

The Scourge of Infection

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A B S T R A C T

“Infection is an inescapable part of life. All creatures feast upon other creatures and in time are feasted upon in a kind of Escheresque food chain. When humans are the meal, we call it infectious diseases.” Rate of infections and range of infections are spreading very fast threatening human well-being. One of the causative micro-organisms of infections is bacteria. Bacteria have evolved for more than 3 billion years and are extremely well-adapted (better than humans) to vicissitudes of changing environment. Bacteria know more about the biology of human cell than most cell biologists. Newer infections are materialising now and old infections are not becoming a part of history. Why? Some pointers are discussed. Our lifestyle changes over millenia, trespassing natural habitats of nature’s other creations, disturbing the natural ecologic balance etc., are all embodied as possible causes of variety of widespread infections. We should remember that death is inevitable. Only the cause of death varies and changes. Man is never going to win a war against micro-organisms. “Infectious disease is one of the few genuine adventures left in the world.” We should learn how to live in symbiosis with microorganisms without producing morbidity. Research should be directed towards reducing premature deaths from any cause. Ways and means should be found out to live a useful, productive full span of life.

The immediate provocation to write this short article was provided by the recent book review on “Secret Agents: The Menace of Emerging Infections”, authored by Madeline Drexler.

The book opens with following frightening lines:

“Infection is an inescapable part of life. All creatures feast upon other creatures and in time are feasted upon in a kind of Escheresque food chain. When humans are the meal, we call it infectious disease.”

The book deals with today’s new and emerging infections. Rate of infections and range of infections are spreading very fast threatening human well being. The book also deals with why certain infections are materializing now and why old infections are not becoming a part of history. We have animal and insect-borne diseases, food-borne diseases, pandemic diseases, antibiotic resistance and fast emerging newer viral diseases. Add to this the possibility of disease spread by bioterrorism—both manmade and natural.

As a response to the WHO’s warning that by the year 2020 to 2025 India will have the world’s largest population of diabetics and coronary artery diseases of an epidemic proportion, we have unduly diverted our attention towards these diseases and infectious disease and infections have been relegated to second/third place. Even the pharmaceutical industries, obviously driven by commercial imperatives are aggressively pushing antidiabetic

and antilipemic medicines into the market. Hardly any sincere effort is made towards discovering and marketing effective anti-infection medicines. However what do the realities dictate? Available statistics from USA indicate that compared to previous decade, both morbidity and admission rates due to infections increased 58% and mortality due to infections increased 22% during the last decade. This does not take morbidity and mortality due to HIV-AIDS into consideration!! I am sure our figures cannot be too different, perhaps worse!! The immediate and the most common cause of morbidity and mortality in the best managed ICUs and ICCUs in our country is still infection, including hospital acquired infection.

Although reasons for this paradox at first sight appear to be difficult to comprehend, the available facts can explain this easily.

Legionnaire’s disease, Lyme disease, toxic shock syndrome, *E. coli* O157:H7 STDs, Ebola virus, Sin Nombre virus (causing pulmonary hanta virus syndrome), bovine spongiform encephalopathy (type of mad cow disease), new variant Creutzfeldt Jakob disease (due to prions) and SARS all made their appearances during last decade. Add to this, recent onset of Bird-flu. List will swell as more and more such diseases make appearances in humans. Must we not ask ‘why’?

We have learnt from our earlier days the Darwin theory of struggle for existence and survival of the fittest. Let us apply

this to modern battle of survival by the Human race and by the Micro-organisms.

