

Inflammatory process play a major role in many chronic diseases.

What is the Major Driving Force of Systemic Inflammation?

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Modern lifestyle encourages people to keep eating frequently. Gut can become 'battlefield'. As Napoleon Bonaparte says the winner would be the one controlling that chaos, both his and his enemies'.

Probiotics and prebiotics are major topics in nutrition, though they sound similar, but have different roles in maintaining health. Probiotics are beneficial bacteria, and prebiotics are food for these bacteria. Recent advances in medical technology are proving that Prebiotics help to grow good gut bacteria.

Hippocrates (460-370 BC), a Greek Physician and Father of Modern Medicine," once famously said: "All disease begins in the gut."

Until 1977, there was a general acceptance that the multiple organ failure was thought to be due in infections. This was influenced by a new thinking in the profession that it could be due to uncontrolled inflammation where the gut may be the site of Multiple Organ Failure. 'The process could start in the gut and Microbiome. Where man meets microbe', the concepts are not new, and found its references even in the Bible, Koran and in Hindu vedas.

Recent technological advancements have provided collection of data describing the structure and functional capacity of the microbiome in a variety of conditions available to the research community. There is consensus that the disruption of the gut Microbia (termed "gut dysbiosis") is influenced by host genetics, diet, antibiotics, and inflammation, and it is intricately linked to the pathogenesis of inflammatory diseases, such as obesity and inflammatory bowel disease (IBD).

Existence of the Inflammatory state is well known in Type II diabetes, Rheumatoid arthritis, cancer, Asthma, Allergies, Inflammatory Bowel Disease (IBD), Autoimmune diseases, pancreatitis, Liver diseases like Cirrhosis and Nash, and many more. In recent years, Inflammatory diseases such as Crohn's, Multiple Sclerosis, Asthma, Type I Diabetes are on the increase. Many types of injuries produce a similar inflammation. He says that inflammation has many diseases.

Do we need this: "infectious diseases (e.g. Mumps, measles, Rubella, TB, coming down due to immunisation?"

Gut microbia, an integral part of the human body, comprise bacteria, fungi, archaea, and protozoa. Macrophages are the key players in the maintenance of tissue homeostasis by eliminating invading pathogens and exhibit extreme plasticity of their phenotypes, such as M1 or M2, which have been demonstrated to exert pro- and anti-inflammatory functions.

Microbia-derived metabolites, short-chain fatty acids (SCFAs) and Gram-negative bacterial lipopolysaccharides (LPS), exert anti-inflammatory or pro-inflammatory effects by acting on macrophages. There is still scope for further understanding the role of macrophages in gut Microbia-inflammation interactions to seek a novel method for preventing and treating inflammatory diseases.

Initially it was difficult to isolate bacteria even though colon has got many hundred species of bacteria till modern

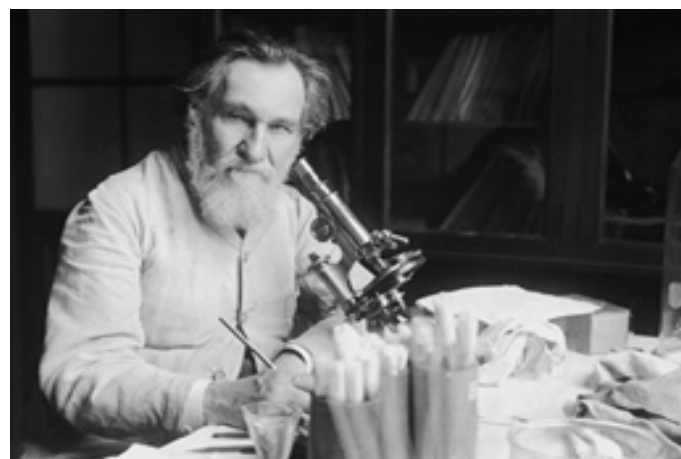
techniques to culture were developed. Change in microbiome disease related and inflammation is disease related and in both changes were found to be parallel to each other.

Ilya Ilyich Mechnikov, a Russian Imperial zoologist known for his pioneering research in immunology tried to find why people in some cultures live longer than others. In his published paper in 1907, he studied 5 different segments around the world to observe that there was only one thing in common in these groups of people was that they all consumed fermented foods. He found in Bulgaria people take fermented milk (He named the bacteria, *Lactobacillus Bulgaricus*). Now there are about a thousand species of bacteria. Elie Metchnikoff, the father of immunology, (1845-1916) investigated intestinal microbes as causative agents in aging, a process he called "auto-intoxication." He believed that lactic acid-producing bacteria (such as those found in yogurt) would suppress the growth of more proteolytic, auto-intoxication bacteria.

Nobel Prize Winner, Dr Lederberg, describes the collective genome of our indigenous microbes (microflora), that a comprehensive genetic view of homo sapiens as life form should include the genes of our microbiome (Microbiota). It includes bacteria, viruses, fungi and archaea.

In the fields of molecular biology and genetics, a genome is all genetic material of an organism and consists of DNA. The genome includes both the genes and the noncoding DNA, as well as mitochondrial DNA and chloroplast DNA. At birth 99% of genome is absent.

Even a 7-day course of anti-biotics wipes out gut bacteria and takes a year to replenish. Sub-therapeutic use of Anti-biotics in farm animals causes changes in the human microbiome when consuming. This is impacted by the modern lifestyle changes Immunisation, decrease in parasitic infection and includes dietary changes in fats, prot-



Nobel Prize winner, Ilya Ilyich Mechnikov, who discovered phagocytes.

-teins, artificial colours, sweeteners, emulsifiers, insecticides, increased use of antibiotics, all cause of the collateral damages.

