Chapter - 2

Review of Literature
REVIEW OF LITERATURE

INFLAMMATION

Introduction

A definition of inflammation is complicated, because the local, vascular and tissue reactions often are accompanied by systemic effects. Burdon-Sanderson 1888 has defined the Inflammation is the local reaction of tissue due to any agent. It is a body defense reaction in order to eliminate or limit the spread of injurious agents as well as to remove the consequente necrosed cells and tissues. If inflammatory response is over vigorous, or persists longer than anti-inflammatory drugs are used to control the inflammation (Swingle et al., 1982).

The word inflammation is derived from the Latin word in flammare meaning to burn (Hurley et al., 1984). It may be evoked by different types of causative factors such as.

1. Physical agents like heat, cold, radiation, mechanical trauma.
2. Chemical agents like organic and inorganic poisons.
3. Infective agents like bacteria, viruses and their toxins.
4. Immunological agents like cell-mediated and antigen-antibody reactions.

A 2000 years ago, Celsus identified 4 Cardinal signs of inflammation as

1. Redness (rubor), is due to persistent dilatation of all blood vessels within the area of injury.
2. Swelling (tumor), is due to increased vascular permeability leads to accumulation of edema fluid.
3. Heat (calor), is due to marked increase in local blood flow.
4. Pain (dolor), is due to stimulation of afferent nerves by tension in tissue.

Later on Virchow added fifth sign i.e.
5. Loss of function (laesa) is due to reflex muscular inhibition due to pain (Herlay et al., 1984)

**TYPES OF INFLAMMATION**

Depending upon the defense capacity of the host and duration of response, inflammatory responses occur in three distinct phases, each apparently mediated by different mechanisms.

1. Acute transient phase characterized by local vasodilatation and increased capillary permeability;
2. A delayed subacute phase, most prominently characterized by infiltration of leukocytes and phagocytic cells.
3. Chronic proliferative phase involving degeneration and fibrosis formation (Insel et al., 1990).

A. Acute inflammation is of short duration and represents the early body reaction and is usually followed by repair.

The main features of acute inflammation are:
1. Accumulation of fluid and plasma at the affected site.
2. Intravascular activation of platelets.
3. Polymorphonuclear neutrophils as inflammatory cells.

B. Chronic inflammation is of longer duration and occurs either after the causative agent of acute inflammation persists for a long time, or the stimulus is such that it induces chronic inflammation from the beginning.
The characteristic feature of chronic inflammation is presence of chronic inflammatory cells such as lymphocytes, plasma cells and macrophages.

**Acute inflammation**

The changes in acute inflammation can be described by

I. Vascular events (Reaction)
II. Cellular events (Reaction)

**I. VASCULAR EVENTS**

Alteration in the microvasculature (arterioles, capillaries and venules) is the earliest response to tissue injury. These alterations include: haemodynamic changes and changes in vascular permeability.

1. **Haemodynamic changes:**

   Immediate vascular response is of transient vasoconstriction of arterioles which follows persistent progressive vasodilatation, may elevate the local hydrostatic pressure resulting in transudation of the fluid into the extracellular space leads to swelling. Slowing or stasis of microcirculation, increased concentration of red cells and raised blood viscosity leads to leucocytic margination or peripheral orientation of leucocytes (mainly neutrophils) along the vascular endothelium. (Hurley et al., 1984) The features of haemodynamic changes in inflammation are best demonstrated by the Lewis experiment.

**Altered vascular permeability :- Pathogenesis.**

In and around the inflamed tissue, there is accumulation of oedema fluid in the interstitial compartment which comes from blood plasma by its escape through the endothelial wall of peripheral vascular bed. In the initial stage, the escape of fluid is due to vasodilatation and consequent elevation in
hydrostatic pressure. This is transudate in nature. But subsequently, the characteristic inflammatory oedema, exudate, appears by increased vascular permeability of microcirculation.

2. **Mechanisms of Increased vascular permeability**

Markedly increased vascular permeability leads to escape of fluid into the extravascular tissue producing oedema-this is termed exudation. Increase in vascular permeability is due to
(a) The endothelial cells develop temporary gaps between them due to contraction of endothelial cells.
(b) Direct injury to endothelial cells.
(c) Endothelial injury mediated by leucocytes.
(d) Retraction of endothelial cells.

II. **CELLULAR EVENTS**

The cellular phase of inflammation consists of two processes.
1. Exudation of leucocytes and
2. Phagocytosis

1. **Exudation of leucocytes**

The escape of leucocytes from the lumen of microvasculature to the interstitial tissue is the most important features of inflammatory response. In acute inflammation, polymorphonuclear neutrophils (PMNs) comprise the first line of body defense, followed later by monocytes and macrophages.

The changes leading to migration of leucocytes are as follows:

a. **Changes in the formed elements of blood**

Due to slowing and stasis, the central stream of cells widens and peripheral plasma zone becomes narrower because of loss of plasma by exudation. This phenomenon is known as margination. As a result of this
redistribution, the neutrophils of the central column come close to the vessel wall, this is known as pavementing.

b. Adhesion or rolling:

Injury leads to neutralisation of the normal negative charge on leucocytes and endothelial cells so as to cause adhesion. Distinct adhesion molecules.

i) Selectins
ii) Addressins
iii) Integrins
iv) Immunoglobulin superfamily adhesion molecule.

c. Cell emigration

After sticking of neutrophils to endothelium, the former move along the endothelial surface till a suitable site between the endothelial cells is found where the neutrophils throw out cytoplasmic pseudopods. Subsequently, the neutrophils lodged between the endothelial cells and basement membrane cross the basement membrane by damaging it locally with secreted collagenases and escape out into the extravascular space, this is known as emigration. The damaged basement membrane is repaired almost immediately. As already mentioned, neutrophils are the dominant cells in acute inflammatory exudate in the first 24 hours, and monocyte-macrophages appear in the next 24-48 hours. However, neutrophils are shortlived (24-48 hours) while monocyte-macrophages survive much longer.

d. Chemotaxis

The chemotactic factor-mediated transmigration of leucocytes after crossing several barriers (endothelium, basement membrane, perivascular myofibroblasts and matrix) to reach the interstitial tissues is called chemotaxis.
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The agents acting as potent chemotactic substances for different leucocytes called chemokines are as follows:

i. Leukotriene B$_4$ (LTB$_4$)
ii. Platelet factor 4 (PF$_4$)
iii. Components of complement system (C$_{5a}$ in particular)
iv. Cytokines (particularly IL-8)
v. Soluble bacterial products (such as formylated peptides)
vi. Chemotactic factor for CD$_4$ + T cells
viii. Eotaxin chemotactic for eosinophils.

There are specific receptors for each of the chemoattractants listed above. In addition, chemotactic agents also induce leucocyte activation that includes, the production of arachidonic acid metabolites, degranulation and secretion of lysosomal enzymes, generation of oxygen metabolites, increased intracellular calcium, and increase in leucocyte surface adhesion molecules.

2. Phagocytosis

Phagocytosis is defined as the process of engulfment of solid particulate material by the cell (cell-eating). The cells performing this function are called phagocytes. There are 2 main types of phagocytic cells;

i. Polymorphonuclear neutrophils (PMNs) which appear early in acute inflammatory response, also called as microphages.
ii. Circulating monocytes and fixed tissue mononuclear phagocytes called as macrophages.

The process of phagocytosis is similar for both polymorphs and macrophages and involves the following 4 steps:

a. Attachment stage (opsonisation).
b. Engulfment stage
c. Secreation (degranulation) stage.
d. Killing or degradation stage.
The antimicrobial agents act by either of the following mechanisms:

i. Oxygen-dependent bactericidal mechanism;

ii. Oxygen-independent bactericidal mechanism; and

iii. Nitric oxide mechanism.

i. Oxygen-dependent bactericidal mechanism:

An important mechanism of microbicidal killing is by the production of reactive oxygen metabolites (O2, H2O2, OH−, HOCl, HOI, HOBr).

NADPH - oxidase present in the cell membrane of phagosome reduces oxygen to superoxide ion (O2−):

\[
\begin{align*}
20_2 & \xrightarrow{\text{NADPH Oxidase}} 20_2^- \\
\text{NADPH} & \xrightarrow{\text{Superoxide anion}} \text{NADP} + H^+
\end{align*}
\]

Superoxide is subsequently converted into H2O2 which has bactericidal properties.

\[
20_2^- + 2H^+ \rightarrow H_2O_2
\]

(Hydrogen peroxide)

This type of bactericidal activity is carried out either via enzyme myeloperoxidase (MPO) present in the granules of neutrophils and monocytes, or independent of enzyme MPO, as under.
a. MPO-dependent killing:

\[ \text{MPO} \]
\[ \text{H}_2\text{O}_2 \quad \text{Cl}^- , \text{Br}^-, \text{I}^- \quad \rightarrow \quad \text{HOCl} + \text{H}_2\text{O} \quad \text{(Hypochlorous acid)} \]

Hypohalous acid which is more potent antibacterial agent than \( \text{H}_2\text{O}_2 \).

b. MPO-independent killing:

\[ \text{OH}^- \]
\[ \text{O}_2^- \quad \text{Haber-Weiss reaction} \]
\[ \text{H}_2\text{O}_2 \quad \text{Fenton reaction} \quad \rightarrow \quad \text{OH}^- \quad \text{(Hydroxyl radical)} \]

Hydroxyl radical (OH\(^-\)) is produced from \( \text{H}_2\text{O}_2 \) have bactericidal activity.

ii. Oxygen-independent bactericidal mechanism.

Some agents released from the granules of phagocytic cells do not require oxygen for bactericidal activity. These include lysosomal hydrolases, permeability increasing factors, defensins and cationic proteins.

iii. Nitric oxide mechanism.

In addition to oxygen-dependent and oxygen-independent mechanisms, recently role of nitric oxide (NO) in inflammatory reaction has been emphasised. NO is produced by endothelial cells as well as by activated macrophages. In experimental animals, NO has been shown to have fungicidal and anti-parasitic action but its role in bactericidal activity in human beings is yet not clear.
CHEMICAL MEDIATORS OF INFLAMMATION:

Currently many chemical mediators have been identified which partake in other processes of acute inflammation as well e.g. vasodilatation, chemotaxis, fever, pain and cause tissue damage. They are released from the cells, the plasma, or damaged tissue itself. They are classified into 2 groups.

A. Cell derived mediators.
B. Plasma derived mediators (plasma proteases).

![Chemical mediators of inflammation diagram]

Fig. 1 Chemical mediators of inflammation.
A. Cell derived mediators

Factors released from tissue cells

(1) Histamine

It is released from various storage depots (granulas of mast cells, basophils and platelets) by a wide variety of inflammatory stimuli, anaphylatoxins, histamine releasing factors, neuropeptides and interleukins. The main actions of histamine are vasodilatation, increased vascular permeability, itching and pain. It is natural mediator of inflammation and responsible for the immediate transient increased permeability seen after many types of mild injury (Lewis's).

(2) Serotonin: (5 Hydroxy tryptamine)

It is found in large amounts in mast cells and in platelets and in lesser amounts in chromaffin cells of GIT, spleen, nervous tissue. The actions of serotonin are similar to histamine but it is less potent mediator than histamine. Serotonin came under notice in 1956 when it was found to be potent permeability factor in the rat (Spector et al., 1963).

(3) Prostaglandins: (PGD₂, PGE₂ & PGF₂α)

Prostaglandins are long chain hydroxy fatty acids. PGD₂ and PGE₂ act on blood vessels to cause increased vascular permeability, vasodilatation and bronchodilatation and inhibit inflammatory cell function. Prostacycline (PGI₂), secreted by vascular endothelium has a powerful inhibitory effect on platelet aggregation and may also inhibit the adherence of leucocytes to vascular epithelium. Thromboxane A₂ (TXA₂) enhances inflammatory cell function by causing platelet aggregation. Mechanism of anti-inflammatory effect of many non-steroidal anti-inflammatory drugs has been shown to be through inhibition of prostaglandin synthesis (Barnes et al., 1988)
(4) Leukotrienes (LT, LTA4, LTB4, LTC4, LTD4, LTE4)

Leukotrienes are produced by action of lipo-oxygenase on arachidonic acid. LTB4 is secreted by neutrophil in inflammatory lesions. It is chemotactic for phagocytic cells and stimulates phagocytic cell adherence i.e. chemotactic for neutrophil and eosinophils.

(5) Lysosomal components:

Cationic proteins and neutral proteins are two most important lysosomal products in inflammation. Cationic proteins can increase vascular permeability either directly or through mast cell and are also chemotactic to monocytes. The neutral protease cause tissue damage and generate chemotactic factors by cleaving C5 and C3 probably also.

(6) Cytokines:

They are polypeptide substances produced by activated lymphocytes (lymphokines) and activated monocytes (monokines). Interleukin-1 (IL-1) and tumor necrosis factor (TNF-α) are formed by activated macrophages while TNF-β and interferon (IF-γ) are produced by activated T cells. Some lymphokines increase vascular permeability and others are chemotactic.

(7) Platelet activating factor (PAF)

It is released from IgE-sensitised basophiles or mast cells, other leucocytes, endothelium and platelets. Actions of PAF as mediator of inflammation are

- increased vascular permeability;
- vasodilatation in low concentration and vasoconstriction otherwise;
- adhesion of leucocytes to endothelium;
- chemotaxis.
(8) Nitric oxide and oxygen metabolites

Nitric oxide (No) plays the following role in inflammation.
- vasodilatation
- anti-platelet activating agent
- possibly microbicidal action

Oxygen derived free radicals produces
- Endothelial cell damage and thereby increased vascular permeability.
- Activation of protease and inactivation of antiprotease causing tissue matrix damage.
- Damage to the other cells.

The actions of free radicle are counteracted by anti-oxidants present in tissues and serum which play a protective role.

B. Plasma derived mediators

These include the various products derived from activation and interaction of four interlinked systems; kinin, clotting, fibrinolytic and complement.

(1) Kinin system

\[
\begin{align*}
\text{Factor XII} & \quad \text{Contact} \\
\downarrow & \\
\text{Factor XIIa} & \\
\downarrow & \\
\text{Prekallikrein activator} & \\
\downarrow & \\
\text{Plasma prekallikrein} & \quad \text{Kallikrein} \\
\downarrow & \\
\text{Kininogen} & \quad \text{BRADYKININ}
\end{align*}
\]

Fig. 2 Pathway of the kinin system.
Bradykinin and kallidin are the two important members of the system. They are formed by the digestion of a plasma glycoprotein (kinininogen) by a proteolytic enzyme kallikrein found in plasma in its inactive form termed prekallikrein, which is activated by tissue and plasma activators. Kinins are destroyed by Kininases present in plasma and tissue. They are among the most potent vasodilators and vascular permeability factors.

(2) The clotting system:

Factor XIIa initiates the cascade of the clotting system resulting in formation of fibrinogen which is acted upon by thrombin to form fibrin and fibrinopeptides. The actions of fibrinopeptides in inflammation are increased vascular permeability, chemotaxis for leucocytes and anticoagulant activity.

(3) The fibrinolytic system.

![Diagram](image)

**Fig. 3** The activation of fibrinolytic system.

This system is activated by plasminogen activator, the sources of which include kallikrein of the kinin system, endothelial cells and leucocytes. Plasminogen activator acts on plasminogen present as component of plasma proteins to form plasmin. Further breakdown of fibrin by plasmin forms fibrinopeptides or fibrin split products (Fig. 3)
The actions of plasmin in inflammation are:

- Activation of factor XII to form prekallikrein activator that stimulates the kinin system to generate bradykinin;
- Splits off complement C3 to form C3a which is a permeability factor; and
- Degrades fibrin to form fibrin split products which increase vascular permeability and are chemotactic to leucocytes.

(4) The complement system

Complement system, consisting of at least 18 proteins, plays an important role in the immunologically mediated inflammation. Anaphylatoxins C3a, C4a, C5a are the important factors released during activation of complement system. (Snynderman et.al. 1986).

The actions of anaphylatoxins in inflammation are

- Release of histamine from mast cells & basophils.
- Increased vascular permeability causing edema in tissues.
- C3b augments phagocytosis
- C5a is a chemotactic for leucocytes.

They promote cell destruction by promoting adherence of cells to the target cells. The final product of the compliment activation C5b complex gets inserted into the bacterial cell wall injuring it leading to cell swelling and rupture (Hurley et. al. 1984)

Types of cells in inflammation and their role in promoting it.

Leucocytes are mainly responsible for destruction of invading microorganisms and clearing the tissue of dead cells. At the later stages of acute inflammation they transform into macrophages. Macrophages do not seem to play any major role in most acute inflammatory reactions. They appear late at the site and their main function is removal of dead bacteria,
dead cells, tissue fragments and fibrin. They also process antigen before presenting to lymphocytes. Leucocytes and macrophages during acute inflammatory lesion secrete lysosomal enzymes thereby increasing the tissue and cell injury. Much of the injury to articular cartilage in rheumatoid arthritis appears to arise in this manner. Eosinophils play a predominant role in immediate type hypersensitivity reactions. They also facilitate antibody mediated killing of parasites. Macrophages, when activated, secrete a large number of biologically active factors, notably lysosomal enzymes. They also secrete some complement factors, lysozyme and interferon. Interleukin-1 (IL-1) secreted by macrophages helps in amplifying immune response. Platelets, besides releasing serotonin, thromboxane and oxygen free radicals produce chemotactic and mitogenic factors (Schleimer R. P., 1985). Epithelial cells (especially bronchial cells) themselves release inflammatory mediators such as Leukotriene B_{4} and 15-hydroxy, 5,8,11,13-eicosatetraenoic acid (15-HETE) (Barnes et al, 1988). Lymphocytes are the specific responder cells of the immune systems and are of two types, i.e. T and B cells. After sensitization they release lymphokines which play important role in increasing vascular permeability and attracting leukocytes into the site of reaction. B-lymphocyte play important role in the formation of humoral antibody and T-cell in cell mediated immunity. Mast cells are widely distributed in most tissues and are particularly numerous near small blood vessels. Mast cells have large basophilic cytoplasmic vesicles (Hurley et al, 1984) which can be discharged by various stimuli. They play a major role during hypersensitivity reactions by releasing considerable amounts of inflammatory mediators like serotonin, histamine and chemotactic factors.

**Functions of the fluid exudate:**

It dilutes toxins and facilitates their transport through lymphatics. Antibodies present in the fluid promote destruction of microorganisms or neutralize the effect of toxins released them. Fibrin network may act as a mechanical barrier for the spread of infection. Through its oxygen and glucose nutrient contents it may nourish the cells (Hurley et al., 1984).
Chronic inflammation

Between acute and chronic inflammation there occurs a wide range of overlapping processes. Those at the halfway point are some times referred to as subacute inflammation.

Inflammation is said to be chronic when its duration is relatively prolonged – often for months, years of even indefinitely. It is provoked by persistence of the causative factor be an infection or an inanimate foreign body. The tissues are infiltrated by mononuclear phagocytes (macrophages, epithelioid), lymphoid cell (lymphocytes, plasma cells or immunoblasts) and fibroblast. Necrosis is also reasonably common in chronic inflammatory lesions. In chronic inflammation lymphocytes and macrophages influence each other and release mediators of inflammation.

Types of chronic inflammation

(1) Nonspecific, when irritant substance produce a non-specific chronic inflammatory reaction with formation of granulation tissue and healing by fibrosis e.g. chronic osteomyelitis, chronic ulcer.

(2) Specific, when the injurious agent causes a characteristic histologic tissue response e.g. tuberculosis, leprosy, syphilis.

Immunologically mediated Inflammation:

Immunologically mediated inflammatory disorders are an important cause of human morbidity and mortality and hence deserve special attention.