As such, the survival value of the human intelligence is not satisfactorily demonstrated, microorganisms (bacteria, viruses, protozoas, typhus, fungi) play the survival game exceedingly well. As the environment changes, microorganisms adapt far more quickly and efficiently than human beings. Humans are multicellular very complex animal, an encumbered species, with too many organs and working parts, which can be strained and derailed easily. Bacteria have evolved for more than 3 billion years and are extremely well adapted to vicissitudes of changing environment. Microbiologist Stanley Falkow remarked "Bacteria know more about the biology of human cell than most cell biologists". Human race produces a new generation every 15-20 years; the bacteria do it almost within 20 minutes and viruses even faster!! Just as genetically superior individuals adapt better in natural selection for survival, the same principle operates far better in microorganisms. Because viruses and bacteria are in enormous numbers they can support considerable variation in their communities, mutate and proliferate freely transmitting their genetic characteristics easily and freely. To exemplify 2% genomic mutational characteristics can occur in viruses in a short span of 2-3 days, the same genetic mutational changes of 2% in humans take approximately 6-8 million years!!

Compared to human genome, viruses are very simple, just either DNA or RNA surrounded by a shell of protein and/or lipid. They can propagate only in live cells or in tissue culture. Viruses hurt us by killing the host cells. Once the viremia occurs and viral infection starts it is difficult to control because our immune responses usually respond rather late to take care of initial phases of infection process.

To begin with bacterial infections may seem easy to control but their certain characteristics are rather disturbing. From a genomic view point, bacteria have only one set of chromosomes instead of two, which means that every gene counts and each advantage due to gene character is conserved and transmitted to the next generation. Because of this, bacteria hurt us in many ways. By their sheer number they can play a game of Arab & Camel (crowding out normal functioning cells), they can cleave cells, may create paralyzing toxins to disrupt normal metabolic pathways, may suppress body's defense mechanisms (both humoral and cellular), and shrug-off drugs and antibodies. They can also generate a massive immune response that itself may be harmful (toxic shock syndrome). They can also produce enzymes that destroy antibiotics. Plasmid in a bacterium helps acquire resistance to antibiotics. Bacteria can pick up genes (phage) from any source: from other bacteria, viruses, fungi etc. and produce toxic gene which can be propagated. For example a toxic gene from *Shigella dysenteriae* was picked up and inserted into harmless *E. coli* to produce *E. coli* O157:H7 which is very toxic and gives rise to hemolytic uremic syndrome.

I also mentioned about infectious agents, prions above. They cause only neurodegenerative disorders. They do not follow the natural laws of biology. They have no reproductive cycle. They exist only in a cell in two states—normal dormant stable state and in a dormant but pathogenic state. How it becomes pathogenic is a mystery yet to be unfolded. These are proteins with a predilection for turning the brain into a spongy mess. There are no nucleic acids in a prion protein. It is a mystery that

such a protein without a nucleic acid should produce a lethal disease. How do they transmit a disease from one animal to another? Prions assume a certain configuration, a peculiar way of folding when in the disease state, which then triggers other prions to fold the same way in a continuous process and in a dominant effect. When they come into contact with other proteins, they turn them into prions, setting a chain reaction till a neurodegenerative disorder is established (in the brain). Once a process starts it is self-perpetuating and no measures can stop it. However, prions cannot reproduce and evoke immune response, nor cause inflammatory response, they are difficult to tackle and treat! One has to destroy and bury the host afflicted with prions. Prions resist heat, UV light, radiation and sterilization!!! The practice of grinding the meat of dead sheep and cows afflicted with prion disease and mixing this (especially the diseased CNS tissue as meat) with the usual fodder and feeding this to other cows is thought to transmit the disease. How does a man escape, if at all, when he eats the brain -meat (beef) from a diseased cow? Can it not lead to an epidemic?

Clearly these are cases where the disease has jumped the species: from animals to humans. This is on the increase. Otherwise how do we explain recent scare of bird flu and SARS making entry into human beings? In fact, during last 25 years about 30 new infectious diseases have made entry into human beings, almost all have come from animals!! Of 150 pathogens linked with emerging infections, almost three-fourths come from animals.

Unfortunately human immune response does not develop *paripassu* with certain viral infections. That is why the mortality of Ebola virus infection and pulmonary hanta virus infection is very high. Human immune response takes a long time to develop when the infection becomes mild. At that point of time microorganism reach a subtle adjustment with human host—a kind of symbiosis, permitting us to survive. It is important to remember that microorganisms require a host to survive; a dead host is a dead end. This is the reason that though *C.botulinum* is a very toxic organism, the mortality has never been considerable at a given time.

