggered from mast cells.
p.m.n. + complement components
dilatation of local blood vessels
blood flow
exudation of plasma proteins
chemotaxis with diapedesis of pmn's, dur to increase in hydrostatic and osmotic pressure.
C3b coated microbe easily adheres to pmn's, resulting in phagocytosis.

II SECOND LINE OF DEFENCE:

Humoral Mechanisms:-

1. Acute phase proteins:-
These are
C reactive proteins (CRP), mannose binding protein, serum amyloid P-component, -antitrypsin, fibrinogen, ceruloplasmin, C9 and factor B.

Any infection produces an increase in 1L1 (endogenous pyrogen) and increased 1L6. These act on the liver, to increase CRP secretion almost 1000-fold in plasma concentration.

CRP further activates complement by classical pathway as does mannose binding protein.

2. Interferons:-
These are a family of broad spectrum antiviral agents present in birds, reptiles and fish also. 14 different - Interferons (INF) produced by leucocytes have been identified.

Fibroblasts and all cell types produce IFNB.

Cells infected with viruses secrete interferons which bind to specific receptors on uninfected neighbouring cells, and this exerts an antiviral effect, by enabling the synthes is of two new enzymes:
1. Protein kinase, which catalyses the phosphorylation of a ribosomal protein and an irritation factor, both of which are necessary for protein synthesis. Thus they reduce on RNA translation.

2. The other enzyme catalyses the formation of short chain polymer of adenylic acid which activates a latent endonuclease. This in turn degrades both viral and host RNA.

This effect is to establish a cordon of uninfectable cells around the site of virus infection, so restraining its spread.

3. Extracellular killing:-

Natural Killer Cells:-

These are large granular lymphocytes. They recognise abnormal glycoproteins which appear on the surface of viral infected cells through lecithin-like receptors on the NK cell surface.

This brings the killer cell and target cell into close opposition, and an extracelluar release of lytic enzymes takes place between the two cells. These polymerise and form transmembrane channels, and lysis of the infected cells takes place.

Some of these lytic enzymes are:

1. Perforin or cytolysin.
2. Tumor necrosis factor V (TFNB).
3. A family of serine proteases termed granzymes.

Eosinophils:-
An extracellular killing mechanism for large parasites like helminths which cannot be phagocytosed is required, and eosinophils are nature's way of dealing with the situation.

They contain a major basic protein (MBP) in the core of the granules as well as a cationic protein and peroxidase in the matrix.

Other enzymes are:

1. Amyl sulfatase B
2. Phosphatase D
3. Histamine.

It also produces granule proteins capable of producing a transmembrane plug. All these substances attack the parasite membrane causing damage and destruction.

PART I (B) : ACCQUIRED IMMUNITY

INTRODUCTION:-

Part I B deals with immune responses that are developed and modified progressively as the individual is exposed to various pathogens.

The main components of the acquired immune system which modify with time and subsequent infections, are the immunoglobulin antibodies which form the humoral system and are mainly produced by B lymphocytes in the lymph nodes and bone marrow.

ANTIBODIES:-

IMMUNOGLOBULIN G (IgG):-

This antibody is the prime workhorse. During 2° response, IgG is the major immunoglobulin to be synthesized.

It diffuses more readily than other immunoglobulins into extravascular spaces, and is the main immunoglobulin that neutralizes bacterial toxins, and binds to microorganisms to enhance their phagocytosis.

It comprises 85% of total serum immunoglobulins. It is the only immunoglobulin that normally crosses the placenta.

IMMUNOGLOBULIN A (IgA):-

This antibody appears selectively in seromucous secretion such as saliva, tears, nasal fluids, sweat, colostrum and secretions of the lung, genito-urinary and gastro-intestinal tracts.

It defends the exposed external surfaces of the body against attack by microorganisms. It is synthesized locally by plasma cells. It functions by inhibiting the adherence of coated microorganisms to the surface of mucosal cells, thereby preventing entry into body tissues

Aggregated IgA binds to polymorphs and can activate the complement pathway.

IMMUNOGLOBULIN M (IgM):-

These antibodies were recognised through the discovery of myeloma protein that did not have antigenic specificity of IgG, A, or M.

Nearly all IgD is present, together with IgM on the surface of a proportion of B lymphocytes. Here they function as mutually interacting and antigen-receptors for the control of lymphocytic activation and suppression.

IMMUNOGLOBULIN E (IgE):-

This antibody is in very low concentration in Serum. Only a small portion of plasma cells synthesize IgE. IgE antibodies are bound with high affinity to the FcERI receptor on Mast cells.

Contact with antigen leads to degranulation of mast cells, with release of preformed vasoactive amines and cytokines and the synthesis of a variety of inflammatory mediators derived from arachidonic acid.

e.g. Hay Fever, Extrinsic Asthma

The physiological role of IgE would appear to be the protection of anatomical sites susceptible to trauma and pathogen entry, by local recruitment of plasma factors and effector cells by triggering an acute inflammatory reaction.

Infectious agents that penetrate IgA defenses would combine with specific IgE on mast cell surface and trigger the release of vasoactive agents and factors chemotactic for granulocytes. This leads to an influx of plasma IgG, complement, polymorphs and eosinophils.

The ability of eosinophils to damage IgG coated helminths and the generous IgE response to such parasites constitute a very effective defense.

PART 2 : IMMUNOLOGY

INTRODUCTION :-

Part 2 describes in detail some of the best known mechanisms of inflammatory responses.

This section would be the most important and poignant from the homoeopathic standpoint, as the factors that may be modifed by homoeopathic remedies are all described here.

One has made use of and quoted most of these mechanisms and mediators of inflammation in Section II of this thesis in order to suggest future scope for research in homoeopathy.

Mediators of Inflammation

Functions include :

1. Acting on smooth muscle wall surrounding the arterioles, to alter blood flow.
2. Acts on venules to cause contraction of endothelial cells with transient opening of the interendothelial junctions and consequent transudation of plasma.
3. Others which facilitates migration of leucocytes from the bloodstream by upregulating the adherence expression of endothelial cells and WBC's.
4. Others which lead the leucocytes to the inflammed site through chemotaxis.

I ACUTE INFLAMMATORY RESPONSE :-

A) The inflammatory stimulus in tissues causes the release of histamine and thrombin, and other mediators

☞This upregulates the P-selector and platelet activating factor (PAF) of the endothelial cells in venules.

☞ This causes the neutophil to roll along the endothelial wall and the PAF docks onto its corresponding receptor.

☞ Next, there is an increased surface expression of LFA-1, MAC-1 (intergrins) which bind the neutrophil firmly to the endothelial surface.

☞ C5a leucotrine-B4now cause the diapedesis of neutrophils.

☞ By the process of chemotaxis, the pmn moves to the inflammatory site.

B) Damage to Vascular endothelium

Results in

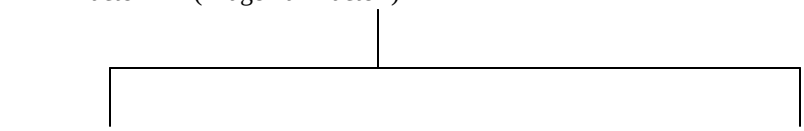
☞activation of platelets by basement membrane collagen and endothelial PAF.

☞this results in aggregation and thrombus formation.

☞adherence to Von Willebrand factor on the Vascular surface.

☞helps in the formation of a platelet plug.

☞Factor XII (Hageman Factor)



Activates the intrinsic clotting system to

Form a fibrin clot at the damaged site.

Activates the plasmin and kinin systems

* This increases vascular permeability.
* Activates the endothelium.
* Autocatalytically amplifies the production of factor XII
* Helps clearing of C3.

C) The ongoing Inflammatory Process

Any injury or infection, after stimulationg this inflammatory response at tissye and vascular endothelial level, further results in a persistent inflammatory process by
☞Secretion of mediators Cytokines, ILI and TNF by tissue macrophages.

☞Endothelial cells, fibroblasts and epithelial cells (i.) Secrete a potent monocyte chemotactic protein MCP-1, which maintains the reaction to infection (ii.) Secrete VCAM-1: homing receptor for VLA-4 positive activated mimouy T-cells, which increases specific antibody production.

D) Regulation and Resolution of Inflammation

Regulation and resolution takes place at the systemic humoral level as well as locally at the cellular level

HUMORAL LEVEL:-

These include component regulatory proteins like C1 inhibitor, C4 binding protein, C3 control protein factors H and I, Complement receptor CRI

- ? Decay accelerating factor (DAF)
- ? Membrane cofactor protein (MCP)
- ? Immunoconglutinin

Proteins which block the membrane attack complex, i.e. CD 59, homologus restriction factor.

CELLULAR LEVEL:-

PGE2, TGFß and glucocorticoids.

PGE2: - Inhibits the lymphocytic proliferation and the cytokine production by T cells and macrohpages.

TGFß :- Deactivates macrophages by inhibiting the production of reactive oxygen intermediates and down regulating MHC class II expression.
It quells the cytotoxic enthusiasm of macrohpages and IFN activated NK cells.

Endogenous glucocorticoids (produced via hypothalamic-pituitary-adrenal axis) exert though control of lipocortin-1

IL-10 inhibits antigen presentation, cytokine production.
Once the inflammatory agent has been cleared, these regulatory processes normalize the situation.

If the trauma has occurred to the tissues, TGFß plays a major role in subsequent wound healing by stimulating fibroblast division and laying down of new extracellular matrix elements.

E) Chronic Inflammation :-

If an antiinflammatory agent persists, either because of 1. Resistance to metabolic breakdown or 2. Inability of a deficient immune system to clear an infectious microbe, then the character of cellular response changes.

Generally, there are the appearance of macrophages as epithelioid cells or giant cells, and the infiltration with lymphocytes that induce pranuloma formation which walls off the persisting inflammatory agent from the remainder on the body.

II. BACTERIAL SURVIVAL STRATEGIES:-

1. Evading phagocytosis by
   (i.) Synthesis of an outer capsule which
   a) does not adhere to phagocytic cells or
   b) physically prevents access of phagocytes to C3b deposited on back wall.

   (ii.) Actively antiphagocytic action by excerting exotonins that poison leucocytes.
   (iii.) Avoid undue provocation of phagocytic cells by adhering to and colonizing only external mucosal surfaces of the body.
2. Challenging the complement system :
   (i.) Some capsules are poor activators of the alternative component pathway
   And
   (ii.) Acclerate complement breakdown by Factor 1 degradation of C3b
   a) Replication motifs of C4 binding protein, complement receptor (CRI) and decay accelerating factor CR3
   b) Production of an integrin-like motif resemblance CR3
   c) Secretion of enzymes which degrade peptides such as C5a (which plays an important role in acute inflammation).
3. Complement deviation
   By secreting a decoy protein they avoid lysis following complement activation.

HOST COUNTER-ATTACK

1. Toxin neutralization :-
   Circulating antibodies neutralize antiphagocytic molecules and other exotoxins released by bacteria.

2. Opsonization of bacteria:-
   a) Independent of antibody :- Serum contains a protein which binds to the bacterial lipopolysaccharide to form complexes. These attach to macrophage CD14 at very low levels to induce phagocytos of the bacteria and TNF secretion.
   b) Augmented by antibody :- Encapsulated bacteria, when coated with antibody (esp. IgG) are more easily cleared by polymorphs and macrophages. This also fixes the complement system esp. C3b. Thus it engages 2 receptors on the phagocyte surface i.e. of IgG and C3b which promotes efficient opsonization.

III. DEFENSE OF MUCOSAL SURFACES
DIAGRAM

1. IgA antibodies afford protection in external body fluids, tears, saliva, nasal secretions, those bathing the surface of the intestine and lungs, by coating the bacteria or viruses and preventing such adherence to mucosal surfaces,

   Also, high affinity of Fc receptors are present on macrophages and polymorphs for IgA and can mediate phagocytosis.

2. If the infectious agent succeeds in penetration the IgA barriers, the next line of defense is IgE.

   Serum IgE is produced fromplasma cells in mucosal tissues and lymph nodes that drain them.

   IgE binds very firmly to the Fc receptors of mast cells and contact with antigen leads to the release of mediators. This results in an acute inflammmatory reaction locally.

   e.g. Histamine
   ☞ increase in valvular permeability
   ☞Transudation of IgG and complement in the area
   ☞Chemotaxis of neutrophils and eosinophils
   ☞local macrophages stimulated by Fc +C3b receptors of the microbe and secrete peptides
   ☞Increase valvular permeability and chemotaxis.

If the opsonized organism is too large for phagocytosis, these cells kill by an extracellular mechanism termed, as Antibody-dependent cell mediated Cytotoxicity.

e.g. in Parasitic infections.

PART 3 : ANATOMY OF THE IMMUNE RESPONSE

INTRODUCTION:-

In trying to anatomically identify the presence of the immune system in the body, an attempt has been made to corelate the immunity of the human body with other complex functions like the Neuro-Endocrine system.

It is obvious then, that there exists a Psycho-Neuro-Endocrino-Immunological AXIS in the body, which when disturbed leads to various dysfunctions and ultimately, disease.

A) ENCAPSULATED LYMPH NODES

Lymph nodes contain a meshwork of reticular cells and their fibres organis ed into sinuses. These act as a filter for lymph, draining the body tissues and possibly bearing foreign antigens.

This enters the subcapsular sinuses by the efferent vessels and diffuses past the lymphocytes in the cortex to reach the macrophages of the medullary sinuses and thence the efferent lymphatics.

What is striking about the organization of the lymph node is that the T and B lymphocytes are largely separated into different anatomical compartments.

B-cell areas

Follicular aggregations of B-lymphocytes are a prominent feature of the outer cortex. They form spherical collections of cells termed **primary nodules**. On antigenic challenge, they form **secondary follicles** consisting of small B-lymphocytes possessing both IgM and IgD on their surface.

Germinal centres contain large B-blasts, a minority of T-cells and follicular dendrite cells. They are greatly enlarged in secondary antibody responses and are regarded as important sites of B-cell maturation and generation of B-cell memory.

The lymphoid tissue forms the white pulp of spleen in circular or elongated areas, within the erythocyte-filled red pulp. The red pulp consists of splenic cords lined with macrophages and venous sinusoids.

'T' and 'B' cell areas are segregated, with T-cells mainly periarteriolar as seen in the diagram. The spleen provides an effective blood filter, removing effete red and white cells, and responding actively to blood borne particulate antigens.

Plasma blasts and mature plasma cells are present mainly in the marginal zone extending to the red pulp.

MUCOSAL ASSOCIATED LYMPHOID TISSUE (MALT)

Subepithelial accumulations of lymphoid tissue without capsule constraints are present in most tracts in the body e.g. respiratory , alimentary and genito-urinary.

These are made up of diffuse collections of lymphocytes, plasma cells, phagocytes throughout the lung and lamina propria of the intestinal wall, or as clearly organised tissue with well formed follicles. The latter, in man, are lingual, palatine, and pharyngeal tonsils.

In the small intestine are the Peyers patches and the appendix.

This 'MALT' forms a separate interconnected secretory system within which cells committed to IgA or IgE synthesis may circulate.

BONE MARROW:-

A few days after a secondary response, activated memory B cells migrate to the bone marrow where they mature into plasma cells.

The bone marrow is a major source of Sr. Ig, contributing to about 80% of the total Ig-secreting cells.

The peripheral lymphoid tissue responds rapidly to antigen but for a relatively short time. The bone marrow starts slowly and gives a long lasting massive production of antibody to antigens which repeatedly challenges the host.

PRIVILEGED SITES:-

Certain selected parts of the body i.e. brain, anterior chamber of the eye and testes, have been designated as privileged immunological sites, as antigens located within them do not provoke reaction against themselves. These areas are protected by strong blood-tissue barriers and have low permeability to hydrophilic compounds and carrier-mediated transport systems.

Immunological responses may cause more damage and these acute inflammations are rarely seen. Very insignificant levels of complement exist for this purpose, unusually high concentrations of immuno-modulators like transforming growth factor ß (TGF ß) endow locally present macrophages with an immunosuppressive capacity.

B) CYTOKINES AND T-CELL ACTIVATION :-

An initial activation of T-cells and T-dependent B-cells involves intimate contact with the antigen-presenting cells. A subsequent profileration and maturation of the response is orchestrated by T-cell **cytokines**, which relay information between cells as soluble messengers.

These T-cell products belong to a group of protein mediators termed cytokines which includes lymphokines, monokines,interlenkins and interferons.

1. Cytokine action is transient and usually short range. They mediate cell growth, inflammation, immunity differentiation and repair.

2. Cytokines have multiple effects on growth and differentiation. Among these is the control on haemopoesis. Stem cells in the bone marrow differentiate into formed elements of blood carefully nurtured through the production of cytokines by stromal cells, i.e.

   GM-CSF (granulocyte-macrophage colony stimulating factor)
   G-CSF (granulocyte colony stimulating factor)
   M-CSF (macrophage colony stimulating factor)
   IL-6, IL-7, LIF (lukaemia inhibitory factor).

3. Network interaction:-

   The complex and integrated relationships between different cytokines are mediated through cellular events. Interaction may occur through a cascade in which one cytokine induces the production of another.
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The complex and integrated relationships between different cytokines are mediated through cellular events.

Interaction may occur through a cascade in which one cytokine induces the production of another.

The amplification of T-cell response following activation is critically dependent upon IL-2. Receptors for IL-2 are not present on resting T-cells, but immediately after activation, they are synthesized . The IL-2 type receptors respond to closely related cytokines also.

The number of receptors on the cell increase under the action of antigen I1-2, and as the antigen is cleared, so the receptor numbers decline, and thus the response to IL-2.

Control mechanisms also come into play, like TGFß - which blocks IL-2 induced proliferation and production of TNF a + ß. Also cytokines IFN, IL-4, IL-10 which mediate mutual antagonism of Th1, and Th2subsets.