Immunologically mediated Inflammation occurs when body attempts to eliminate foreign substances. It occurs in the following sequence of events:

(i) Binding of recognition component of immune system to the antigen;
(ii) Activation of an amplification system and
(iii) Initiation and production of local inflammatory reaction by the
inflammatory mediators as described above (Snynderman et al., 1986).

Four types of inflammation of immune systems are recognised:

1. Allergic Inflammation:
   Certain antigens stimulate production of IgE antibodies, which bind to
mast cells and basophils through their FC receptors and trigger the release of
large amount of inflammatory mediators from these cells leading to severe
inflammatory lesion at the affected site, e.g. asthma, urticaria and seasonal
rhinitis.

2. Inflammation Mediated by Cytotoxic Antibody:
   Binding of complement fixing antibodies to cells leads to activation of
complement system leading to destruction of such cells through release of
inflammatory mediators and macrophages e.g., haemolytic anaemia
associated with systemic lupus erythematosus.

3. Inflammation Initiated by Immune Complexes:
   Sometimes inflammatory lesion results from local deposit of immune
complexes. When the amount of immune complex is greater and beyond the
capacity of phagocytic cells - degranulation of phagocytic cell occurs against
the complex leading to tissue destruction. Activation of respiratory burst in the
inflammatory cells, also adds to the destruction, e.g. rheumatoid arthritis,
glomerulitis, etc.

4. Delayed Hypersensitivity Reaction:
   This reaction is important for the destruction of tumor cells, viruses and
intracellular parasites. Antigen is first encountered by macrophages which
alter and present it to T-lymphocytes which contain receptors for the antigen as well as antigen on the macrophage. This binding leads to production of lymphokines (interleukin 2, Y-interferon and lymphocyte derived chemotactic factor) from lymphocytes and interleukin from macrophages. These play important role as inflammatory mediators (Snynderman et al., 1986) e.g. tuberculosis, sarcoidosis etc.

**Inflammation in rheumatoid arthritis:**

Synovial membrane, which lines diarthroidal joints, is a thin, richly vascularised connective tissue. It contains two types of cells. Type A cell is similar to a fixed macrophage possessing phagocytic capability. Type B cells appear to be mainly concerned with secretion of hyaluronic acid. Beneath the synovial membrane fibroblast produce type I and II collagen. All the main features of inflammation are seen in synovitis in rheumatoid arthritis. In early stages proliferation of both A and B cells is seen. Polymorph neutrophils are the predominant cells present in synovial fluid and immune complexes can also be demonstrated in them. Other features are proliferation of small blood vessels, local accumulation of inflammatory cells, the lymphocytes, plasma cells, macrophages and sometimes mast cells. Activation of polymorph neutrophils leads to the degranulation of inflammatory cells with consequent release of lysosomal contents. They along with toxic oxygen products formed through respiratory burst cause tissue destruction. Immune complexes tend to bind to collagenous tissue and cartilage and may attract deposition of degradative contents of inflammatory cells.

Many causative agents for R.A. have been suggested but none have been demonstrated conclusively. It is likely that some as yet unidentified agent localises in the synovium leading to plasma cell induction through B-lymphocyte resulting in the production of antibodies and rheumatic factors. Simultaneously activating T-lymphocyte leading to synthesis of lymphokines. Combination of causative factor with antibody as well as complexing of antigen-antibody activates complement and kinin forming system. Neutrophils
and macrophages ingest immune complexes in the synovial fluid and as well as those embedded in cartilage matrix—this leads to release of lysosomal contents and production of toxic oxygen radicals causing injury to cartilage cells. Secretion of collagenase, PGs, hydrolytic enzymes activation of plasminogen further adds to the tissue destruction (Snynderman et al., 1986).

**Naturally occuring inflammatory modulators:**

Since inflammation is essentially a protective response, it should not last longer than required to achieve it. The normal self containing nature of the inflammatory response is due to the action of various endogenous modulatory factors. Certain factors are released from the injured tissue itself (anti-inflammatory factors released from irritated tissue ITAIF) which limit the response, α2 macroglobin and antitrypsin act as antiproteases (Nataraja et al., 1985, Bonta et al., 1977). Acute phase reactant proteins (orosomucoid, ceruloplasmin and heptaglobin) may function as endogenous inhibitors of inflammation (Glenn et al., 1968).

Steroids, oestrogen and insulin are also reported to produce anti-inflammatory effect. Oestrogen effect is reported to be through lysosomal membrane stabilisation, inhibition of prostaglandins synthesis and induction of hepatic anti-inflammatory factors.

Superoxide desmutase (SOD) produces anti-inflammatory effect through scavenging superoxide radicals (O$_2^-$) which together with H$_2$O$_2$ give rise to hydroxy (OH⁻) and singlet oxygen (1O$_2$) which are involved in pathogenesis of inflammation (Bhaskar Rao et al., 1986).

Some mediators of inflammation also have micro feed-back mechanism through which their formation and release are regulated, e.g. histamine and proslaglandins (Dipasquale et al., 1973).
Prostaglandin, Arachidonic acid and Inflammation:

The prostaglandins (PGs) are a complex group of oxygenated fatty acids that have been detected in virtually all mammalian tissues so far examined. They include some of the most potent natural substances known and are important both as bioregulators and as participants in pathological states. The prostaglandins are not stored free in tissues, but are synthesized as a result of membrane perturbations that cause the release of free fatty acids, generally arachidonic acid, from esterified lipid sources. The release of arachidonic acid can be brought about by a wide variety of hormones either directly or indirectly (S. L. Hong et al., 1976), as well as by inflammatory or immunological stimuli (J. L. Humes et al., 1977, R. J. Bonney et al., 1979), Calcium ionophores (E. G. Lapetina et al., 1979), Ultraviolet light (N. A. Plummer et al., 1977) and Melittin, the membrane active component of bee venom (A. Hassid et al., 1977), tumor promoting agents (K. Ohuchi et al., 1978) and even mechanical agitation (R. J. Flower et al., 1976). The free arachidonic acid then reacts with prostaglandin cyclooxygenase, the first enzyme of the prostaglandin biosynthetic sequence. This enzyme oxygenates arachidonic acid to the endoperoxide intermediate PGG2, which is then converted to a variety of other biologically active products. The nature of which is determined by the enzyme content of the tissue under consideration. For example, platelets make primarily thromboxane A2 (TXA2) whereas the aorta forms prostacyclin (PGI2).

With special reference to PGE2, an oxygenated fatty acid with a cis double bond, a trans double bond, two hydroxyl groups, a carbonyl. And a five-membered ring joined to the two side chains at carbones-8 and 12. Prostaglandins E2 and E1 are derived from other eicosanoids (fatty acids with 20 carbon atoms) with PGE3 having an additional cis double bond at carbon-17, and PGE1 being devoid of the double bond at carbon-5. However, the E2 prostaglandins, derived from arachidonic acid, are the most abundant.
The nature of these products is depicted in Fig. 4

Variations on the ring give PGD$_2$ by interchanging the carbonyl and hydroxyl or PGF$_2$ with a hydroxyl group at carbon-9. Compounds with other rings and similar side chains such as the endoperoxides (PGG$_2$ and PGH$_2$). TXA$_2$ and PGI$_2$ are also physiologically active. Strictly speaking TXA$_2$ devoid of a prostanoic acid skeleton, is nor prostaglandin. These structures are reviewed elsewhere in detail (R. J. Flower et al., 1976).
Biosynthetic Pathways for Arachidonic Acid Oxygenation

Fig. 5 Biosynthesis of the products of arachidonic acid by Cyclooxygenase pathway.
**Cyclooxygenase:**

The precise mechanism for releasing free fatty acid precursors of prostaglandins has not been elucidated. It is generally agreed, however, that they originate largely from phospholipid reserves in cell membranes. Although Phospholipase A: has been recognized as an important enzyme in the release of these precursor acids, recent studies with platelets implicate a phosphatidyl inositol specific phospholipase C, yielding diacylglycerides and subsequent arachidonic acid (S. Rittenhouse-simmons et al., 1979). However, the importance of this new pathway in other cell types has not yet been established. Of the three substrate fatty acids-5,8,11,14-eicosatetraenoic acid (arachidonic acid), cis-8,11,14-eicosatrienoic acid and cis 5,8,11,14,17-eicosapentaenoic acid, the first (arachidonic acid) is the most relevant to prostaglandin physiology. It is the only one that is converted enzymatically to an active thromboxane and prostacyclin. As shown in figure 5, Arachidonic acid is oxygenated to PGG₂ by prostaglandin cyclooxygenase, and this hydroperoxy acid is largely converted to PGH₂ by a hydroperoxidase. PGH₂ is then a substrate for thromboxane synthetase, PGI₂ synthetase. PGD₂ isomerase or PGE₂ isomerase and this pathway appear to predominate in most cells. The alternative pathway, the direct conversion of PGG₂ to 15-hydroperoxy PGE₂ (B. Samuelsson et al., 1974) and hydroperoxy TXA₂ (S. Hammarstrom et al., 1980), has been demonstrated with isolated enzymes but does not appear to be important in vivo.

The action of non-steroidal anti-inflammatory drugs (NSAID’s) on the cyclooxygenase, the first enzymatic step in the oxygenation sequence, necessarily regulates the synthesis of all subsequent compounds. When prostaglandins were first associated with inflammation, only the PGE’s and PGF’s were recognized as biologically active (S. Bergstrom et al., 1949, 1957, 1960). Consequently, these substances, sometimes referred to as primary prostaglandins, were implicated as inflammatory mediators. However, in 1973, PGG₂ and PGH₂ previously thought to be ephemeral intermediates, were
isolated (B. Samuelsson et al., 1965). Despite having a half-life of only few minutes, this substances have biological activities exceeding those of the primary prostaglandins.

Although PGE₂ and PGF₂ have opposing actions in special instances, with the discovery of TXA₂ and PGI₂ (M. Hamberg et al., 1975, S Moncada et al., 1976), the possibility of other prostaglandins having opposing effects surfaced. TXA₂ has a half-life of seconds and is most potent of the eicosanoids in contracting aortic tissue and triggering platelet aggregation. In fact, there is substantial evidence that TXA₂ is the major prostaglandin-related mediator of platelet aggregation (M. Hamberg et al., 1975). In contrast, PGI₂ relaxes aortic tissue and prevents platelet aggregation by antagonizing the actions of TXA₂ in these tissues (S. Moncada et al., 1976). Since NSAID’s inhibit cyclooxygenase and there by depress the formation of these products, those mentioned above must now also be considered as potential inflammatory mediators. However, despite the isolation of the biologically active compounds PGG₂ and PGH₂ the original concept of the endoperoxides being intermediates in inflammation appears to be correct. Addition of these precursor endoperoxides to various tissues gives response characteristic of the enzymatic makeup of that tissue, that it they cause TXA₂ synthesis in platelet and PGI₂ synthesis in aorta. Further evidence for the obligatory metabolism of PGH₂ to such active products is the finding that potent TXA₂ synthetase inhibitor OKY-1555 (T. Miyamoto et al., 1980) inhibits the ability of PGH₂ to trigger platelet aggregation (E. A. Ham et al.,).

Increase in Endogenous Prostaglandin during Inflammation

Studies of relative concentrations of cyclooxygenase-derived products in numerous inflammatory lesions (For review, R. J. Flower et al., 1977) have led to the conclusion that PGE₂ and PGF₂ concentrations increase in number of inflammatory conditions. In addition, both PGI₂ and TXA₂ have been identified in inflammatory exudates (G. A. Higgs et al., 1979).
The origin of cyclooxygenase-derived products in inflamed joints has not been established. The PMN's phagocytic cells essential for the initiation of acute inflammation, are relatively poor producers of prostaglandins (P. Davics et al., 1977). Another Phagocytic cell, the monocyte, is somewhat more productive, and the macrophage derived there from releases large amounts of PGE_2 and PGI_2 in response of inflammatory stimuli (J. L. Humes et al., 1977). TXA_2 production by this cell has also been reported (S. I. Murota et al., 1979). The low capacity of PMN's to produce prostaglandins and occurrence of acute inflammation in the absence of macrophages, suggest that cyclooxygenase-derived compounds are produced locally during the initial stage of inflammation. For example, interstitial and synovial cells have the capacity to produce copious quantities of prostaglandins (J. M. Dayer et al., 1979). The macrophage subsequently contributes to chronic inflammation. However, irrespective of the source, it is clear that there are high concentrations of cyclooxygenase-derived products in the inflamed joints and that reduction of these concentrations is associated with reduced inflammation.

### Cyclooxygenase-derived Products Mimic Symptoms of Inflammation:

Although there may be some overlap among the causes of the symptoms of acute inflammation, it is convenient to divide these symptoms into three categories: erythema, edema and pain. At a time when only PGE's and PGF's were identified as major biologically active prostaglandins, subdermally administered PGE's were shown to cause itch and flare responses in the human forearm whereas PGF's were inactive (E. W. Horton et al., 1963). Additional studies in animals have confirmed the efficacy of PGE's as vasodilatory agents capable of inducing erythema (G Kaley et al., 1971, S. H. Ferreira et al., 1974). However, neither PGE's nor PGF's fully induce edema or pain. Nevertheless, the edema and pain response caused by histamine or bradykinin could be enhanced dramatically by PGE, leading to the suggestion that PGE's are modulators of inflammation.
Although this interpretation fitted most facts at that time, it did not explain the capability of NSAID’s, acting at the cyclooxygenase level, to suppress all three symptoms of inflammation. With our current realization that other biologically active products are derived from cyclooxygenase and that bradykinin releases arachidonic acid from cell membranes, it is now possible to suggest that PGF$_2$ acts in conjunction with other products of this biosynthetic pathway and thereby, accounts for the efficacy of NSAID’s. (S. H. Ferreira et al., 1974).

Recently, PGI$_2$ has been shown to potentiate the effect of histamine and bradykinin in carrageenan-induced rat paw edema (E. M. Davidson et al., 1978). In a comparative study of the effects of PGE$_2$, PGI$_2$, PGD$_2$ and PGF$_2$ on plasma exudation and blood flow, both PGE$_2$ and PGI$_2$ potentiated the action of bradykinin. The effects of PGD$_2$ and PGF$_2$ however, were too small to have physiological significance. Although PGI$_2$ was five to ten times less potent than PGE$_2$ (E. A. Higgs et al., 1978), PGI$_2$ proved considerably more effective than PGE$_2$ in inducing pain (S. H. Ferreira et al., 1979). The ability of PGI$_2$ to cause hyperalgesia seems to relate to its capacity to stimulate adenosine 3',5' monophosphate (cyclic AMP) (I. Fridovich et al., 1975), a property characteristic of the E-type prostaglandins (F. A. Kuchi et al., 1974). Thus, these limited studies support a role for PGI$_2$ in inflammatory conditions.

Considering the extreme lability of TXA$_2$, it would be very difficult to establish its ability to trigger inflammatory responses. However, studies show that OKY-1555, an extremely potent inhibitor of TXA$_2$ synthesis with no appreciable cyclooxygenase inhibition (T. Mryamoto et al., 1980), has no effect on mouse ear edema (J. L. Humes et al.).
COX-1 and COX-2: Two isoforms of cyclooxygenase:

An early clue to the existence of COX-2 came from a study of cell-growth signalling pathways, which pointed to a unique inducible gene product related to the known COX i.e. COX-1 (Herschman et al., 1996). Meanwhile investigators looking at PG production in response to cytokines and other inflammatory factors observed increases in COX activity that could only arise by increased expression of another cyclooxygenase (Raz et al., 1988). Immunoprecipitation techniques allowed the isolation of the COX-2 protein and the identification of the two distinct isoforms. Subsequent research established that the COX-1 and COX-2 proteins are derived from distinct genes that diverged well before birds and mammals (Reed et al., 1996).

Properties of COX-1 and COX-2:

COX-1 is constitutively expressed in most tissues and performs a housekeeping function to synthesize PGs with normal cell regulatory activity. It is a membrane-bound haem and glycoprotein with a molecular weight of 71 kDa. It cyclizes arachidonic acid and adds the 15 hydroperoxy group to PGG2 and then reduces the molecule to PGH2 both through its own peroxidase activity. COX-2 with a molecular weight of 70 kDa has similar functions. However, it is not found to any appreciable extent in resting cells. On the other hand, it is expressed considerably after exposure to fibroblasts, cytokines etc. Levels of COX-2 protein increase in parallel with over-production of prostaglandins in many cells and tissues in chronic inflammation. Both COX-1 and COX-2 are homodimeric proteins. With the availability of purified COX-1 and COX-2 enzymes of different origins and by various methods, including recombinant technology, the classical NSAIDs could be readily tested and were shown to inhibit both COX-1 and COX-2, some of them in fact inhibiting the first more than the second. A logical outcome of the recognition of the role of the two COX forms appeared to be that a selective COX-2 inhibiting NSAID should not have the principal side effects associated with use of the earlier drugs, such as gastrointestinal inhibition and ulcers as well as renal perturbations (Hawkey et al., 1999, Vane et al., 1996).
Additionally, since COX-2 over expression is observed in diseases like alzheimer's and colorectal cancer, selective COX-2 inhibitors may have useful therapeutic benefits in such conditions (Dubois et al., 1998). COX-2 selective NSAID treatment may be an important advance in the prevention of preterm delivery (Sewdy et al., 1997). The design of a selective COX-2 inhibitor would be desirable and possible if structural differences could be identified between the two isoforms and exploited, although doubts have been raised to temper this optimism, since among other reasons, COX-2 has also useful physiological functions which may suffer in the process of inhibition (Wallace et al., 1999). The situation is confounded further by the preliminary data on COX-3 which is expressed in the 'resolution' phase of the inflammatory process. Since this has anti-inflammatory activity, the administration of selective COX-2 inhibitors at this stage may actually retard the healing phase (Willoughby et al., 2000).

Cyclooxygenase-2 - An attractive target for fruitful drug design:

Cyclooxygenase, an enzyme involved in the conversion of C-20 acids to prostaglandins, occurs in two isoforms. A third isoform has been recently encountered. COX-1 has a gastroprotective function. COX-2, induced at the site of injury, is responsible for the expression of pro-inflammatory prostaglandins. Despite overall similarities, COX-1 and COX-2 show subtle differences in amino acid composition at the active sites. COX-2 has valine at positions 8, 9 and 5, 2, 3, while COX-1 has isoleucine, resulting in larger space availability in the former. Further, the presence of valine at position 4, 3, 4 in COX-2 as against isoleucine in COX-1 allows a grate mechanism to operate in favour of the former. Molecular modelling studies explain the preferential COX-2 inhibitory activity of some nonsteroidal anti-inflammatory agents like celecoxib (Vane et al., 1996), rofecoxib (Vane et al., 1998), nimesulide (Bakhle et al., 1996), meloxicam (Hart et al., 1999), nabumetone (Vane et al., 1990) and etorolac (Raz et al., 1988) in terms of binding, destabilizing and intermolecular energies.
The revolution in biology over the past two decades has resulted in radically new approaches and opportunities for drug discovery. There has been an incredibly rapid increase in the rate of determination of three dimensional structures of biomolecules. Many of these macromolecules are important drug targets and it is now possible to use the knowledge of the three dimensional structure as a good basis for drug design. This area has attracted immense attention in the last few years and a large number of original research articles and a good number of scientific and popular review articles have been published. Aspirin or acetylsalicylic acid, the prototype of nonsteroidal anti-inflammatory agents (NSAIDs) was first produced and marketed by Bayer in March 1999. NSAIDs are even today among the most widely used therapeutic agents with a total annual sale in excess of US$ 10 billion. They are used for the treatment of a broad spectrum of pathophysiological conditions such as headaches, discomfort associated with minor injuries and alleviation of severe pain caused by inflammatory and degenerative joint diseases such as osteo and rheumatoid arthritis (Dubois et al., 1998).