Let us now consider infections and why they persist

We have our known old infections and new emerging infections. Unfortunately known old infections have not been consigned to a dustbin of history. Dysenteries, tuberculosis, plague, enteric fever, brucellosis, cholera, rabies, and even small pox are still there with us and worldwide they still have considerable mortality. In fact, tuberculosis has become a serious problem due to MDR organisms and avian tuberculosis has started taking roots in humans. This is probably due to increasing number of AIDS/HIV +ve individuals in the society. Morbidity and mortality due to several organisms causing pneumonia have significantly increased during the last decade. Why? Few important reasons follow:

Let us consider some of the widely known facts

1. Infectious microorganisms love two things: (a) crowding and (b) poor sanitation—dirtiness. Migration from rural to urban areas is the order of the day leading to overcrowding in urban areas. Statistics show that in the year 1900, only 2% of world population lived in cities with a population > 100,000. However it is estimated that by the year 2020,

almost 60% population will be in cities with population more than 100,000. Once microorganisms gain a foothold in an overcrowded population, they spread rapidly.

2. Poor sanitation due to overcrowding, poverty, unsafe water supply is well known causes of outbreak of epidemics in mega cities. The Nipah virus epidemic of Malaysia in 1998 is noteworthy. The mortality was almost 30% amongst those infected.
3. Old age population is fast growing worldwide. At the time of independence average age of India was 37 years, but to day it stands at 64 years!! In 1900 only 4% of US population was above the age of 65, whereas it is almost 20% to-day. And it is well known that self immunity both humoral and cellular declines significantly in elderly making them an easy prey to common infections.
4. Add to this widespread use of immunosuppressive drugs and certain hormonal treatments to treat cancers and other ailments. We all know the havoc wrought by unmitigated use of corticosteroids in the 80s—they suppress immunity and increase the susceptibility to the most common pathogens. Even disease-modifying treatments expose the human beings to heightened incidence of infection. So, on one hand we try to lengthen the life-span in such incurable diseases and on the other hand we expose them to infections. Shall we ever be able to strike a balance?
5. We should always keep in mind the dictum: What is potent for good is equally potent for evil. This applies to our newer and stronger antibiotics. While they are good to combat virulent infections but they are equally bad to produce serious side effects including toxic shock syndrome. But bacteria are smart enough. It takes almost a decade or more to produce a new antibiotic whereas bacteria can acquire resistance to a new antibiotic almost within 20 minutes!! Do we have an idea that after discovering artemisinin compounds to fight malaria, almost during last 12 years we have had no new compound to fight malaria, while morbidity and mortality due to malaria is rising throughout the world!! In fact, as the WHO pronounced in the nineties that we are losing the battle against mosquitoes. Almost 500 million people are infected yearly with mosquito-borne diseases; nearly 3 million die. Big four mosquito-borne diseases worldwide are Malaria, dengue, yellow fever and several viral encephalitides. The same can be said about antibiotics too. We have no newer class of antibiotic in the last decade. Unfortunately it is observed that microorganisms develop resistance to newer later antibiotics much quicker than was the case with old generation of antibiotics. Most organisms today are resistant to quinolone antibiotics, notably to ciprofloxacin.
6. Modern technologies make life easier not only for humans but also for pathogens. The classical example is spread of Legionnaires' disease which is acquired from moist soil.

Now let us talk about new, emerging infections. These probably have widespread distribution due to change in our culture and lifestyle, disturbing the Nature's ecological system.

1. Travel has become a part of our life. So infection in one region quickly travels globally. Just think of the recent SARS epidemic and scare worldwide. Or a global warning of

a plague emanating from India in 1995? Airport malaria is a well known entity. After all mosquitoes and microorganisms neither require passports nor visas to travel! Cargo vessels and airplanes are well known sources of travel for mosquitoes, rodents and microorganisms.