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CYTOKINES : THEIR ORIGIN AND FUNCTION

CYTOKINE	SOURCE	EFFECTOR FUNCTION
	INTERLEUKINS	
IL-1	M? , fibroblasts	Proliferation activated B- & T-cells Induction PGE2 & cytokines by M? Induction neutrophil & T-adhesion molecules on endothelial cells Induction IL-6, IFN-ß1 & GM-CSF Induction fever, acute phase proteins, bone resorption by osteoclasts
IL-2	T	Growth activated T-and B-cells; activation NK cells

IL-3	T, MC	Growth & differentiation hematopoietic precursors Mast cell growth
IL-4	CD4 T, MC, BM stroma	Proliferation activated B-, T-, mast & hematopoietic precursor Induction MHC class II and Fc? R on B-cells, P75IL2R on T-cells Isotype switch to IgG1 & IgE M? APC & cytotoxic function, Mf fusion (migration inhibition)
IL-5	CD4, T, MC	Proliferation activated B-cells; production IgM & IgA Prolifetation eosinophils; expression p55 IL-2R
IL-6	CD4 T, M? , MC, Fibroblasts	Growth & differentiation B- and T-cells effectors, & hematopoietic precursors Induction acute phase proteins
IL-7	BM stromal cells	Proliferation pre-B, CD4-CD8-T-cells & activated mature T-cells
IL-8	Monocytes	Chemotaxis & activation neutrophils Chemotaxis T-cells
IL-9	T	Growth and proliferation T-cells
IL-10	CD4 T, B, Mf	Inhibits IFN? secretion Inhibits mononuclear cell inflammation
IL-11	BM stromal cells	Induction acute phase proteins
IL-12	T	Activates NK-cells
Il-13	T	Inhibits mononuclear phagocyte inflammation
COLONY STIMULATING FACTORS		
GM-CSF G-CSF M-CSF Steel factor	T, Mf , fibrolasts MC, endothelium Fibroblasts,endothelium Fibroblasts, endothelium, epithelium BM stromal cells	Growth granulocyte & Mf colonies Activates M? , neutrophils, eosinophils Growth mature granulocytes Growth macrophage colonies Stem cell division (c-kit ligand

TUMOR NECROSIS FACTORS		
TNF a TNF ß	M? , T T	Tumor cytotoxicity ; cachexia Induction acute phase proteins Antiviral & anti-parastic activity Activation phagocytic cells Induction IFN?, TNFß, IL-1, GM-CSF & IL-6 Endotoxic shock
INTERFERONS		
IFNa	Leukocytes	Anti-vira; expression MHC1
IFNß	Fibroblasts	
IFN?	T	Anti-viral; M? activation

		Expression MHC class I and II on M? & other cells Differentiation of cytotoxic T Synthesis IgG2a by activated B Antagonism several I1-4 actions
		OTHERS
TGF-ß	T , B	Inhibition I1-2R upregulation and IL-2 dependent T- and B-cell proliferation Inhibition (by TGF-ß1) of IL-3 + CSF induced hematopoiesis Isotype switch to IgA Wound repair (fibroblast chemotaxin) and angiogenesis Neoplastic transformation certain normal cells
LIF	T	Proliferation embryonic stem cells without affecting differentiation

Mf = macrophage; MC = mast cell; BM = bone marrow; IL = interleukin; GM-CSF = granulocyte-macrophage colony stimulating factor; TGF-B = transforming growth factor-B; LIF = leukemia inhibitory factor.

12. Cytokine action is transient and usually short range. They mediate cell growth, inflammation, immunity differentiation and repair.

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    Interaction may occur through a cascade in which one cytokine induces the production of another.

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    Control mechanisms also come into play, like TGFß - which blocks IL-2 induced proliferation and production of TNF a + ß. Also cytokines IFN, IL-4, IL-10 which mediate mutual antagonism of Th1, and Th2 subsets.

C) Immune Processes and Neuro-Endocrine Factors

Immunological cells have receptors which enable them to receive signals from a whole range of hormones such as corticosteroids, insulin, growth hormone, estradiol, testosterone, ß -adrenergic agents, acetylcholine, endorphins and enkephalins.

In general glucocorticoids and androgens deepen immune responses, whereas estrogens, growth hormones, thyroxine and insulin enhance immune function.

Glucocorticoids are secreted in response to stress, like extreme changes in temperature, fear, hunger and physical injury.

It is presumed that glucocorticoids function by suppressing Th1 and augmenting TH2 cells. Hence, individuals with a genetic predisposition to high levels of stress-induced glucocorticoids would be expected to have an increased susceptibility to infections with intracellular pathogens such as M. leprae, which require effective Th1 cell-mediated immunity for their eradication.

Estrogen influences a more active immune response in females, causing a higher serum Ig and secreted IgA levels, a higher antibody response to T-independent antigens, relative resistance to T-cell tolerance and a greater resistance to infections.

Stress and circadian rhythms at the physiological level, modify the functioning of the immune system. By Pavlovian conditioning in rats, it is possible to show a suppression of conventional immune responses and enhancement of NK cell activity. Thus there is every possibility that an adverse effect of psychological factors such as bereavement, divorce and mental trauma produce a depression of the immune function, a study now termed as" PSYCHO-IMMUNOLOGY ".

Conversely, IL-1 and another lymphokines are capable of stimulating glucocorticoid synthesis through the pituitary-adrenal axis. Also, there seems to be an interaction between inflammation and repair. Mast cells are often abundant, IL-6 induces neurite growth and IL-1 and enhances production of nerve growth factor.

Also IL-1 increase slow-wave sleep when introduced into the lateral ventricle of the brain. Both IL-1 and interferon produce pyrogenic effects through their action on the temperature controlling centre.

CIRCUITS:-

Two network interactions between the immune and neruo-endocrine systems have been reasonably established.

1. The increased synthesis of glucocorticoids under the influence of IL-1, a lymphokine, and a thymus hormone is generated during an immune response.

   In turn, glucocorticoids exert a feedback suppression by influencing several processes including production of IL-1 and IL-2.
2. An intimate relationship between hormone receptor, hormone, antihormone and anti-idiotype exists, where antireceptor antibodies are developed. Its relevance is important in the pathogenesis of autoimmune disorders directed against hormonal receptors.

D) Effects of Diet, Exercise, Trauma and Age on Immunity

The greatly increased susceptibility of undernourished individuals to infection may be attributed to many factors such as - poor sanitation and personal hygiene, overcrowding and inadequate health education.

But protein-calorie malnutrition produces atrophy of lymphoid tissues and 50 % reduction in circulating CD4 T-cells resulting in serious impairment of cell-mediated immunity. Antibody reponses, though intact

are of lower affinity. Phagocytosis of bacteria may be normal, but subsequent intracellular destruction is defective.

Deficiencies in pyridoxine , folic acid and vitamins A, C and E result in generally impaired immune responses. Vitamin D is an important regulator. It is produced by the UV-irradiated dermis and also by activated macrophages. The hypercalcemia associated with sarcoidosis is attributed to the production of Vitamin D by macrophages in active granulomata. This vitamin is also a potent inhibitor of T cell proliferation and of cytokine production by Th1 cells. Thus a neat feedback loop exists at the sites of inflammation where macrophages activated by IFN produce Vitamin D which then suppresses the T-cells making interferon. It also downregulates antigen presentation by macrophages and promotes multinucleated giant cell formation in chronic granulomatous lesions.

Zinc deficiency also greatly affects the biological activity of thymus hormones and has a major effect on cell mediated immunity as a result. **Iron** deficiency impairs the oxidative burst in neutrophils since the flavocytochrome NADP oxidase is an iron containing ezyme.

Oils which have a C-3 double bond (as in fish oils) are protective in autoimmune diseases, perhaps due to and increased synthesis of immunosuuppressive prostaglandins. Yet a reduced fat intake ameliorates age-related diseases of autoimmunity. **Exercise**, particularly severe exercise, induces stress and raises plasma levels of cortisol, catecholamines, IFN, IL-1, ß- endorphin and metenkephalin. This can lead to reduced IgA levels, immune deficiency and increased susceptibility to infection.

Multiple **traumatic injury**, surgery and major burns are also immuno-suppressive and so contribute to the increased risk of sepasis. Post-trauma corticosteroids, prostaglandin E2 released from damaged tissue, bacterial endotoxin of gut flora - all have an immuno-suppressive influence.

PART 4 : IMMUNE SYSTEM BREAKDOWN

INTRODUCTION :-

The diseases of the future consist primarily of the breakdown of the normal physiological functioning of the immune system, a total deviation in which the body expresses itself as

A) Immunodeficiency or
B) Hypersensitivity.

It is a sign of the immune system out of control, moving towards deterioration.

Both these clinical expressions are quite difficult to control in the long term, and most patients regress further into deterioration.

It is still difficult to describe what role homoeopathy could play. But keeping the last remaining immunological processes going - in AIDS patient's and restricting to a certain extent the further damage by hypersensitivity reactions, could well be a major contributing factor.

A) IMMUNODEFICENCY

1. PRIMARY (DIAGRAM)

2. SECONDARY :

1. **AIDS:-**

AIDS has a high incidence in Africa, but a majority in male homosexuals in the rest of the world. Other risk groups are intravenous drug users, haemophiliacs receiving factor VIII from pooled plasma, and infants of sexually promiscuous or drug-addicted women.

There is a sudden onset of immuno-deficiency associated with opportunistic infections involving commonly Pneumocyctis carini, Cytomegalovirus, Herpes Simplex virus, Fungi-like Candida, Asperigillis and Cryptococcus, and the protozoan Toxoplasma. Additionally there is an exceptional susceptibility for Kaposi's sarcoma.
Commonly many patients feature in the group of ARC (AIDS Related Complex) which is characterised by fever, weight loss, and lymphadenopathy.

HIV is an RNA retrovirus, which utilises a reverse transcriptase to convert its generic RNA into the corresponding DNA. This integrates into the host genome were it can remain latent for long periods. The envelope glycoprotein of HIV binds avidly to cell surface CD4molecules initiating a fusion with the T-cell, and infection.

In vitro, an important discovery was that suspensions of single follicular dendritic cells from human tonsil can be infected with HIV by a process that does not involve CD4. These infected cells permit viral replication and can re-infect T-cells.
Also, complexes of virus with antibody may also facilitate entry into T-cells through Fc receptors.

TNF, which upregulates HIV replication, is present in elevated concentrations in plasma of HIV-infected individuals in the advanced stage.

Natural History of the Disease
Stages

1. HIV infection
2. Early retroviral syndrome
   - ? Fever, myalgia, arthralgia
   - ? Viremia and positive test for blood p 24 - a dominant neucleocapsid antigen
3. Immune response to circulating antibodies to p 24 and envelope proteins gp 120 and gp 41
   Production of gp 120 specific cytotoxic T cells
4. Viremia is curtailed and sequestration of HIV lymphoid tissue
5. Follicular hyperplasia and infection of follicular dendritic cells (FDC) caused by trapping of viral particles complexed by antibody and complement
6. Follicles thus become the principal site for viral replication and infection of other cells of the immune system
7. Follicular involution occurs which finally leads to a gradual degeneration of the FDC network
8. CRUCIALLY, circulating CD4T cell numbers fall progressively

9. A level less than 50 ¯3 of CD4T cell numbers results in depressed cell mediated immune responses to common antigens with a failure to produce antigen-specific cytotoxic T cells
10. The patient is now wide open to life-threatening infections caused by normally non-pathogenic (i.e. opportunistic agents such as Pneumocystis Carini and cytomegalovirus.

AIDS patients also bave hyper-gamma globulinaemia and large numbers of B cells which spontaneously secrete Ig in culture. This suggests that they are polyclonally stimulated. A small proportion of HIV-inffected T cells express membrane TNF and these can induce polyclonal B cell activation.

DIAGNOSIS :-

Diagnosis of AIDS amy be made on the following criteria :

1. Opportunistic infections
2. Low CD4count with normal CD8 count

   (* Absolute CD4count of 200 cells/M1

   * Percentage of CD4lymphocytes may be a more reliable indicator of prognosis than absolute counts as the percentage does not depend on calculating a manual differential)
3. Raised IgG and IgA levels
4. Poor skin tests of CMI
5. Increased IFN and neopterin preceding subsequent loss of CD4cells
6. Lymph nodes biopsy - abnormalities and drastic changes in germinal centres
7. Sr. p 24 antigen positive in active disease
8. Weight loss:-
   High TNF levels cause a decrease in lipoprotein lipase antivity. This decreases the syntheses of fatty acids and promotes the breakdown of fats, resulting in weight loss.

High interferon levels may also result in decreased clearance of triglycerides.

Anorexia and malabsorption also contribute to weight loss.

An increased metabolic rate exists even in asymptomatic HIV infected persons resulting primarily in muscle wasting.

B) HYPERSENSITIVITY

When an individual has been immunologically primed, further contact with the antigen leads to boosting of the immune response. However, sometimes an excessive reaction may take place, leading to gross tissue changes if antigen is present in large amounts or if the humoral and cellular immune state is at a heightened level.

These are termed as hypersensitive reactions and a state of hypersensitivity.

TYPE 1 HYPERSENSITIVITY:-

a.) ANAPHYLAXIS

Anaphylaxis is an excessive allergic reaction in the body mediated by the reaction of the allergen with IgE antibodies bound strongly to the surface of the mast cell. This is followed by degranulation of mast cells and the release of histamine, heparin, eosinophil and neutrophil chemotactic factors and platelet activating factors.

Various Interleukins, GM -CSF and other cytokines are also released. In normal circumstances these mediators help to orchestrate the development of a defensive acute inflammatory reaction. But when there is a massive release of these mediators, their bronchoconstrictive and vasodilatory effects predominate and become distinctly threatening.

b.) ATOPIC ALLERGY:-

Localised IgE mediated anaphylactic reactions to extrinsic allergies such as gram pollens, animal danders and faeces from mice in house dust are becoming increasingly common.

Mechanism of allergic response.

c.) **FOOD ALLERGY**:-

IgE sensitisation to food allergies in the gut, especially to egg white and cow's milk, occurs in early infancy through breast feeding, with allergen passing into mother's milk.

Food additives such as sulfiting agents can also cause adverse reactions. Contact of the food with specific IgE on mast cells in the gastrointestinal tract may produce adverse reactions such as diarrhoea and vomiting. Otherwise the allergen may be allowed to enter the body by causing a change in gut permeability through mediator release. This allergen may then complex with antibodies and cause distal lesions by depositing in joints, or it may diffuse freely to other sensitised sited such as skin or lungs.

This produces a local anaphylactic reaction. Hence - eating strawberries may produce urticarial reactions, or eggs may precipitate an asthmatic attack in these sensitised individuals.

Genetic Factors:-

A familial predisposition also exists in the development of atopic allergy suggested to be linked to the inheritance of an HLA halotype within one family. High IgE levels in the blood suggest a higher likehood of becoming atopic.

TYPE II ANTIBODY-DEPENDENT CYTOTOXIC HYPERSENSITIVITY (ADCH)

Some examples of this type of reaction:

1. Transfusion reactions:-

ABO blood groups are a dominant system of classifying different polymorphic constituents of the human red cell membrane.
If an individual is Blood Group A, he would be tolerant to antigens closely similar to A. He would only form cross reacting antibodies capable of agglutinating B red cells. Similarly an O individual would make anti-A and anti-B antibodies. On transfusion , mis-matched red cells will be coated by the isohemaglutinins and cause severe reactions.

2. Rhesus incompatibility:-

The Rhesus (Rh) blood groups form the other major antigenic system, the Rh D-ve blood group can readily be sensitized by red cells from a baby carrying Rh D antigens. This occurs most often at the birth of the first child, when a placental bleed can release a large number of the baby's erythrocytes into the mother. The antibodies formed thus are predominantly of the IgG class and are able to cross the placenta in any subsequent pregnancy.

Reaction with the D-antigen on the fetal red cells leads to their destruction through opsonic adherence, giving hemolytic disease of the newborn.

Rh D-'ve mothers are now treated prophylactically with small amounts of IgG-anti-D at the time of birth.

TYPE III IMMUNE COMPLEX MEDIATED HYPERSENSITIVITY

The body may be exposed to an excess of antigen over a protracted period in a number of circumstances, persistent infection with a microbial organism, autoimmunity to self components and repeated contact with environmental agents.

The union of such antigens and antibodies to form an insoluble complex at fixed sites within the body may well give rise to acute inflammatory reactions.

The outcome of the formation of immune complexes in vivo depends not only on the absolute amounts of antigen and antibody, which determines the intensity of the reaction, but also on their relative proportions which govern the nature of the complexes and hence the distribution within the body.

In antibody excess and mild antigen excess, the complexes are rapidly precipitated and tend to be localized to the site of introduction of antigen, Whereas in moderate to gross antigen excess, soluble complexes are formed.

Some Type III Reactios are

1. Farmers lung disease i.e. ARTHUS TYPE REACTION:-

Here patients are sensitized to thermophilic actinomycetes which grow in mouldy hay. The patient has severe respiratory difficulties within 6-8 hours of exposure to dust of mouldy hay.
Inhalation of bacterial spores present in dust from the hay introduces antigen into the lungs and a complex-mediated hypersensitivity reaction occurs. " Anaphylatoxin " is generated which degranulates mast cells. The intravascular complexes cause platelet aggregation and vasoactive amine release, and as a result erythema and edema increase.
There is also infiltration of polymorphs due to chemotactic factors. These changes produce the severe respiratory difficulties.

2. Disease resulting from circulating complexes.

(i.) SERUM SICKNESS:-
A condition termed serum sickness was observed about 8 days after injection of large doses of horse serum (antidiptheria).

A rise in temperature, swollen lymph nodes, a generalised unrticardial rash and painful swollen joints associated with low serum complement and transient albuminurea is observed. This results from the deposition of soluble antigen-antibody complexes formed in antigen excess.