**Prostaglandin Biosynthesis and Anti-inflammatory Activity:**

The discovery that aspirin and idomethacin block the synthesis of prostaglandins (J. B. Smith et al., 1971) lead many laboratories to investigate the involvements of prostaglandins in inflammation. There are several points in the biosynthetic pathway at which it might be possible to suppress the formation of primary prostaglandins. The cyclooxygenase was established as the site of action of NSAID’s because the uptake of molecular oxygen was blocked by these compounds (W L. Smith et al., 1972).

Acute inflammation is commonly measured by the edema induced in a rat paw by subplantar injection of carrageenan (C. A. Winter et al., 1963). It is also possible to measure edema in a mouse ear caused by topical application of phorbol esters (C. G. Van Arman et al., 1974). In both tests they effected increases in tissue weight within a few hours. The anti-inflammatory activity of
a compound is assessed by administering it topically, intraperitoneally, or orally and measuring the decrease in the edematous weight gain.

Anti-inflammatory drugs:

A good correlation has been demonstrated between the capacity of a variety of structures to inhibit prostaglandin synthesis in vitro and their ability to suppress inflammation in the rat paw edema assay (E. A. Ham et al., 1972). Particularly convincing is the correlation between optical isomers of two pairs of NSAID's, one pair structurally related to indomethacin and other belonging to the aryl acetic acid series. In both instances, the (+) isomer was significantly more active than (-) isomer on cyclooxygenase and foot edema, and clinical studies on the indomethacin related pair gave similar results (E. A. Ham et al., 1972). Several other laboratories have further strengthened the correlation (C. Takeguchi et al., 1972). Nevertheless, there are also instances in which inhibitors of cyclooxygenase are not effective anti-inflammatory agents. However, metabolic stability and appropriate pharmacokinetic properties are essential to the action of any drug in vivo, and the accumulation after ingestion of effective NSAID's in inflamed joints has been determined by radiographic studies (P. Graf et al., 1975). Considering these added factors, the correlation between the activity of NSAID's as cyclooxygenase inhibitors in vitro and their anti-inflammatory activity in vivo is very convincing.

Glucocorticoids:

Glucocorticoids express anti-inflammatory activity by means of a complex series of cellular responses. In general, they interact with a specific cytosolic receptor and ultimately alter protein synthesis. A most of effects results from this action, among which is decreased release of arachidonic acid from phospholipids (R. J. Grgelewski et al., 1975). Since only unesterified fatty acid are used by the cyclooxygenase, (Fig. 8), this depresses all cyclooxygenase derived products. For example, bradykinin-stimulated
synthesis of prostaglandins in isolated 3T3 cells was blocked by dexamethasone which thus acted as an inhibitor of arachidonic acid release (S. L. Hong et al., 1976). It appears that glucocorticoids effect this inhibition by steroid-directed synthesis of a specific protein (R. J. Flower et al., 1979).

The superior efficacy of steroidal compared to non-steroidal anti-inflammatory drugs is consistent with ability of the former to induce responses in addition to inhibition of prostaglandin biosynthesis. For example, macrophages are essential to chronic inflammation and release both prostaglandins and tissue-destructive lysosomal enzymes. In studies with cultured cells, indomethacin completely blocked formation of PGE$_2$ and PGl$_2$ but had no effect on lysosomal enzyme release, Dexamethasone inhibited both (J. L. Humes et al., 1977, R. J. Bonney et al., 1978). Nevertheless despite their potential therapeutic advantages, adverse side effects of steroids such as bone degeneration and supresson of the immune response limit their use as anti-inflammatory agents.
Lipoxygenases:

![Diagram](image)

**Fig. 6 Biosynthesis of the products of arachidonic acid by Lipoxygenases pathway.**
Lipoxygenases:

Mammalian lipoxygenase enzymes provide a competitive route for oxygenation of free arachidonic acid (figure 6) (M. Hamberg et al., 1974). Many cells possess both lipoxygenase and cyclooxygenase. However, despite their identical substrate requirements, the former is insensitive to NSAID's. The primary products of arachidonic acid and lipoxygenases are hydroperoxyeicosatetraenoic acids (HPETE's). Although the example in figure 2 (5-HPETE) has substitution at the fifth carbon, the location varies among cell types with substitution also being possible at the 5, 8, 9, 11, 12 or 15 positions. Whereas polymorphonuclear leukocytes (PMN's) can form HPETE's with substitution at each of the first five position concurrently (E. J. Goetzl et al., 1979), other cells such as platelets, which are reported to generate only 12-HPETE, are more selective (D. H. Nugteren et al., 1975). These hydroperoxides can be metabolized to either the analogous alcohol, or to leukotrienes. The alcohols result from peroxidatic reduction which occurs rapidly with any of the hydroperoxides. In contrast, the leukotrienes are formed only from 5-HPETE by epoxide formation (leukotriene A) with subsequent ring opening either with water to give a diol (leukotriene B) (P. Borgeat et al., 1979) or with glutathione to give the slow reacting substance of anaphylaxis (leukotriene C) (R. C. Murphy et al., 1979). Since the various compounds in these class are only now being elucidated, and variations on these basic structures have already been identified, it appears likely that a large number of leukotrienes will eventually be found.

Involvement of Lipoxygenase Products in Acute Inflammation:

The involvement of the products of the lipoxygenase enzymes in inflammation is based on rather tenuous evidence. The finding that 12-hydroxy-5,8,10,14 - eicosatetraenoic acid (12-HETE) is chemotactic to PMN'S drew attention to this phenomenon since the influx of these cells is essential for initiation of inflammatory responses (S. R. Turner et al., 1978). Other products of the lipoxygenase pathways, including the hydroperoxy
eicosatetraenoic acids (HPETE's) and the corresponding HETE, are also chemotactic to PMN's. The order of activity in the latter case being 5-HETE > 8-HETE > 11-HETE > 12-HETE, 15-HETE. However, the recent report that leukotriene B (5, 12-dihydroxy-6, 8, 10, 14-eicosatetracnoic acid) is more chemotactic by several orders of magnitude than other lipoxygenase products suggest this to be the truly relevant lipoxygenase product in inflammation (A. W. Ford et al., 1980, E. J. Goetzlet al.).

Although the chemotactic property of lipoxygenase products seems very secure, attempts to relate this property to inflammation by employing enzyme inhibitors are difficult to evaluate because of the absence of inhibitors that are specific for the lipoxygenase pathway. Unlike NSAID's, which block cyclooxygenase at concentrations that have no effect on lipoxygenase, all effective lipoxygenase inhibitors known to us also inhibit cyclooxygenase in varying degrees. Compounds with mixed activities against both enzymes but with a preference for lipoxygenase inhibition have not provided convincing evidence in support of the concept that the lipoxygenase pathway is important in acute inflammation. A more definitive statement regarding the involvement of this pathway in inflammation awaits the discovery of more selective inhibitors.

Mode of action of anti-inflammatory drugs:

Anti-inflammatory drugs have different mechanisms of action. Some may prevent components of the early inflammatory responses from manifesting themselves. Some drugs interfere with proliferative connective tissue phase of inflammation such as cytotoxic agents and while others may act by eliminating the noxious stimulation like microbial infection or formation of urate crystals.

The vascular phase of the early acute inflammatory response is mediated through release of many mediators by the cells into the infected area. Drugs interfering with the activity of these mediators or preventing their formation can be expected to produce anti-inflammatory activity.
Antihistamine and antiserotonin drugs produce transient anti-inflammatory effect. All the acidic non-steroidal anti-inflammatory drugs (NSAIDs) produce anti-inflammatory activity by inhibiting the enzyme cyclooxygenase, activity of which is the rate limiting factor for the synthesis of prostaglandin. Part of steroidal activity is mediated through inhibition of release of arachidonic acid the precursor for prostaglandin and leukotrienes the most potent chemotactic agent synthesis. Attempts are being made to prepare leukotriene antagonists.

Inflammatory response can also be suppressed by prevention of cell emigration from blood vessels to the injured area or by inhibiting the release of lysosomal enzymes or by inhibiting the activity of released factors. Steroids inhibit stabilization of lysosomal membrane besides inhibiting cell emigration. Many NSAIDs like indomethacin also act by increasing membrane stabilization. Gold preparations suppress the increased phagocytic activity of the neutrophils that occur in rheumatoid arthritis. The preparation may react with collagen and stabilise it preventing its denaturation which may be the cause of initiation of self disturbing response. The inflammation seen in gout is reduced by colchicine probably by preventing cell immigration and release of chemotactic factors from the neutrophil.

Inflammation, especially of immunological origin, can be suppressed by agents which interfere with the antigen processing by macrophages and secretion of lymphokines (Interleukin-1) e.g. steroids. Agents scavenging toxic oxygen radicals may also produce anti-inflammatory effect e.g. superoxide dismutase.

Anti-inflammatory activity can be produced by agents inhibiting proliferation of fibroblasts and preventing deposition of both the ground substance and collagen in connective tissue (e.g. steroids, cytostatic and cytotoxic agents like cyclophosphamide).
Chapter - 2

Review of Literature

The exact mechanism through which the drugs like penicillamine and chloroquine produce antirheumatic activity is not clear. Elucidation of this may provide an opportunity to develop drugs with specific antirheumatic activity. Drugs which increase the production of endogenous anti-inflammatory factors may be beneficial therapeutically. However, no such drug has been developed so far.

New Approach:

The recent trend is towards developing drugs with immunomodulatory function with a view to set right altered immune response in rheumatoid arthritis. This is based on the premise that rheumatoid arthritis is an immunodeficiency disease in the sense that suppressor T-lymphocytes are not functioning normally, thus allowing the unchecked autoimmune response to manifest itself and that the underlying cause of rheumatoid arthritis is persistent infection.

Levamisole has received lot of attention. It is found to be effective clinically but produces unacceptable toxic effects. Cyclosporin A and natural products like interferon, bestatin and lentinan, which are reported to be effective clinically, have been shown to possess immunomodulatory effects (Asherson et al., 1991).

Anti-lymphocyte immunotoxin, anti-interleukin-2 receptor antibody, interleukin toxin and antithymocyte globulin are receiving increased attention as possible therapies in rheumatoid arthritis.

Need for further research on anti-rheumatic drug:

Rheumatoid arthritis, due to its widespread prevalence throughout the world, chronic and disabling nature and onset in early adulthood, is considered as one of the most important diseases. Inspite of availability of a wide range of anti-inflammatory agents with diverse mechanisms of action
and chemical configuration it remains a difficult disease to treat. This is mainly due to non-availability of specific targeted therapy to set right the pathological changes in the affected parts. The search for an effective therapy is hampered by the nonavailability of information on the causative factor. Among the available drugs, steroid offer significant improvement but their use is to be set with serious untoward effects. Non-steroidal anti-inflammatory drugs offer only symptomatic relief from the pain and inflammation associated with the disease without altering the course of the disease and they also cause serious side effects mainly injury to the gastric mucosa. These two factors have sustained the interest of investigators in medicinal plants which offer vast reservoir of source material for undertaking search for a 'ideal' anti-rheumatic drug. It is pertinent to mention here that a number of plant products are reported to possess immunomodulatory effect and may prove to be useful in rheumatoid arthritis. In the following pages an attempt has been made to enumerate plants with anti-inflammatory activity reported by various authors in the past few years.
ARTHRTIS

Introduction

Arthritis means disease of the joints, specifically when joints are inflamed. On the other hand, rheumatism refers to aches and pains from the muscles and other structures outside the joints. These cover a wide range of disease states, comprising more than 100 conditions. There have been many attempts at classification but none of them is wholly satisfactory, because the etiology of most of the diseases is obscure. But the five common types are.

(Prakash K. Pispati et al.,)

1. Caused by wear and tear, or mainly degenerative in nature, such as osteoarthritis.

   This is the most common form of arthritis. The cartilage, or the "shock absorber" inside the joint, gradually deteriorates over a period of time, and the bones around it thickens and grows stiff. This process occurs primarily in weight-bearing joints, and is associated with little inflammation. Osteoarthritis of knees and hips are common examples; when it occurs in the neck, it is called cervical spondylosis.

2. Inflammatory, such as rheumatoid arthritis.

   In this condition, the body's defense or immune system goes wrong and the body's "soldiers" (white cells in the blood), instead of attacking invading bacteria, attack the joints, resulting in arthritis. The membrane lining within the joint gets severely inflamed, and the underlying cartilage and bone are also gradually affected. Severe pain and stiffness in the joints of the extremities may even lead to disability.
3. **Caused by defects in body chemistry, such as gout.**

   This sort of inflammation usually affects one or two large joints. In gout, there is excess uric acid in the blood and this gets deposited as injurious crystals in the joints, producing very intense pain.

4. **Many other kinds of arthritic diseases are a mix of both wear and tear and inflammatory changes.**

   There are also some which are caused by infection, either when the bacteria themselves are carried in the blood to the joint (causing septic arthritis), or when the arthritic symptoms occur as a reaction to some infection elsewhere in the body (as in the case of rheumatic fever and reactive arthritis). In the latter, it seems as though the infection, which may be anything from a sore throat to dysentery, can indirectly trigger off changes in the joints, though no bacteria are actually transported through the blood stream to the joint.

5. **Soft tissue rheumatism:**

   This is when tissue around the joint are affected by injuries and, as a result, degenerate or become inflamed. Examples would be frozen shoulder, tennis elbow, sprains, strains, and similar aches and pains.

   Unless the condition is acute and severe, most patients go to self-medication with analgesics before they seek advices.
ANATOMY AND PHYSIOLOGY OF JOINTS AND RELATED STRUCTURES:

Two types of joints are affected by rheumatic disease, synovial and cartilaginous. The former allow a wide range of free movement and so include all the 'hinge' joints of the limbs; the latter allow only limited movement and include primarily those of the vertebral column and the pubic symphysis (the anterior joint between the two pubic bones). Synovial joints vary in size, number of articulating surfaces, shape, range of motion and type of motion. Cartilaginous joints are involved primarily in degenerative and traumatic problems, whereas problems in synovial joints tend to be inflammatory.

Figure 7 exhibits type of joint involved in the legs, arms, fingers and feet. A generalized diagram is given in Fig. 1 from which it can be seen that the two opposing bones are covered with a firmly attached 1-3 mm layer of tough hyaline cartilage (articular). The cartilage is radiolucent, giving the appearance of a joint space on X-ray, though the two layers of cartilage are normally in close contact. The bearing surfaces of the cartilage are lubricated with a small volume (less than 4ml in knee joint) of viscous, pale yellow synovial fluid containing a hyaluronate-protein complex, albumin and some white cells, electrolytes, etc. The synovial fluid does not normally clot but if there is inflammation, fibrinogen enters the fluid, which is then able to clot like normal inflammatory exudates. Inflammation also increases the volume and pressure of fluid within the joint. The fluid is produced by the surrounding synovial membrane, which contains cells that secrete fluid and other phagocytic cells. The whole is surrounded and stabilized by a tough, fibrous capsule which may be thickened in places and by ligaments which further strengthen the joint. However, joint stability depends largely on the strengths of the attached and surrounding muscles, one of the object of physiotherapy to strengthen the muscles and to reinforce the joints. Some joints have additional structures, e.g. the tough, fibrous cartilage of the menisci in the knee joint, which helps to absorb stresses and further improves stability.
SYNOVIAL JOINTS

Typical synovial joints exhibit congruent articular cartilage surfaces supported by subchondral and metaphyseal bone and stabilized by joint capsule and ligaments. Inner surfaces, except for articular cartilage, covered by synovial membrane (synovium).

Fig. 7: Structure of synovial joints

Joint pain derives primarily from the stretching and inflammation of the fibrous structures (capsule and ligaments) and the periosteum, the thin layer of tissue which covers all bones in the body; sensation in the synovial tissues is poor. Inflammation often results in joint deformity because the limb is held in a position which provides the maximum joint volume, to accommodate the increased volume of synovial fluid.
Cartilaginous Joints

The arrangement of the joints in the vertebral column are covered with a thin layer of hyaline cartilage, similar to synovial joints, but are separated by intervertebral discs consisting of a strong fibrous capsule filled with a proteoglycan gel, thus providing an effective shock absorber.

Synovial Sheaths and Bursae

These occur where closely opposed structures move relative to each other, especially where skin or tendons need to move freely over bony surfaces. Bursae are enclosed clefts of synovial membrane supported by dense connective tissue, the synovium sometimes being continuous with that of an adjacent joint. The central potential space is normally filled with a capillary film of Synovial fluid which permits free movement to occur between the two layers of synovium.

Synovial sheaths occur around tendons which pass under ligaments or through fibrous tunnels, e.g. the carpal tunnel in the wrist. The sheath consists of a closed, double walled Synovial cylinder enclosing a capillary film of Synovial fluid. The inner wall is attached loosely to the tendon and the outer to the bones, ligaments or other adjacent structures. This arrangement again permits free movement of the tendon through surrounding tissues, similarly to the bursae.

Inflammation of the bursae or sheaths causes the accumulation of fluid, with swelling, tenderness, pain and restriction of movement.

Ganglia are synovial herniations (bulges) from a tendon sheath or joint.

Joint Nutrition and Repair

The synovial membrane is supplied with blood and nutrients from and underlying bed of vascular connective tissue. Nutrients for the chondrocytes, which are responsible for synthesizing all of the components of the joint
cartilage, diffuse through the synovial fluid which also transports waste products from the cartilage. There is normally a slow turnover of joint cartilage, which contains a unique collagen (Type II) plus highly hydrophilic proteoglycans. When this is compressed, the structural water (held by hydrogen bonding) is released from the proteoglycans and regained when the force is removed. This mechanism temporarily increases the fluid volume and makes it less viscous, thus cushioning stresses and facilitating movement. In adults the Chondrocytes do not normally replicate but repeated trauma reactivates their division. The resultant increased metabolism accelerates the dismantling and regeneration of damaged cartilage.

In degenerative joint disease, the composition and size of the proteoglycan molecules is altered and the rate of repair no longer keeps pace with that of degradation. Further, the Type-2 collagen fibrils are replaced with the commoner, less suitable Type -1 collagen which is characteristic of skin and tendons. Changes also occur in the underlying bone, with new bone formation occurring at the margins of the articular cartilage to form osteophytes (bony outgrowths).
RHEUMATOID ARTHRITIS

Introduction:

Rheumatoid arthritis is usually a chronic, progressive, inflammatory, systemic disease, which primarily affects Synovial joints. The commonest extra articular features are anaemia, soft tissue nodules (subcutaneous, pulmonary and pericardial), vascularitis, sicca syndrome and fibrosing alveolitis.

Etiology and epidemiology:

The trigger factors and the basis of the prolonged, intense inflammatory process are largely unknown. Despite intensive research and our much greater understanding of immuno-pathology, current explanation is speculative. Although it has been suggested that there is a persistent viral antigenic stimulation, no virus has yet been found and bacterial causes (eg. Proteus mirabilis) are also disputed. There is a high incidence of HLA-DR1 and DR4 genes in RA patients, and DR4 carriers have a high reactivity to mycobacterium tuberculosis. Interestingly, T-cells clone from the sivonoal fluid of RA patient seem to react with tubercular antigens. There may be an association between DR4 and T-cell receptor genes. The concept of RA as an autoimmune disease is popular, and there is some evidence to suggest that there is an imbalance between T-helper and T-suppressor cell activity, with a deficiency of the latter.

About 1.5% of the population in the UK is affected, with a 3:1 female/male pre menopausal sex ratio, the incidence being equal in both sexes in the elderly. The peak period of onset is between 35 and 55 years of age, though it can start at almost any age. Minor racial and geographical variations occur.
Natural history

The onset of RA is normally insidious, poly articular (several joints affected) and symmetrical, the small joints (PIP, MCP, MTP, wrists) being affected first. Although a mono articular onset, usually in the knee or the wrist, occurs in some 20% of patients. Fatigue and malaise may precede joint symptoms by several months.

