Inflammation and Disease

Current Medical Thinking and Herbal Strategies – Part 1

Introduction

Invertebrates with no true circulatory system (eg. earthworm) respond to an irritant by surrounding it with specialised cells (haematocytes) which then ingest it. If the damage is very severe, the invertebrate simply rejects the injured portion of its anatomy as a prelude to its regeneration. In higher animals such as humans, the local reaction to injury is much more complex because of the evolution of the circulatory system, and the disappearance of the kind of regenerative powers seen in the earthworm.

The local reaction to injury is called inflammation (from the Latin word *inflamare* meaning 'to burn'. Four cardinal signs signify inflammation:

- Red (erythema)
- Hot (heat)
- Swollen (inflammation)
- Tender (pain)

Given the extent of disturbance, it goes without saying that there will undoubtedly be a loss of function too. Some experts classify this as the fifth cardinal sign. Although any tissue may suffer injury, inflammation is essentially the reaction to injury of the living microcirculation and its contents. Although the physiological mechanisms of inflammation haven't changed over the years, the theories and our understanding of its purpose and clinical significance has.

Current Medical Thinking

Researchers are linking inflammation and the inflammatory response to an ever-wider array of chronic illnesses. Uncontrolled chronic inflammation is now considered a major component of many widely occurring diseases, including asthma, atherosclerosis, peripheral vascular disease, Alzheimer's disease, cancer, ADHD, diabetes and osteoporosis. This is in addition to the established pathophysiology of a range of skin disorders, joint disorders, metabolic disorders and homeostatic imbalances of inflammatory origin. Examples of current medical thinking include novel approaches in the resolution of inflammation:

- angiogenesis and cancer (areas for R_x targeting)
- autoimmunity and RA
- impact of stress on inflammatory disorders of the GIT
- chronic inflammation and Alzheimer's

- biochemical markers of inflammation esp. CRP (C-Reactive Protein). Others incl. adiponectin, MCP-1, CD40 ligand and Lp-PLA(2)

A certain amount of focus these days seem to be on how active a process inflammation is and the control of it. Also, there is considerable interest in the connection between inflammation in one area of the body and others eg. gum disease and other conditions.

Biochemical Mechanisms & Principles of Inflammation

Inflammation is the body's response to injury (stimuli). These stimuli can constitute any of the following:

- physical – damage to skin or other tissue or organ
- chemical – noxious chemicals/poisons
- microorganisms – toxins produced by them
- immunological – hypersensitivity reactions

Categorising the <u>type</u> of inflammation is important as this will (to a large extent) determine the treatment rationale. In short, inflammation is either <u>acute</u> or <u>chronic</u>.

acute - of short duration
- 4 cardinal signs on examination
eg, bacterial infection, flu, sprained ankle

chronic - prolonged phase of inflammation (depending on nature of injury)
- usually there is a preliminary & sometimes recurrent acute episodes
- inflammation & repair occur simultaneously with persistent
- suppuration (pus formation) & ulceration leading to fibrosis (scarring)
eg. chronic bronchitis, RA, IBD

Main Features of Acute Inflammation

1. dilation of blood vessels (heat & redness)
2. increased vascular permeability (heat & redness)
3. emigration of WBC along with inflammatory exudate (swelling & pain)

Physiological Significance of Inflammation

1. Clot formation localises pathogens and prevents loss of blood at the site if injury
2. Inflammatory exudate contains antimicrobial agents eg. Ab, complement
3. Inflammatory exudate is continually drained via the lymphatic so that pathogens and/or their toxins are drained into the lymph nodes leading to the initiation of an immune response

Suppuration
Suppuration is an intermediate situation with 2 main components:

1. very large granulocytes (a type of WBC that incl. neutrophils) are summoned to the site of injury (usually by chemotactic influence of certain bacteria such as *S.aureus*).
2. the exuded WBC are killed in large numbers by the bacteria and their bodies liquefied by their own lysozymal enzymes to form a creamy, viscous fluid rich in lipids, proteins and nucleic acids – this fluid is known as **pus**. The mass of bacteria, dead, dying and liquefied WBC and surviving inflamed tissue is termed an **abscess** *eg. when present in skin it is called a boil or sometimes a carbuncle if very large*

Note: the painful abscess is the price we pay for survival since it is an inevitable result of confining certain dangerous bacteria to one part of the body rather than allowing them to disseminate.