The capillary membranes commonly affected are those of the skin, joints, kidneys, and heart. As the antibody synthesis increases, antigen is cleared ant the patient normally recovers.

(ii.) Immune Complex Glomerulonephritis :-
The deposition of immune complexes in glomerulo basement membrane is a long lasting disease dur to persistent antigen of chronic infections or autoimmune disease.

This is commonly seen following infections with so-called " nephritogenic " streptococci, or nephrotic syndrome in children associated with quartan malaria wher complexes with antigens of the infecting organism are deposited on the glomerulobasement membrane.
Immune complex nephritis can also arise in the course of chronic viral infections.
DIAGRAM

TYPE IV CELL-MEDIATED (DELAYED-TYPE) HYPERSENSITIVITY

This form of hypersensitivity is encountered in many allergic reactions to bacteria, viruses, and fungi; in contact dermatitis resulting from sensitization to certain simple chemicals; and in the rejection of transplanted tissues.

The **MANTOUX** reaction is the best known example. Previous infection with mycobacterium induces a state of cell-mediated immunity. The reaction is characterised by erythema and induration which appears only after several hours (hence termed delayed) and reaches a maximum at 24 - 48 hours, thereafter subsiding. The infiltration consists of monouclear cells, i.e. lymphocytes and cells of the monocyte-macrophage series.

Tissue damage produced by type IV Reactions

1. Infections:- The development of a state of cell-mediated hypersensitivity to bacterial products is probably responsible for the lesions associated, with bacterial allergy such as cavitation, caseation and general toxaemia seen in human tuberculosis as also the granulomatous skin lesions found in patients with borderline form of leprosy.

   When the battle between the replicating bacteria and the body defenses fails to be resolved in favour of the host, persistent antigen provokes a chronic local delayed hypersensitivity reaction.

   Continuous release of lyphokines from sensitized T lymphocytes leads to the accumaltion of large numbers of macrophages bearing bacterial antigens on their surface. Tissue damage further occurs due to cytotoxicity by lymphokine-activated macrophages.

   Morphologically, this combination of cell types with proliferating lymphocytes and fibroblasts associated with areas of fibrosis and necrosis is termed a " chronic granuloma " and it represents an attempt by the body to wall off a site of persistent infection.

   Granulomas can also arise from persistence of indigestible antigen-antibody complexes (foreign bodies/ inorganic materials such as talc) within macrophages . In these there is an absence of lymphocytes. DIAGRAM

   Skin rashes in small-pox and measles and herpes simplex may be due to a delayed type of allergic reaction, with extensive damage to virally infected cells by cytotoxic T -lymphocytes.

   Sarcoidosis, a disease of unknown etiology affects ly mphoid tissue and involves the formation of chronic granuloma.

   CONTACT DERMATITIS :- It is a delayed type reaction in the skin, which is produced by foreign materials capable of binding to body constituents, possibly surface molecules of the Langerhan's cells, to form new antigens. The reaction ischaracterised by mononuclear cell infiltrate peaking at 12 -15 hours accompanied by edema of the epidermis with microvescicle formation.

TYPE V STIMULATORY HYPERSENSITIVITY

In this situation, the antibody reacts with a key surface component such as a hormone receptor and " switches on " the cell.

An example of the thyroid hypersensitivity in Grave's disease. When Thyroid Stimulating Hormone (TSH) of pituitary origin binds to the thyroid cell receptors, adenylcyclase is activated and the cyclic AMP " second messenger " is generated, which aids to stimulate the thyroid cell. Instead, thyroid stimulating antibody present in the sera of thyrotoxic patients, an auto antibody, is directed against a site of TSH reception and produces a similar reaction as TSH, and thyrotoxicosis results.

TOXIC SHOCK SYNDROME is characterised by hypertension, hypoxia, oliguria and microvascular abnormalities caused by elements of the innate immune system independently of the operation of acquired immune response.

These involve an excessive release of TNF, IL-1 and IL-6 and intravascular activation of complement.

Septic shock associated with gram negative bacteria is primarily due to lipopolysaccharide (LPS) endotoxin.

Gram positive organisms cause release of TNF due to direct action on macrophages and stimulation of selected T-cell families by the enterotoxin superantigens.

Aggregation of platelets by S. Aureus induces disseminated intravascular coagulation.

PART 5 : AUTOIMMUNE DISEASES

INTRODUCTION:-

A deviation from the normal immunological reaction takes place in some individuals, where lymphocytes produce auto-antibodies to normal body " self " components.

Homoeopathic remedies have a very positive action on the immune system in these conditions. The homoeopathic similimum especially the " constitutional " could reduce the inflammatory process locally as also the indiscriminate production of autoantibodies. It could possibly also enhance the normal functioning of the organs involved by stimulating their physiological processes into normal function.

Modern Medicine has yet a very minimal cure for these diseases, and apart from supplementary treatment and palliative drugs, have nothing much to offer. Hence Homoeopathy could have a very good scope in CURING these diseases on long term treatment especially **before** too much tissue destruction has taken place.

At one end are the " Organ-Specific " Diseases with organ-specific autoantibodies, e.g. Hashimoto's disease of the thyroid, where a specific lesion of the thyroid exists involving infiltration by mononuclear cells (lymphocytes, histiocytes and plasma cells), destruction of follicular cells and germinal centre formation, accompanied by the production of circulating antibodies with absolute specificity for certain thyroid constituents,e.g. ANA, Anti-thyroid mitochondrial antibody.

Moving towards the centre of the spectrum are those disorders where the lesion tends to be localised to a single organ, but the autoantibodies are non-organ specific.
e.g. Primary Biliary Cirrhosis, where the small bile ductule is the main target of inflammatory cell infiltration, and serum antibodies present are mainly mitochondrial but not liver specific.

At the other end of the spectrum are the " Non-organ specific " or " Systemic " autoimmune diseases, broadly belonging to the class of **rheumatological disorders** e.g. Systemic Lupus Erythematosis (SLE) where both lesions and auto-antibodies are not confined to any one organ. Pathological changes are widespread , and are primary lesions of connective tissue with fibrinoid necrosis. They are seen in the skin butterfly rash on the face, kidney glomeruli, serous membranes and blood vessels. The formed elements of blood may also be affected.

A bizzare collection of autoantibodies are found, some of which react with DNA and other constituents of all cells in the body.

I) NATURE AND NURTURE: POSSIBLE CAUSES OF AUTOIMMUNITY.

1. Genetic Factors in Autoimmune diseases :-

Autoimmune phenomena tend to aggregate in certain families, e.g. 1st degree relatives (siblings, parents, children) of patients with Hashimoto's disease show a high incidence of thyroid antibodies and of overt and subclinical thyroiditis. The proportion with autoantibodies is higher in these families, where more than one member is affected.

Similarly, in families of pernicious anemia patients, gastric parietal cell antibodies are prevalent in relatives who are wont to develop achlorhydria and atopic gastritis.

2. Cell influence in autoimmunity :-

There is a general trend for autoimmune disease to occur far more frequently in women than men. Pregnancy is often associated with amelioration of disease severity particularly in rheumatoid arthritis. There is a striking relapse of R.A. after giving birth, at which there are drastic hormonal changes including the loss of placenta. Commonly postpartum hypothyroidism is precipitated in women with pre-existing thyroid immunity.

3. Environmental factors :-

(i.) Sun exposure often triggers the skin lesions of SLE.
(ii.) Organic solvents can initiate the basement membrane autoimmunity, which results in Good Pasture's Syndrome.
(iii.) Drugs can induce diseases like SLE, myasthenia gravis and autoimune haemolytic anemia.
(iv.) Infectious microorganisms can cause autoimmune diseases in genetically predisposed individuals.
a) Acute rheumatic fever with A Streptococcal Pharyngitis.
b) Autoimmune Myositis with B3 Coxsackie Virus
c) Takayasu's Arthritis may be linked to Mycobacterium Tuberculosis
d) HLAB27 related Reactive Arthritis may stem from Old Chlamydia, Yersinia or Salmonella infections.

4. Autoimmunity may also arise through bypass of T-helper cell regulatory mechanisms, along with other defects in regulatory mechanisms.

5. **CYTOKINES** have a large part to play in **inducing** autoimmunity. In studies carried out, it was observed that transinfection of mice pancreas with IFN gene on the insulin promoter produced an inflammatory reaction and diabetes.

This must have been a result of autoimmunity, since a normal pancreas grafted into the same animal suffered a similar fate. This implies that unregulated cytokine production, producing, a local inflammatory reaction can initiate autoimmunity perhaps by increasing the concentration of processed autoantigens available to professional antigen-persenting cells. Naïve T-cells perform avidly due to upregulated adhesion molecules and previously anergic cells also become responsive to antigen.

Conversely, Cytokines can also be used to **correc**t autoimmune disease.

(i.) IL-1 cures D.M. in non-diabetic mice.
(ii.) TNF prevents the onset of SLE symptoms in New Zealand Black & White hybrid mice.
(iii.) TGFß1 is known to protect against collagen arthritis and relapsing E.A.E.
(iv.) Cultures of synovial cells of R.A. spontaneously reproduce high levels of IL-6, TNFa and GM-CSF, which strongly activate macrophages, but very little of IFN? or TNFß (which reduce inflammatory activity) and hence remain in persistent autoimmune activity.

II PATHOGENIC EFFECTS OF HUMORAL ANTIBODY

A) BLOOD :-

- The erythrocyte antibodies play a role in the destruction of red cells in autoimmune haemolytic anemia.
- Some children with immunodeficiency associated with very low white cell counts have a serum lympho-cytotoxic factor, which requires complement for its activity.

- Lymphopenia occuring in patients with SLE and RA may also be a direct result of antibody, since nonagglutinating antibodies coating WBC's have been observed in these cases.
- In Wegener's Granulomatosis, cytokines prime polymorphs, translating proteinase III to the cell surface. This reacts with antibody and activates the cell causing degranulation and generation of reactive oxygen intermediates. Endothelial cell injury occurs as a consequence v.o.i. and superoxide anion, thus causing vasculitis.
- Platelet antibodies may be responsible for Idiopthic thromobocytopenic purpura (ITP).

B) SURFACE RECEPTORS

1. THYROID :-

In certain situations, antibodies to the surface of a cell may stimulate rather than destroy, as seems to be the case in thyrotoxicosis (Graves Disease). Thyrotoxicosis has also been found with undue frequency in families of Hashimoto's patients.

Antibodies were discovered on TSH receptors by Adams and Purves that acted in the same manner as TSH i.e. through the adenyl cyclase System Thyroid stimulating antibodies (TSAB) act independently of the pituitary-thyroid axis. Iodine uptake of the gland is unaffected by the administration of thyroxine or triiodothyroxine, whereas normally this would cause feedback inhibition and suppression of uptake. The enlargement of the thyroid in this disorder is due to the antibodies, which react with a growth receptor and directly stimulate cell division as distinct from metabolic hyperactivity. In contrast, sera from patients with primary myxedema contain antibodies capable of blocking the mitogenic action of TSH, thereby preventing the generation of follicles which is a feature of the enlarged Hashimoto's goitre.

2. MUSCLE :-

The transient muscle weakness seen in a proportion of babies born to mothers with myasthenia gravis is due to the transplacental passage of IgG, capable of inhibiting neuromuscular transmission. Antibodies to muscle acetylcholine receptors (ACh-R) in myasthenics are consistently found along with depletion of these receptors within the motor and plates.

3. STOMACH :-

In pernicious anemia the underlying histo-pathologic lesion is an atrophic gastritis in which chronic inflammatory mononuclear invasion is associated with degeneration of secretory glands and failure to produce gastric acid. The development of achlorhydria is accelerated by the inhibitory action of antibodies to the gastric proton pump (ATPase) located in the membrane of the secretory canaliculi, and also probably the gastric receptors.

C) OTHER TISSUES :-

1. **GASTRO-INTESTINAL TRACT :-**

Some patients with autoimmune atrophic gastritis diagnosed by achlorhydria and parietal cell antibodies, develop Vit. B_{12} deficiency much later, which precipitates pernicious anemia. Probably the autoallergic destruction is balanced by the regeneration of mucosal cells (hence steroid may restore gastric function in patients with pernicious anemia).

However, the balance would be upset if the patient produced antibodies to intrinsic factor in the lumen of the GIT. These would neutralise the small amount of intrinsic factor still available and the body would move into negative balance for B_{12}. The symptoms of B_{12} deficiency, pernicious anemia and sometimes subacute degeneration of the cord would appear a considerable time later, when the liver stores become exhausted.

In Celiac disease, the acquired tolerance to dietary protein seems to break down, and T-cell sensitivity to wheat gluten can be demonstrated subsequently. B cell stimulation would result in secretion of IgA endomysial antibodies, which are exclusive to patients with Celiac disease.

2. GLOMERULAR BASEMENT MEMBRANE :-

There exists a deposition of C3 and IgG in the basement membrane of the glomerular cappilaries, producing glomerulonephritis; glomerulobasement antibodies may be detected in the serum even after nephrectomy.

3. **HEART** :-
Congenital complete heart block has been attributed to neonatal lupus erythematosus. IgG anti-Ro reaches fetal circulation by transplacental passage, and binds to neonatal rather than adult cardiac tissue and alters the transmembrane action potential by inihibiting repolarisation. Maternal heart is unaffected.

III ORGAN SPECIFIC ENDOCRINE DISEASE

1. Autoimmune thyroiditis :-
The inflammatory infiltrate in autoimmune thyroiditis is usually essentially mononuclear cells, which indicates T-cell mediated hypersensitivity.
But there is considerable diversity in the autoimmune response to the thyroid, leading to tissue destruction, metabolic stimulation, growth promotion or mitotic inhibition, which in different combinations accounts for the variety of forms in which autoimmune thyroid disease presents.

2. Insulin Dependent Diabetes Mellitus (IDDM) :-
This involves chronic inflammation infiltration and destruction of the specific tissue i.e. insulin producing cells of the pancreatic islets of Langerhans. This condition is all T-cell mediated.

3. Multiple Sclerosis (MS) :-
It is postulated that MS could be an autoimmune disease as it has a resemblance to experimental allergic encephalomyelitis -a demyelinating disease leading to motor paralysis, produced in rats by immunization with myelin basic protein.

IV PATHOLOGICAL EFFECTS OF COMPLEXES WITH AUTOANTIGEN

1. Rheumatoid Arthritis :
Morphological Evidence: The joint changes in rheumatoid arthrites are produced by the malign of the synovial cells, as a pannus overlaying and destroying cartilage and bone. The synovial membrane, which surrounds and maintains the joint space, becomes intensely cellular as a result of considerable immunological hyperactivity. This is evidenced by large numbers of T-cells mostly CD4 invarious stages of activation, usually associated with dendrite cells and macrophages. Clumps of plasma cells are frequently observed and sometimes even secondary follicles with germinal centres are present, as though the synovium has become an active lymph node. Indeed, it has been estimated that the synthesis of immunoglobulins by the synovial tissue ranks with that of a stimulated lymph node. Also, there is widespread expression of surface HLA - DR (Class II), T and B cells, dendritic and synovial lining cells and macrophages are all positive signifying high activity. The thesis is that this fiery immunological activity provides an intense stimulus to the synovial lining cells which undergo a Dr Jeckyll to Mr. Hyde transformation into the invasive pannus. This brings about joint erosion through release of destructive mediators.

IgG Autosensitization and Immune Complex Formation : The synthesis ofautoantibodies to IgG-Fc region known as antiglobulins or rheumatoid factors, are the hallmark of the disease. The majority have IgM antiglobulins which react in the classical latex and sheep cell agglutination tests. These as will as sero-negative patients have elevated levels of IgG antiglobulins.

Plasma cells in the synovium presumably synthesize the IgG antihlobulins which tend to aggregate and can be regularly detected in the synovial tissues and in the joint fluid where the give rese to typical acute inflammatory reactions with fluid exudates.

IgG galactose provides an early marker for future clinical disease and can be of prognostic value. In patients that develop RA, it has been detected that IgG is abnormally glycosylated i.e. the percentage IgG-

Fc sugar groups completely lacking galactose in the IgG i.e. the agalacto IgG of RA patients is always higher than in controls and can go to as high as 60 %. This contributes to the autogenicity.

Production of Tissue Damage : Immune complexes are stabilized by multivalent Fe binding molecules, IgM rheumatoid factor and Clq. These when present in the joint space may initiate an " Arthritic " reaction leading to the influ x of polymorphs. Their inter-reaction results in the release of reactive oxygen intermediates and lysosomal enzymes like neutral proteinases and collagenase. These damage the articular cartilage by breaking down proteoglycans and collaagen fibrils.

The aggregates may also stimulate the mactophage like cells of the synovial lining. Also, there is a release of TNF and GMCSF from activated T-cells which also stimulates the macrophages. The activated synovial cells grow out as a malign pannus over the cartilage and at the margin of thes advancing granulation tissue, mactophage can activate chondrocytes to exacerbate cartilage breakdown, and osteoclasts to bring about bone resorption, wich is a further complication of severe disease.

Subcutaneous nodules are granulomata possibly formed through local production of insolubilzed self-associating antiglobulins.