Occasionally, there is an abrupt onset with marked systemic symptoms. This acute form has a better prognosis and, following recovery, many years may pass before another attack. Even less common is a palindromic onset, with acute episodes affecting one joint for hours or days, followed by remissions and exacerbations affecting other joints at interval of days to months. RA often remains inactive in pregnancy (75%) of women, and this may be related to the suppression of interleukin-2 production or to the levels of hormone dependent fetal proteins. There is some evidence to suggest that both susceptibility to RA and the disease activity are related to sex hormone level, which may act by modulating T-cell responses.

Disease activity waxes and wanes unpredictably and spontaneously, so patients who experience a remission while taking or using some product will naturally, though often mistakenly, attribute their improvement to that. This demonstrate one of the principal problems in the evolution of new anti arthritic drugs: the large number of patients have to be used in very well designed trial over long period to obtain statistically meaningful results.

Pathology

Initially, there is an inflammatory reactions in the synovial membrane (fig 8). The cell lining the synovium multiply, the surface become thickened and covered with villi, and fibrin is deposited from the inflammatory exudates.
Normal Joint

Osteoarthritis

Rheumatoid Arthritis

Fig. 8: Progression of joint damage in Rheumatoid arthritis
The deeper layers become infiltrated with lymphocytes and plasma cells and the latter produce rheumatoid factors (RFS). Most patients become sero +ve within a year of symptom onset and show high RF titres. However, there are few neutrophills in the synovium though they are the commonest cells in the synovial fluids. Phagocytosis of the immune complexes formed in the fluid results in an increase in the oxidative metabolism, liberating damaging free radicals and lysosomal enzymes which attack tissues.

If the inflammation proceeds, the synovial margin develops outgrowth of metabolically active pannus which dissolves underlined cartilages and bones to produce the characteristic erosions. If the disease progression is sufficiently severe, the supporting ligaments become weak and the joints will sublux (become partially or completely dislocated) and be deformed and non functional. Eventually, the joint may become fibrosed and ankylosed (stiff, non functional) but pain free. This progression of changes is illustrated in fig. 8. The tendons and tendon sheaths undergo changes similar to synovial changes described above.

The mechanisms responsible for these changes are unknown, but both immunological and free radical damage have been postulated. It has been suggested that deposition of iron in the synovial tissues, which does occur, promotes free radical damage, so chelating agents have been used to treat some patients with sever RA this is a developing field.
OSTEOARTHRITIS

Osteoarthritis is a common disease usually presenting after the age of 40 years and is more common in females. After the age of 65 more than 40% of the people have osteoarthritis. Though the ankles, hips, shoulders and small joints of the hand and feet may be involved the commonest joints to be affected are the knee joints. Osteoarthritis of the knee joints is one of the commonest causes of disability in humans, and is one of the commonest reasons for which patients come to a physician. Osteoarthritis was initially thought to be a degenerative disease with no cure, but now is seen as a dynamic process, which results from alterations both in degenerative and reparative processes, and with exciting prospects of medical intervention. Osteoarthritis has a very variable progression with some patients rapidly progressing to disability, whereas others many continue to have very mild symptoms for a long time, without any disability. In such a setting it is difficult to evaluate long-term benefits of drugs. Advances in research methodology have allowed for the development of scales for evaluating the progression of osteoarthritis and evaluating response in patients on drug therapy. (Bellamy N. et al.,1988, Leguesne M, et al.,1994, Das SK, 1998). Medicines for osteoarthritis may be drugs, which only reduce pain (symptom modifying) over short periods of time (like NSAIDs), or for a longer period of time (Symptomatic slow acting drug for OA, SYSDOA). Medicines with potential for treatment of osteoarthritis are now being evaluated both for symptom modification and structure modification.

Osteoarthritis (OA) primarily is due to breakdown of articular cartilage with poor repair. Both the increased breakdown of articular cartilage and the poor reparative mechanisms are targets for therapeutic maneuvers. Cartilage is composed of proteoaminoglycans. Exogenous polysulfated glycosaminoglycans and glycoaminoglycan peptide complex have been evaluated for symptom modification and structure modifying effects.
Glucosamine sulfate (Noack W, et al., 1994) and chondroitin sulfate (Morreale P, et al., 1996) (one of the glycosaminoglycans) are now marketed as drugs or nutritional supplements in many countries.

The viscosity of synovial fluid is dependent on hyaluronan or hyaluronic acid, which acts as lubricant when joint motion is slow and as a shock absorber when the movement is fast. In osteoarthritis the synovial fluid is of poor quality and not viscous enough and may not save the joint from damage. Moreover, articular cartilage is an avascular tissue, which derives its nutritional supply from the passage of synovial fluid in the intercellular matrix. The cartilage imbibes the synovial fluid at the time of knee unloading and expels it at the time of knee loading. The quality of synovial fluid dictates the nutrition obtained by the cartilage. Attempts have been made to improve the quality of synovial fluid by injecting 'hyaluronan', which increases the viscosity of synovial fluid (Viscosupplementation). The mechanism of action may include anti-inflammatory properties and stimulation of endogens hyaluronan synthesis. These drugs are now commercially available for clinical use.

Inflammation is considered to be an important mediator of cartilage damage in osteoarthritis. Most patients have subclinical inflammation where as a few patients develop recurrent acute inflammation in their knee joints. Various enzymes like collagenases, elastases etc, collectively called matrix metalloproteinases (MMP), are important mediators of inflammation and also of articular cartilage damage. Drugs which inhibit these MMP's are being developed. Chemically modified tetracyclines (CMT), which do not have antibacterial activity but inhibit the MMP's are being evaluated. Of the various CMT’s, CMT 8 seems to have reasonable activity (Ryan ME, et al., 1996). These drugs are not available for clinical use as yet.

New therapies are being tried out for the regeneration of degenerated cartilage. Of interest is the role of growth hormone and other growth factors.
including insulin like growth factors and TGF beta. These stimulate proteoglycan synthesis and possibly new cartilage formation. It may also be possible to plant synthetic matrix at sites of damaged cartilage which may contain growth factors and chondrocytes (Solchaga L A et al., 1999). One novel therapy is to introduce a polymer in the joint, which spreads inside the joint and covers the articular surface with a layer of polymers similar to the "Nlon" treatment to a car engine.

With these medicines and therapeutic strategies physicians are likely to help patients with early osteoarthritis, in preventing progression or in delaying the development of end stage joint disease. However for those who have developed end stage joint disease the orthopedic surgeons come in as angels and provide a useful and painless mobility with the help of artificial prosthesis by way of knee replacement surgery.

Table : 2

Classification of OA

I. Idiopathic
   A. Localized OA
      1. Hands: Heberden's and Bouchard's nodes (nodal), erosive inter-phalangeal arthritis (nonnodal), 1st carpometacarpal joint.
      2. Feet: hallux valgus, hallux rigidus, contracted toes (hammer/cock-up toes), talonavicular.
      3. Knee:
         a. Medial compartment
         b. Lateral compartment
         c. Patellofemoral compartment
      4. Hip:
         a. Eccentric (superior)
         b. Concentric (axial, medial)
         c. Diffuse (coxae senilis)
5. Spine:
   a. Apophyseal joints
   b. Intervertebral joints (disks)
   c. Spondylosis (osteophytes)
   d. Ligamentous (hyperostosis, Forestier’s disease, diffuse idiopathic skeletal hyperostosis

6. Other single sites, e.g., glenohumeral, acromioclavicular, tibiotalar, sacroiliac, temporomandibular

B. Generalized OA includes 3 or more of the areas listed above (Kellgren-Moore)

II. Secondary

A. Trauma
   1. Acute
   2. Chronic (occupational, sports)

B. Congenital or developmental
   1. Localized diseases: Legg-Calvé-Perthes, congenital hip dislocation, slipped epiphysis
   2. Mechanical factors: unequal lower extremity length, valgus/varus deformity, hypermobility syndromes
   3. Bone dysplasias: epiphyseal dysplasia, spondyloepiphyseal dysplasia, osteonchondrostdrophy

C. Metabolic
   1. Ochronosis (alkaptonuria)
   2. Hemochromatosis
   3. Wilson's disease
   4. Gaucher's disease

D. Endocrine
   1. Acromegaly
   2. Hyperparathyroidism
   3. Diabetes mellitus
   4. Obesity
   5. Hypothyroidism
E. Calcium deposition diseases
   1. Calcium pyrophosphate dihydrate deposition
   2. Apatite arthropathy

F. Other bone and joint diseases
   1. Localized: fracture, avascular necrosis, infection, gout
   2. Diffuse: rheumatoid (inflammatory) arthritis, Paget's disease, osteopetrosis, osteochondritis

G. Neuropathic (Charcot joints)

H. Endemic
   1. Kashin-Beck
   2. Mseleni

I. Miscellaneous
   1. Frostbite
   2. Caisson's disease
   3. Hemoglobinopathies

Table: 3
Risk Factors for OA

- Age
- Female sex
- Race
- Genetic factors
- Major joint trauma
- Repetitive stress, e.g., vocational
- Obesity
- Congenital/developmental defecta
- Prior inflammatory joint disease
- Metabolic/endocrine disorders


ETIOLOGY

The disease may be classified into two groups:

- Primary: of unknown origin, and
- Secondary: consequent on trauma, Joint malalignment, etc.
Synovial fluid

Osteoarthritic joint

Loss of cartilage and formation of cyst and osteophytes

It usually develops gradually over a period of several years and sometimes it may suddenly flare up. Slowly, as the cartilage starts eroding, the disease progresses and bony "outgrowths" form at the outer edges of the joint. The synovial membrane and the capsule also thicken and are inflamed. All this leads to painful movements and stiffness.
Primary osteoarthritis

Important factors include the following.

- **Ageing:** Osteoarthritis is not result of ageing but age allows many of the other causes to damage the joint, hence the disease is associated with the ageing population.

- **Obesity:** Obesity is a risk factor for knee OA and hand OA. Obesity plays an even larger role in the etiology of the most serious cases of knee OA.

- **Genetic predisposition:** primary generalized OA (PGOA), in which there is widespread early joint involvement, is sex linked (1.5 times more common in women) and tends to run in families, as does the development of Heberden’s nodes, i.e. bony enlargement of the DIP (terminal linger) joints. Less common are the similar Bouchard’s nodes at the PIP (middle finger) joint. Involvement of the first MCP (thumb) joint gives the hand a squarish appearance. PGOA is unusual in Black populations and is particularly common in people of British descent but is not related to climatic or environmental factors. There is no association with HLA antigens.

- **Wear and tear:** The subchondral bone is known to undergo microfractures in normal use and repeated fracture and healing result in bone changes which reduce its ability to absorb shocks. Further, muscle weakening with lack of exercise and advancing age results in loss of adequate joint support, thus allowing abnormal joint movement which causes further cartilage damage. However, wear and tear does not, of itself, necessarily produce OA.

- **Major trauma and repetitie joint use** are also important risk factors for OA. Anterior cruciate ligament insufficiency or meniscus damage (and meniscectomy) may lead to knee OA.


**Chapter - 2**

Review of Literature

- **Congenital defects**: Abnormal positioning of bones due to congenital defects can cause arthritis in the long run.

- **Abnormal enzymes**: Though not conclusively proved, it is suspected that some abnormal enzyme released by the cartilage cells may lead to cartilage breakdown and joint destruction.

**Secondary osteoarthritis**

This is the result of accelerated wear due to joint damage or malfunction. The disease may develop insidiously over up to 60 years, and is a consequence of defective collagen repair.

**Signs and Symptoms**

The weight bearing joints (hip, knee) are principally affected though involvement of the smaller joints (e.g. hands) may also contribute to disability. Unlike RA, there is no systemic (extra-articular) involvement. The predominant features are as follows.

Some conditions which commonly predispose to secondary osteoarthritis, Trauma: obesity, fractures, dislocation, sports injuries, joint surgery.

- Genetic and congenital: conditions affecting joint alignment, haemophilia, acromegaly, hyperparathyroidism, chondrocalcinosis, ochronosis

- Postinflammatory: rheumatoid arthritis, gout, pseudogout, septic arthritis

- Bone disease: Paget's disease.

- Pain: onset is gradual, initially after exercise but later occurring at night and at rest
Stiffness may be severe after a period of rest, but transient, and patients often complain of stiffness on rising ("morning stiffness") lasting up to about 15 min. This should be compared with the situation in RA in which morning stiffness may be severe and prolonged.

Loss of function is extremely variable and may occur early, even though pain is light. However, even gross joint changes may not be accompanied by significant functional impairment, though there may be limitation of movement;

Joint swellings are hard (Heberden's and Bouchard's nodes) due to osteophytes (outgrowths at the bone ends), or may be softer and partly due to inflammation. The inflammation and tenderness may occur in the early stages and during the acute exacerbations, lasting a few weeks, which occur without apparent cause and tend to occur in joints are over-used;

The joints most commonly involved are:
(a) Cervical and lumbar spine,
(b) DIP joints (Heberden's nodes, normally spared in RA),
(c) PIP joints (Bouchard's nodes, less common),
(d) Hips,
(e) Knees,
(f) Feet, especially the first MTP joint (large toe), which takes the heaviest loading.

Laboratory and Radiographic finding
The diagnosis of OA is usually based on clinical and radiographic features. In the early stages, the radiograph may be normal, but joint space narrowing becomes evident as articular cartilage is lost. Other characteristic radiographic findings include subchondral bone sclerosis, subchondral cysts, and osteophytosis. A change in the contour of the joint, due to bony remodeling, and subluxation may be seen.
No laboratory studies are diagnostic for OA, but specific laboratory testing may help in identifying one of the underlying cause of secondary OA.

TREATMENT

Treatment of OA is aimed at reducing pain, maintaining mobility, and minimizing disability. For those with only mild disease, reassurance, instruction in joint protection, and an occasional analgesic may be all that is required; for those with more severe OA, especially of the knee or hip, a comprehensive program comprising a spectrum of nonpharmacologic measures supplemented by an analgesic and/or NSAID is appropriate.

Nonpharmacologic Measures - Reduction of joint loading

OA may be caused or aggravated by poor body mechanics. Correction of poor posture and a support for excessive lumbar lordosis can be helpful. Excessive loading of the involved joint should be avoided. Patients with OA of the knee or hip should avoid prolonged standing, kneeling, and squatting. Obese patients should be counseled to lose weight.

Rest periods during the day may be of benefit, but complete immobilization of the painful joint is rarely indicated. In patients with unilateral OA of the hip or knee, a cane, held in the contralateral hand, may reduce joint pain by reducing the joint contact force. Bilateral disease may necessitate use of crutches or a walker.

Physical therapy

Application of heat to the OA joint may reduce pain and stiffness. A variety of modalities are available; often, the least expensive and most convenient is a hot shower or bath. Occasionally, better analgesia may be obtained with ice than with heat.
It is important to note that patients with OA of weight-bearing joints are less active and tend to be less fit with regard to musculo-skeletal and cardiovascular status than normal controls. An exercise program should be designed to maintain range of motion, strengthen periarticular muscles, and improve physical fitness. The benefits of aerobic exercise include increases in aerobic capacity, muscle strength, and endurance; less exertion with a given workload; and weight loss. Those who exercise regularly live longer and are healthier than those who are sedentary. Patients with hip or knee OA can participate safely in conditioning exercises to improve fitness and health without increasing their joint pain or need for analgesics or NSAIDs.

Disuse of the OA joint because of pain will lead to muscle atrophy. Because periarticular muscles play a major role in protecting the articular cartilage from stress, strengthening exercises are important. In individuals with knee OA, strengthening of the periarticular muscles may result, within weeks, in a decrease in joint pain as great as that seen with NSAIDs.

Drug Therapy of OA

Therapy for OA today is palliative; no pharmacologic agent has been shown to prevent, delay the progression of, or reverse the pathologic changes of OA in humans. Although claims have been made that some NSAIDs have a "chondroprotective effect," adequately controlled clinical trials in humans with OA to support this view are lacking. In management of OA pain, pharmacologic agents should be used as adjuncts to nonpharmacologic measures, such as those described above, which are the keystone of OA treatment.

Although NSAIDs often decrease joint pain and improve mobility in OA, the magnitude of this improvement is generally modest—on average, about 30% reduction in pain and 15% improvement in function. In a double-blinded, controlled trial in patients with symptomatic knee OA, an anti-inflammatory dose of ibuprofen (2400 mg/d) was no more effective than a low (i.e.,
essentially analgesic) dose of ibuprofen (1200 mg/d) or than acetaminophen (4000 mg/d), a drug with essentially no anti-inflammatory effect. Other studies confirm that an analgesic dose of ibuprofen may be as effective as anti-inflammatory doses of other NSAIDs, including the potent agent, phenylbutazone (400 mg/d), in symptomatic treatment of OA. Even in the presence of clinical signs of inflammation (e.g., synovial effusion, tenderness), relief of joint pain by acetaminophen may be as effective as that achieved with an NSAID. Nonetheless, if simple analgesics are inadequate, it is reasonable to cautiously prescribe an NSAID for a patient with OA.

It should be recognized that concern over the use of NSAIDs in OA has grown in recent years because of side effects of these agents, especially those related to the gastrointestinal (GI) tract. Those at greatest risk for OA, i.e., the elderly, appear also to be at greater risk than younger individuals for GI symptoms, ulceration, hemorrhage, and death as a result of NSAID use. The annual rate of hospitalization for peptic ulcer disease among elderly current NSAID users was 16 per 1000-four times greater than that for persons not taking an NSAID. Among those age 65 and older, as many as 30% of all hospitalizations and deaths related to peptic ulcer disease have been attributed to NSAID use. In addition to age, risk factors for hemorrhage and other ulcer complications associated with NSAID use include a history of peptic ulcer disease or of upper GI bleeding, concomitant use of glucocorticoids or anticoagulants, and, possibly, smoking and alcohol consumption.

In patients who carry risk factors for an NSAID-associated GI catastrophe, a cyclooxygenase (Cox-2-specific NSAID may be preferable to even a low dose of a nonselective Cox inhibitor. In contrast to the NSAIDs available to date—all of which inhibit Cox-1 as well as Cox-2—two Cox-2-specific inhibitors (CSIs), celecoxib and rofecoxib, are now available. Systemic glucocorticoids have no place in the treatment of OA. However, intra- or periarticular injection of a depot glucocorticoid preparation may provide marked symptomatic relief for weeks to months. Because studies in animal models have suggested that
glucocorticoids may produce cartilage damage, and frequent injections of large amounts of steroids have been associated with joint breakdown in humans, the injection should generally not be repeated in a given joint more often than every 4 to 6 months.

Intraarticular injection of hyaluronic acid has been approved recently for treatment of patients with knee OA who have failed a program of nonpharmacologic therapy and simple analgesics. Although relief of knee pain is achieved more slowly after hyaluronic acid injection than after intraarticular glucocorticoid injection, the effect may last much longer after hyaluronic acid injection than after glucocorticoid injection, JIRA-2001.

**Nutritional Therapy for Osteoarthritis:**

**Glucosamine and Chondroitin**

**Introduction to Glucosamine:**

Glycosaminoglycans are the main components of cartilage, and glucosamine is one of the building blocks of glycosaminoglycans. In vitro studies have shown that incorporation of glucosamine is the rate-limiting step in the production of glycosaminoglycans. In theory, the administration of glucosamine to an individual with osteoarthritis may stimulate the production of glycosaminoglycans and prevent the continued erosion of the cartilage. Thus, the use of glucosamine as a dietary supplement has become popular among individuals suffering from osteoarthritis.