Inflammation and the Nervous System (NS)
Many experiments have shown that inflammation proceeds unmodified in the absence of any nerve supply. This does not mean, however, that the NS is unable to influence the inflammatory reaction. At the simplest level, the red flare that surrounds the skin reaction to mild trauma (the triple response*) is abolished if the sensory or vasomotor nerves are blocked or cut.
** a simple way of demonstrating the early phases of acute inflammation*

On a more complex level, hypnosis, suggestion and emotional factors have been shown to significantly influence the inflammatory response particularly, in the sensation of pain. Equally, there is ongoing research interest in psychosomatic disorders where emotional factors seem likely to play a major role.

Pain
The heat, redness and swelling of acute inflammation (due to vascular dilation and increased vascular permeability) results in pressure on sensory nerve endings by the exuded fluid and detected as pain. This is particularly the case if the space in which it can expand is limited but it is partly due to the release of bodily substances which stimulates these nerves. These substances are collectively referred to as chemical **mediators** of inflammation (see table below) and have wide-range actions.
eg. histamine, serotonin, kinins, prostaglandins are all linked to pain.
eg. other chemicals liberated by nervous stimuli or cell injury eg Ach or K^+ may also be painful

Mediator	Main source
Histamine	Mast cells or basophils
Kinins (eg. bradykinin, leucokinins)	From blood cell precursors by proteases and WBC
Prostaglandins (E_1 & E_2) & acidic lipids	Polymorphonuclear leucocytes, monocytes and basophils
Slow reacting substances	Mast cells and basophils
Complement components	Derived by activation of classical or alternative pathways
Clotting system components (fibrinopeptides)	Blood and tissue fluids
Cytokines	Lymphacytes & macrophages (WBC)

Significance of Pain

The survival value to the host of pain is obvious as it sends a signal that there is injury/damage and that part of the body needs to be favoured and rested. However, the reverse is true if body function is limited because of the pain itself.

Hypersensitivity

The normal acquired immune mechanisms perform a useful function in combating infection. However, disadvantageous reactions can unfortunately occur at the same time.

eg. *release of inflammatory mediators that, whilst helpful in phagocytes serum Ab or complement to the site of infection, can also cause damage to tissue cells.*

Even cellular immune reactions can result in the destruction of host cells. These disadvantageous reactions are called hypersensitivity reactions or **allergies**. There are 4 types:

Type 1 IgE Ab attached to mast cells react with Ag (sometimes called allergen) and trigger the release of histamine, a slow-reacting substance of anaphylaxis and eosinophil chemotactic factor. This is the mechanism of many common forms of **allergy** eg. atopic allergy (hayfever, eczema, asthma), urticaria

Type 2 IgM or IgG Ab react with Ag (often a drug or microbial product) attached to tissue cells, such as WBC or RBC. This results in **complement activation** and lysis of the cell.

Type 3 IgM or IgG Ab form complexes with Ag and activate complement. Chemotactic factors and other inflammatory mediators are generated and tissue damage results. This is sometimes called **immune complex disease** and is responsible for vasculitis and kidney damage

Type 4 Sensitised T-lymphocytes (WBC) interact with Ag for eg. products of mycobacteria or sometimes even simple chemicals attached to body proteins. Lymphokines are released and can cause inflammation. These reactions are sometimes called **delayed**

hypersensitivity responses or **contact dermatitis** when simple chemicals are involved.

Note: genetic factors in allergy must be considered so family history and previous exposure and events are important clinical considerations. Other important points include:

- the IgE levels of normal individuals are low (approx. 0.1 mg/dL) and are controlled by a dominant gene. The higher the level of IgE, the greater the chance of allergic predisposisiton
- ragweed allergy is closely associated with the DW2 locus of HLA (Human Leucocyte Antigen). The HLA is the name of the major histocompatibility complex (MHC) in humans and contains a super locus (of which the DW2 is one) contains a large number of genes related to immune system function
- immune hyperactivity particularly of IgE response to a wide range of Ag is a feature if allergic individuals

Other factors include: degree of exposure to Ag (allergens)
nutritional status of the individual
presence of chronic infections
acute viral infections

Autoimmunity

Whilst immunological responses to foreign agents are powerful, sometimes the body starts to produce Abs against its own tissues. When this happens, there is always a potent disease mechanism at play. There are two general categories of autoimmune disease:

Organ specific diseases: thyroiditis (Hashimoto's Disease)
haemolytic anaemia
pernicious anaemia

Non-organ specific diseases: SLE
RA

Between these two extremes lie a number of conditions such as:

Juvenile diabetes	- Ab produced against pancreatic islet Ag and WBC Ag
Primary biliary cirrhosis	- Ab produced against mitochondria of various cells
Active chronic hepatitis	- Ab produced against smooth muscle Ag and nuclei

Another strand of autoimmune disease is extra-articular disease which is less well understood but can include:

anaemia
rheumatic nodules
vasculitis
eye disease (eg. episcleritis)
nerve lesions (eg. peripheral neuropathy)
pericarditis
pleurisy
lymphadenopathy
splenomegaly
general malaise

Examples of associations between HLA type and some diseases:

Disease	HLA	Frequency in %	
		Patients	Controls
Ankylosing Spondylitis	B27	90	9.4
Reiters Disease	B27	79	9.4
Acute Anterior Uveitis	B27	52	9.4
Subacute Thyroiditis	B35	70	14.6
Idiopathic Hemochromatosis	A3	76	28.2
	B14	16	3.8
Psoriasis vulgaris	CW6	87	33.1
Coeliac Disease	DR3	79	26.3
Idiopathic Addison's Disease	DR3	69	26.3
Insulin-dependent Diabetes (IDD)	DR3	56	28.2
	DR4	75	32.2
Myasthenia Gravis	DR3	50	28.2
	B8	47	24.6
Systemic Lupus Erythematosus (SLE)	DR3	70	28.2
Multiple Sclerosis (MS)	DR2	59	25.8
Rheumatoid Arthritis (RA)	DR4	50	19.4
Hashimoto's Thyroiditis	DR5	19	6.9
Pernicious Anaemia	DR5	25	5.8

HLA = Human Leucocyte Antigen (or Major Histocompatibility Complex/MHC)

Markers of Inflammation

A number of different biomarkers have been shown to be clinically relevant not only in the onset of inflammation but also to predict risk (eg. CRP in CVD). This holds significant potential for new therapeutic possibilities in conventional treatment strategies. Other markers include:

- o adiponectin
- o monocyte chemoattractant protein 1 (MCP-1)
- o CD40 ligand
- o lipoprotein-associated phospholipase A(2) or Lp-PLA(2)

Conventional R_x

Drug therapy very much depends on the condition being treated, whether it is acute or chronic and largely dictated by other considerations such as patient profile, severity and response to initial treatment. Routine drug-based anti-inflammatories fall into 2 major groups:

- o NSAIDs (non-steroidal anti-inflammatory drugs)
- o Steroids-based anti-inflammatories

Both types of drugs have adverse effects and depending on the duration of treatment, not all patients respond favourably to long-term prescription without encountering problems and/or complications as a consequence. It is this without doubt, that patients most seek help from natural therapies and CAM alternatives to either treat or manage a range of inflammatory conditions.

Homeostatic Imbalance and Inflammation

The very nature of inflammation means that homeostasis is significantly compromised and this has profound and often devastating endocrine, metabolic, cellular and systemic effects. Consequential effects can be addressed by a symptomatic approach (clinical features) but a more holistic approach is very often necessary if the cause and nature of inflammation is such that only a comprehensive examination which considers all influences to the clinical presentation proves effective especially in the long term.

New Research & Novel Mechanisms

Whilst inflammation may not be the causative factor in some widely occurring diseases, it is now believed to contribute to disease progression, tissue dysfunction and ultimately organ failure in these diseases. Resolution of inflammation was once considered a passive process but in recent years, evidence has emerged that this biochemically active process and more recent results have established some of the chemical mediators involved. Elucidation of biochemical pathways contributing to the resolution of inflammation has provided many new anti-inflammatory targets and an opportunity for resolution-based pharmacology for the treatment and prevention of inflammatory disorders.

Studies examining the mechanisms of inflammation and the process of resolution (healing & repair) leading to new therapeutic possibilities include the following:

- atherosclerosis
- acute inflammation
- endogenous anti-inflammation
- inflammation, healing & angiogenesis in the eye
- endogenous mediators

References:

1. e-briefing paper January 25, 2011, symposium at the New York Academy of Sciences titled Novel Mechanisms in the Resolution of Inflammation: Implications in Health and Disease

2. BSI website for basic concepts and principles in immunology http://www.immunologyexplained.co.uk/

3. To find out more on current research into gum disease and other conditions see eg: http://www.perio.org/consumer/mbc.top2.htm

4. Information on biochemical markers in inflammation, see http://www.ncbi.nlm.nih.gov/pubmed/15823493