Manifestations	Cytokines Involved
1. Synovial tissue Inflammation	
a) Increased adherence ofpost capillary venules	IL-1, TNFa, IL-6, IL-2, IFN?.
b) Chemotaxis of T-cells	IL-8
c) T cell activation and proliferation	IL-1, TNFa, IL-6, IL-2, IFN?.
d) B cell differentiation and antibody formation	IL-1, TNFa, IL-6, IL-2, IFN?.
e) Increased expression of HLA antigens	IFN?, TNFa, GM-CSF
f) Macrophage Activation	IFN?, GM-CSF, M-CSF, IL-2
2. Synovial Fluid Inflammation	
a) Increased adherence of post capillary venules	IL-1, TNFa, IFN?.
b) Chemotactic for PMN	TNFa, IL-8
c) Activation of PMN	TNFa , GM-CSF, IL-8
3.Synovial Proliferation	
a) Fibroblast Growth	PDGF, IL-1, IGF, FGF,TGFß , EGF
b) Neovascularization	TNF , FGF, TGFß .
4. Cartilage and bone damage	
a) Activation of Chondrocytes	IL-1, TNFa .
b) Activation of fibroblasts	IL-1, TNFa .
c) Activation of osteoblasts / osteoclasts	IL-1, TNFa .
5.System Manifestations	
a) Fever, Constitutional Symptoms	IL-1, TNFa .
b) Acute phase reactants	IL-1, TNFa , IL-6.

EGF= Endothelium Growth Factor
FGF= Fibroblast Growth Factor
GM-CSF= Granulocyte, Macrophage Colony Stimulating Factor
IFN= Interferon
IGF=Intermediate Growth Factor
IL=Interleukin

M-CSF= Macrophage Colony Stimulating Factor
PDGF= Pre Dendritic Growth Factor
TGF= Transforming Growth Factor
TNF = Tumour Necrosis Factor

2. <u>Systemic Lupus Erythematosus</u>

SLE is an autoimmune disorder where autoantibodies are formed against soluble components of the body

e.g. Formed elements of blood, clotting factors, IgG, cardiolipn, ß2-glycoprotein 1; as also to nucleoproteins and Sm ribonucleoprotein. These antibodies have continual access to these components and complexes are formed that give rise to lesions similar to those occurring in serum sickness. The most common finding in these patients is a defect in the early classical complement components i.e. Clq and C4 deficiency, which prevents effective clearance.

As detailed earlier, a rich variety of autoantigens in lupus exists, the most pathognomic being double standate DNA (ds-DNA). The complexes of DNA and other nuclear antigens together with immunoglobulin and copmlement grow in size to become large aggregates in capillaries. These are also visible in the electron microscope especially on the epithelial side of the glomerular basement membrane as amorphous lumps.

During the active phase of the disease, Sr. complement levels fall as components are affected by the immune aggregates in the kidney and circulation. Deposition of these complexes is widespread where organ involvement is 98 % for joints amd muscle, 64% for lung, 60 % for blood, 60 % for brain, 20 % for heart and 40 % for kidney lesions.

Antibodies	Incidence %	Antigen detected	Clinical Importance
Antinuclear Ab	95	Multiple nuclear and cytoplasmic antigens	Negative test makes SLE diagnosis unlikely
Anti DNA	70	DNA	Anti-ds-DNA is disease specific Anti-ss-DNA is not Associated with nephrites and clinical activity
Anti Sm	30	Protein complexed to 6 species	Specific for SLE
Anti RNP	40	Protein complexed to U1RNA	High titre in polymyositis, scleroderma, lupus, MCD. If present in SLE without DNA less chances of nephritis
Anti Ro (SSA)	30	Protein compelled to Y1-Y5RNA	Associated without Sjogrens syndrome, Subacute cutaneous lupus, Inherited complement deficiency, Congenital heart block
Anti La (SSB)	10	Phosphoproteins complexed with RNA protein III transcriptase.	Always associated with AntiRo.
Antihistone	70	Histone	More frequency in drug induced LE (95 %)
Anticardiolipin	50	Phospholipid	Arterial / Venous thrombosis, thrombocytopenia, valvular heart dysfunction. Spontaneous abortion, prolonged PTT, false VDRL
Antierythrocyte	60	Erythrocyte surface antigens	A small proportion of these

			patients develop hemolysis
Antiplatelet		Platelet surface	Associated with thrombocytopenia
Anti lymphocyte	70	Lymphocyte surface antigens	Leukopenia / Abnormal T cell function
Antineuronal	60	Neuronal and Lymphocyte surface antigens	In CSF high IgG correlate with diffuse CNS lupus.

HOMOEOPATHIC CONSIDERATIONS IN IMUNOLOGY

INTRODUCTION

It is a widely accepted idea in homoeopathic circles that our medications have a modifying effect on the so-called PNIE axis, i.e. the Psycho Neuro Immuno Endocrine axis.

The human body has a particular balance of functions indicated by the emotional status, immunological status and endocrine status. That is, should any of these functions be modified by any cause, such as external or environmental stress, as well as internal stress, the changes are manifested as alterations in this axis, which finally percolate down to the somatic / physical level.

The vigour of expression at the somatic level would thus depend on the amount of change that has taken place in the individual, and the capacity of the individual to respond and recover from this state with his internal reserves. This capacity is termed in homoeopathy as the **SUSCEPTIBILIT**Y of the person.

Thus to consider or study the immunological status of an individual from the homoeopathic standpoint, one needs to clearly assess the susceptibility of the person and all the factors that affect or modify it.

The second important aspect of cure of immunological diseases is with regard to the choice of the remedy. It is essential that the remedy is a **SIMILIMUM or "CONSTITUTIONAL"** , i.e. based on both mental and physical generals of the patient. Only this remedy would obtain a continous, lasting cure and have a modifying effect on the immune system as well as the PNIE axis as a whole Section II studies these aspects.

My interst in the topic of immunology is due to the fact that extensive knowledge and details are available to us already; with which, if our homoeopathic principles are applied, it could possibly be ascertained just how our homoeopathic medications bring about a change and cure, as against palliation or suppression.

Since today, we are plagued by numerous **INCURABLE** diseases that are essentially autoimmune in nature, the superiority of our branch of medicine in being able to tackle these diseases at the **root** is apparent ; and to prove this, numerous immunological parameters exist that could be made use of. Section II deals with these suggestions of mine, with laboratory details.

PART 1

A) SUSCEPTIBILITY

Susceptibility is defined as the inherent capacity of an individual to react with external morbid stimuli. This reaction may vary in intensity for each individual, and it is in gaugeing the quality of this reaction that one is able to detect the level of susceptibility at that particular point of time.

Various factors affect the susceptibility of an individual and these include:-

1. AGE; - Children have a high level of susceptibility as their reactions are generally intense and acute. Hence, high potencies are suitable in their treatment.
   Adults have a moderate to high susceptibility and this has to be gauged individually.
   Older people have a low susceptibility and hence are more prone to chronic diseases with chronic, mild symptoms.

2. SEX:- Females tend to have a higher state of susceptibility than males.

3. IMMUNITY: - The immune status of an individual is directly proportionate to the susceptibility of an individual. Therefore good immune status speaks of a good susceptibility and vice-versa.

4. SUPPRESIVE TREATMENT:- Suppresive treatment, whether homoeopathic or allopathic, has a detrimental effect on the immune system and the susceptibility as a whole.
   E.g. - Long continued superficial homoeopathic specific medication without similimum and antimiasmatic back up.
   Steriods, antibiotics, shock treatment in pschyiatric patients in allopathy.

5. NUTRITION: - Poor nutrition lowers the susceptibility considerably and the patient is unable to resist infection.

6. OLD DISEASES AND INHERITED MIASM:- Past diseases suffered as well as Family history of diseases are an important indication of susceptibility of a patient. They modify the present disease reaction, depending on whether the disease was curative or suppresive, and whether the recovery was complete or incomplete. Most chronic diseases have their basis in the fundamental or inherited miasm, due to which the consitution has a vulnerability to particular diseases.

The SUSCEPTIBILITY of an individual plays an important part in the recovery process as well as responsiveness to medicine. Similarly, one needs to prescribe the homoeopathic remedy in accordance with 2 of Hanemann, which states that
"The highest ideal of cure is rapid, gentle and permanent restoration of the health or removal and annihilation of the disease in its whole extent, in the shortest, most reliablen and most harmless way, on easily comprihensible principles".

In order to do this, one needs to gauge the susceptibility of the individual from the earlier mentioned criteria, as well aas from the disease reaction ineach particular case. A proper choice of the Similimum ceeds to be supported with a proper choice of posology, inorder to be ideally effective. The correct potency then "satisfies" the morbid susceptibility and modifies it resulting in a cure from within. The healthy susceptibilityis then able to withstand infection due to a healthy functioning immune system.

Other poignant aspects of the susceptibility of an individual is his ability to be most "susceptible" or vulnerable to that remedy which bears a complete homogeniety to its state.

Any stimulus (here the similimum in its correct potency) which is given to a diseased or healthy person, if it is homogeneous, will produce a reaction. In a diseased person it will result in a cure; while in ahealthy person it will result in a fantastic, lucid proving of the drug.

Though a heterogenous / non-similimum will also produce a reaction of the individual's susceptibility, the effect is very short and partial, and not healing in nature.

B) SIMILIMUM OR CONSTITUTIONAL REMEDY.
The similimum is a remedy that satisfies the following characteristics as outlined in 24
1. It covers the TOTALITY of the symptoms of the disease.
2. Its pathogenic effects are known
3. It has been tested on healthy provers
4. It has a power and tendency to produce an artificial morbid state similar to that of case of the disease in question.

The similimum then necessarily follows HERING'S LAW OF CURE or THE LAW OF NATURE which states:

"The cure always takes place from above downwards, within outwards, from an organ of greater importance to one of lesser importance, in the reverse order of appearance of symptoms".

How does one reach the choice of this similimum?

It is very important that the physician is an "unprejudiced observer" while recording the case history, and has a keen mind to discern that which is peculiar to the case and give adequate importance to it.

A method followed, which yields good results as far as obtaining a descriptive, complete history is given below

1. Chief cimplaint:-
   Details with regard to Location, Sensation, Modalities and Concomitants.
2. Enumerate all Associated Complaints with Location, Sensation, Modalities, Concomitants.
3. Physical Generals:- Craving, Aversions in Food and Drinks; Tongue, characteristics; Thirst; Perspiration: Distribution, Odour; Bladder and Bowel Habits; Thermal State; Sleep and Dreams; Sexual Habits; Other Habits.
4. Mental Generals, Including "Life Space" : i.e. entailing details of family enviroment and relationships.
5. Past History of Diseases.
   Family History of Diseases.
6. In Females:- Menstrual and Obstetric History
7. In children:- Birth History, Milestones, Mother's Obstetric History.

Once this history is obtained, an Analysis of the symptoms is done in order to obtain the most characteristic symptoms, peculiar to the patient.

This is then further synthesized in order of their importance as given below

1. Mental Generals
2. Sleep and Dreams
3. Physical Generals
4. PQRS Symptoms
5. Particulars form the chief complaint and associated complaints.

This forms the **TOTALITY** or **PORTRAIT** of this disease.

The next step is Repertorization of the totality of symptoms and Selection of the remedy which bears complete similarity to the picture.

Once the remedy is chosen, its posology and frequency of repetition is based on the susceptibility of the individual as ascertained from the history.

PART 2

Introduction:- This section deals with a variety of postulations and suggestions that I have personally made taking into account all the information gathered in Section I of this thesis. With the wealth of information, and advancement in science and technology taking place, one needs to see homoeopathic remedies with a new perspective, to add on to what our Masters have done over the decades.

The following are personal theories and postulations and would need a lot of research to prove, even if they do seem probable. I now seek to venture into the unknown and a few errors are bound to be present. The emphasis is mainly, on the line of thinking, the possibilities that exist, rather than on being especially accurate.

A) INFLAMMATIONS AND INJURIES

Homoeopathic remedies have a widespread application in inflammations and injuries, and as if by magic, healthy granulation tissue appears, wounds begin to heal and inflammations subside. How does this happen?

I have taken the liberty of postulating various possibilities, taking into account the pathogenic nature of a few well known remedies. Similarly, many other remedies could be understood in a similar manner.

I) REPERTORIAL SYMPTOMS:-

[Ref: Synthetic Repertory, Pg. 318, Vol 2]

(Mostly 3 mark or 2 mark drugs have been chosen)

Inflammations:-

(i.) Blood Vessels of :- ARN, ARS, BAR-C , SULPH
Ant-t, Cuprum, Ham., Kali-c., Puls.

Arteritis:- **Calc., Kali Iod., nat-I**

Phlebitis:- ACON, BRY, CALC, LACH, RHUS-T, VIP.
All-c, ant-t, arn, ars, bell, both, calc-f, cham, chin, ferr ham, iod, kali-c, led, Lyc.
Lycps nat-s, puls, sep, sil, sulph.

(ii.) Bones of :- FL-AC, MERC, MEZ, PHOS-AC, PULS, SIL, STAPH.
Acon, ang, asaf, aur-i, aur-m, bell, calc, calc-sil, kali-I, lac-ac, lyc, mang, nit-ac, phos, phyt, psor, sulph, symph.

Osteomyelitis :- gun-powder, sil.

Periostitis:- FL-AC, MERC, MEZ, PHOS-ac, PULS, SIL, STAPHL, SYMPH.
Acon, apis, ars, asaf, aur-m, bell, ferr-I, ferr-p, guaj, hecla, iod, kali-bi, kali-l, mang merc, merc-c, nit-ac, phyt, psor, sil, staph, still, symph.

(iii.) Granulations, proud flesh
:- ARS, SIL.
Alumn, anac, ant-t, calc, calen, kali-m, lach, merc, sabin.

(iv.) Heal, slow tendency to
:- HEP, LACH, NIT-ac, PETR, SIL, SULPH.
All-c, bar-c, bor, calc, carb cham, graph, merc, merc-c, rhus staph, tub.

(v.) Suppurating:- **bell, bufo, calc, calen, cham, chin, hep, merc, nat-m, puls, sil, sulph.**

II) REMEDIES

From the above remedies, a few have been chosen and discussed in detail. An attempt has been made to explain a postulate on the probable mode of action of these remedies on the immunological system. A few hints have been given to us by the Masters, and we now need to update this with recent discoveries, in research.

"Homoeopathic peculiar" symptoms have not been considered here.

1. ACONITUM NAPELLUS:-

SPHERE OF ACTION:-

Repertory:- Acute inflammatory changes in blood vessels, phlebitis, joints/ synovitis, wounds, swellings.

Materia Medica:-

1. It is the first remedy in inflammations and inflammatory fevers.
2. Serous membranes and muscular tissue come under its sphere of action.
3. Aconite causes only functional disturbances and cannot produce tissue change.
4. **Before** the onset of exudation in the beginning of inflammation.
5. Purpura miliaris.

IMMUNOLOGICAL INTERPRETATION:-

From the above information, it would be expected that aconite stimulates the initial mediators, of inflammation such as:-

Histamine; Thrombin; P-Selectine; Platelet activating factor; Integrins (LFA-1, MAC-1); C5a; Leucotrine-B4.

It is these mediators that enable chemotaxis to the inflammatory site and produce the first signs of inflammation.

SCOPE FOR RESEARCH:-

a. It is possible that repeated doses of Aconite in a selected potency would cause a positive increase of the above factors in the blood or at an inflamed site. This would be a type of proving for Aconite which can be carried out both in vivo with laboratory animals, or in vitro, detecting changes of these mediators in a sample of blood.

b. It would be interesting to study the modifying action of Aconite on the above mediators in vivo, in acute inflammatory condition that already exists.

c. Laboratory studies cimilar to that suggested in 'A' could be done on mice, in order to detect
   (i.) levels of the above suggested mediators in the blood with a structured programme
   (ii.) Tissue histopathology following repeated dosing.

2. ARNICA

SPHERE OF ACTION:-

Repertory:-

1. Inflammation of blood vessels, esp. post traumatic
2. Prophylaxis of tetanus.
3. Abscesses & suppurations;
   Helps to abort the process in acute situations
4. Wound healing
5. Bites.

Materia Medica:-

1. Produces conditions similar to those resulting form injuries, falls, blows and contusions.
2. Septic conditions
3. Prophylactic of pus infection.
4. Affects the venous system inducing stasis.
5. Relaxed blood vessels, echymosis, haemorrhage.
6. Tendency to tissue degeneration, septic conditions abscesses that do not mature.
7. Rheumatism and traumatism of muscular and tendinous tissue.

IMMUNOLOGICAL INTERPRETATION:-

A) In the presence of Vascular endothelium damage,
Arnica probably

- Promotes platelet plug formation by
Factor XII activation
Kinin and plasmin production.

B) It promotes the ongoing inflammatory process by
- Increase of cytokines IL1, TNF,
Monocyte chemotactic protein
- Activation of receptor VCAM-1

C) It encourages resolution of inflammation at the cellular level:-

PGE2 , TGF, glucocorticoid at the humoral level:- Stimulus complement regulatory proteins like C1 inhibitor, C4 binding protein, C3 control protein, factor H-1
:- Stimulates Decay accelerating factor DAF
:- Controls the production of proteins blocking the membrane attack complex lide CD5A and homologus restriction factor.

SCOPE FOR RESEARCH:-

It would be interesting to study the effect of Arnica in tincture and various potencies on the above detailed proteins and mediators of inflammation; i.e. its ability to modify their secretions and thus cause symptomatic improvement.

In what way Arnica assits the resorption of extravasated blood in various injuries as well as in hematomas and intracerebral bleeds.

3. APIS MELLIFICA

SPHERE OF ACTION:
Repertory:- 1. Cellulitis.
2. Chronic inflammation of serous membrane.
3. Aborts suppuration / abscesses
4. Thrombosis
5. Wounds

Materia Medica:-
1. Acts on cellular tissues causing edema of skin and mucous membranes.
2. Oedema, dropsial effusions and anasarca
3. Ersypelatous inflammations
4. Acute inflammations of parenchymatous tissues.
5. It produces serous inflammation with effusions.

IMMUNOLOGICAL INTERPRETATION:-

The possible mediators influenced by Apis could be:-
Histamine
Thrombin
P-selectin and platelet activating factor C5a, Leucotrine-B4.
Kinin and Plasmin systems which increase vascular permeability
Monocyte chemotactic proteins. (MCP-1) which maintains reaction to infection.