2. Our methods to raise livestock have changed and also horticultural habits. Nipah virus infection occurred due to faulty methods of pig raising and so also mad cow disease.
3. In some parts of the world, the shift from extended families to nuclear ones has created a need for day-care facilities for babies and children. Not all such centers are monitored adequately and therefore infection in one child could result into a small epidemic rather quickly.
4. Transgression into the natural habitat of animals and plants by humans has led to many serious diseases for which we are not prepared. AIDS probably was acquired from green monkeys of Africa, Lyme disease for encroaching upon rain forests of South America and Ebola virus due to encroachment upon jungles of Africa. Coastal population growth and especially in India practice of polluting the rivers through the practice of bathing and washing animals and sewage disposals has led to contaminations in fishes and crabs with human wastes, fostering transmission of bacterial and viral diseases. Polluting rivers with industrial effluents have changed the aquatic biology. Human encroachment on rain forests may give rise to haemorrhagic fever viruses and perhaps HIV's mysterious cousin viruses. Avian tuberculosis in humans probably also falls into this category.
5. Recent trend towards organ transplant—using animal organs in humans may be fraught with dangers. Using pig organs may give rise to infection akin to AIDS because of porcine endogenous retroviruses which are in donor pig's DNA and may interact with human viruses (which may be benign) to produce a new strain of virus which could be dangerous and lethal. The preparation of certain vaccines and biological products by harvesting "active principles" of organs of live or dead animals is also fraught with dangers, due to hidden viruses or due to prions. Injections of gonadotropins and human growth hormones prepared by harvesting pituitary obtained at autopsy markedly increased the incidence of CJD in Australia. Fortunately hGH is now prepared by recombinant DNA technology.
6. Antibiotics are used not only by the humans but are also fed to the livestock (almost ½ the total stock of antibiotics produced is used in livestock). Pathogens thriving in these livestock acquire resistance and when the same pathogens produce infections in humans, they are already resistant to the antibiotics right from the start. This is more often seen in hospital-acquired infections.
7. The immediate concern is emergence of deadly virus infections as they are not only difficult to treat but the body also is rather slow in developing antibodies/immune response to viral infections.
8. Exodus from villages to urban cities may create problem. Infection lurking in barren villages may acquire serious epidemic proportion should it travel to overcrowded urban areas where the immunity to the said infection may be low.

9. We do not know enough about emergence of new viruses. Recently Corona virus of SARS was a new entity. Its full characteristic has not yet been identified. It is established that even PrP from animals can take a toll of human beings. Can avian flu which recently has taken a heavy toll of farm poultry, not be contracted by humans?
10. Recent possibilities that even so called lifestyle change diseases may have an infectious background: for example there may be an element of infection in atherosclerosis, type I diabetes mellitus, multiple sclerosis, Crohn's disease and even Guillain-Barre syndrome. In due course, perhaps, many more may be added to this list.

As early as 1930, the biologist Hans Zinsser wrote: "Infectious disease is one of the few genuine adventures left in the world." How true.

What are our defenses?: A few pointers

Proper sanitation, potable water supply, adequate immunization, rational use of antibiotics and keeping physically fit are some

"dos". The 'don'ts' include pollution, overcrowding, and messing with our natural ecology systems, avoidance of drugs, tobacco and alcohol. We also need to focus our research towards vaccines and the production of biologic products for human use by recombinant DNA technology.

There are other measures which are beyond our control. How dramatically will gene therapy alter this picture, we do not yet know, not counting the problems of gene therapy itself!

Moral

Death is inevitable. Only the cause of death varies and changes. Man is never going to win a war against micro-organisms. Aim should be how to live in symbiosis with organisms without producing morbidity. Research should concentrate upon reducing premature deaths from any cause. Ways and means should be found out to live a useful, productive full span of life.

REFERENCES

1. Secret Agents: The menace of emerging infections; Madeleine Drexler; Joseph Henry Press.