- *Ciprofloxacin is the worst:* One dose of broad-spectrum antibiotic, reduces 1000 species to 250 species of microbiota. Stress of previous antibiotic therapy on outcome of Gram-negative severe sepsis. 30% mortality if a patient had any type of antibiotic 6 months prior of operation.
- *PPI- Omeprazole/ H2RA, Vasopressors:* Cause change in pH, decreased pO2 including pCO2
- *Opioids:* Decreases motility and bacterial clearance mechanism. It also alters bacterial pathogenicity. Pseudomonas becomes aggressive. It attaches to the mucosa. Normally they live happily in GUT.
- The intestinal environment of surgical injury transforms Pseudomonas Aeruginosa into discrete hypervirulent morphotype capable of causing lethal peritonitis.
- Artificial sweeteners and emulsifiers have dramatic influence on host microbiome.
- *Microbiome:* Metabolises drugs, produce Vitamins, SCFA (Saturated Fatty Acids), Amino Acids, Modulation of Hormone secretions, modulates immune function, maintains mucosal barrier function.

Has our Fear of 'bacteria, made us more susceptible to diseases?

GUT MICROBIOME is affected by DIET, Drugs, Stress, Infant feeding, Birthing process, Life cycle changes, Geography.

Relationship of microbiome and some common illnesses.

- *Overeating:* In general, it is safe to say that the obesity is blamed on the lifestyle choice and often counts for lack of will power, and that may be considered as a Psychological issue! It is simply a problem of overeating and not a single disorder. Probably there are several dozen phenotypes or more clinically meaningful types where the inflammation is strongly associated with obesity.
- *Transferable obesity:* Interestingly, there is low grade inflammatory process in Adipose tissue in Obese patients. And, the obesity is considered as transportable from an obese person to thin person by transferring the Microbiome of obese person to lean person.⁶
- *Impact of the western diet:* Decreases diversity, increases firmicutes, Decrease Bacteroidetes, increases body fat, amount of increase in at roughly linear with changes in microbiome. Gut microbiota decreases insulin resistance.
- *Functions of Microbiome:* Microbiome Metabolises drugs, produce and metabolise nutrients like Vitamins, Saturated Fatty Acids, Amino Acids, Modulation of hormone secretions, modulates immune functions, maintains mucosal barrier function. Microbiome should be treated like an organ.

Bacteria metabolise 5FU and makes it more active to kill cancer cells.

Factors impacting on Gut microbiome: Stress (Exercise, metabolic, psychological), Geography (6 hours of flight to a different area changes) infant feeding, birthing place (home or hospital). Medical practices like vaccinations, Antibiotics and Hygiene and Host genetics. This leads to Dysbiosis.

What happens in Dysbiosis: Dysbiosis leads to altered intestinal permeability and changes in microbiome. Broad

spectrum antibiotics cause changes within a few hours. Microbiome species are reduced from over 1200 to mere few hundred. PPI, vasopressors cause change in pH, decrease pO2 and increase pCO2. Opioids decrease gut motility and gut clearance mechanism, alters bacterial pathogenicity. These also decrease luminal nutrient delivery. Even working in the hospital alters gut bacteria in healthy individuals. Pseudomonas when exposed to opioids they become aggressive. Bacteria gets attached to mucosa. It is important to maintain healthy microbiome during illness.

How does Probiotics help us?

Multiple mechanisms described to support concept of microbe involved in systemic inflammatory regulation.

1. Competitive inhibition of pathogens.
2. Enhance Heat Shock Protein in gut.
3. Tight junction protein synthesis-holds the intestinal cells together preventing absorption of toxins from lumen of gut.
4. Enhance mucosal blood flow. Right bacteria increase blood from 30-50%.
5. Stimulate gut immunity.
6. Increase return of GI motility.
7. Helps maintains microbiome diversity in colon.
8. Butyrate (Fermentative product) enhances neutrophil killing chemotaxis, resolution of inflammation, anti-neoplastic. Microbiome transports Butyrate it to blood.

Leaky Gut Syndrome.

It means Increased Intestinal permeability-here intestinal wall exhibits permeability. It is controversial syndrome. Diseases associated with Leaky Gut are IBD, IBS, Coeliac, Type I Diabetes Mellitus, AIDS, Multiple sclerosis, Autism, Migraine, Food sensitivities. Little objective data supports Fibromyalgia, Depression, Allergies, and skin disorders. No objective data supports Weight gain or Chronic Fatigue Syndrome.

Microbiome and Brain functions:⁷ Gut communicates with brain via Vagus nerve. 90% of Vagus fibre from gut go to brain and not vice versa. Hence health of the Gut can affect the brain.

Clinical use of probiotics: The pool of beneficial microbes can be resupply by Dietary prebiotics. Other way is Refaunation (FMT)-Faecal transplantation!

Role of Probiotics in pregnancy and maternal outcomes:⁸ Gestational Diabetes: Pre-eclampsia: reduced by 50% in high-risk pregnancies. Inflammatory markers: Reduced ENTEROCOLITIS IN NEONATES: There is some reduction in mortality 9.8 vs 6.8%. A four-Probiotics regimen reduces postoperative complications after colorectal surgery in a double-blind Placebo controlled study.⁹ SEPSIS: about 40% reduction in Sepsis in healthy neonates. Cost one dollar a week. C Diff diarrhoea: 60% decrease with probiotics.

There is a greater challenge for the practitioners in the primary care to exercise their capacity towards somewhat a 'holistic approach' in managing patients with relative risks. Intestine constantly battles between Barrier function and selective absorption. Variety of bacteria living in the gut affects our health.

Judicious use of antibiotics when required and encouraging use of probiotics may be helpful in General Practice.