Apis probably helps resolve excessive inflammatory edema esp. at the cellular level, by increasing or promoting the early production of PGE , TGF , and glucocorticoids.

ILIO also inhibits antigen presentation and cytokine production..

In chronic inflammatory conditions it probably
- Enhances toxin neutralisation with the help of circulating antibodies.
- Increases IgE production that stimulates mast cells to increase the inflammatory process, so that opsonization takes place at the earliest.

SCOPE FOR RESEARCH:-

It would be interesting to study the action of Apis at the cellular tissue level with respect to the mediators of inflammation
1) Either producing the edema
2) Or quick resolution of the edema.

Toxin neutralisation may be another important function of Apis Mellifica, esp. in insect bites and allergies.

4. BOTHROPS LANCEOLATUS

SPHERE OF ACTION:-

Repertory:- 1. Thrombosis
2. Phlebitis / Milk leg
3. Symphangitis
4. Injuries- extravasations with

Materia Medica:-
1. The venom of this snake is most coagulating
2. Thrombosis and thrombotic phenomena which present as CVA's with hemiplagia and aphasia-"paralysis of the tongue"
3. Lymphatics swollen
4. Gangrene

Textbook of Haematology by Williams states that Batroboxin is the defibrinating agent in Bothrops venom. It releases fibrinopeptide A from fibrinogen leading to fibrin formation with subsequent removal from the circulation.

IMMUNOLOGICAL INTERPRETATION:-

A) It is obvious that Bothrop has an effect at that stage of pathology where damage has occurred to vascular endothelium due to various causes like fluctuating B.P., injury, infection.

Once damage has occurred to the cadothelial wall, there is:-
(i.) Activation of platelets by endothelial PAF
(ii.) Aggregation and thrombus formation
(iii.) A platelet plug forms which adheres to Von Willebrand factor on the vascular endothelium
(iv.) Factor XII is stimulated which then activates the intrinsic clotting system.

B) The second inference is that Bothrops could prevent thrombus formation and definitely break down thrombii which have already formed. This probably happens by its defibrinating effect.

C) The haemorrhagic tendency in Bothrops as in all snake poisons is generally due to the destruction of clotting factors in the blood, e.g. Factor VIII, prothrombin, thromboxane as well as other mediators involved in the intrinsic clotting system.

SCOPE:-
1. All the above named mediators could be repeatedly measured in laboratory animals as well as frequent biopsies taken to detect time changes and thrombus formations.
2. In vivo, when Bothrops is indicated in a patient, one may measure modifications in the levels of the mediators promoting thrombus breakdown in response to its administration.

5. CALENDULA

SPHERE OF ACTION:-
Repertory:- 1. Absecesses and suppurations
2. Wounds - esp. to stimulate exhuberant granulations, proud flesh.

Materia Medica:-
1. Promotes healthy granulation of wounds with rapid healing.
2. Hemostatic after tooth extraction
3. Promotes favourable cicatrization, with least amount of suppuration.

IMMUNOLOGICAL INTERPRETATION:-

It promotes the ongoing inflammatory process towards resolution. Therefore it could have a modifying effect on:-
Tissue macrophages which secrete the necessary mediators like IL-1, TNF.
Endothelial cells, fibroblasts and epithelial cells are stimulated into producing various factors for healing.
At the cellular level:-
PGE2, TGF and glucocorticoids resolve the inflammatory process. TGF plays a major role by stimulating fibroblast division and layin down of extracellular matrix.

SCOPE FOR RESEARCH:-

The main sphere of action of Calendula could be interpreted by studying its action a the cellular level, especially with TGF, PGE , and glucocorticoids.

Hence a detailed study of these factors, with frozen sections and blood levels in laboratory animals should shed a lot of light on this matter.

Also investigating the process of healing in a controlled study of patients with chronic injuries or non-healing wounds or bed-sores should give us valuable information on Calendula's properties.

6.HEPAR SULPHURIS CALCAREUM

SPHERE OF ACTION:-

Repertory:-1. Cellulitis - acute
2. Synovitis - chronic inflammation
3. Abscesses and suppuration aborts or hastens suppuration
4. Wounds - slow healing.

Materia Medica:-

1. Unhealthy skin -every little injury suppurates
2. Abscesses - suppurating glands
3. Chronic and recurrent urticaria.

IMMUNOLOGICAL INTERPRETATION:-

Hepar Sulph probably improves the process for resolution of inflammation by

(i.) Enhancing suppuration by stimulating tissue macrophages, endothelial cells, fibroblasts and epithelial cells.
This in turn increases phagocytosis and pus formation.
Also stimulation of the humoral system occurs to produce cytokines especially IL2 which amplifies T-cell response.

(ii.) Aborts suppuration:-
At the humoral level through stimulation of complement regulatory proteins, decay accelerating factor, immunoglobina and other proteins blocking the membrane attack complex.

At the cellular level:-
PGE inhibits the lymphocyte proliferation and cytokine of T-cells and macrophages.
TGF quells the cytotoxic enthusiasm of macrophages and IFN activated Natural Killer Cells.

(iii.) Wound healing is promoted by TGF which stimulates fibroblast division and laying down of extra cellular matrix.

(iv.) Urticaria:- Indicates Hepar Sulph action on Type 1 Hypersensitivity; i.e. it modifies IgE production and mast cell activation.

SCOPE FOR RESEARCH:-

1. To document the action of Hepar Sulph, the mediators one can consider are IL-2, tissue macrophages that promote suppuration; PGE , TGF that enhance resolution.
2. Type 1 Hypersensitivity reaction may be studied in laboratory animals by documenting IgE production and mast cell activation.

6. LACHESIS

SPHERE OF ACTION:-

Repertory:- 1. Phlebitis
2. Cellulitis
3. Abscess & suppurations: acute onset
4. Wounds
5. Increases Granulation tissue.

Materia Medica:-

1. Lachesis "decomposes" the blood, rendering it more fluid, hence a haemorrhagic tendency is marked.
2. Boils and carbuncles with echymosis around
3. Purpura, Cellulitis.

PHYSIOLOGICAL ACTION:-

A) Snake poisons when inoculated spread by lymphatic flow. There is immense local tissue destruction by direct necrosis of tissue which causes blood and fluid to extravasate. There is a dramatic onset of swelling which increases local pressure producing ischaemic damage. This gives rise to echymosis and severe pain.

B) They have marked haematological effects which cause abnormalities in clotting mechanisms, red cell morphology, platelet count and function, and a bleeding tendency. The main modes of action are:
   1. Local platelet consumption at the site of injury.
   2. Activation of prothrombin to thrombin causing platelet aggergation.
   3. Platelet activating proteins which promote platelet destruction; e.g. fibrinolysis, hemolysis

4. Hypofibrinogenemia with or without thromobocytopenia due to enzymes which clot fibrinogen directly or via activation of factor X or prothrombin
5. Various proteins that act as anticoagulants, procoagulants, fibrinolysins, haemolysins and haemorrhagins.

SCOPE FOR RESEARCH:-

1. It would be interesting to study the mediators of inflammation that are modified by Lachesis. It is obvious that acute phase proteins as well as other agents promoting or controlling the dramatic onset of cellulitis with haemorrhagic extravasation may be acted upon by Lachesis.
2. Identification of those elements in the blood that enhance the tendency to bleed
   a) Increased platelet count
   b) Increased prothrombin / thrombin levels
   c) Altered thromboxane levels
   d) Altered fibrinogen levels.

7. SILICA

SPHERE OF ACTION:-

Repertory:-1. Inflammation - bones
- osteomyelitis
- bursae
- cellulitis

2. Chronic inflammation of serous membranes and joints
3. Slow repair of broken bones
4. Abscesses - hastens suppuration
5. Granulation tissue - proud flesh
6. Slow healing wounds.

Materia Medica:-

1. Silica can stimulate the organism to reabsorb fibrotic conditions and scar tissue.
2. Abscesses, quincy, cheloid growth.
3. Suppurative processes - ripens abscesses since it promotes suppuration
4. Promotes the expulsion of foreign bodies from tissues.

IMMUNOLOGICAL INTERPRETATION:-

Silica plays a major role in chronic inflammation or in acute inflammation, after suppuration has set in.

1. Hence it probably modifies or enhances the function of tissue macrophages which further secrete mediators like cytokines, IL-1, TNF. This in turn increases the resolution of inflammation by activating the lymphocytes resulting in a granuloma formation.
2. To hasten suppuration, the process of phagocytosis is enhanced by
   (i.) A serum protein which forms complexes with bacterial lipopolysaccharides, attaches to macrophages which induces phagocytosis and increased TNF secretion.
   (ii.) An improved humoral response and immunoglobin production also accelerates phagocytosis.
3. Resolution of inflammation:
   To enhance the resolution of inflammation, Silica probably has an action at the cellular level, especially with TGF which deactivates macrophages quelling their cytokine enthusiasm by inhibiting the production of reactive oxygen intermediates.

   TGF also helps subsequent wound healing by stimulating fibroplast division and laying down of extracellular matrix.
4. Keloids / Scar tissue:-

It is difficult to explain exactly how Silica causes resorption of keloids, as there is no documented physiological explanation for this. But silica "CONSTITUTIONS" tend to have hypertrophied scars, and silica modifies this excessive fibrous tissue deposition probably by control of TGF.

SCOPE FOR RESEARCH:-

Studying the above changes under the action of Silica in histopathological sections in laboratory animals would give us good information about its properties. The most modified mediators may be TGF under the action of Silica.

C) AUTOIMMUNE DISEASES

Autoimmune diseases are a recently recognised entity, and their terminology did not exist in the days when repertories were written. Hence one would not find relevant rubrics in any repertory.

APPROACH:-

How does one approach autoimmune diseases from a homoeopathic standpoint ? We understand that autoimmunity is a general disease of the body; i.e. Auto-antibodies circulate in the blood which, for some reason have been developed by the body's deviant immune system.

Homoeopathic medication thus, has to have a modifying effect on the immune system as a whole, bringing back the deviation to normal.

As explained in Section I, autoimmune diseases are classified according to the target of the autoimmune antibodies, which range from Organ Specific antibodies to Systemic or non-organ specific antibodies. These are produced by CD5 cells as part of the 'natural' antibody spectrum.

There is a tendency though, for more than one autoimmune disorder to occur in the same individual and when this happens, the association is often between diseases within the same region of the autoimmune system (Table on pg 55.)

Thus Hashimoto's disease may be seen with pernicious anemia; conversely in pernicious anemia patients, thyroiditis and thyrotoxicons are common (thyroid antibodies have been demonstrated in 50 % of pernicious anemia patients, i.e. two populations of antibodies are present, one with specificity for the thyroid and the other for the stomach).

At the non-organ specific end of the spectrum, Systemic autoimmune disease such as SLE is clinically associated with R.A. and several other disorders which are themselves uncommon, e.g.hemolytic anemia, ideopathic leucopenia, thrombocytopenie purpura, dermatomyocytis and Sjogren's syndrome. Antinuclear antibodies and antiglobulin (rheumatoid) factors are a general feature.

Patients with organ specific disorders are slightly more prone to develop Ca in the affected organ, whereas generalised lymphoreticular neoplasia shows up with uncommon frequency in non-organ specific disease.

For this thesis, we will consider the following clinical conditions.

1. Hashimoto's Thyroiditis / Primary Myxedema
2. Grave's Disease
3. Myasthenia Gravis
4. Rheumatoid Arthritis
5. Systemic Lupus Erythematosus.

1. HASHIMOTO'S THYROIDITIS

ANTIGEN:- Thyroglobulin
ANTIBODY:- Antibodies to several thyroid constituents such as antithyroglobulin and antimicrosomal antibody.

SYMPTOMATOLOGY:-

A) **EARLY**:- Weakness, fatigue, muscle cramps, cold intolerance, constipation, lethargy, dryness of skin, headache, menorrhagia.
Physical findings:- Occasionally present are brittle nails, thinning of the hair c coarseness, pallor, por turger of the mucosa; delayed return of deep tendon reflexes is often found.

B) **LATE**:- Slow speech, absence of sweating, weight gain, peripheral edema, pallor, hoarseness, muscle cramps, aches and pains, dyspnoea, deafness. Amenorrhea or menorrhagia, galactorrhea.
Physical findings:- Puffiness of face / eyelids, thickening of tongue, hard pitting edema, effusions - pleural / peritoneal, pericardial cavities as well as joints, Pulse rate slow, Cardiac enlargement.

In Part 5, II B and III of Section I, we explain the existence of inflammatory infiltrate which speaks of an associated T-cell mediated hypersensitivity. Presently the diagnosis is established with Antithyroid titres. The higher the titre, more active and progressive is the disease, whereas low titres signify latent disease. The inflammatory changes on FNAC are also diagnostic.

How does homoeopathy contribute in these cases ? Let us first understand this disease from the homoeopathic perspective. The patient's immune system deviates from normal, but only enough to produce self-antibodies localized to a specific organ. Here the susceptibility is good and hence restricts the disease process to a single organ. If the proper homoeopathic treatment is given, progrssive improvement could take place.

If the patient does not get a 'good' homoeopathic treatment, the impaired immune function deteriorates further, the disease process continues, and more organs become involved until finally, malignancy of the affected organs develops.

What is the miasmatic background in this condition ?

Though individual to each case, the predominant miasm in autoimmune disease is TUBERCULOSIS. The reaction of the individual to the antibody is entirely dependent on the predominant miasm which produces the ultimate clinical picture, i.e. either hypo- or hyperthyroidism. In this case, hypothyroidism manifests, where chronic inflammation is associated with destruction of cells producing hypersensitivity.

Hypothyroidism and its symptoms though, do suggest a good **SYCOTIC** background as well. But further disease progression would be complete destruction and thus **SYPHILITIC.**

The homoeopathic approach in hypothyroidism could be 3-fold:
1. Constitutional Similimum.
2. Replacement / Supplementation therapy
3. Anti-miasmatic remedy.

1. Constitutional Similimum:-

This is obtained on the basis of symptom similarity of the "Mental and Physical Generals". What we seek to achieve here is a change in the emotional "imbalance" or "deviation" which has initially caused the immune system to malfunction destructively.

Secondly, resolution of the chronic inflammatory changes within the gland has to take place over a period of time.

Thirdly, correction of the abnormal immune response, i.e. to **stop** the production of antithyroid antibodies

a) First, by reducing and neutralising by some innate mechanism, the existing circulating serum antibodies.
b) Then, by correcting the autoimmune deviation of the immune system. But this process would possibly take a long period of time, even upto 5- 10 years. To reverse the initial deviation which could have started very much before the actual time changes had begun to occur, and further bring this to normal, requires time. Of course, symptomatic improvement is always present.

2. Replacement / Supplementation therapy

For this reason, the Replacement or Supplementary treatment comes into play, till the organ recovers enough from the inflammatory change that interfere with its function.

Homoeopathic preparations of Thyroidinum in various potencies could be selected as replacement . Conversely, I am presently not averse to replacing the inadequate hormone with "Levothyroxine", i.e. commercially prepared thyroxine hormone in an adequate dose. This can be subsequently reduced as the thyroid function improves.

Thyroxine is a very important hormone for all functions of the body, as well as basic cellular metabolic processes; and failure to replace it in the body results in malfunction of almost all organs of the body as the disease progresses.

3. Anti Miasmatic:-

The destructive effect of antibodies in this disease must have a miasmatic base, and to ensure a complete improvement one needs to include the miasmatic drug in the treatment process. As each case is individual, an antisycotic or antitubercular drug needs to be interposed at appropriate times.

Very often improvement is stalled or inadequate for want of the use of the correct antimiasmatic remedy.

LABORATORY PARAMETERS:-

A regular follow up on immunological and other parameters is necessary to gauge the improvement in the patient.

1. Antithyroid antibody levels or Anti Microsomal antibody levels - widely considered only of academic importance or for diagnosis only, as there is apparently no control over the 'activity' of the dis ease, and waxing and waning is expected.

   Fluctuating or reducing levels would help us gauge the remedy requirement of the patient. One could probably predict the potency and repetition of the remedy.
2. FNAC of the thyroid gland would determine the amount of inflammation and infiltration of the gland.

   A comparative study over a period of time would suggest and improvement or deterioration in the chronic inflammatory process. Unfortunately, this test is invasive in nature.
3. Improvement in T4 and radio-iodine uptake could be an indicator to the function of the thyroid under homoeopathic treatment, as simple replacement therapy would not enhance thyroid function.

   Similarly, lower requirement of replacement medication would indicate and improved thyroid function.

GRAVES' DISEASE

ANTIGEN:- Cell surface TSH Receptors
Growth receptors

ANTIBODY:- Thyroid stimulating antibodies
TSAb.

SYMPTOMATOLOGY:-

1. Weakness, sweating, restlessness, nervousness, irritablity, easy fatigueability
2. Unexplained weight loss inspite of ravenous appetite.
3. Quick movements with incoordination varying from fine tremulousness to gross tremor.
4. Tachycardia; warm, thin soft, moist skin; exopthalamus; goitre with a bruit.

As explained in part II B and III of Section I, there is always an associated T-cell midiated hypersensitivity contributing to the thyroiditis.

There is a considerable diversity in the autoimmune response to the thyroid antibodies, possibly due to different constitutional and miasmatic backgrounds. I Graves' disease, there is metabloic stimulation resulting in hyperfunctioning of the gland.

Also there is growth promotion due to growth receptor antigens and hence an enlargement of the thyroid gland or goitre is observed. This enlargement is also contributed by the mononuclear cell infiltration of thyroiditis.
How does homoeopathic treatment help in "curing" Graves' disease?

To postulate on the mechanism of action of the indicated homoeopathic remedy, we can consider both, the control of antibody production and thus thyroid function, as well as modification of chronic inflammatory changes The idea is, as explained earlier, to modify the basic deviation of the immune system and thus control further progress of the disease.