**Absorption and distribution**

After the oral consumption, 90 percent of glucosamine sulphate is absorbed from the stomach and is rapidly distributed in the body. Articular cartilage concentrates glucosamine to a greater extent than any other structural tissue. (Setnikar I. et al., 1993).
Mode of action:

i. Glucosamine stimulates chondrocytes - the cells that produce proteoglycans and collagen.

ii. Glucosamine acts by actually helping the body repair the damaged and eroded cartilage. It does so by stimulating the production of collagen and proteoglycans. Glucosamine is the major building block of proteoglycans and provides the building material for the manufacture of proteoglycans.

iii. Glucosamine is also needed to make water binding protein glycosaminoglycans in the cartilage matrix. Thereby water retention capacity of the cartilage improves. Hence nourishment of the cartilage also improves.

iv. At the same time, glucosamine also regulates cartilage metabolism, helping to keep cartilage build-up and break-down mechanisms balanced.

v. Further, glucosamine stimulates synovial production of hyaluronic acid (HA), which is primarily responsible for the lubricating and shock absorbing properties of synovial fluid. Hyaluronic acid has anti-inflammatory and analgesic properties.

(Kelly J. S. 1988, McCarty, M.F., 1988).

Therapeutic uses

Glucosamine sulphate might be supportive in:

- kidney stones
- osteoarthritis
- wound healing

A Glucosamine sulphate deficiency in humans has not been reported. There is no need for people other than those with osteoarthritis to routinely supplement their diet with glucosamine sulphate. So it has specific therapeutic value.
Duration of therapy

The positive effects of glucosamine sulphate are more apparent when it is used consistently over time. Like any other nutritional product, it has a gradual influence. Studies have, shown remarkable benefits within four to eight weeks of supplementation, using 500mg three times daily.

Chondroitin

Introduction

Chondroitin is the major glycosaminoglycan species in cartilage, and consists of repeating disaccharide units of N-acetylgalactosamine and glucuronate substances from the cartilage, deficiency of which leads to loss of resilience and thinning and the onset arthritis.

Mode of Action

i. Chondroitin help attract fluid into the proteoglycan molecules which is important for two reasons:
   - The fluid acts as a spongy shock absorber
   - The fluid sweeps nutrients into cartilage

ii. Chondroitin stimulates the production of cartilage matrix molecules that serve as building blocks for healthy new cartilage.

iii. Chondroitin protects existing cartilage by inhibiting action of certain enzymes.

As mentioned earlier, articular (joint) cartilage has no blood supply, so all of its nourishment and lubrication comes from the liquids that ebbs and flows as pressure to the joint is applied and released. Without this fluid, cartilage would become malnourished, thinner and more fragile. Like glucosamine, chondroitin helps attract this fluid into the proteoglycan molecules. (Palmoskil, J.J., and Brandt K.D., 1980).
Chondroitin stimulates the production of proteoglycans, glycosaminoglycans, and collagen, the cartilage matrix molecules that serve as building blocks for healthy new cartilage. (Roetta G., 1991).

**Glucosamine and Chondroitin in the Treatment of Osteoarthritis**

Glucosamine and Chondroitin used together successfully address the causes of cartilage damage at the cellular level. Between them they meet all the requirements for “true” chondroprotective agents.

Therefore Glucosamine and Chondroitin:

- Enhance cartilage cell macromolecule synthesis (glycosaminoglycans, proteoglycans, collagens, proteins).
- Enhance the synthesis of hyaluronan (the substance that gives the joint fluid its thick viscosity, providing lubrication between the synovial membrane and cartilage).
- Inhibit the enzymes that degrade the cartilage cell macromolecules.
- Mobilise thrombi, fibrin, lipids, cholesterol deposits in synovial spaces, and blood vessels in surrounding joints.
- No drug or supplement can achieve all this alone.
- But Glucosamine and Chondroitin working together can do!

Therefore, what Glucosamine and Chondroitin do, is to supplement the ingredients naturally present in the body thereby relieving the damaging effects of osteoarthritis and decreasing signs and symptoms. Second line agents in the treatment of Rheumatic Diseases, (Dixon J.S. et Furst D.E.)

**Conclusions**

Use of glucosamine and chondroitin sulphate are newer options in management of osteoarthritis. Early results are encouraging and experience with these drugs in long-term may change the entire spectrum of disease management.
Orthopedic Surgery:

Joint replacement surgery should be reserved for patients with advanced OA in whom aggressive medical management has failed. In such cases total joint arthroplasty may be remarkably effective in relieving pain and increasing mobility.

Arthroscopic removal of loose cartilage fragments can prevent locking and relieve pain. Chondroplasty (abrasion arthroplasty) has also and some popularity as treatment for OA.

Other Types of Arthritis

Gout

This is a type of arthritis that has been known since time of the Greeks and Romans. It mainly affects men after the age of 40 and is unusual in women, except those past the manopause.

Cause

Gout is caused by crystals of uric acid forming particularly in the joints, skin and kidneys. Uric acid is one of the end products of the body’s chemical processes. Victims in gout have higher level of uric acid in the blood than normal beings due either to increased amounts being formed or reduced amounts of acid being passed out by the kidneys into the urine. This uric acid normally remains dissolved in the blood. But under certain conditions when the blood becomes too full of it, the uric acid forms needle-shaped crystals in the joints which bring about an attack of gout.

It has been recognized for a long time that gout may be inherited. Certain races, such as the Maoris of New Zealand and other Polynesian races, are prone to gout. Thus in people with defects of body chemistry they might have inherited producing high blood levels of uric acid, many factors
may trigger off an attack. Examples of these are injury to a joint, an operation, and certain drugs such as ‘diuretics’ (water-pills used to get rid of excess body fluid). Contrary to popular belief, diet and drinking alcohol in moderation are not important factors. Nevertheless, foods rich in ‘purines’, which the body converts into uric acid, such as liver, kidney, meat extracts, sardines and fish roe and certain drinks such as port, burgundy and other red wines may contribute to a person developing gout.

**Symptoms**

During an attack, the big toe, which is affected in 75% of cases, becomes acutely painful tender, hot and swollen over a few hours. The sufferer may be awakened in the early hours of the morning, having gone to bed happily the night before. Other joint, such as the knee or wrist, may be similarly affected, and sometimes more than one joint at a time. Without treatment, the acute attack subsides over one or two weeks.

Repeated attacks may occur after several weeks or months. These intervals become shorter if the condition is left untreated. The joint gradually becomes damaged by the arthritis. This is chronic gout in which ‘tophi’ or chalky lumps of uric acid crystals remain in the joint and also form under the skin, a typical place being the ear lobe.

Another important complication of gout is kidney stones containing uric acid. This may cause severe ‘colic’ pains in the stomach. Some people pass the stones out in the urine in the form of gravel or fine sand. In chronic cases the kidneys themselves also become damaged and occasionally fail to function properly. This is a potentially serious situation in which poisonous waste products, normally removed by the kidneys, accumulate in the blood.
Treatment

Although gout cannot be cured, in the sense of curing an infection with antibiotics, treatment is so effective that drugs can relieve both the acute symptoms and prevent further attacks. Before starting treatment the doctor may want to do a blood test to measure the uric acid. Other tests for some patients are X-rays and looking for crystals in the joint fluid.

The acute attack has traditionally been treated by a drug called colchicine. But, although it is effective, it can have unpleasant side-effects, such as stomach pains, diarrhoea and vomiting. It is a mitotic poison. It has, therefore, been replaced by other drugs such as indomethacin and phenylbutazone, that will be prescribed in a suitable dose. These drugs control inflammation and should relieve the symptoms quickly, often within couple of days. Side-effects, such as indigestion, are not a problem when they are taken for a short period. It is helpful for a person known to have gout to keep a supply of tablets with him and take them at the start of the early warning symptoms.

If the attacks are frequent, the joints have been damaged by gout, there are obvious tophi or the blood levels of uric acid are very high. The above drugs are unsatisfactory, the doctor may decide to put the patient on a drug that helps the kidneys flush out the excess uric acid from the body. In other words it brings down the level of uric acid in the blood and reduces the chances of a gouty attack. For successful treatment these tablets must be taken regularly and virtually for life.

A newer and better drug is called allopurinol, which has only minor side-effects. It has brought about a revolution in the treatment of gout and actually prevents the body from forming uric acid. Apart from the conditions mentioned above, it is of particular benefit in patients who tend to form kidney stones, since the drug reduces the flow of uric acid through the kidneys. Allopurinol, which lowers the blood uric acid levels and prevents crystals form-
ing in the joints and elsewhere, has no effect on the symptoms during an attack. Treatment with this drug needs to be regular and lifelong. Often two drugs are prescribed, one like allopurinol and the other such as a small dose of colchicine or indomethacin, especially in the early weeks after an acute attack, to stop further pain and swelling.

Because treatment is now so effective, keeping to a strict diet and other measures are not so important. However, it would be wise for affected people not to over-indulge in alcohol and the foods rich in purines. Obese people should lose weight and the doctor will advise whether drinking plenty of fluids is necessary. Finally, certain drugs, for example diuretics (water-pills) and aspirin, tend to raise the level of uric acid in the blood and should be avoided if possible. Today, a gouty person under adequate medical supervision should be spared the prospect of further suffering from an otherwise crippling disease.

Ankylosing spondylitis

This apparently difficult term refers to inflammation and arthritis of the joints of the spinal bones (vertebrae) that tend to become stiff, rigid and fused together (ankylosis). It is not as rare as was once thought and affects men about five times more frequently than women. Typically, it starts in young men in their twenties.

Cause

Although the cause is not known, research has shown that hereditary factors are very important. A gene type or genetic marker called ‘HLA-B27’ has recently been discovered in more than 90 per cent of patients. This means not only that someone with this B27 marker has a much higher chance of developing spondylitis, but also the condition is more common among relatives of that person. What exactly triggers the arthritis in these people is, however, not understood. Research workers are trying to establish if some kind of infection may be responsible.
Symptoms

In most cases the first symptom is gradually developing pain and stiffness in the lower back that is worse in the morning on waking up. This may also be felt in the buttocks and back of the thighs. The backache is due to inflammation of the sacro-iliac joints between the base of the spine (sacrum) and the hip bones. This inflammation gradually spreads up the spine (lumbar and dorsal) and even the neck may become stiff. Back movements are restricted with a slowly increasing stooped posture due to forward curving of the spine and in bad cases of the neck as well. Chest expansion is also reduced due to inflammation in the joints between the ribs and the vertebrae. Normal breathing itself is unaffected.

Other joints such as the shoulders, hips and knees may be involved with this arthritis, sometimes as the first evidence of the disease. In rare cases, the small joints of the hands and feet are affected. Rheumatic pains may occur in soft tissues. Spondylitis is a chronic condition, its natural course is often mild with a tendency to become inactive over the years. Some people have only occasional aches and pains which don’t bother them a great deal. Others go through periods of active disease which makes them feel generally ill, but this gradually subsides. In many people the upper part of the back, neck and other joints are never affected. In a few, however, the whole spine may become rigid by bony fusion of the joints and disease of the hips may be quite disabling.

Complications may occur, though all of these, except the first, are rare. These include inflammation of the eyes, leaky heart valves, defective beating of the heart, inflammation of the lungs and fractures of the rigid spine. Occasionally, symptoms similar to ankylosing spondylitis may be seen in people with other disorder such as a colitis, an inflammation of the bowel.
Chapter - 2

Review of Literature

Treatment

The doctor is able to confirm the diagnosis by X-rays of the sacro-iliac joints and spine which will usually show the typical changes. He may also do blood tests to look for the 'B27' marker and to check how active the disease is, before starting treatment. He will encourage the patient to remain mobile and live as active a life as possible. Rest appears to lead to increasing stiffness and fusing of the joints and, if really needed, should be kept to a minimum.

Physiotherapy and swimming are useful to relieve stiffness. The physiotherapist will teach the patient how to carry out a regular daily programme of home exercises, particularly breathing and spinal exercises. Advice on posture during sitting, standing and walking is important; a firm mattress helps the patient to sleep in a good position. There is evidence that this routine prevents spinal and joint deformities from taking place or getting worse.

When the disease is active, the doctor may advise a short period of bed rest, especially if there is pain and swelling of the hip or knee. He will prescribe drugs to relieve pain and inflammation. While aspirin type medication may be all that is necessary, other drugs such as phenylbutazone and indomethacin are also very effective in controlling both acute and chronic symptoms. They should always be taken under medical supervision, mainly because of potential side-effects on the stomach and bone marrow.

Surgical operations are only occasionally needed to replace a damaged joint, such as the hip, with a metal and plastic joint. Rarely, an operation to straighten a badly bent spine may be needed, but it is not without risk. Most patients can live full and comfortable lives without needing these types of treatment.
Arthritis in children

Children are liable to be affected with most of the types of arthritis that affect adults, except osteoarthritis. Examples are arthritis due to infection that may produce a septic joint, which can be cured by antibiotic treatment, and arthritis may complicate virus infections such as German measles, mumps and glandular fever. In these cases the arthritis is temporary and does not leave behind any damage to the joints.

Juvenile chronic arthritis

There is, however, a group of conditions called juvenile chronic arthritis. From the name one can guess that this arthritis occurs in children (before their sixteenth birthday), and tends to last a long time. The causes are not known, though the factors discussed before also apply here.

Treatment of juvenile chronic arthritis:

After a physical examination, blood tests and X-rays, the patient is advised medication to relieve pain and inflammation. This may take the form of soluble aspirin or a similar preparation, and other drugs like indomethacin may also be used in a suitable children’s dose. Other treatment will depend on the individual case and any other complications. A few children may need an operation to correct joint deformity in the later stages. When the child is very ill, bed rest is necessary. The affected joints may also have to be supported in splints to prevent them becoming deformed. Appropriate physiotherapy to maintain joint movement and muscle strength is also important. Hydrotherapy in a warm pool may be very comforting to the sick child. These and other measures will usually be done in a hospital with suitable facilities.

Still’s disease

The majority of children (70 per cent) fall into this group. This disorder is named after Dr George Frederick Still, a physician from King’s College Hospital, London, who has described the arthritis in 1897. Girls are more
frequently affected than boys, commonly between the first and fifth birthdays. The usual symptoms are those of an arthritis affecting one or more joints and an early sign may be the child developing a limp or a reluctance to move its arm. The painful joints become warm, stiff and swollen. The child soon looks unwell and stops playing. In some cases there may be high fever, skin rash, enlarged glands, liver and spleen, with little joint pain. Inflammation of the covering of the heart (pericarditis) can develop and the child may be quite ill. The most frightening complication is inflammation of the eyes (iritis) which can lead to blindness. Because young children cannot or may not complain of defective eye sight, it may be necessary to have regular eye checks to detect and treat it as early as possible.

**Soft-Tissue Rheumatism**

This has come to be accepted as meaning pain and stiffness in the muscles, tendons, ligaments and other similar ‘soft tissues’ of the body.

So-called ‘fibrositis’ is probably the commonest condition affecting the soft tissues. There has been a good deal of controversy among doctors about this diagnosis and the label has fallen into disfavor, mainly because there is no proof of any inflammation when the tissue is examined under the microscope. It has therefore been replaced by the term ‘soft-tissue rheumatism’.

Very few people go through life without experiencing this form of rheumatism. It affects men and women, both young and old, and is the most common and mildest of the rheumatic diseases. It usually subsides spontaneously or with simple remedies and never causes crippling.

**Causes**

The causes are many and varied. The commonest is some strain or injury This may be related to bad posture or over-using a limb or other part of the body. Some people experience symptoms after a fall or unusual exertion
for example, carrying heavy shopping, lifting, home decorating or simply over-exerting while on holiday. Many injuries during sports may cause soft-tissue rheumatism. Psychological factors may also be important: anxiety and worry may actually produce symptoms or make them worse. Emotional upset can make people feel achey and depressed. These tensions may be no more than those we meet in everyday life.

Draughts, the cold and damp, contrary to popular belief, don't cause rheumatism, though they seem to make symptoms worse.

**Symptoms**

Most parts of the body can be affected and the usual symptoms are pain, stiffness and difficulty in using the painful part. The area, if pressed, may also be uncomfortable and tender. In what used to be called 'fibrositis', there is pain in the neck and shoulder region, which may also affect the chest wall. Pain is usually nagging and persistent and may be present in the morning. However, it wears off during the day, only to return towards the evening when the person is tired at the end of a day's work. Even everyday activities like driving or watching television may bring on the pain. Headaches can be part of the picture and may be mistaken for migraine, which is an entirely different disorder.

Often there are localized areas of tenderness or 'trigger spots'. Pressing over these spots may reveal painful nodules, previously called 'fibrositic nodules'. An important underlying cause for such symptoms is degenerative change (spondylosis) affecting the cervical (neck) or dorsal (back) spine. Some degree of pain on neck movement or tenderness along the spine is not uncommon.

An acute wry neck, in which the person wakes up in the morning with a very stiff painful neck, is a distressing condition. The unfortunate sufferer holds the head in a twisted position due to spasm of the neck muscles.
Although exposing oneself to a draught is given as the common cause, a more likely explanation in some 'injury', like sleeping with the neck in an awkward position, when the muscles are relaxed, producing irritation of the structures in the neck. Fortunately, the condition subsides within a week or so, though occasionally there may be twinges of pain for a longer time.

If the symptoms occur in the chest area, especially in the front, the individual may be worried about heart trouble. However, chest pains that occur as short sharp twinges are harmless and not due to heart disease. They are usually made worse by becoming anxious, and palpitations (being conscious of the heart beats) may then be present. If the chest muscles are tender, a virus infection may be the cause.

The shoulder itself may be affected by pain especially on moving the arm. It usually follows some sort of strain or injury, with the inflammation of one or more tendons and tenderness around the shoulder. Sometimes, the whole capsule (fibrous covering) of the shoulder joint is affected and this is called 'frozen shoulder'. The name shows how limited movement of the shoulder can be.

The lumbar region of the back may also be affected by soft-tissue rheumatism, which in common language is called 'lumbago. This type of backache may be acute or chronic and is thought to have similar features to the neck and shoulder symptoms described earlier. Here again there are trigger spots of tenderness and an important underlying cause may be lumbar spondylosis.

Bursitis, or inflammation of a bursa in the outer part of the shoulder, may be another cause of pain. This can also occur over the point of the elbow, where the bursa becomes swollen with fluid.
Inflammation of the sheaths of tendons is a good example of a condition due to over-use. The tendons to the thumb may be inflamed and produce pain in the outer side of the wrist. Other wrist or finger tendons may also be affected. A ‘trigger finger’, in which a snapping noise occurs when the digit is moved, can affect any finger. In middle-aged women, a frequent cause of burning pain or pins and needles in the fingers is something pressing on a nerve in the wrist. The symptoms commonly wake the person at night and shaking the hand helps; usually this is not a serious condition. Occasionally there are well known causes, such as rheumatoid arthritis; a lazy thyroid gland or simply being pregnant, which produce some swelling of the tissues with increased fluid.

Most of the types of rheumatism described in the arm also occur in the legs. Bursitis and tendonitis (inflammation of a tendon) may cause pains in the buttock and hip area. ‘Housemaid’s knee’ is a painful swelling of the burs in front of the kneecap and is brought about by a lot of kneeling. Pins and needles may be felt in the thigh because the ligament in the groin is pressing on a nerve. Strains or sprains of ligaments may happen around the knee or ankle. Tendinitis around the ankle, particularly of the Achilles tendon, is another cause of ankle pain. Pain under the heel, made worse by walking, is due to inflammation of a ligament where it is attached to the bone. Heel pain, of course, may also occur as part of an arthritis, such as ankylosing spondylitis. Other causes of pain in the feet and toes are usually due to, or at least made worse by, badly-fitting shoes. Sometimes pressure on the nerves may produce pins and needles or numbness in the feet.

