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General introduction

Every individual or human being desires to live a healthy and respectful life. There is an age old saying “health is wealth.” Every country desires that its subjects remain healthy to keep itself prosperous and progressive. In spite of the best efforts to achieve this goal, human suffering has become synonymous with the rapid advancements made in technology. It has taken competition to break neck levels and the young generations have given the health parameters a go by. Commercialization in agriculture has assured in a green revolution, yields have increased with bioengineered crops but the nutritional components have progressively decreased. The current day lifestyle of fast food and non exercise has led to a spurt in non communicable and metabolic related diseases.¹

If lifestyle diseases are self created destruct buttons, infections have reared its head in spite of the best attempts to tackle them. Charles Darwin’s statement “survival of the fittest” works aptly in this scenario. Microorganisms and parasites are rapidly adapting to new environs with ever increasing reports of drug resistance.¹

Drug discovery programmes today are not restricted to a single country, so also are the markets. Pharma majors invest heavily in research, but their agenda is mainly commercial. Countries with deep pockets also have extensive budgets with investment in drug research focused to their health care needs. Many drugs in the past are due to serendipity, with universities contributing substantially. Academic involvement is significant and academic research, however small, can be a contributor to the development of science and beneficial to mankind at large.

Introduction to Infections

Rapid growth in population, especially in the developing countries is leading to challenges in combating infectious diseases. Reports state that there are 17 infectious diseases, which include the likes of leprosy, tuberculosis, malaria, leishmaniasis etc., to be endemic in 149 countries, with over one billion people being exposed to them. The World Health Organization has raised the ante and has suggested to the various affected countries to be more focused on disease control.
Most of these diseases are vector borne or communicable. Climate change has also been a contributing factor in slowing down vector control programmes. Favourable changes in the weather suiting to the growth of vectors have generated new transmission zones with an increased spread of infections.\textsuperscript{2}

Tropical countries, including India are prone to certain common infections like malaria, dengue, chikungunya, filariasis, tuberculosis, leprosy, leishmaniasis, typhoid etc. The geographical distribution of some of them is localized depending on the regional climatic conditions. 6,60,000 deaths were reported in 2012 due to malaria of which 95\% was in Africa.\textsuperscript{3} A cohort study by Neeraj Dhingra and colleagues suggest that the mortality rates of malaria in India are much higher than reported. They attribute this to a similarity of malarial symptoms with other infections like typhoid, ricketsial fever etc., thereby making malaria go unnoticed. Symptomatically similar typhoid has a fatality rate of 2 lakh deaths per year across the globe.\textsuperscript{4,5}

Dengue and chikungunya, spread by the mosquito \textit{Aedes aegypti} has been widespread. Improper sanitation and hygiene has let to their rapid growth and an estimated 2/5\textsuperscript{th} of the world’s population is exposed to them.\textsuperscript{6} A positive aspect of the WHO report is that the combined efforts of the countries has shown a decreased incidence by 17\% and a 26\% reduction in morbidity for the period 2000 – 2010.\textsuperscript{7}

There is a lot of concern with reference to tuberculosis (TB). The World Health Organization in its latest report states that over 8.6 million people developed tuberculosis in 2012 with 1.3 million TB related deaths.\textsuperscript{8} Some reports suggest that there are a million missing patients who are actually positive but undiagnosed and one million infected children.\textsuperscript{9,10} A significant 13\% of this infected population were HIV positive. The report also states that India alone accounted for a staggering 26\% of the reported cases. The organisation has stressed the need for better diagnostic methods to detect the infection at early stages especially multi drug resistant tuberculosis (MDR-TB). Patients with MDR-TB are resistant to the first line drugs rifampicin and isoniazid.\textsuperscript{8} The advent of modern techniques like GeneXpert has helped to identify as many as 64,000 cases in India alone.\textsuperscript{11} Experts believe that TB is a silent epidemic which has mutated very fast in the last twenty years leading to
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MDR-TB and extremely drug resistant tuberculosis (XDR-TB) with the first case of
XDR-TB reported in the year 1997 at Sewri. Even though there are thirteen drugs
available in the management of tuberculosis, it is difficult to treat drug resistant
varieties. Reports of XDR-TB in Africa have been frightening and according to
WHO, accounts for 9.6% of MDR-TB cases. It is now believed that a wrong diagnosis
and treatment of XDR-TB as MDR-TB complicates the further treatment. Attempts
are being made to develop fixed dose combinations for treatment of TB, especially in
children. Another mycobacterial infection that prominently bags the headlines is
leprosy. 58% of the 2,32,857 leprosy cases reported worldwide were from India.
Though there has been a substantial reduction in the number of cases, there needs
to be some more work done till leprosy is completely eradicated.

An area of concern is the development of resistance to antibiotics. This has impeded
global efforts in containing infections. Higher rising incomes and higher rates of
hospitalization have let to the higher use of antibiotics. There is also rampant over
the counter sales of antibiotics without prescription in many countries including
India. Microorganisms, when exposed to sub optimal doses of antibiotics develop
resistance by undergoing mutations and these strains are increasingly transmitted.
Some of the well documented drug resistant strains are methicillin resistant
Staphylococcus aureus (MRSA), Escherichia coli ST131 and Klebsiella ST258.
Resistance is more to β lactam class of antibiotics, with a 10 fold increased incidence
in the last 20 years. The evolution of hospital MRSA was directly attributed to the
indiscriminate use of quinolone antibiotics. Recently, the gene responsible for
resistance in the malaria parasite Plasmodium falciparam was also identified.