A bipronged approach to treatment in these cases would be required. But as the symptoms are aggressive, the treatment approach should also necessarily be aggressive.

1. Constitutional Similimum.

It is imperative to derive the complete similimum in these cases, in order to effect any changes. The so-called "incurable" cases are the result of one's inability to obtain the similimum. Once decided on the basis of symptom similarity in physical and mental generals, the remedy needs to be repeated frequently to have and adequate impact. The doses then need to be gradually increased in frequency and potency, as the improvement occurs.

This would be observed at the emotional, symptomatic as well as investigative levels.

2. Antimiasmatic Remedy.

The proper interposition of the indicated antimiasmatic remedy is essential for the progress of the case. Graves desease has essentially a Tubercular Miasmatic background. But one needs to take Past History and Family History into consideration, in deciding the appropriate Miasm.

Tuberculinum in1M potency is the drug of choice and is frequently indicated.

LABORATORY PARAMETERS:-

1. T3 T4 TSH levels should be done frequently to evaluate the status of the thyroid function and disease improvement. The first response, along with symptomatic improvement would be and increase in TSH levels, along with a reduction in T3 T4 levels.

2. TSAb levels as well as AMA and ATA
   Changing levels would give an indication on the activity of the disease.

3. FNAC of the thyroid gland:-
   This would document the recovery of thyroid tissue from chronic inflammation and improvement of the level of thyroid sensitivity.

Appendix 1 has two cases presented by Dr.P. M. Barvalia, an authority on Thyroid Research in Bombay. They give a clear indication of line of treatment and support the philosophical interpretation suggested above.

3. MYASTHENIA GRAVIS

ANTIGEN:- Skeletal and heart muscle
Acetylcholine receptors
ANTIBODY:- To the ACL receptor in 80 % of cases
To muscle, usually if associated with thymoma.

SYMPTOMATOLOGY:-

1. Fluctuating weakness of commonly used voluntary muscles, producing symptoms such as diplopia, ptosis, and difficulty in swallowing.
2. Activity increases the weakness of affected muscles.
3. Weakness is usually localised to a few muscle groups, esp. ocular muscles, or may become generalized
4. Symptoms of ten fluctuate in intensity during the day, and this diurnal variation is superimposed on a tendency to longterm spontaneous relapses and remissions.

Clinically: Weakness and fatigueability of affected muscles, esp. ocular palsies and ptosis which is asymmetrical, but pupilary responses are normal.

HOMOEOPATHIC APPROACH:-

These symptoms are due to a varying degree of block of neuromuscular transmission due to autoantibodies binding to acetylcholine receptors, which efectively reduce the number of functioning Ach receptors.

As with other autoimmune diseases, the scope of homoeopathic medicines is to first reduce the antibody levels and, at the same time, reduce the antigenicity of the acetyl choline receptors.

Secondly, to increase the number of available receptors possibly by regeneration of depleted receptors at the motor end plates.

As with other autoimmune diseases, the treatment is
1. Constitutional and
2. Antimiasmatic.

Here the predominant miasm is probably Sycotic with Tubercular overtones. Hence, depending on the history of the patient, the proper antimiasmatic remedy should interposed at regular intervals.

LABORATORY DATA:-

1. A diagnosis is generally made on detection of antibody to Ach receptor.
- Regular titers would indicate improvement and remission
- Since a latent period of re mission could take place, a regular follow up over a period of 2 to 3 years is necessary before one is completely sure of a cure.

2. Electrophysiological demonstration of a decrementing muscle response to repetitive 2 to 3 Hz stimulation of motor nerves indicates the disturbance of neruomuscular transmission As sustained improvement in these observations in specific areas could also indicate a cure.

3. Alternatively, Needle electromyography of affected muscle shows a marked variation in configuration and size of individual motor unit potentials.

Also single fibre electromyography reveals a variability in the time between 2 muscle fibre action potentials from the same motor unit.

Repeated electromyography when the patient is on treatment, would indicate success or failure of the homoeopathic remedy to control the disease. A properly selected remedy should reduce this variable tendency of the readings.

4. RHEUMATOID ARTHRITIS

ANTIGEN:- IgG
ANTIBODY:- Antiglobulin to IgG.

SYMPTOMATOLOGY:-

1. Prodromal systemic symptoms of malaise, fever, weight loss and morning stiffness.
2. Insidious onset in small joints with centripetal and systemic progression.
3. Joint selling associated with stiffness, warmth, tenderness and pain. Stiffness is more early morning improving during the day. Its **duration** is a useful indicator of activity of the disease.
4. Extra-articular manifestations are sub-cuaneous nodules, pleural effusion, pericarditis, lymphadenopathy, splenomegaly, with leucopenia and vasculitis.
5. Late symptoms are thickening of periarticular tissue, flexion deformities, subluxation, fibrosis, ankylosis. Dryness of eyes and other mucous membranes. Arthritis resulting from rheumatic vasculitis.

HOMOEOPATHIC APPROACH:-

Specifics for joint inflammation, in my opinion, ar of little value and a waste of time. Pain can be so intense, that homoeopathic remedies fail to have an effect.

The only successful and long term treatment is RA is that of a deep-acting constitutional similimum.
How does this work at the immunological level ?

It is well documented that cytokines like TGF 1 are known to protect against collagen arthritis and relapsing EAE. Also cultures of synovial cells of RA spontaneously produce high levels of IL-6, TNF and GM-CSF which activate macrophages, but very little of INF or TNF (which are protective) and hence remain in persistent autoimmune activity (cf. Section I Part 5 sub-section IV; Appendix 1).

The autoimmune process of immune complexes stimulate activated T-cells to produce TNF and GM-CSF, and theit interaction with polymorphs releases reactive oxygen metabolites and lysozomal enzymes. This produces **tissue damage** and **pain** with infammation.

This immunologival change can be predicted by a galacto IgG. This change causes a T-cell mediated hypersensitivity reactionwhich further contributes to the acute inflammatory changes in the joint and subsequent pannus formation. Subcutaneous nodules are similarly formed.

The properly prescribed similimum would possibly effect changes as below.

1. Reduction of pain and inflammation. This takes place probably
a) by reducing the mediators of inflammation, like reactive omygen metabolites, lysozomal enzymes like neutral proteinases and collagenase.
b) Reduction in TNF, GM-CSF,and IL-6 secretion by T-cells that maintain the inflammatory changes.
c) Increased secretion of IFN which have resolution properties.

2. **Arresting the damage** taking place on articular surfaces is secondary to the initial response of reduction in inflammatory changes. Once the inflammation is under control, subsequently the ability of the immune complexes to be stabilised by multivalent binding may be interfered with.

Ultimately there is no stimulus for activated synovial cells, which form the pannus over the cartilage, and breakdown of tissue at the margin is slowly reduced. This process would require a very long term treatment of nothing less than 4 - 5 years. But progress under change should demonstrates a change in the above indicators.

LABORATORY PARAMETERS:-

Measure	**Normal**	**Group I (Non-inflam.)**	**Group II (Inflam.)**	**Group III (Septic)**
Volume	3.5	Often 3.5	Often 3.5	Often 3.5
Clarity	Transparent	Transparent	Transparent - opaque	Opaque
Colour	Clear	Yellow	Yellow or Opalescent	Yellow / Green
WBC	200	200 - 3000	3000 - 5000	50,000
PMN %	25 %	25 %	50 % or more	50 % or more
Culture	Negative	Negative	Negative	Usually positive
Glucose	Nearly equal to serum	Nearly equal to serum	25, lower than serum	25, much lower than serum

Group I	**Group II**	**Group III**
(Non-inflammatory)	**(Inflammatory)**	**(Septic)**
* Degenerative joint disease	* R. A.	* Pyogenic bacterial Spesis
* Trauma	* Gout / Pseudogout	
* Osteochondritis dessicans	* Reiters Syndrome	
* Osteochondromatosis	* Alkylosing Spondilitis	
* Neuropathic arthropathy	* Psoriatic arthritis	
* Early or subsiding inflammation	* Arthritis accompanying U. Colitis and Regional Enteritis	
* Hypertrophic Osteoarthropathy	* Rheumatic fever	
* Pigmented Villonodular Synovitis	* SLE	
	* PSS	
	* Tuberculosis	
	* Mycotic Infections.	

When the diagnosis of RA has been established, a regular examination of joint fluid e.g. every 6 months could be a good indicator of improvement under homoeopathic medication. One would expect

i.) clarity to improve from opaque to transparent
ii.) Colour to improve from yellow / opaque to clear
iii.) WBC count to reduce in joint fluid
iv.) PMN's 25 %
v.) Glucose levels to rese upto serum levels.

2**. Rheumatoid factor** :- IgM antiglobulin
IgG antiglobulin in Sr. negative patients.

(i.) Antibody titre is indicative of activity of the disease.
(ii.) IgG antiglobulins presumably synthesised in the synodial tissues can be detected also in joint fluid. Since they tend to aggregate, reduction in these aggregations could also be used to indicate improvement with medication.
(iii.) Periodic synovial membrane biopsy:

To detect a) cellularity i.e. CD4 cell count, dendritic cells, macrophages.
b) Clumps of plasma cells.
c) Secondary follicles with germinal centres.

d) Expression of surface HLA -DR (class II) of all cells.

Reduction at all these levels could further indicate improvement under treatment if serially observe and compared over a period of years.

It should be stressed that once severe destructive pathological changes hace taken place, they would probably be irreversible under any treatment. Hence catching the disease process early is of prime importance.

Also, use of certain drugs like Steroids or Gold Salts hamper the action of homoeopathic medications. Patients who come after such treatment are usually advanced cases, and hence have a poor prognosis.

5**. S.L.E.**

ANTIGEN:- Soluble components: - Formed elements of blood.
- Clotting factors
-IgG
-Cardiolipin
- 2glycoprotein
:- Sm. Ribonucleoprotein
:- Nucleoprotein

ANTIBODY:- High titre Antinuclear Antibody (ANA)
Anti DSDNA Antibody
Phospholipid Antibody

The American Rheumatism Association has proposed that the diagnosis of SLE can be made with reasonable probability if 4 of the 11 following criteria are present, serially or simultaneously during any interval of observation.

1. Malar Rash
2. Discoid Rash
3. Photosensitivity
4. Oral ulcers
5. Nonerosive arthritis
6. Serositis
7. Renal disorder
8. Neurologic disorder
9. Haemotologic abnormality (haemolytic anemia, leucopenia,lymphopenia, or thrombocytopenia).
10. Immune dysfunction (positive LE preparation, antinative DNA, anti-Sm, false positive syphilis VDRL for more than 6 months.
11. Positive Antinuclear antibody.

CLINICAL SYMPTOMATOLOGY:-

1. Fever, anorexia, malaria, weight loss.
2. Skin lesions:- butterfly rash on the face.
Discoid lupus, typical fingertip lesions,
Periungal erythema, nail fold infarcts, sphincter haemorrhages. Alopeia.
3. Raynaud's phenomena in 20 % of patients.
4. Joint symptoms in 90 % of patients
- with or without active synovitis, rarely deforming.

5. Ocular - Conjunctivitis, photophobia, transient and blurring of vision.
- Cotton wool spots i.e. "cytoid bodies" on retina, representiing degeneration of nerve fibres due to occulusion of retinal blood vessels.

6. Restrictive lung disease
-Pleurisy, pleural effusion, broncho-pneumonia, pneumonitis.

7. Pericardial effusion; Myocarditis and hypertension, Cardiac arrythmias.
8. Abnormal pains, ileus, peritonitis which may result from vasculitis. Right colon is especially affected.
9. Neurological complications

- Psychosis, Organic Brain syndrome, seizures, peripheral and cranial neuropathies, transverse myelitis and strokes.

10. Several forms of glomerulonephritis may occur including mesengial, focal proliferative and membraneous.
11. Arterial and venous thrombosis, Lymphadenopathy. Splenomegaly.
12. Hashimoto's thyroiditis. Haemolytic Anemia. Thromobocytopenic purpura.

HOMOEOPATHIC APPROACH:-

SLE is one of the most difficult diseases to treat and control, not only in modern medicine but in homoeopathy too. This is largely due to the fact that the antibody is systemic and not restricted to one particular area of the body. It speaks of a generalised immune system deviation which is a largr problem than a single organ problem.

The vascular system is mainly attacked with antibodies formed to blood components and deposited wherever capillary perfusion exists.

One understands, that symptomatic SLE develops very much after the disease process had originated. Homoeopathy could endeavour or restrict the disease to the skin and other less importand organs, and prevent its progression deeper to the important organs . One can thus arrest the disease i.e. reduce the development of immune complexes and the tendency of these complexes to deposit themselves along the basement membranes. Alsol, early aggregations and depositions could be cleared up by phagocytosis before they grow large enough to be symptomatic.

Most probably, the homoeopathic similimum improves the function of the early classical complement components Clq and C4 that enhances effective clearance of these immune complex aggregations.

The similimum would also reduce the intensity of the symptoms and would be required to be repeated very frequently, even daily or twice daily with gradually increasing potencies, probably life long. Antimiasmatic remedies also need to be interposed frequently.

LABORATORY PARAMETERS (refer to page 66):-

I Tests to detect disease activity:-

(i.) Serum complement:-
Decreased serum complement indicates increased disease activity. Whereas increased serum complement signifies a decreased activity and remission.
This is a good guide to prognosis on homoeopathic medication.

(ii.) Anti-native DNA antibody levels also correlate with disease activity.

(iii.) Leucopenia, lymphopenia and thrombocytopenia also indicate activity and should improve on treatment with homoeopathic medication.

(iv.) Raised ESR is always a good indicator of disease activity.

II. Antiphospholipid antibodies are of 3 types (refer Appendix 1)

(i.) One responsible for false positive for syphilis; VDRL 10 - 20 %.

(ii.) Second is lupus anticoagulant -7 % which is a risk factor for venous and arterial thrombosis and miscariage . Also idintified by prolongation of activated PTT.

(iii.) Anticardiolipin antibodies -25 % which cause fetal death in pregnant patients with Lupus. These patients have a poorer prognosis, but it would be interesting to study the effect of similimum on them.

C) FEVERS

INTRODUCTION:

It is obvious that homoeopathic medicines have a modifying effect on most types of fevers. The following chapter is an attempt to understand how possibly these remedies prove effective, with an ecdeavour to suggest a future scope for research.

We will study this in two parts:
A) Physiological consideractions.
B) Homoeopathic Observations.

A) **Physiological Considerations**:

Fever is an elevation of body temperature above normal circadian variation, as a result of a change in the thermo-regulatory centre, located in the anterior **thalamus.** A normal body temperature is maintained despite enviromental variations, due to the ability of the thermo-regulatory centre to balance heat production by tissues, notably muscles and the liver, with heat dissipation. With fever the balance is shifted to increase core temperature.

Hyperthermia is an elevation of body temperature above the hypothalamic set point due to insufficient heat dissipation e.g. as is seen in exercise, perspiration, inhibiting drugs, hot ecvironment.

Pyrogens:
Substances that cause fever are called pyrogens and may be either exogenous or endogenous. Exogenous pyrogens are from outside the host, whereas endogenous pyrogens are produced by the host generally in response to initiating stimuli usually triggered by inflammation or infection.

The majority of exogenous pyrogens are micro-organisms, their products or toxins e.g. In Gram negative bacteria, an endotoxin (lipopolysaccharide) LPS is found on the outer membrane. Gram positive organisms alo produce potent exogenous pyrogens, which include lipoteichoic acid, peptidoglycan and various exotoxins and enterotoxins.

In vivo, LPS is capable of producing fever in humans with a little as 1 ng/kg. The exogenous pyrogens act primarily by inducing the formation of endogenous pyrogens: by stimulation of the hosts' cells, generally monocytes and macrophages.

But LPS may act directly on endothelial cells in the brain to generate fever, whereas many endogenous products result in the release of endogenous pyrogens, thereby causing fever. Such endogenous pyrogenous substances include antigen-antibody complexes with complement cleavage products, steroid hormone metabolites, bile acids, and some cytokines.

Endogenous pyrogens are polypeptides produced by a variety of host cells, particularly monocytes / macrophages. Endogenous pyrogens (EP) produced either systemically or locally gain entrance to the circulation and produce fever at the level of the thermo-regulatory centre of the hypothalamus.

Two leucocyte EP's exist IL-1, IL -1. These are also produced by endothelial cells, B lymphocytes, natural killer cells, fibroblasts, smooth muscle cells, keratinocytes and glial cells. Because of the ubiquitous production of these and other interleukins, cell derived inflammatory polypeptides and growth promoting peptides the more general term cytokine has been adopted to refer to these substances. The major pyrogenic CYTOKINES are IL-1ß, TNF, TNR, lymphotoxin interferon and IFN, IL- 6. If these are administered intravenously to humans chills and fever occur within one hour.

Hypothalamic Control of Temperature:
The metabolic rate of humans consistently produces more heat than is necessary to maintain core body temperature at 37° C, assuming a neutral enviroment. Body temperature is controlld by the hypothalamus. Neurons in bothe the preoptic anterior hypothalamus and post hypothalamus receive two kinds of signals: one from peripheral nerves that reflect receptors for warmth and cold, and the other from the temperature of the blood bathing the region. These two signals are integrated by the thermo-regulatory centre of the hypothalamus to maintain normal temperature . Also present is a specialized vascular network called: Organum vasculosum laminae terminalis (OVLT) supplying some clusters of neurons.

It is likely that,
Endogenous pyrogens from circulation stimulate

?

Endothelial cells of the OVLT

?

Release arachidonic acid metabolites esp. PG-E2 Cyclic AMP

?

Preoptic /anterior hypothalamus region

?

Raises the thermo-regulatory set point

?