**Treatment**

The doctor may request X-rays and blood tests, but these are not usually necessary to make a diagnosis or he may simply want to make sure that there is no other cause for the aches and pains. Many people don’t even go ‘to see a doctor, since simple home remedies, such as a hot water bottle, rubbing in a liniment such as oil of wintergreen or methyl salicylate, can give relief. The enthusiastic person may even buy a heat lamp to use whenever necessary.
If the symptoms don't get better soon, the family doctor is usually consulted, who may prescribe anti-inflammatory or pain-killing medication, either tablets or an ointment to be applied on the painful area. An explanation of the cause of the symptoms usually reassures the patient that nothing serious is wrong. Sometimes the doctor may find himself providing psychological support to the patient, but in only a few cases are anti-depressant tablets really needed. Avoiding the cause, such as over-use or whatever physical stress, prevents the condition from recurring. In foot troubles, attention to proper footwear, with padded insoles, is a sensible move. In some cases, a period of rest initially may be advisable.

If simple measures don't work, other treatment is necessary. Physiotherapy may be very effective. This can be in the form of heat, such as short-wave diathermy or ultrasonic treatment, cold in the form of an ice-pack, or can involve mobilization or manipulation, mechanical traction, frictions or massage, exercises on land or in a hydrotherapy pool. A combination of different treatments is usually used and the aim is to relieve pain and improve the function of the affected structure. The therapist will also advise the patient on suitable posture and exercises at home, depending on the individual case.

Rest splints, for the wrist for example, may also occasionally be used. A local anaesthetic and cortisone (steroid) can be dramatically successful. This may the repeated if necessary. Only rarely is surgery required, to relieve, for example, persistent pressure on a nerve or troublesome trigger finger.

**Drug Treatment and Surgery**

Treatment of arthritis and rheumatism should be the responsibility of the doctor and all patients should be under medical supervision. This is particularly important when treatment with drugs is concerned. The common drugs used in arthritis are discussed below There is reference mainly to rheumatoid arthritis, though the principles of treatment will be the same for other forms. Surgical operations are also dealt with.
Aims of treatment

To manage arthritis successfully the doctor will have a programme of treatment that needs to be carried out over a long period, since the types of arthritis we are talking about are also chronic (long-lasting). The patient must persevere with the advice given and indeed be 'patient', since success doesn't come overnight. The treatment will not cure the arthritis, like curing a chest infection with antibiotics, but it will make it better-keeping joint inflammation under control, preventing the joints from becoming deformed, and helping to cope with any disability.

This programme will include combined treatment with two or more of the following measures: drugs and surgery; and rest, physiotherapy, occupational therapy and other rehabilitation procedures. All of these may be used to some extent over a period of time, but we confine ourselves here to drugs and surgery. When dealing with drugs, remember that brand names (indicated by beginning with a capital letter in our text) may change from time to time as new drugs come on the market, and can vary from country to country.

Anti-inflammatory drugs

Self-diagnosis and treatment is dangerous! Some aches and pains are minor and soon, go away, but others are more serious and long-lasting. If some of the symptoms of arthritis seem to apply to you, do not immediately assume you have a serious problem, go to see your doctor and get his opinion first.

Since relieving pain forms an important part of treatment, virtually every patient will benefit from drugs that fight inflammation and thus reduce pain and swelling. These Drugs, however, will not affect the underlying disease.
The best example of an anti-inflammatory drug is aspirin. Because it is commonly used to relieve headaches and other minor pains, it is not unusual for people to remark that the doctor only prescribed aspirin! However, when taken in suitably large doses, it is a very effective drug in rheumatoid arthritis. Side-effects, like indigestion and stomach ulcers, can be troublesome, and soluble or coated tablets may be better for the individual patient. A recently-introduced liquid preparation containing aspirin and paracetamol seems even better tolerated. But a disadvantage of these drugs, to a greater or lesser extent, is that they may cause the patient to lose a small amount of blood in the gut, which in some cases produces an iron-deficiency anaemia. This type of anemia can be easily treated with iron tablets or injections.

There are other drugs which trials have shown to be as good as aspirin. One of these is indomethacin, commonly available as Indocid capsules or suppositories. It is useful in reducing the morning stiffness of rheumatoid arthritis if taken last thing at night but it can also be taken in divided doses during the day. Side-effects do occur in some patients and consist of headaches, dizziness and indigestion.

Within the past few years, more anti-inflammatory drugs have been introduced. These, like aspirin and indomethacin, can be used to treat rheumatoid and other forms of arthritis and rheumatism. Examples are naproxen (available as Naprosyn tablets and suppositories) and fenoprofen (Fenopron tablets). Different patients respond differently to these drugs and it may be necessary for the doctor to switch to another drug to obtain maximum benefit.

Corticosteroids

These are often called by their shortened name of ‘steroids’ and include drugs like cortisone. They are the most effective drugs in reducing the signs of inflammation in joints. Prednisone and prednisolone are the most frequent drugs prescribed, and they are taken by mouth. But the risk of serious
side-effects to those taking steroids in high doses for a long time have made these drugs much less popular than they were 10 or 15 years ago, and they are now used with caution.

Nevertheless, there are special situations where steroids are prescribed. If the dose of, say, prednisolone tablets, is kept as small as possible, the risk, of side-effects is low. In any case, patients should carry a ‘steroid card’ or other indication of such treatment so that, if they develop a serious illness or are in an accident, the attending doctor knows and will give more steroid as a temporary-measure. This must also be done before any operation, since steroid treatment tends to reduce the body’s own cortisone production, which therefore is not available in times of need. Patients should also remember not to stop the drug suddenly, since the arthritis may flare up badly. The dose must always be reduced gradually, unless the patient hasn’t been on steroids for long.

There is one situation where steroids are frequently used, without the above serious effects. Injections of steroids directly into a painful joint or into inflamed tendon sheaths provide temporary but welcome relief.

Long-acting drugs

Gold is the best example of this and has to be given by injection: a brand of this is Hyocrisin. This has been used for the treatment of rheumatoid arthritis for over 50 years, and more recently it has also been given to children with juvenile chronic arthritis. Doctors are still not sure how it works, though what is certain is that it accumulates slowly in the body and patients will not notice any benefit until 10 to 12 weeks after the first injection. The patient will continue to improve after this. Unlike the anti-inflammatory drugs, gold relieves inflammation slowly and gradually to switch off the disease. The doctor will prescribe a small test dose, followed by weekly injections for 20 weeks or so. If all goes well, the injections are given at longer intervals, say, once a month, for as long as they are tolerated and keep the patient free from active arthritis.
Gold works well in about two-thirds of patient and is usually given together with other treatment. Once the patient has begun to respond, the doctor may decide to reduce or even stop other medication. It will not reverse damage or deformity already present. There is controversy at present whether gold does, in fact, heal joint erosions, though actual proof is difficult to obtain.

There is another long-acting drug that have been introduced more recently in the treatment of rheumatoid arthritis. This is penicillamine (brand name : Distamine). Unlike gold, which is given by injection, this is given in tablet form. In other respects this is very similar to gold- it take several weeks to work, seem to control the underlying disease process, have much the same success rate and side-effects, except this is also able to cause indigestion. this, therefore need careful medical supervision and is not advisable in pregnant women, while penicillamine can be given to children and young people, azathioprine should not be used during the child bearing years because of the risk of genetic damage.

**Surgery**

Great strides have taken place in surgical techniques in the past decade or two and everyone has heard of the dramatic improvement that an artificial joint can make to the life of a disabled arthritic. But surgery means much more than this.

If a single joint is persistently troublesome and swollen, for example the knee or wrist, synovectomy (removal of the bulky, inflamed joint lining) may produce good relief for a year or two. Such an operation may also be usefully done on the finger tendons, where clearing the sheaths will improve finger movements.

Various operations have been devised to prevent or correct deformity, of the finger or repairing them. Sometimes, bits of bone may have to be removed to relieve pain, as in the wrist and toes. A bunion operation is an example of
how the bones are shaved and the joint reshaped. Occasionally, to make a useless joint stable, it may need to be fused together, as in the wrist or knee.

Plastic and metal joints may give new life to the arthritic sufferer. The greatest success so far has been with replacing hip joints and restoring their function in patients with rheumatoid arthritis, osteoarthritis, or ankylosing spondylitis. Other artificial joints are available for the knee, ankle, shoulders, elbows, wrists and fingers. Intensive research is going on to understand the working of these different human joints and thus make artificial implants safe and effective for the patient.

Implications of the Actions of NSAID's:

Despite the convincing evidence that, as a class, NSAID's suppress inflammation by acting at the level of the cyclooxygenase, these compounds have also been shown to inhibit a number of other enzymes, indomethacin, because of its wide use and availability, has been particularly well studied and is known to inhibit prostaglandin 15-dehydrogenase, phosphodiesterase, dopa decarboxylase, histidine decarboxylase, a platelet peroxidase, diglyceride lipase, and a protein kinase (R. J. Flower et al., 1974). However, with the possible exception of the kinase, the concentration required to inhibit these enzymes is 100 - to 1000 - fold greater than that necessary to inhibit the synthesis of prostaglandins.

Recent work shows that NSAID's are capable of interacting with two sites on the cyclooxygenase (J. L. Humes et al). Occupation of the secondary site does not necessarily inhibit catalytic activity. Although occupancy appears to be essential for cyclooxygenase inhibition. This supplementary site may be simply a lipophilic pocket in the enzyme that inhibits a high affinity for the corresponding nonpolar moiety of the inhibitor, a concept consistent with the structure of NSAID's (J. L. Humes et al.,) The high affinity of NSAID's for albumin and the remarkable correlation of this property with the efficacy of these compounds as anti-inflammatory drugs...
indicate that this lipophilic region is common to many proteins and enzymes (R. Gryglewski et al., 1974). Hence, the wide range of activities of high concentration of NSAIDs may simply be a reflection of an interaction with this commonly occurring lipophilic site and have little bearing on the catalytic component of action of NSAIDs.

Since NSAIDs almost fully prevent the formation of prostaglandins in vivo, as reflected by urinary metabolites (M. Hamberg et al., 1972), and only occasionally have deleterious effects, prostaglandins appear on the one hand to be involved primarily in pathological responses. On the other hand, prostaglandins can mimic hormone action by triggering a specific membrane receptor to increase intracellular cyclic AMP formation favouring a regulatory as well as pathological role (F. A. Kuchi et al., 1970). Indeed, the fraction of the prostaglandins involved in cellular regulation may be small compared to the total prostaglandins output. Those detected as urinary metabolites would be found primarily in tissues with unusually high bio-synthetic capacity such as the kidney (E. Anggard et al., 1972).

Furthermore, anti-inflammatory action depends on accumulation of a drug at the inflamed site as well as on its innate activity, and NSAID's concentrate in the stomach, kidneys, and inflamed joints (P. Graf et al., 1975). Since prostaglandins are known as cytoprotective agents in the stomach wall (A. Robert et al., 1974) and as mediators of renal blood flow, salt and water loss, and angiotensin release (A. R. Whorton et al., 1973), this accumulation explains the side effects of NSAIDs often observed in these particular organs. Thus, in most tissues where prostaglandins are essential modulators, because of pharmacokinetic considerations their synthesis may not normally be depressed sufficiently by NSAIDs to interfere with their regulatory role. In addition, some prostaglandins are antagonistic, for example, PGI₂ prevents platelet aggregation, whereas TXA₂ promotes it. In view of this relationship, depressing both compounds by inhibiting the cyclooxygenase (Fig. 5) would not be as consequential as decreasing only one. Therefore, although
prostaglandins may increase and be intimately involved in certain pathological states, they are also important under normal physiological conditions.

**Mode of action of anti-inflammatory agents:**

Corticosteroids inhibit the activity of phospholipase A and hence reduce the release of arachidonic acid and ultimately inhibit the formation of proinflammatory prostaglandins. Vane et al., 1971 made the seminal proposal in 1971 that in contrast to steroids, NSAIDs exerted their activity by inhibiting cyclooxygenase (COX), a dual function enzyme. Prostaglandins are formed by the oxidative cyclization of the central 5 carbons within 20 tuto polyunsaturated fatty acids. The key regulatory enzyme of this pathway is COX, also known as PGH synthase, which catalyses the conversion of C-20 acids with varying degrees of unsaturation to prostaglandins PGG$_2$ and PGH$_2$. The latter is subsequently transformed to a variety of eicosanoids such as PGE$_2$ and thrombaxane TXA$_2$. Apart from the activity to bring about cyclization, COX has also peroxidase activity which leads to the hydroxylation of cyclopentenes through endo-peroxidation. All NSAIDs in clinical use have been shown to inhibit COX, leading to a marked reduction in PG synthesis (Simon et al., 1996). The inhibition by aspirin is due to irreversible acetylation of the cyclooxygenase component of COX, leaving the peroxidase activity unaffected (vander et al., 1980). In contrast, NSAIDs like indomethacin or ibuprofen inhibit COX reversibly by competing with the substrate, arachidonic acid, for the active site of the enzyme (Vane et al., 1990). All the activities of NSAIDs such as prevention of pathological overproduction of pro-inflammatory prostaglandin and the physiological formation of prostanoids are explained well by the postulate of inhibition of prostaglandin synthesis. The unwelcome ulcerogenic and renal side effects of NSAIDs such as aspirin and ibuprofen have been related to the inhibition of production of prostacyclin, which has a cytoprotective effect on the gastric mucosa and regulation of kidney function. It thus appeared that the ulcerative effect of classical NSAIDs was an inevitable price to be paid for the desired anti-inflammatory activity,
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until the discovery that COX existed in two isoforms, COX-1 and COX-2. More recently, the presence of a new isoform COX-3 has been speculated upon (Willoughby et al., 2000).

FUTURE DIRECTION IN THE ANTI-INFLAMMATORY DRUG DEVELOPMENT

The main therapeutic indication of the anti-inflammatory drugs is in the treatment of rheumatic disorders. At present the major constraint in finding suitable treatment to rheumatoid arthritis (RA) is the lack of knowledge about its aetiology. Thus at least part of the future efforts to find out a suitable remedy to RA will depend on gaining new sight into its aetiology and predisposing factors like genetic susceptibility advances in the understanding of the immuneresponse in RA, immunogenetics, identification of microbial agents as the cause of certain types of disorders, data obtained from epidemiological studies of patients with RA. Meticulous documentation of responses obtained to therapeutic molalities will certainly help in formulating new therapies and mode of treatment. The observation that genetic susceptibility of RA is determined by certain genes within the major histo-compatability complex (MHC) has drawn the attention of researchers into this field and appreciable progress is being made in the area. However, the precise shape of the genetic link to disease progression is not clear, T-cell receptor is likely to be an important element in determining the susceptibility. This will be one of the areas for future investigations especially T-cell receptor gene polymorphism.

Brief summary of the current concept about the sequence of events leading to synovities and destruction of surrounding structures in rheumatoid arthritis would be helpful in identifying the area for future investigation to obtain anti-rheumatic remedies. It is hypothetized that an unidentified antigen localises in the joint synovium and is phagocytozed by type A synovial cells.
The antigen is not completely destroyed and diffuses into the joint space, where it may adhere to cartilage. Binding of the antigen processed by macrophage, to B lymphocytes induces their differentiation into plasma cell. Activated plasma cells produce antibodies against (including RA factors), the antigen. Activation of T-lymphocyte triggers lymphokines synthesis followed by blastogenesis (Snyderman et al., 1988). Local formation of immune complexes following the combination of antibody with antigen as well as combination of immune complexes with RA factors, or self-association of rheumatoid factors activates complement as well as kinin forming systems (Snyderman et al., 1988). The results will be production of inflammatory products such as C5a, arachidonic acid metabolites, kinins and fibrinopeptides, which diffuse into the synovium and synovial blood vessels. These products initiate the inflammatory process causing marked increase in the vascular permeability and attracting polymorphonuclear leukocytes and macrophages. These inflammatory cells ingest the abundant immune complexes in the fluid, release lysosomal enzymes and generate superoxide anions. This causes destruction of hyaluronate polymers in the joint fluid, as well as injury to the cartilage (Snyderman et al., 1988). Production of cytokines and growth factors like interleukines (IL), tumour necrosis factors (TNF), tumour growth factor-β (TGF-β) and platelet derived growth factor (PDGF) in the synovium, add further to the destruction through further accumulation and activation of macrophages, fibroblasts and lymphocytes (Snyderman et al., 1986).

The unique structure of the joint space is important, as enzymes present in synovial fluid or released and synthesized locally by the cells of the proliferative synovial lesions contribute to the pathological changes. The cartilage-degrading lysosomal enzymes-collagenase and elastase are primarily derived from inflammatory cells. Proteinases released by dying cells may aid in superficial cartilage destruction by uncrosslinking collagen fibrils. Macrophages produce prostaglandin (PGs), hydrolytic enzymes, collagenase,
plasminogen activator, IL-1, TNFα and TGFβ collagenase is produced in large quantities by synovial cell that has an unusual dendrite appearance. Collagenase synthesis by this cell is greatly enhanced by IL-1 (Snyderman et al., 1988). The migration of the synovium (pannus) on to the cartilage may be directed by the deposition of the antigen there (Snyderman et al., 1988).

Deminalisation is the final stage of the destructive process. It may result from the combined elements present initially in the inflammatory and later in the proliferative responses. Demineralisation of bone occurs before tissue is susceptible to collagenolytic enzymes. In RA synovitis, PGs stimulate calcium release from the bone matrix (Synderman et al., 1988, Goodwin et al., 1984). Other arachidonic acid metabolites are responsible for long-term leaching of mineral from bone matrix. Lymphocyte derived oseoclast-activating factor (OAF) may also participate in demineralisation of connective tissue activating peptides (CTAPs) and specific lymphokines such as lymphocyte-derived chemotactic factor for fibroblasts (LDCF-F), which attract and stimulate fibroblasts to produce collagen and may contribute to the fibrosis in the destroyed ankylosed joint (Snyderman et al., 1988).

None of the available anti-inflammatory and anti-rheumatic drugs provide satisfactory treatment in RA. Non-steroidal anti-inflammatory drugs (NSAIDs) provide symptomatic relief without altering the course of the disease. Corticosteroids often provide dramatic relief in some diseases but produce unacceptable toxic effects. Certain cytotoxic agents like methotrexate provide substantial relief but their administration is attendant with serious toxicity (Swingle et al., 1986). Anti-rheumatic drugs like gold preparation, penicillamine, and chloroquine also produce serious toxic effects (O’ Duffy et al., 1984).

In the light of the above situations, attempts are done at several centers throughout the world to obtain better anti-inflammatory and anti-rheumatic drugs.
All the above available NSAIDs inhibit the enzyme cyclooxygenase leading to PG synthesis inhibition which is considered to be their main mechanism for producing anti-inflammatory effect. NSAIDs administration, especially for long term in RA, produces serious gastric and renal toxic effects that have been attributed to PG synthesis inhibition (Ashershon et al., 1991). At present the research in the field of NSAIDs development is centred around the following approaches.

1. Random synthesis of newer chemical entities (NCE) and their screening.
2. Attempt to obtain specific inhibitors for suppressing one or more mediators of inflammation.
3. Development of prodrugs with the intention of providing drugs with greater toxicity to efficacy ratio.
4. Developing controlled release or targetted delivery systems (Naik et al., 1993).

Number of new chemical entities have been synthesized and screened for anti-inflammatory activity (Naik et al., 1993).

Based on the fact that leukotrienes (especially LTB4) and other products of arachidonic acid metabolism through lipoxygenase pathway are chemotactic and chemokinetic for polymorphonuclear leukocytes and LTB4, in addition to being chemotactic is capable of stimulating PMNs to produce inflammatory substances, including superoxide, hydrogen peroxide and hypochlorus acid, attempts were made to obtain drugs with comparatively better specificity for inhibiting lipoxygenase enzyme. The first such inhibitor to become available, benaxoprofen, was found to produce serious toxic effects hence was withdrawn shortly after its introduction. Thus usefulness of such drugs in the treatment of RA remains to be evaluated. However, this is an active area of research and there is a possibility of introduction of many such drugs in the future.
Attempts to develop drugs with greater gastric irritancy to anti inflammatory ratio lead to the introduction of drugs like etodalac (Kantor et al., 1987) in which existence of large difference between AIF dose and the dose causing gastric irritation has been observed in experimental animals. This has been explained as a possible difference in the enzyme activity at different sites (Kantor et al., 1987). However no conclusive evidences are available on the difference in cyclooxygenase activity at different sites if such difference exists. It would be a potential target for the drug designing with activity at specific site.