Inflammation

Inflammation can be defined as series of pathological changes associated
with local vascular reactions and cellular responses of living tissue to an injury
insufficient to kill the tissue. It is the body’s defence mechanism in order to eliminate
or limit the spread of an injurious agent and is characterized by local heat, redness,
swelling, pain and loss of function. Depending upon the duration and the mode of
onset, the inflammatory reaction can be classified as acute, sub-acute or chronic.
Acute inflammation is characterized by a sudden onset and as a short course which may last for a few minutes to several hours. On the other hand, sub acute inflammation is set to last for one to six weeks or more. Chronic inflammation is known to last for months to years and is characterized by proliferation of connective tissue and blood vessels with presence of lymphocytes, plasma cells and histocytes but absence of polymorphs. Another prominent feature is the denaturation of proteins that occur in the region of inflammation.

The root cause for inflammation could be a variety of chemotactic factors which could be any one among the following: Membrane derived lipid substances like eicosanoids & platelet activating factors, Vasoactive amines, cytokines, lysosomal proteases etc., the most common however being the eicosanoids.

The arachidonic acid pathway is well known to be the primary mechanism for the generation of pain and inflammation. The arachidonic acid itself is derived from lipid hydrolysates that are supplied from the diet. At the cellular level, the enzyme phospholipase A2 converts the phospholipids to arachidonic acid. This arachidonic acid is acted upon by two major enzyme systems: namely lipoxygenases and cyclooxygenases. Together, they regulate various immune defenses and pain mediating responses in the body and maintain homeostasis.

The enzymes 5-lipoxygenases and 12-lipoxygenases metabolize the arachidonic acid to various leukotrienes which bring about vasoconstriction and vascular permeability, promote adherence of leucocytes to vascular endothelium and induce bronchial smooth muscle contraction. The role of 5-LOX in inflammation is well established. Modulating the activity of these intermediates has helped in the better management of asthma.

The prostaglandins, obtained as the major products of action of cyclooxygenases on arachidonic acid show significant physiological activity when activated. Thromboxanes help to increase vascular permeability and in the aggregation of platelets, the prostacyclines decrease vascular tone and decrease platelet adhesion, the prostaglandin D2 increases hyperalgesia in sensory apparent nerve fibres whereas the prostaglandins E1, E2, F1 & F2 are known to increase vascular
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permeability, increases hyperalgesia in sensory apparent nerve fibres, cause inflammation, reduce gastric acidity. Both isoforms of the enzyme cyclooxygenase, namely COX 1 and COX 2 are expressed in various cells and tissues. It is well established that COX 1 is expressed more in the stomach and prominently involved in the regulation of acid levels, whereas COX 2 is expressed in tissues only during an injury and releases eicosonoids which regulate inflammation. Regulation of COX 2 is therefore a primary focus area in the management of inflammation.

Arthritis is a very common occurrence these days. Eating habits and non-exercise have let to obesity. Lack of synovial fluids is known to increase friction resulting in the inflammation of the joints. Patients suffering from arthritis are subject to chronic medication and under such circumstances, patient safety becomes critical. The current strategies of NSAID research are to develop selective COX 2 inhibitors. Drugs like celecoxib, rofecoxib have been introduced in the past for the management of chronic inflammation.

Figure 1: Scheme of Arachidonic acid pathway
Reactive oxygenated species

As reported in the initial part, lifestyle related diseases are quite common. Extremely stressful life and the enormous level of pollution that one is exposed to has affected the health of the common man. Free radicals are extensively produced in the body due to various chemo stimuli. These reactive oxygenated species are known to damage various tissues in the body. The role of antioxidants in scavenging these free radicals is well known.  

The reactive oxygenated species are formed due to different mechanisms which could be due to ionizing radiations, byproducts of cellular respiration or due to defence mechanisms of neutrophils and phagocytes. The electrons lost in electron transport chain attack molecular oxygen to form superoxide ion. These superoxide ions are capable of attacking various mitochondrial membranes and fatty acid side chains, thereby damaging them. The body has its own defence against these destructive reactive species like the enzymes superoxide dismutase and catalases which scavenge these radicals. It is also well established now that antioxidants also go a long way in combating this reactive species.  

Combating the menace of free radicals is either by prevention or by scavenging of already existing free radicals. Various enzyme, metals and vitamins work in tandem to remove these reactive oxygenated species.  

a) Anti-oxidative enzymes: These are superoxide dismutase, catalase, and glutathione reductase. They are synthesized in the body and convert reactive oxygenated species like superoxides and hydroxyperoxides into non-reactive oxygen molecules.  

b) Metal Chelating antioxidant: The role of metal ions in accelerating lipid oxidation is of paramount importance, especially the transition metals like iron and copper. The initiation step of oxygen oxidation requires removal of a hydrogen atom which are catalysed by these metals.
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c) Singlet oxygen-quenching antioxidants: Singlet oxygen is highly reactive towards any molecule with electron or lone pairs of low ionization energy.

d). Radical scavenging antioxidants: These can donate hydrogen atoms to free radicals, can scavenger free radicals and prevent lipid oxidation. Eg: vitamin C, albumin (hydrophilic), vitamin E, carotenoids (lipophilic)