A) Higher setting sends signals to various efferent nerves particularly those sympathetic fibres innervating the peripheral blood vessels. ✍ Initiate vasoconstriction and promote heat conservation.

B) Cerebral cortex: Initiating behavioural changes seeking warm enviroment, clothes, special posturing.

C) Shivering (involuntary muscle contraction) is another mechanism to increase heat production.

If the hypothalamic set point is reset downward by the disappearance of stimulating endogenous pyrogens or by inhibition of local prostaglandin syntheses by cyclo-oxygenase inhibitors such as aspirin, ibuprofen or acetominophen, then vasodilatation and sweating dissipate heat through radiation and conduction from the skin.

These are also endogenous ANTIPYRETIC substances such as arginine vasopressin, adenocorticotropin, and melanocyte stimulating hormone and corticotropin releasing hormone, each of which seems to alter the ability of endogenous pyrogens to stimulate prostaglandin production .
Several peptides MODULATE responses in fibrile diseases called cytosine antagonists and inhibitory cytokines.

Biological activities of IL-1, TNF and IL-6.
It is important to distinguish between the critical physiological roles of local IL-1 and TNF and the high systemic blood levels often seen with severe life threatening diseases.
IL-1 and TNF:

1. Mediate local phagocyte cell emigration and activation and the release of lipid-derived mediators such as PG E2, thromboxane and platelet activating factor.
2. IL-1 induces IL-8 synthesis which is a potent neutrophil and monocyte chemotactic factor.
   ✍ IL stimulates the release of enzymes from neutrophils
   ✍ Enhances the host attack on invading microbes.
3. Vasodilatation,
   Induction of adhesive glycoprotein,
   T and B cell activation,
   Enhanced phagocyte cell killing,
   Are directly or indirectly mediated by these cytokines.
4. Acute phase response is stimulated mainly by IL-6.
   This cytokine produces:
   - ? Changes in protein synthesis in the liver
   - ? Sr. Albumin levels decrease.
   - ? Production of acute phase proteins including antiproteases, complement components, fibrinogen, ceruloplasmin, ferritin, haptoglobin.
   - ? C-reactive protein which in turn binds to damaged and necrotic cells and some micro-organisms, may increase 1000 fold.

- ? Sr. amyloid A (SAA) protein may increase markedly and be deposited in various organs to cause secondary amyloidosis.
- ? Sr. Fe and Zn levels are decreased, depriving invading microbes of these critical growth factors.

5. IL -1 and TNF mediate local and systemic inflammatory effects. In combination small amounts may cause refractory hypotension and multiorgan system failure.
   Suppression of either of these two cytokines could bace a significant therapeutic effect by blocking their synergistic toxicity.
6. IL -1 induced activation of T and B cells is greater at 39° C than at 37° C.
   IL -1 and TNF increase loss of mean body mass and cause anorexia, contributing to the cachexia of chronic febrile states.
   IL -6 levels correlate better with the amount of fever and other pathologiv findings in a variety of infectious diseases than IL -1 and TNF, because of the persistence of IL -6 in the circulation.

Why is fever necessary?

1. The elevation of the body temperature in many situations ensures survival.
2. The growth and existence of several bacterial species are impaired at higher temperatures.
3. Temperatures in the febrile range appear to increase the phagocytic and bactericidal activity of neutrophils and the cytotoxic effects of lymphocytes.

Each elevation of body temperature of 1° C there is and increase in O_2 consumption of 13 % and increased caloric and fluid consumption.
The increased metabolic demand may stress the foetus during pregnancy and patients with marginal cardiac or cerebral vascular supply.
IL -1 and TNF accelerate muscle catabolism, leading to a loss of body weight and negative nitrogen balance. Essentially, skeletal muscle is utilized as an energy source, with liberation of aminoacids for gluconeogenesis and for the synthesis of acute phase proteins and formation of clones of immune cells.
Fever reduces mental activity and can produce delirium and stupor. Childres are particularly prone to develop seizures with fever.

Homoeopathic Observations in Fever:

It has been clearly documented in the history of homoeopathy that homoeopathic remedies possess "fever producing" properties and thus "fever curing" properties too. Hahnemann's discovery of homoeopathy was linked to the "fever producing" properties of Cinchona bark. This prompted him to take the bark himself in order to document whether this fact was true or not, and to his surprise, he did develop chills and fever as in Malaria fever.

Subsequently, numerous remedies were proved including Aconite, Arsenic Album, Eupatoreum Perflolatum, Belladona, Byronia, Hepar Sulph, to name a few. The pyrogenic effects of most homoeopathic remedies have been documented in Allen's 'The Therapeutics of Fevers' along with those distinguishing characteristics which are purely homoeopathic in nature.

What is essential in making use of a homoeopathic remedy for fever is that the remedy is a similimum, either specific for the acute episode or if constitutional symptoms are predominant, then the deep acting chronic remedy is indicated. Allen states in 'The Therapeutics of Fevers', " But of this I am sure that the objective and subjective symptoms of which he [the patient with fever] complains are in every respect similar to those produced on the healthy subject by Cinchona" (the remedy).

Mechanism of Action:

It would be interesting to postulate exactly how the homoeopathic remedies prove curative in fevers. It is obvious, that these drugs enhance the host reaction or modify it to overcome the infective stimulus as well as ensurs a good recovery. But how does this happen ?

Lately, a lot of new information has been discovered about the mechanism of fever and the biological changes that contribute to hyperthermia. This has been detailed above. Taking into account all this information, one may be able to postulate the possible mode of action of homoeopathic re medies.

Homoeopathic drugs could hace a direct action on endogenous antipyretic substances such as arginine, vasopressin, adeno-corticotropin, alpha-melanocyte stimulating hormone, corticotropin hormone each of which seems to alter the ability of endogenous pyrogens to stimulate prostaglandin production. But the major pyrogenin substances are CYTOKINES, and general term that includes interleukins (IL -1ß , IL -1a), Tumour Necrosis Factor (TNFa), TNFß , lymphotoxin, interferon (IFN -a) , IL -6. Hence, the homoeopathic remedies should also have a modifying influence on the cells producing these cytokines such as endothelial cells, B lymphocytes, natural killer cells, fibroblasts, smooth muscle cells, keratinocytes and glial cells.

SCOPE FOR FESEARCH:

(Refer page 110: Biological activities of IL -1 , TNF and IL -6)

In order to suggest possible areas for research, it would seem sensible to document the changes produced on three major cytokines: IL -1, TNF and IL -6. This could be done in two types of circumstances.

1. Laboratory animals:
   These animals could be regularly dosed with the homoeopathic drug to be studied. Daily variation in the levels of the above cytokines could be measured and interpretations made. Apart from this, one could keep track of:
   a) Protein synthesis of the liver.
   b) Serum Albumin levels
   c) Presence and levels of acute phase proteins like antiproteases, complement components, fibrinogen, ceruloplasmin, ferritin and haptglobin.
   d) Levels of C-reactive protein.
   e) Levels of PGE2, thromboxane and platelet activating factor.

2. In Patients with Fever:
   This could only be possible in an institutional set up, like a hospital, where patients are admitted for treatment with fever. Here, while regular investigations are being done, one may also detect the levels of the proteins and enzymes as mentioned above, as well as the levels of IL -1 , IL-6, TNF.

   Once the homoeopathically chosen remedy has been aministered, a steady check on the improvement of the patient needs to be done to ascertain just how this remedy is acting. For patient comfort, it would be preferable to withdraw blood only once a day to do the various blood investigations mentioned earlier.

CONCLUSION

Homoeopathic remedies have a definite effect on the immune system, through various mechanisms, either directly or through hormonal changes, emotional changes, salt-electrolyte variations and other metabolic functions. The relevant immunological and physiological mechanisms which could be modified by homoeopathic remedies have been detailed in Section 1.

A lot of work needs to be done to prove and document this. This thesis has suggested a number of laboratory methods and procedures with this aim in mind, and identifies various mediators of inflammation that could be modified by homoeopathic drugs directly.

The specific action of certain remedies on the immune system, as described in Section 2, is indicative of the power contained in the infinitesimal dose, when homoeopathically prescribed. The superiority of our medication in this regard is uparalleled and only with further research will this fact be accepted wouldwide. Regarding the therapeutics of hypersensitivity diseases and autoimmune diseases, various ongoing clinical trials

manifest the curing capacity and healing possibilities of the Similimum. These conditions are the next frontier that science needs to find a " cure " for, and the Similimum, I believe, is the only long-term safe and permanent solution.

APPENDIX

A few clinical cases of autoimmune thyroiditis and rheumatoid arthritis presented in the Indian Journal of Homoeopathic Medicine

Dr. Praful Barvalia:- AUTOIMMUNE THYROIDITIS

These cases are from a Thyroid Research Project and were presented in the Indian journal of Homoeopathic Medicine. These cases have been scientifically explained and demonstrate the effectiveness of homoeopathic medicines in these " incurable autoimmune diseases ", when the similimum is identified and basic homoeopathic concepts are applied.

CASE 1
NAME:Mrs. U. A. D.
Age: 35yrs. M.S. 12yrs.
Spouse : 37yrs. Occupation : Cloth Merchant.
Siblings : Bro. 30yrs Sis. 45yrs & 40yrs.
Children : Sons : 12yrs & 9yrs.

Chief Complaint :
THYROID Autoimmune thyroiditis :"hypothyroid phase"
Since 10 mths. Swelling+++, lethargy, weight gain : 6 kg.
Face & Legs esp.

Past History :
TYPHOID followed by JAUNDICE 10 mths . back . Lasted for 3 weeks.
Evening rise of fever, with sever cramps and tetany during fever.

Patient as a person :
Perspiration : offensive
Menstrual function : Normal. Backache and pain in legs < before menses.

Life space appreciation:
The patient is a Jain Gujurati lady from a joint family. She lost her mother in childhood due to accidental burns. Her 15 yr.old elder sister shouldered the responsibility. She claims she had no problems in childhood. Both her father and sister were irritable and there were a lot of restrictions. She was a quiet and reserved child.
She married at the age of 23 yrs.into a joint family where her husband is the second of 3 brothers. He is a self-made person who came to Bombay at a young age and established a good business. Subsequently he brought his family.
The elder brother-in-law (b-I-l) is indolent with poor resources while the younger b-I-l is slightly mentally retarded. There has always been some friction with her elder s-I-l, but she would never retaliate. They are living separately for the last 7 yrs.
The younger b-I-l is quite untidy in his work and impolite as well. The mother-in-law's partial attitude towards him adds fuel to the fire. The patient could never sort this out and would remain vexed. Her husband says that she appears extremely quiet while inside she would be boiling . She would cry alone, but would not let them know.
Two years back an arrangement was worked out leading to partial separation of the house, where the connecting door remains open while the kitchens are separate. In spite of this there are ample occasions for "tensions" and eventually she fell sick.

Dreams: Nil

Thermal State : CHILLY
Bath : Hot water around the year.
Covering : Always Woolen in winter. Fully covered.
Fan : Slow in winter.

Physical Examination:
Oedema+ on face, ankle, shin of tibia.
Pulse : 124/minute B.P.: 150/90, 160/94 Weight : 65 kgs.

Investigations :
2.4.92 : Antithyroid Antibody Titre : POSITIVE [l : 160]
(Titre above 1:40 is considered significantly positive for anti microsomal antibody and is indicative of Autoimmune thyroiditis.)
T.S.H. = 95 IU/ml
E.S.R. = 08.

Discussion :
Basically we find the patient extremely **reserved**, non-communicative and intensely **vexe**d due to inter-personal conflicts. She could bever sort out her difficulties and her emotions accumulate within, causing a deep impact on her psycho-sommatically. This appreciation led to the diagnosis of **Magnesium Carb**.and Natrum Mur as D/D. The problem with communication and an inability to retaliate favoured Magnesium rather than Natrum. Also, the evening rise of fever, cramps and tetany during fever, favour Mag. Carb.
The evolution of disease is quite consistent with the concept of adaptation to stress. Massive emotional disturbances broke down the patients' resistance and she developed fulminating acute illnesses which bore a constitutional stamp. This was followed by the precipitation of an Autoimmune disease in the Hypothyroid phase, which speaks of a dominant **Tubercular Maism.**

Inference : Susceptibility = Moderate : Reactivity =Moderate.
Immunity = Distorted
Sensitivity = High
Structural changes = Moderate
Suppression = Nil
Potency selected : 200. Initially infrequent doses, later multiple doses as required.
Treatment started : 7.7.1993 Mag. Carb.200 Three Doses. Placebo for one week.

FOLLOW-UP TREATMENT

DATE	**1**	**2**	**3**	**4**	**5**	**6**	**Prescription**
	Lethargy	**Mental fatigue**	**Swelling ; Face**	**Swelling : ankle / leg**	**Pulse / B.P.**	**Wt. / Other sympts.**	
12.7.93	>20 %	>20 %	SQ	SQ	140/90	SQ	S.Lx7 days
19.7.93	>20 %	SQ	SQ	SQ	-	Tetany once	Mag.Carb 200 III
26.7.93	>20 %	>40 %	>20 %	>20 %	-	-	Mag.Carb 200 III
9.8.93	>20 %	>++	>++	>++	P= 120BP 140/90	64 Kgs	Mag.Carb 200 III every week
20.12.93	>+++	>+++	>+++	>+++	134/90	63 Kgs	Mag.Carb 200 tds
3.1.94	>+++	>+++	>+++	<20 %	136/90	63 Kgs	Mag.Carb 1 M H

From 9.8.93 upto 20.12.93 Mag Carb 200 was repeated HS x3, every week. All the above mentioned subjective criteria improved by 50 % but the weight remained stagnant and the B.P. was 140/104, hence the posology was reviewed on 18.10.93 and the patient was put on multiple doses….. initially daily HS, then BD, and then TDS. From 3.1.94, the patient was kept on Mag. Carb 1 M HS. Her B.P. stabilized to 130/90, and weight to 62.
Clinically : **Euthyroid**
Anithyroid Antibody Titre : Negative.

CASE 2
NAME : Mrs. AJS
Age : 36 yrs.
Qualification : B.E. (1979) M.E. (1981)
Father : B. Sc. (Physics), Statistical Officer suffering from D.M., Ca. Mandible
Mother : B. A. Housewife
Siblings : 4 Sisters :- 37 yrs. (M.Sc.), 26 yrs. (B Pharm.), 21 yrs expired 1983, 24 yrs.
Married : August 1983
Husband : M. Tech., Consultancy

Chief Complaint :
Spine Severe pains
Since 8 mths. Weight loss (4 Kgs. In 2 mths.)
Routine investigations and Thyroid Hormones : N.A.D.
Treated with Calcium supplements.

Thyroid Swelling on face
June 1993 Change of voice
Since 6 mths. Weight gain 6 kgs. Over last 4 months.
On repeat investigations diagnosed as having hypothyroid. Was put on T. Eltroxin 2 O.D.
T.S.H.= More than 60
Antithyroid antibody Titre : Positive 1 :400

Associated Complaints :
Sinusitis Pain > Steam Inhalations
Since 5 yrs. Nose block

Patient as a person :
Cr./Av.: Nothing particular
Perspiration : Moderate, No stains
Offensive recently
Menses : Regular. Dark red
Stains indelible since the beginning
Thermal State : sun : <papules on skin
Fan ; <Heaviness of Head, Stiffness of hand
Covering : Only in winter, 2 sheets
Bath : Hot in all seasons
C3H2
Sleep : Normal
Dreams : Occasional, frightful, used to scream in sleep before. Robbers, Examination.

Life Space :
The patient is from a well-educated family of Baroda. She is the second of five sisters. Her father had a transferable job but her mother remained in Baroda for the children's education. Her father is a strict disciplinarian, and wants things done on time and perfectly. Her mother is very calm and quiet. The patient used to have tiffs with her elder sister but would eventually let go of things. Overall the family environment was protective and they shared healthy relationships with each other.
The patient decided to do Engineering against her parent's wishes as they wanted her to be a Doctor. She did appear for an open medical entrance exam, she was still fascinated by her maternal uncles who were engineers.

In school she used to take part in extra-curricular activities like games, dancing, debates, etc. She did not have any anticipatory anxiety before going on stage. Before exams, she would rarely get nervous, even if they were told that the correction was going to be strict. In college she confined herself to academics only. She stood 3rd in B.E. and 1st in M.E.

When the patient was in her final year B.E. her third sister developed Intususception. Though she was operated upon immediately she did not survive. The surgeon later confessed that he had not given her prophylactic antibiotics. This was a great shock for the entire family. They decided against filing a case as they would not gain anything by it. The patient cried during the interview while describing this incident.

The patient married in Bombay into a conservative family comprising of her father-in-law (FIL), mother-in-law (MIL), 1 elder sister-in-law (SIL) who is a spinster and her husband. Her husband was in service the first two years, then later started his own consultancy. Her FIL was trading in steel but retiered five years back. Her MIL is a very irritable person. They have frequent conflicts, but the patient prefers to remain quiet to avoid aggravating the situation. She had initially taken up a job when her in-laws were in America. When they returned, they did not approve of it. Her husband asked her to leave the job. She tried to argue about their difference in attitudes towards her and her SIL , her husband tod her not to make any comparisons. She resigned her job without further hesitation. The family makes a lot of demands on her although they have a full time servant. Her SIL interferes in everything and expects the patient to do all the work. Her husband supports them and keeps insulting her. His attachment towards his mother and sister and his insensitivity towards his wife, leads to serious conflicts between her husband and wife. Once they even considered separation, but they later patched up.

The patient described an incident while her husband was away on tour, when her SIL gave her food mixed with insecticide with the help of the maid-servant, who later confessed to her. Initially she did not believe it, but when she was convinced, she told her husband. They got it tested in a laboratory, which proved positive. Her husband's eyes were poened. They decided to live separately, but before that her SIL separated with insinuations of the patient poisoning her. The patient avoided telling her parents about all this to avoid hurting them. But when her MIL accused her of poisoning her SIL in front of her mother, she had to give the whole story to her innocence. Now her In-laws shift between her's and her SIL's house. She does her duty towards, them, but her MIL continues to find fault with her.