Sulindac and Nabumetone are the prodrugs which require metabolism in the body to get converted to active metabolites. Sulindac is reported to possess “renal sparing” affect. Incidence of gastropathy and nephropathy are reported to be less with Nabumetone (Mangan et al., 1987). However, no comparative studies are available to establish the therapeutic efficacy of these prodrugs over established NSATDs.

Attempts were also made to exploit differences in pharmaco-kinetic properties to develop drugs with optimum duration of activity which would require only once a daily drug administration that would help in better patient compliance in comparison to short acting NSAIDs which may require frequent dosing and maintenance of optimum plasma level with long acting drugs like phenylbutazone is difficult (Kaintor et al., 1987).

Reduction of phospholipase A2 catalysed release of arachidonic acid from membrane phospholipid is reported to be one of the mechanism of anti-inflammatory activity of glucocorticoids. Since arachidonic acid is the substrate for synthesis of eicosanoids of both cyclooxygenase and lipoxygenase pathway, decrease in its availability shall lead to decrease in the availability of all eicosanoids which would have profound effect on inflammatory reactions. Though glucocorticoids produce this effect indirectly through stimulating the synthesis of a natural inhibitor (macrocortin or lipomodulin), attempts were
made to prepare compounds with direct inhibitory effect on phospholipase A2. This resulted in the synthesis of compounds like fluroketones, acenapthazener, benzylamines, dioxa phosphozener etc. all of which have been reported to produce good anti-inflammatory activity (Naik et al., 1993). However, data on their clinical evaluation is lacking. This will be one of the areas for future active exploration.

Bone marrow-derived leukocytes, particularly neutrophils are responsible for much of the damage observed during inflammatory reaction (Uurch et al., 1991). T-lymphocyte play active role in the maintenance of chronic inflammatory diseases (Taurgo et al., 1985). Drugs modulating activities of these cells could be potential disease modifying agents. A series of N. (Fluorenyl-os-methoxy carbonyl) amino acids, have been screened by Burch et al. These compounds are reported to act not by inhibiting lipid metabolic enzymes, they are not steroids and they donot increase the circulating levels of endogenous glucocorticoids. Instead they block recruitment of neutrophils into inflammatory sites and inhibit T-cell activation in in vitro. It remains to be seen whether they will turn out to be useful as anti-rheumatic drugs after clinical evaluation or not.

Drugs which are effective in arresting the progression of RA are termed disease modifying drugs or disease modifying anti-rheumatic drugs (DMARDs). Currently available drugs that appear to be DMARDs include the aminouinoline, antimalarials, gold preparations, penicillamine, azathioprine and glycophosphamide (Swingle et al., 1986). They are presumed to act by interfering with activities of the cells involved in the immunological responses. The presumed mechanism of action involved in the anti-rheumatic activity of gold are inhibition of phagocytic activity in macrophages and polymorphonuclear leukocytes, inactivation of complement components in serum and synovial fluid and inhibition of transformation of lymphocyte (Swingle et al., 1986). penicillamine can affect both cellular and humoral immunity. Azathioprine modulates the activity of helper-T cells and may reduce the levels
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of circulating monocytes and neutrophils. Alkylating agents affect cells in the "s" phase of rapid proliferation and have profound effect on B-cells and humoral immune mechanism (Swingle et al., 1986). Future efforts in the groups would be to attempt to design drugs with lesser toxicity and better clinical efficacy through manipulation of their structure. Targetted drug administration device could be helpful in reducing the toxicity of drugs like gold and Alkylating agents.

Attempts have been made to treat RA through administration of immunomodulatory drugs like levamisole and cyclosporin A. The rationale for immunomodulation therapy in RA is based on the following premises that (Swingle et al., 1986). RA is an immunodeficiency disease in the sense that suppressor T-lymphocytes are not functioning normally, thus allowing unchecked autoimmune response to manifest itself and (2) the underlying cause of RA is a persistent infection. Levamisole an immunopotentiating agent, was found to be effective clinically but its therapeutic utility is restricted by unacceptable toxic effects (Swingle et al., 1986). Cylosporin A is another immunomodulatory agent which is relatively specific in its action in inactivating T-helper inducer lymphocytes by blocking IL-2 production. It has also been found to inhibit gamma interferon and IL-3 productions. It has the tendency to produce nephrotoxicity and neurotoxicity. Undoubtedly this will be one of the areas which is going to attract greatest attention in future since lymphokines play important role in activating T-lymphocytes and continuous proliferation of T-lymphocytes (Reasor et al., 1986). Gamma interferon is another product secreted by lymphocytes which has immunoregulatory activity in addition to being antiviral(Snyderman et al., 1988). Some of the recent development related to this field are the development of antilymphocytic immunotoxin (PGN), anti-interleukin-2 IL-2 receptor antibody (PGH) and interleukin-2 toxin (Ashershon et al., 1991,Coperton et al., 1989, Banrjee et al., 1988). But these are still experimental stage. Anti CD antibodies and anti-lymocyte globulin have also been tried with same success. Attempts have been made to treat RA patients with apheresis and total lymphoid irradiation.
Next line of therapeutic agents are likely to be directed towards treating the disease by preventing the deposition of immune-complexes, suppressing the immune response and modulating the immune mechanism.

In another related development attempts are being made to influence the synthesis of inflammatory eicosanoids through dietary modification. Preclinical studies have shown that dietary eicosanoids prolong the survival of NZB, NZ10-F1, m♂c*(Wilkens et al., 1987), and decrease susceptibility to collagen induced arthritis (Wilkens et al., 1987) The effects of dietary supplemation with marine fish oil containing isosapentaenoic acid (EPA) on the clinical manifestation of RA have been evaluated (Asharshon et al., 1991). The results were modest however there has been impressive down regulation of pro-inflammatory mediators such as leukotriene-84, interleukin-J9), and TNF. Long term studies are needed to assess the long lasting benefit accruing from such efforts. However, this will certainly receive the attention of future investigators.

Therafectin (amiprilese)-is a non-metabolizable hexose sugar with both anti-inflammatory and immunomodulatory effects with a low toxicity profile. After positive response in animal screening*, open and randomized clinical trials are reported to be in progress. A prospective, multicentric, randomized 12 week study against placebo, comprising a total of 221 patients, showed the drug to possess significant anti-inflammatory activity and a favourable safety profile when used as a sole anti-rheumatic therapy in patients with active RA3, and the quest for obtaining new chemical entities for specific alteration of immunological and anti-inflammatory pathways resulted in isolation of retinoids like orgotain, isotretinion, etretinate, manolides etc from natural sources- thus pointing towards possibility of obtaining new anti-inflammatory drugs from natural sources mainly medicinal plants.
Another area which has not received sufficient attention is the possibility of increasing the activity of endogenous anti-inflammatory agents. For example, tissue destructive potential of the lysosomal proteases is regulated by protease inhibitors such as, macroglobulin and, antiprotease. These antiproteases are present in serum and in synovial fluids and inhibit proteases by binding to them and covering their active sites.
Review of Literature of Three Plants

Fenugreek - (METIHI)

Common Name(s): Fenugreek, methi

Scientific classification

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Hindi          | Methi            |
Gujarati       | Methi            |
English        | Methi            |

History

The herb has been used for centuries as a cooking spice in Europe and remains a popular ingredient in pickles, curry powders, and spice mixtures in India and Asia. In folk medicine, fenugreek has been used in the treatment of boils, cellulitis, and tuberculosis. It was a key ingredient in a 19th century patent medicine for dysmenorrheal and postmenopausal symptoms. It also has been recommended for the promotion of lactation. Fenugreek seeds have been used as an oral insulin substitute, and seed extracts have been reported to lower blood glucose levels. The maple aroma and flavor of fenugreek has led to its use in imitation maple syrup. Madar Z. et al., 2002.
Overview

Fenugreek (Trigonella foenum-graecum) is used both as an herb (the leaves) and as a spice (the seed). It is cultivated worldwide as a semi-arid crop. The name fenugreek or foenum-graecum is from Latin for “Greek hay”.

The yellow, rhombic fenugreek seed is frequently used in the preparation of pickles, curry powders and pastes. The young leaves and sprouts of fenugreek are eaten as greens and the fresh or dried leaves are used to flavor other dishes. The dried leaves (called kasuri methi in Urdu) have a bitter taste and a strong characteristic smell. It is also one of the ingredients in the making of khakhra, a type of bread.

Fenugreek is mainly used as digestive aid. It is ideal for treating sinus, lung congestion, reduces inflammation and fights infection.

Dried fenugreek seed

Supplements of fenugreek seeds were shown to lower serum cholesterol, triglyceride, and low-density lipoprotein in human patients and experimental models of hypercholesterolemia and hypertriglyceridemia (Basch E. et al., 2003). Several human intervention trials demonstrated that the antidiabetic effects of fenugreek seeds ameliorate most metabolic symptoms associated with type-1 and type-2 diabetes in both humans and relevant animal models (Basch E. et al., 2003; Srinivasan, 2005). Fen is currently available commercially in encapsulated forms and is being prescribed as dietary supplements for the control of hypercholesterolemia and diabetes by practitioners of complementary and alternative medicine.

In recent research, fenugreek seeds were shown to protect against experimental cancers of the breast (Amin et al., 2005) and colon (Raju et al., 2006). The hepatoprotective properties of fenugreek seeds have also been reported in experimental models (Raju and Bird, 2006; Kaviarasan et al., 2004; Thirunavukarsasu et al., 2003).
Fig. 10 Fenugreek (plants with ripening fruits). Note the long pods!

Fig. 11 Dried fenugreek seeds
Chapter - 2

Review of Literature

Plant Description

A member of the bean family, fenugreek grows as an erect annual with long, slender stems reaching 30 to 60 cm in height. The plant bears grey-green, tripartite, toothed leaves. White or pale yellow flowers appear in summer and develop into long, slender, sword-shaped seed pods with a curved, beak-like tip. Each pod contains about 10 to 20 small, yellowish-brown, angular seeds. These are dried to form the commercial spice. The plant thrives in full sun on rich, well-drained soils and has a spicy odor that remains on the hands after contact.

Chemical Constituents

The presence of several of the alkaloids such as methylamine, dimethylamme and trimethylamine as well as choline, neurin and betain was noted (Nadkarni, 1927). The seed contains the alkaloid trigonelline (Kirtikar and Basu, 1980). Trigonelline is hygroscopic and easily soluble in water but is insoluble in ether, chloroform and benzol (Dymock et al.). Air dried seeds contain 0.38% trigonelline, and 3mg% nicotinic acid (Chopra et al., 1958). Fenugreek contains about 28% of mucilage. It yields by hydrolysis the sugar manose and galactose.

The drug contains about 22% of proteins, 6% of fixed oil, a saponin and two alkaloids, trigonelline and choline (Wallis, 1985). Diosgenin is contained in the oily embryo. Indian sample were found to contain 0.7% to 0.8% steroidal sapogenin with diosgenin to yomogenin ratio of 3:2. Young seeds contain small amount of carbohydrates consisting mostly of sucrose, glucose, fructose, myoinositol, galactinol, stachyose and traces of galactose and raffinose. Ghoshal et al., (1970) reported the presence of three C27 Steroidal sapogenins viz. tigogenin, yuccagenin and digitogenin alongwith those already reported. Diwidar et al., (1973) reported the presence of neotigogenin in Fenugreek plants for the first time. Seshadri (1973) reported the presence of vitexin and its isomer isovitexin in the seeds of Trigonella Foenum-graecum.

Fenugreek Uses and Pharmacology

The use of fenugreek has been limited by its bitter taste and pungent odor. Isolation of the biologically active components or production of a debittered extract, which would allow greater use of the plant, have been investigated. 1

Cholesterol-lowering effects

Fecal bile acid and cholesterol excretion are increased by fenugreek administration. Another hypothesis attributes the cholesterol-lowering activities to the fiber-rich gum portion of the seed that reduces the rate of hepatic synthesis of cholesterol. It is likely that both mechanisms contribute to the overall effect. (Madar Z, et al., 2002).

The defatted fraction of fenugreek seeds which contains about 54% fiber and about 5% steroidal saponins, lowered plasma cholesterol, blood glucose, and plasma glucagon levels from pretreatment values in both groups of dogs and rats. (Valette G. et al., 1984, Singhal PC. et al., 1982, Yadav UC. et al. 2004). Administration of the fiber-rich fraction of fenugreek to diabetic rats lowered total cholesterol, triglycerides, and low density lipoprotein (LDL). (Hannan JM. et al., 2003). The level of high density lipoprotein (HDL) was increased.

Glucose-lowering effects

The galactomannan-rich soluble fiber fraction of fenugreek may be responsible for the antidiabetic activity of the seeds. (Madar Z. et al., 2002). Insulinotropic and antidiabetic properties also have been associated with the amino acid 4-hydroxyisoleucine that occurs in fenugreek at a concentration
of about 0.55%. In vitro studies have indicated that this amino acid causes
direct pancreatic á-cell stimulation. Delayed gastric emptying and inhibition
of glucose transport also have been postulated as possible mechanisms. (Gupta
A. et al., 2001).

The defatted fraction of the seeds lowered blood glucose levels, plasma
glucagons, and somatostatin levels; carbohydrate-induced hyperglycemia also
was reduced in dogs. (Ribes G. et al., 1984). Glycemic control was
improved in a small study of patients with mild type-2 diabetes mellitus. 16 A
reduction in glycosylated hemoglobin (HbA 1c) levels and increased insulin
sensitivity were observed in fenugreek recipients.

Anti-inflammatory effects

Rats treated with a single dose of fenugreek extract 100 or 200 mg/kg
showed a dose-related response when treated with carrageenin. Inhibition of
inflammatory swelling was 45% and 62% in the lower and higher dose groups,
respectively, compared with 100% in untreated animals. (Sur P. et al., 2001).

Antioxidant effects

High levels of polyphenolic flavonoids (more than 100 mg per 100 g)
have been isolated from fenugreek seeds. These have been associated with
dose-dependent protection of erythrocytes from antioxidant damage in an in
vitro study. (Kaviarasan S. et al., 2004).

Other uses

Diosgenin, a precursor used in commercial steroid synthesis, is
extracted from the seeds. Because the seeds contain up to 50% of
mucilaginous fiber, they have been used in the preparation of topical
poultices and emollients; internally this ability to swell in volume has been
utilized to relieve constipation and diarrhea. Reduction in cataract incidence
has been demonstrated in diabetic rats receiving an extract of fenugreek

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seeds and leaves. (Vats V. et al., 2004). Oral administration of fenugreek seed fractions resulted in dose-dependent gastric protection against the effects of ethanol (a necrotizing agent). (Pandian RS. et al., 2002).

**Dosage**

Studies in patients with type-2 diabetes mellitus and hypercholesterolemia have used 5 g/day of seeds or 1 g/day of a hydroalcoholic extract of fenugreek. (Gupta A. et al., 2001).

**Pregnancy/Lactation**

Fenugreek has documented uterine stimulant effects and has been used in traditional medicine to induce childbirth and hasten delivery by promoting uterine contractions. Avoid use in pregnancy.

**Adverse Reactions**

When ingested in culinary quantities, fenugreek usually is devoid of adverse reactions. However, a case of hypersensitivity to curry powder has been linked to ingestion of the spice. (Ohnuma N. et al., 1998).

**Toxicology**

The acute toxicity from a large dose of fenugreek has not been characterized, but may result in hypoglycemia. It is probable that toxicity is low; the LD 50 of fenugreek extract was more than 1 g/kg when administered intraperitoneally to rats. (Sur P. et al., 2001).
Turmeric (HALDI)

Other Names: Curcuma, Curcuma species, Indian Saffron

Scientific classification

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Hindi       Haldi
Gujarati    Halad
English     Turmeric

History

Turmeric is native to Indonesia and southern India, where it has been harvested for more than 5000 years. It has served an important role in many traditional cultures throughout the East, including being a revered member of the Ayurvedic pharmacopeia. While Arab traders introduced it into Europe in the 13th century, it has only recently become popular in Western cultures. Much of its recent popularity is owed to the recent research that has highlighted its therapeutic properties. The leading commercial producers of turmeric include India, Indonesia, China, the Philippines, Taiwan, Haiti and Jamaica.
Overview

Turmeric is the primary anti-inflammatory plant of ayurvedic medicine (Indian traditional medicine). Over the last several years, there has been increasing interest in turmeric and its medicinal properties. This is partially evidenced by the large numbers of scientific studies published on this topic. Turmeric (Curcuma longa), a flowering plant in the ginger family, is widely used as a food coloring and is one of the principal ingredients in curry powder. Turmeric has long been used in both Ayurvedic and Chinese medicine as an anti-inflammatory, to treat digestive disorders and liver problems, and for the treatment of skin diseases and wound healing. The active ingredient in turmeric is curcumin, which has been the subject of numerous animal studies—but as of yet, very few studies on people demonstrating various medicinal properties. The curcumin in turmeric reduces inflammation by lowering histamine levels and increasing production of natural cortisone by the adrenal glands, Arora R. B. et al., 1971. Turmeric is also an antioxidant with a similar power to that of Vitamin C and E. Antioxidants provide cell protection by ‘mopping up’ unstable oxygen molecules called free radicals that can otherwise cause cell damage which is associated with ageing and many diseases of older age. Curcumin has been shown, for example, to stimulate the production of bile and to facilitate the emptying of the gallbladder. It has also demonstrated in animals a protective effect on the liver, anti-tumor action, and ability to reduce inflammation and fight certain infections. Arora R. B. et al., 1971.

Plant Description

A relative of ginger, Turmeric is a yellow-flowered perennial plant found in India and throughout Asia it grows 3 to 5 feet high in the tropical regions of Southern Asia, with trumpet-shaped. Turmeric is fragrant and has a bitter, somewhat sharp taste.
Parts Used

The aboveground and underground roots, or rhizomes, are used in medicinal and food preparations. These are generally boiled and then dried, turning into the familiar yellow powder.

Chemical Constituents

The active substance of turmeric is the polyphenol curcumin, also known as C.I. 75300, or Natural Yellow 3. Systematic chemical name is (1E,6E) 1,7-bis (4-hydroxy-3-methoxyphenyl) 1,6 heptadiene-3, 5-dione. It can exist at least in two tautomeric forms, keto and enol. The keto form is preferred in solid phase and the enol form in solution.
Fig. 13 Chemical Structures of naturally occurring curcuminoids

Medicinal Uses and Indications

While turmeric has a long history of use by herbalists, most studies to date have been conducted in the laboratory or in animals and it is not clear that these results apply to people. Nevertheless, research suggests that turmeric may be helpful for the following conditions.

Digestive Disorders

(stomach upset, gas, abdominal cramps): The German Commission E (an authoritative body that determined which herbs could be safely prescribed in that country and for which purpose[s]) approved turmeric for a variety of digestive disorders. Curcumin, for example, one of the active ingredients in turmeric, induces the flow of bile, which helps break down fats. In an animal study, extracts of turmeric root reduced secretion of acid from the stomach.
and protected against injuries such as inflammation along the stomach (gastritis) or intestinal walls and ulcers from certain medications, stress, or alcohol. Further studies are needed to know to what extent these protective effects apply to people as well.

**Osteoarthritis**

Because of its ability to reduce inflammation, turmeric may help relieve the symptoms of osteoarthritis. A study of people using an Ayurvedic formula of herbs and minerals containing turmeric as well as Withania somnifera (winter cherry), Boswellia serrata (Boswellia), and zinc significantly reduced pain and disability. While encouraging for the value of this Ayurvedic combination therapy to help with osteoarthritis, it is difficult to know how much of this success is from turmeric alone, one of the other individual herbs, or the combination of herbs working in tandem.

**Atherosclerosis**

Early studies suggest that turmeric may prove helpful in preventing the build up of atherosclerosis (blockage of arteries that can eventually cause a heart attack or stroke) in one of two ways. First, in animal studies an extract of turmeric lowered cholesterol levels and inhibited the oxidation of LDL ("bad") cholesterol. Oxidized LDL deposits in the walls of blood vessels and contributes to the formation of atherosclerotic plaque. Turmeric may also prevent platelet build up along the walls of an injured blood vessel. Platelets collecting at the site of a damaged blood vessel cause blood clots to form and blockage of the artery as well. Studies of the use of turmeric to prevent or treat heart disease in people would be interesting in terms of determining if these mechanisms discovered in animals apply to people at risk for this condition. Ramirez-Tortosa MC. et al., 1999.
Chapter - 2
Review of Literature

Cancer

There has been a substantial amount of research on turmeric's anti-cancer potential. Evidence from laboratory and animal studies suggests that curcumin has potential in the treatment of various forms of cancer, including prostate, breast, skin, and colon. Human studies will be necessary before it is known to what extent these results may apply to people. Doral T. et al., 2001., Kawamori T. et al., 1999.

Improved Liver Function

In a recent rat study that was conducted to evaluate the effects of turmeric on the liver's ability to detoxify xenobiotic (toxic) chemicals, levels of two very important liver detoxification enzymes (UDP glucuronyl transferase and glutathione-S-transferase) were significantly elevated in rats fed turmeric as compared to controls. The researchers commented, "The results suggest that turmeric may increase detoxification systems in addition to its antioxidant properties... Turmeric used widely as a spice would probably mitigate the effects of several dietary carcinogens." Curcumin inhibits free radical damage of fats (such as those found in cell membranes and cholesterol), prevents the formation of the inflammatory chemical cyclooxygenase-2 (COX-2), and induces the formation of a primary liver detoxification enzyme, glutathione S-transferase (GST) enzymes. When the rats were given curcumin for 14 days, their livers' production of GST increased by 16%, and a marker of free radical damage called malondialdehyde decreased by 36% when compared with controls. Luper S. A. et al., 1999.

Bacterial Infection

Turmeric's volatile oil functions as an external antibiotic, preventing bacterial infection in wounds.
Wounds

In animal studies, turmeric applied to wounds hastens the healing process.

Cosmetics

Turmeric is currently used in the formulation of some sunscreens. Turmeric paste is used by Indian women to keep them free of superfluous hair. Turmeric paste is applied to bride and groom before marriage in India. The turmeric is said to give glow to skin and also keeps some harmful bacteria away from the body.

Relief for Rheumatoid Arthritis

Clinical studies have substantiated that curcumin also exerts very powerful antioxidant effects. As an antioxidant, curcumin is able to neutralize free radicals, chemicals that can travel through the body and cause great amounts of damage to healthy cells and cell membranes. This is important in many diseases, such as arthritis, where free radicals are responsible for the painful joint inflammation and eventual damage to the joints. Turmeric's combination of antioxidant and anti-inflammatory effects explains why many people with joint disease find relief when they use the spice regularly. In a recent study of patients with rheumatoid arthritis, curcumin was compared to phenylbutazone and produced comparable improvements in shortened duration of morning stiffness, lengthened walking time, and reduced joint swelling.

A Potent, Yet Safe Anti-Inflammatory

The volatile oil fraction of turmeric has been demonstrated significant anti-inflammatory activity in a variety of experimental models. Even more potent than its volatile oil is the yellow or orange pigment of turmeric, which is called curcumin. Curcumin is thought to be the primary pharmacological agent in turmeric. In numerous studies, curcumin's anti-inflammatory effects have
been shown to be comparable to the potent drugs hydrocortisone and phenylbutazone as well as over-the-counter anti-inflammatory agents such as Motrin. Unlike the drugs, which are associated with significant toxic effects (ulcer formation, decreased white blood cell count, intestinal bleeding), curcumin produces no toxicity.

Available Forms

Turmeric is commercially available in the following forms:

- Capsules containing powder
- Fluid extract
- Tincture

Bromelain enhances the absorption and anti-inflammatory effects of curcumin, the best studied active ingredient of turmeric; therefore, bromelain is often formulated with turmeric products.

The following are doses recommended for adults:

- Cut root: 1,500 to 3,000 mg per day
- Dried, powdered root: 1,000 to 3,000 mg per day
- Standardized powder (curcumin): 400 to 600 mg, 3 times per day
- Fluid extract (1:1) 30 to 90 drops a day
- Tincture (1:2): 15 to 30 drops, 4 times per day

The appropriate dose of turmeric for this child would be 1/3 of the adult dosage.

Precautions

The use of herbs is a time-honored approach to strengthening the body and treating disease. Herbs, however, contain active substances that can trigger side effects and interact with other herbs, supplements, or
medications. Turmeric and curcumin are considered safe when taken at the recommended doses. However, extended or excessive use of curcumin may produce stomach upset and, in extreme cases, ulcers. (Note: normal therapeutic doses of turmeric protect from ulcers. Turmeric should not be taken by those who have been diagnosed with gallstones or obstruction of the bile passages without explicit direction from a qualified practitioner. While pregnant women needn't avoid foods containing turmeric, its use as a medicinal herb is not recommended during pregnancy because the effects are not fully known.

Turmeric has shown protection in animals from the development of ulcers due to NSAIDs. NSAIDs include indomethacin, ibuprofen, and many other drugs that are often prescribed for pain and inflammation, such as that of arthritis.

Turmeric, powder 2.00 tsp 16.04 calories

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**Nutritional Profile**

Turmeric is an excellent source of both iron and manganese. It is also a good source of vitamin B6, dietary fiber and potassium.

**Safety**

Turmeric is not a commonly allergenic food and is not known to contain measurable amounts of goitrogens, oxalates, or purines.
Mechanism of antiinflammatory actions of curcumin and boswellic acids.

Curcumin from Curcuma longa inhibited the 5-lipoxygenase activity in rat peritoneal neutrophils as well as the 12-lipoxygenase and the cyclooxygenase activities in human platelets. In a cell free peroxidation system curcumin exerted strong antioxidative activity. Thus, its effects on the dioxygenases are probably due to its reducing capacity. Boswellic acids were isolated from the gum resin of Boswellia serrata and identified as the active principles. Boswellic acids inhibited the leukotriene synthesis via 5-lipoxygenase, but did not affect the 12-lipoxygenase and the cyclooxygenase activities. Additionally, boswellic acids did not impair the peroxidation of arachidonic acid by iron and ascorbate. The data suggest that boswellic acids are specific, non-redox inhibitors of leukotriene synthesis either interacting directly with 5-lipoxygenase or blocking its translocation. (Ammon HP et al., 2006) Deshpande UR, et al., 1998., Gururaj A. et al., 2002., Hieaka H. et al., 2002. Kang BY, et al., 1999.
Boswellia - (SALAI GUGGAL)

Common name: Frankincense

Scientific classification

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Species

Boswellia frereana
Boswellia papyrifera
Boswellia sacra
Boswellia serrata

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<td>Gujarati</td>
<td>Guggal</td>
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Description:

Boswellia serrata is a moderate to large branching tree found in India, Northern Africa, and the Middle East. Strips of bark are peeled away, yielding a gummy oleo-resin which contains oils, terpenoids, and gum. Up to 16
percent of the resin is essential oil, the majority being alpha thujene and
p-cymene. Four pentacyclic triterpene acids are also present, with \( \beta \)-Boswellic
acid being the major constituent.

Extracts of this gummy exudate have been traditionally used in the
Ayurvedic system of medicine as an anti-arthritic. These gum resins are also
known as guggals. S. Nityanand et al., showed the guggal of Commiphora
mukul to be an effective hypolipidemic agent, but it does not have the anti-
inflammatory action of the gum resin of Boswellia serrata. B serrata is a
moderate or large branching tree with a bole 3.5 to 4.5m in height and 1.0 to
1.5 m in girth, generally found in dry hilly areas “of Aravalli ranges in Rajasthan,
M.P., Gujarat, Bihar, Assam, Orissa, as well as in central peninsular region of
A.P., Assam etc. The gum is tapped from the incisions made on the trunk of
the tree, which is then stored in specially made bamboo baskets and
converted to different grades of material according to flavour, colour, shape &
size. The fresh gum obtained from tree is hot dry with a pleasant flavour and
slightly bitter in taste.

**Medicinal Uses:**

The gum is credited with astringent, stimulant, expectorant, diuretic,
diaphoretic, antipyretic, stomachic emmenagogue, ecbolic and antiseptic
properties. It is reported to be useful in ulcers, tumours, goitre, cystic breast,
diarrhoea, dysentery, piles, asthma, bronchitis, chronic laryngitis, jaundice,
syphilitic and skin diseases It is used in the preparation of an ointment for
sores and is used with butter in syphilis, in convulsions, orchiopathy, cough,
stomatitis and arthritis (The Wealth of Asia, 1996, pandit et al., 1988, Orient
1993, Dhanvantari et al.,). It is also used in various Unani and Ayurvedic
preparations. It act both as internal and external stimulant. It is expectorant,
diuretic and stomachic. It is also reported to be used in fever, dysentery, skin
and blood diseases, convulsions, mouth sores and diabetes, uterine and
menstrual diseases, gonorrhoea, rheumatism etc.
Pharmacological Activity:

The gum-resin is reported to possess sedative and marked analgesic activity. The defatted extract of the gum exudate (oleo-gum-resin) was found to possess marked anti-inflammatory and anti-arthritis activity against adjuvant arthritis in experimental animals and was free from toxicity or any other side effects. It was also shown to possess marked cholesterol and triglyceride lowering activity. Clinical trials on rheumatic patients have shown promising results. Boswellic acids isolated from the gum resin inhibit, in a concentration dependent manner, 5-lipoxygenase product formation with an IC50 of 1.5 micromole. Chronic toxicity studies in healthy monkeys revealed that the drug was devoid of bio-chemical, hematological and other toxicities (Pachnanda et al., 1981, Safayhi et al., 1992, Gupta et al., 1987).

In a detailed investigation, Singh et al have conclusively established that defatted alcoholic extract of the gum resin (95%) has marked anti-inflammatory activity in carrageenan induced oedema in rats and mice and dextran oedema in rats. It was also effective in formaldehyde induced arthritis in rats. Detailed pharmacological studies conducted at RRL Jammu have shown that defatted alcoholic extract of Salai Guggal is Active against rheumatoid arthritis and related ailments like osteoarthritis, juvenile rheumatoid arthritis, soft tissue fibrositis and spondilitis without any side effects. Boswellic Acid (B.A.) was found equally effective in established adjuvant arthritis indicating its possible usefulness as an anti-arthritis agent. This effect was more marked on arthritis in dogs. B. A. inhibited the arthritis increased value of total leucocytes counts, serum transaminase levels, ESR in these test models.

Mechanism of Action:

Animal studies performed in India showed ingestion of a defatted alcoholic extract of Boswellia decreased polymorphonuclear leukocyte infiltration and migration, decreased primary antibody synthesis, (Sharma
et al., 1988, 1989) and caused almost total inhibition of the classical complement pathway. (H. Wagner et al., 1989) In vitro study of the effects of \( \beta \)-Boswellic acid on the complement system, the extract demonstrated a marked inhibitory effect on both the classical and alternate complement systems. (Knaus et al., 1996) An investigation of Boswellia's analgesic and psychopharmacologic effects noted that it "was found to exhibit marked sedative and analgesic effects" in these animals (Menon et al., 1971).

In vitro testing revealed Boswellia specifically, and in a dose-dependent manner, blocks the synthesis of pro-inflammatory 5-lipoxygenase products, including 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B4 (LTB4), (Ammon et al., 1991) which cause bronchoconstriction, chemotaxis, and increased vascular permeability. (Robertson et al., 1987). Other anti-inflammatory plant constituents, such as quercetin, also block this enzyme, but they do so in a more general fashion, as an antioxidant; whereas, Boswellia seems to be a specific inhibitor of 5-lipoxygenase. Safayhi et al., 1992, Ammon et al., 1991. Boswellia has also been observed to inhibit human leukocyte elastase (HLE), which may be involved in the pathogenesis of emphysema. HLE also stimulates mucus secretion and thus may play a role in cystic fibrosis, chronic bronchitis, and acute respiratory distress syndrome. (Rall et al., 1996, Safayhi et al., 1997).

It is known that, non-steroidal anti-inflammatory drugs can cause a disruption of glycosaminoglycan synthesis which can accelerate the articular damage in arthritic conditions (Lee et al., 1969, Palmowski et al., 1979, Dekel et al., 1980, Brandt et al., 1984). A recent in vivo study examined Boswellia extract and ketoprofen for their effects on glycosaminoglycan metabolism. Boswellia significantly reduced the degradation of glycosaminoglycans compared to controls, whereas ketoprofen caused a reduction in total tissue glycosaminoglycan content (Reddy et al., 1989).
Apoptosis of leukemia cells is increased by acetyl-11-keto-beta-boswellic acid (AKBA) but not by amyrin, a structural analog without effect on 5-lipoxygenase. DNA laddering and PCR indicates inhibition of topoisomerase Hoernlein 1999.

Acetyl-11-keto-beta-boswellic acid (AKBA) inhibition of 5-lipoxygenase is allosteric (non competitive) and calcium dependent Sailer 1998. Leukotrienes B4 and C4 from ionophore stimulated PMNLs were inhibited by acetylboswellic acids (IC50=8.5 microgm/ml), 11-keto-beta-boswellic acid (IC50 = 3 microgm/ml), or MK886 (IC50=0.0068 microgm/ml) Wildfeuer 1998.

Nonredox type 5-lipoxygenase inhibitors generally are activated by glutathione. However, no such redox-dependent effects were observed with acetyl-11-keto-beta-boswellic acid, Werz 1998.

Acetyl-11-keto-beta-boswellic acid inhibited DNA, RNA and protein synthesis in HL-60 cells with IC50 = 0.6, 0.5, & 4.1 microM, respectively, and inhibited cell growth but not viability, Shao 1998.

Human leukocyte elastase is inhibited by acetyl-11 -keto-beta-boswellic acid (IC50 = 15 micro Mole), beta-boswellic acid, amyrin & ursolic acid, but not by 18beta-glycyrrhetinic acid. Ursolic acid and amyrin do not inhibit 5-lipoxygenase Safayhi 1997.

5-Lipoxygenase inhibition requires the 11-keto and a hydrophilic group on C4 of ring A of boswellic analogs. Potency of AKBA was only slightly diminished by deacetylation or by reduction of the carboxyl to alcohol. It is inhibited by amyrin Sailer 1996.

5-Lipoxygenase inhibition by AKBA is reduced by noninhibitory pentacyclic triterpenes, concentration-dependently. This is not due to nonspecific lipophilic interactions, because cholesterol, cortisone, testosterone (4 rings) lack effect, safayhi 1995.
Curcumine inhibits 5-lipoxygenase in rat peritoneal neutrophils and 12-lipoxygenase & cyclooxygenase in human platelets while boswellic acid only inhibits 5-lipoxygenase and did not impair the peroxidation of arachidonic acid by iron and ascorbate Ammon 1993. Carrageenan-induced rat paw edema was reduced by four species of the plant family Burseraceae, Boswellia dalzielli, Boswellia carteri (gum olibanum), Commiphora mukul and Commiphora incisa Duwiejua 1993. C3-convertase of the classical complement pathway is inhibited by boswellic acid @ 100 micrograms, Kapil 1992. Papaya latex induced inflammation was reduced by prednisolone, aspirin, indomethacin, phenylbutazone, ibuprofen, piroxicam, chloroquine, levamisole or a mixture of boswellic acids, Gupta 1992.

Among boswellic acid isomers, acetyl-11-keto-beta-BA (AKBA) induced the most, pronounced inhibition of 5-lipoxygenase with IC50 of 1.5 microM. It did not impair cyclooxygenase and 12-lipoxygenase, Safayhi 1992. Inhibition of 5-lipoxygenase and its products (LTB4 & 5-HETE) are inhibited by ethanolic extracts of the gum resin exudate of Boswellia serrata, Ammon 1991. Leucocytes of BSA-induced arthritis in rabbits decreased by boswellic acids (25, 50 and 100 mg/kg/day), Sharma 1989. Glycosaminoglycan content in rats was decreased in the ketoprofen-treated group but unaltered in the boswellic acids or salai guggal treated groups Reddy 1989. Antibody production and cellular responses to sheep red blood cells in mice was inhibited by Boswellia ethanolic extract, Sharma 1988. Arthritis associated elevation of urinary hydroxyproline (free, total, nondialysable and dialysable), hexosamine and uronic acid was slightly decreased in the acute phase and significantly decreased in the chronic phase by boswellic acids in rats Kesava Reddy 1987. Arthritis elevation of beta-glucuronidase is reduced by boswellic acids or salai-guggal, Kesava Reddy 1987.

Carrageenan or dextran induced edema and formaldehyde induced arthritis were reduced by Boswellia extract. It lacked any analgesic or anti-pyretic effects and no significant effect was seen on cardiovascular, respiratory and central nervous systems, Singh 1984.
Chapter - 2

Review of Literature

Chemical Constituents:


(1) Volatile Oil or Lower Terpenoids:

Steam distillation of fresh gum resin yields upto 10-16% of essential oil with characteristic odour. (Guenther E. S., 1943) The monoterpenes indentified in the oil includes u-pinene (6.4%), u-thujene (50%), d-limonene (4.5%), P-cymene (14%), Cardinene (4%), Geraniol (0.8%) and elemol (1.3%), terpeneol, β-pinene, methyl chavicol and phellandrene, camphene, d-borneol, verbenon and verbenol. (Bhargawa P. P., 1963, Girgune J. B. and Garg B. D. 1979, Dennis T. J. 1980).

2) Higher Terpenoids:

Major fraction (25-35%) of the oleo-gum resin. First isolation of B.A. in 1898 by Tschirch et al., Simpson et al., (1938) (1941) have described the constitution of α and β-Boswellic Acid. Ruzicka et al., (1940) converted α-Boswellic Acid into β-Amyrin. It has now been well established that said anti-inflammatory and anti-arthritic activities are due to the presence of β-Boswellic Acid and other related pentacyclic triterpene acids. (Mahajan B. 1993, 1995). Based on β-Boswellic acid structural modification are being carried out at RRL Jammu by Yadav et al., (1984) by condensing β-Boswellic acid with different aromatic amines in order to enhance the activities.

(3) Carbohydrates:

Carbohydrate or sugar also constitute the major fraction (45-60%) of the gum resin. Preliminary examination indicated the presence of disachcharides along with oligo and polysaccharides. Identified sugar as arabinose, xylose and galactose. Moisture 10-11%, volatile oil 8-9%, Gum 20-23%, insoluble matter 4-5%. (Malandkar M. A., 1925).
The boswellic acids are organic acids, consisting of a pentacyclic triterpene, a carboxyl group and at least one other functional group. Alpha-boswellic acid and beta-boswellic acid, C30H48O3 both have an additional hydroxyl group; they differ only in their triterpene structure. Acetyl alpha-boswellic acid and acetyl-beta-boswellic acid, C32H50O4, replace the hydroxyl group with an acetyl group.

**Boswellia serrata** (Salai Guggal)

![Structure of boswellic acids](image)

**α -boswellic acid**

**β -boswellic acid**

**11-keto-β -boswellic acid**

Fig. 14 Structure of boswellic acids