A few years ago, her husband was away,when she wanted to take up a job, but her In-laws refused to let her go for the interview. She wrote to her husband complaining about this, asking him why he married a qualified woman when he only wanted a housewife. Her husband wrote to his parents to let her do what she wants. She then took up a job as a lecturer in an Engineering College. Her husband is more supportive now and helps her in the house-work whenever required, though he still insults her at times.

Discussion:

Here is a sensitive person who has experienced the tortures of MIL and SIL along with her husbands insensitivity towards her and yet she has no bitterness towards them. She has an independent temperament with an ability to stand firm in adverse circumstances, and a strong drive which helped her carry on and helped her adapt to her environment. Although she has paid the price at the physical level in the form of **Autoimmune Thyroiditis**, she has shown a stability at the level of the mind. This clinched the diagnosis of Silica. At the physical level a) Dreams of robbers b) Menses: Stains fast, supported the diagnosis of Silica.

If we examine the sequence of events, we observe a wounded psyche.
— Followed by backache and weight loss
—— Breakdown with Autoimmune Thyroid disease,
Manifesting in a hypothyroid state. This would indicate a **Tubercular Miasm**.
Susceptibility : Moderate
Similarity : Total
Sensitivity : Moderate
Structural changes : Moderate hypothyroid state
Miasm : Tubercular
With this understanding, treatement was started with the 200 potency.

FOLLOW UP TREATMENT:

Date	Backache	Weakness	Face	Pulse	Other	Treatment

			Swelling		**Symptoms**	
1/7/92	-	-	-	-	-	Sil. 200 III H.S.
8/7/92	>	>	>	100/48		Sil. 200 III H.S. Eltroxin stopped
15/7/92	>	0	>	100/48		Sil. 200 III H.S.
22/7/92	>	0	>			Sil. 200 H.S x 7d
29/7/92		0	>			Sil. 200 H.S. x 7d
5/8/92	>	<	>		Mind-relaxed	Sil. 200 H.S. x 7d
14/8/92	<	<	>		Hdk 4d; cough ++; thirst inc; chilly	Ars Alb 30; Tds x5d
19/8/92	>	>	>	100/46.5		Sil. 200 H.S. x 7d
26/8/92	SQ	SQ	>	TSH 0.5		Sil. 200 II H.S.
9/9/92	>	>	>			Placebo
23/9/92	>	>	>		Face: Papules-scars	Sil. 200 II H.S.
7/10/92	>	>	>	>+	>	Sil. 200 II H.S.
21/10/92	>	>	>	86/46.6	Emotional+ Cries on seeing sad movies	Sil. 200 III H.S.
4/11/92	>	>	>	80/46.5		Sil. 200 III H.S.
11/11/92	>	>	>	86/46.5		Placebo
2/12/92	>	>	>	100/47.5		Placebo
9/12/92	>	>	>	100/47.5		Placebo
16/12/92	>	>	>	100/47.5		Sil. 200 I H.S.
23/12/92	>	>	>	106/47.5		Sil. 200 I H.S.
6/1/93	>	>	>		Nausea <morning; bitter taste in mouth	Ars Alb 200; 6 hrly
8/1/93	SQ	SQ	>		>	Sil. 200 II H.S.
12/1/93	>70 %	>70 %	>70 %			Sil. 200 III H.S. weekly
11/2/93	>	>	>			Placebo
18/2/93	Overall >					Sil. 200 H.S. x 8d
4/3/93	Overall >					Placebo

Investigation:

Date T T TSH Antithyroid antibody

7/4/92	168	12.5	-	
25/6/92	-	>60	+ve 1:400	
16/8/92	-	0.5	-	
28/10/92	-	-	0.5	-ve<1:100
1/2/93	-	-	1.8	-

Analysis:
Both the patients are now asymptomatic euthyroid and antithyroid antibody test became negative. Both patients had presented with a significant rise in ATA titre and symptoms of thyroid hypofunction. In the early phase of treatment one patient had a severe backache and the other suffered from two acute illnesses.

Let us make some **clinico-immuno-pathologic correlations** to have a better appreciation of the state of susceptibility and posology indicated.
It is necessary to revise briefly the natural evolution of the disease. A variety of abnormalities in hormone biosynthesis is seen in patients with Hashimoto's Disease. This can lead to hyper-secretion of TSH.
First stage: Characterized by the presence of thyroid hyperfunction. Serum TSH levels and RIAU are increased. The patient is still eumetabolic, indicating that the glandular response to compensate for the abnormalities in hormone biosynthesis.
Second stage: With the passage of time the ability of the thyroid to respond to TSH decreases. RIAU and Sr. T concentration progressively approach sub-normal values. The next step in the evolution of complete thyroid failure is the development of "sub-clinical hypothyroidism".

Our patients are in the first stage (rather a terminal phase of this stage) as the T3 and T4 values are normal, TSHis high but less evidence of hypo-functioning. Thus the susceptibility is moderate. Through multiple doses it is possible to combat autoimmune activity faster and restore the balance. One can afford to be aggressive but with utmost precaution taking care of the sensitivity. One can then withdraw Eltroxin faster, if the patient is already on it or avoid it if it has not been started yet.
When the patient presents in the second stage, with significant autoimmune destruction of the thyroid, one's approach is quite different.

The prodromal phase of the disease gives us valuable information. In the first case, acute fever with constitutional symptoms indicates the constitutions' fight to deal with the stress. Then localization occurs, followed by signs of exhaustion. This phenomenon has been explained in **Henseley's concept of stress**. His ideas of general adaptation syndrome and local adaption syndrome, if abstracted further and adapted to comprehend the evolution of chronic disease, would help us handle the state of susceptibility better, and so satisfy it as desired by Stuart Close, and thus achieve an **Ideal Cure**.

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The following cases of Rheumatoid Arthritis, haave been presented in the Indian Journal of Homoeopathic Medicine. The authors have clearly applied the concepts and principles of homoeopathy in the therapeutic management of this disease, and have been successful clinically. They illustrate some of the principles presented earlier, on Rheumatoid Arthritis in Section II.

CASE I
R.K. was a young male patient, 21 years old with Juvenile Arthritis since the last 10 years. He had a moderately severe oligoarthritis in low grade, continuous over the last 10 years. Severe exacerbations occurred 2 or 3 times a year, lasting for 1 month each. This was treated withNSAID's and steroids.
Currently, he is in a progressively worsening exacerbation for the last 1 month, with moderate synovitis (++) in multiple joints and spine, a lot of stiffness (+++), with restriction of movements (++) and synovial thickening.
In the natural history and course of Juvenile Arthritis, this case falls in the category leading eventually to S.S.A.(Seronegative Spondylo Arthropathy) having a bad prognosis overall.
This diagnosis and prognosis suggests a low susceptibility. This is further supported by the low grade residual inflammations of multiple joints, non febrile exacerbations with severe stiffness and relatively scanty characteristics. Constant suppressive treatments also contributed to this to some extent. The Life Space below gives us further idea of how mental suppression and inertia also reflect this.

Life Space:
The patient lost his father at 6 years of age from chronic alcoholism. His mother had to play the role of both parents. He has a 22 yr. Old sister who is working and was engaged to be married 6 months back. He seemed to be carrying a heavy emotional burden regarding the pathetic state of the family, the difficulties his mother was facing, financial problems, etc. This was aggravated by his disappointment that his maternal uncle was not helping them as much as he should. Now an additional anxiety is his sister's dowry. With the increasing pain, the patient became more anxious (+++) and worried.
If he woke up with pain in the morning he would not go to work. Otherwise he would work less or come away early. He felt helpless and quite hopeless. He never communicated these feelings to his mother or his sister. He felt his disease was incurable and he would be unable to help his sister. He decided he did not care if his sister's engagement was broken as he was unable to take any more tension. He felt she would find another suitable match. Fully aware of the expectations of his mother and sister, he realised that he could not face this challenge.

Discussion:
This history manifests chronic suppressions, ongoing vexation and anxiety, leading to an almost paralysed state of mind and body. We also see a dominant sycotic miasm.
The remedy selection was based on the overall disposition. The attachment to his suffering mother, his despondency, an apprehensive attitude, aggravation of complaints from anxiety in contrast to avoiding genuine worry about his sister's alliance, with an overall self-centered sensitivity under stress. This along with other physical data led us to the choice of Kali Carb as the chronic remedy.
Even though the patient seemed to be in acute distress, with pains, < on initial movements,> continued motion, > warmth, along with bodyache, the tempatation to prescribe Rhus Tox was avoided. The chronic remedy covers the picture well and an unclear "acute picture" favours the prescription of Kali Carb.
Kali Carb was given in 30 potency in multiple doses. Improvement was short lasting and the potency was raised to 200 and subsequently to 1M. After 5 weeks of treatment there was considerable relief, but on withdrawal of Indomethacin there was an increase in inflammation of all involved joints. At this stage Thuja 1M 1dose was introduced as intercurrent. The next few weeks his response was munch better and Thuja was repeated once every week. A definite remission set in after 2 months with withdrawal of all NSAID's . Within 6 months there was hardly any complaint, and the patient has remained well for 2 years. He now needs infrequent doses of constitutional for mild synovitis or upper respiratory tract infection.

CASE II
A patient presented with the onset of Sjogren's syndrome at the age of 61 years in June 1990. It stated with acute parotiditis followed by non-improving dry eyes dry mouth joints were involved in March'92 knees - hands -elbows -back. The whole process occurred with mild to moderate intensity. She had morning stiffness of just 30 mins, even when we saw the patient in Sept. '92. The lachrymal glands were non-secreting by then. She was on artificial tears and artificial mouth secreting agents as well as on steroids and NSAID's. There were hardly any characteristics, while the pathology had crossed the functional zone and had to structural changes. She had bilateral O.A. of the knees: synovitis + but not very warm and tender; minimum edema feet. Hb 11.9 ESR 40 mm. Urine Routine: 15 - 20 pus cells/hpf. CxR; Interstitial parenchymal markings visible at sensitivity -ve. Pulmonary Function Test: NAD.
Parotid Sialography : NAD Histopathology Oral Mucosa: Hydropic changes and minonuclear infiltration in submucosa.
Thus we see all reflections of low susceptibility in the evolution of functional and structural changes. This slowly evolved case also had interesting psychosomatic dynamics in the background.
The lady and her husband were from a lower middle class family, that had come up in life after considerable struggle. Both took extreme care of their three children, 2 sons and a daughter. Both sons obtained Phd degrees and the daughter studied upto M.Sc. They also bought a large flat to accommodate the future large joint family. The ilder son one day declared that he was marrying a girl from another caste. This shock was not yet absorbed when the married couple decided to live separately as they did not like the "style of living". The second son had a good opportunity and went to USA to study. The lady was quite disappointed and lonely initially, but later felt guilty about the training she had given to her children!
The sadness and self-reproach lingered from 1986 to 1988, with a few ineffectual attempts at reconciling with her elder daughter-in-law and son. In 1988 her daughter passed through a series of complication during her

pregnancy, and the patient experienced a lot of anxieties and worries. She subsequently developed a full-fledged Sjogren's syndrome picture.
Silica was selected as the constitutional remedy, on the basis traits of conscientiousness, and sustainence in adaptation, in correlation with other data. The patient improved gradually with Silica 30 in multiple doses. All allopathic drugs were withdrawn except the artificial moistening agents to replace tears and saliva. Thuja 1M as antimiasmitic was prescribed 3 to 4 times to push the patient out of sycotic inertia. She also started having a few secretory spells from the salivary glands, with good control over other problems.

CASE III

Mr. R.S., a native of U.P. , 27 years of age, married for 5 years.
Hindu, Non-vegetarian, working as a glass cutter at a "Tabela."

Location/ ODP	Sensation/ Pathology	Modality/ R	Concomittants
Joints: Since 11 years.	Usual Symptomatology:		
Sudden onset with ankles	Pain ++ +++ +++++	Usually admitted as in-pt.	Chilly
Progress rapid 5+ in all episodes	With / without fever Swelling HOT, TENDER	Stay variable: 15 days to 7 months	Appetite: Ravenous (will eat 3 meals!)
Ankles back knees elbows	STIF all over	< Winter < Rains, getting wet	Cr. = Spicy items
1st relapse: 6 months	Deformities (Flexion type)		
2nd relapse: 1yr.			
3rd relapse: 1 yr. 8 months	Immobile in bed . Had to be carried to the toilet	Rx Phenyl butazone Disprin, Steroids.	
Then relapsing every 6 mths.			
Current exacerbation Since 6 mths. Hips, Knees, Fingers, Back, Elbows	Morning stiffness: 3 hours Pain++ Swellings+++	<Warmth locally <Touch >Rest	

Other Symptoms:
Weight loss worse with every attack.
No skin rash, No mouth ulcers, No contributory drug history.
No GIT/GUT complaints, No generalised edema;
No respiratory symptoms
No muscle weakness or vascular symptoms

Associate Complaints:
GUT burning in urination < during fever

Patient as a person:
Lean
H/o Suppuration of ears many years back
Rx Ayurveda. Cured.

Cr= Pungent , Spicy (esp. during exacerbations.)
Sleep disturbed because of thooughts.
Thermal: Dislikes fan, prefers to keep the room closed. Uses thick warm cotton quilts in winter.
Habituated to cold baths from childhood. Generally cannot tolerate cold weather. CHILLY
Habits: Tobacco 10 - 12 times a day since seven years.

Life Space:

The patient was too depressed to tell us much. He had lost everything due to this "monstrous"illness i.e. his land, his siblings' support, his wife, financial resources etc. Two hours of case taking could not ellict much about his past interpersonal relationships except for the above. He was attached to his mother who lived with him in the village. He did not even ask us when he would improve with the medication.

Physical Examination:
Peroneal spasm+; Knees:-varus Rt>Lt
Rt hip tender +; terminal abduction painful
Dorsolumbar spine tender
Schober's -ve
Chest expansion 3/4 inches.

Investigating results:
RA +ve 1:40
HLA B27+ve
ESR:90
Bilateral O.A.changes with gross varus in knees.
SI joints: sclerosis, with fusion areas
Lt hip joint: destruction of the femur.

Discussion:
We see a rapid course of illness with characteristics, early damaging effects on the joints, progressive weight loss, poor general condition, depression and exhaustion. Early fibrous activity with deformities, easy prostration, voracious appetite and weight loss all point towards the tubucular miasm. Low susceptibility is reflected in the fast travel towards structural damage and deformities and frequent severe exacerbations.
Keynote Symptoms: (1) Appetite increased during fever. (2) Desires spicy 5+ (3) Slowness and Indifference. These lead us to a small group of remedies. When correlating the rapid pace of illness, easy choice. Since he was in a severe exacerbation multiple doses were prescribed. But he had a very brief improvement even after PHOS.1M 4hourly.
Tub. Bov 1M, one dose was introduced as intercurrent and this accelerated the improvement, while PHOS 1M was continued in multiple doses. This controlled the acute exacerbation.
Once remission set in, he improved faster and then began to prove PHOSPHORUS(with symptoms like a sudden spell of drowsiness, early moming 4 am diarrhoea with urgency and prostration). This disappeared within 2 - 3 days leaving behind a stable remission.

ANCILLIARY MANAGEMENT:

1. Psychological Management:
In case 1, the patient was encouraged to be regular at work as well as advised to take a loan for his sister's wedding.
The lady in case 2, was allowed to express her feelings and was reassured that all her efforts for her children were not wasted. In fact they were now well settled due to her contribution in their life.
The depressed young man in case 3, was given a lot of sympathy and reassurance initially. Later he was advised to get additional part time work and save money to buy back his land.
All cases do need some level of psychotherapy individual to their case.

2. Scientific Withdrawal of Suppressive Agents.
In patients who are already on steroids for a long time do face problems during homoeopathic treatment. It is better not to stop the steroids immediately but to taper it off gradually over a period of time while on homoeopathic medication. This is in order to prevent a strong exacerbation or systemic problems due to pitutary adrenal axis disturbances. Also the patient may lose confidence in the physician. Temporally though, one may replace steroids with NSAIDS.

3. Adequate Physiotherapy:
Medical management alone cannot take care of ligament laxity, muscle spasm, postural, contractures, joint deformities, etc. Physiotheraphy is therefore important. The different modalities in physiotheraphy are

adequate rest, immobilisation, special splintage supports, traction, range of motion exercises, muscle strengthening exercises, gaot training, short wave diarthermy, local heat fomentation, local ice packs, ultrasonics, T.N.S., etc.
The judicious combination and choice from these and motivating the patient psychologically for mobility, may go a long way in keeping the patient from getting a painful deformity and ultimately becoming crippled. The patient should be encouraged to use as many joints as possible.
Physiotheraphy may sometimes remove static blocks in treatment. Eg. A young lady with polyarticular RA was improving in all other aspects except in her cervical pain, stiffness and torticollis. A custom made well padded cervical four post collar did the trick. She had to use it only for some weeks and now she is freely moving her neck.

4. Surgical procedures:
One needs to keep an open mind for the reasonable utility of surgical procedures. Arthroscopic procedures like synovial biopsy in undiagnosed monoarticular cases, synovectomy for debulking the diseased tissue to reduce mechanical problems, cartilage burring for isolated deep cartilage craters, are some of the useful ancillary surgical procedures.
For tendons and soft tissues, release of contractures and synovectomy may be indicated. For deformed and unsalvageable joints, arthrodesis or total joint replacement may be required.

5. Diet:
Restrictions are advised by us only in hyperuricemia i.e. stop red meats, sea food, pulses and food made from pulses, cashew-nuts. We encourage natural haematinics and a high protein diet in RA with anemia.

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