

Mon Jan 17 14:35:22 EST 2000

In the history of human encounter with infectious disease, the current millenium's defining year is better lodged at about 1877, than at an arbitrary '000 C.E. That year saw the consolidation of the germ theory of disease, through the researches on anthrax by Louis Pasteur and Robert Koch. It was soon followed by effective veterinary vaccines for anthrax, and then the systematic search for every other disease-causing microbe: the golden age of microbiology had begun. It was soon enriched by the discovery of filtrable viruses, particles too small to be seen with the conventional microscope, or to be cultivated on artificial media. There had been many anticipations of germs: Fracastoro had sung in 1546 of "seminaria" (seeds) to account for the spread of the "French Disease" (syphilis). The terrified targets of the Black Death in Europe after 1346 had some intimation of contagion though distracted by scapegoatery of witches and Jews. Edward Jenner had developed vaccination for smallpox in 1798, by purely empirical routes and little or no insight into its mechanisms (a cross-reacting virus variant and the host's immunological response). Leeuwenhoek, in 1684, with his simple new microscope, had visualized bacteria among the animalcules seen in scrapings from his teeth. On the therapeutic side, Jesuit missionaries in Peru had noted the native Indians' use of Cinchona bark, and brought this to Europe in 1637 for the treatment of malaria. This quinine was one of the small handful of medications available to physicians prior to 1877 that actually worked any benefit. (We can think of a few other botanicals: opium, digitalis, willow bark [salicylates], but none for infection.)

These scattered landmarks appear in sharp contrast to the ever growing tidal advance of scientific enquiry that succeeded the pioneers of 1877: the institutionalization of microbe hunting and of the systematic enjoyment of scientific analysis of disease processes and of the microbial world. Sanitary reform had not waited for these scientific advances -- mounted in revulsion at the squalor and the stinks of the urban slums that followed upon the industrial revolution in England and the U.S. Although flawed in detail, the hygienic movement that tried to scrub up dirt and sewer smells did have some health impact in mid 19th century, though it failed when fleas, mosquitoes and sewage leakage into water supplies were ignored.

As witness to the millennial ascent, vital statistics were also diligently recorded after 1900 for the U.S. as intelligence for the quest for new knowledge and its application to the struggle for public health. The U.S. experience is graphically displayed in (Fig. 1) depicting life-expectancy at birth through the century. Similar trends applied to most other industrialized countries, with lags and disparities for economically and socially depressed sectors. The outstanding message is the near doubling of lifespan from 47 years in 1900 to 77 at present. (Count 74 for males, 80 for females -- a gap partly explained by the female double-X-chromosome's buffering against accumulated recessive mutations, and illustrated by male-prevalence of conditions like color-blindness and hemophilia.) As shown in Fig. 2, the decline in mortality ascribable to infectious disease accounted for almost all of the improvement up to 1950, when life expectancy had reached 68. Besides the major improving trends, we also observe the jaggedness, the year-to-year fluctuations in the graphs 1900-1950, again attributable to sporadic outbreaks of particular infections (typhoid fever, tuberculosis, scarlet fever) which no longer loom large in numerical statistics. Outstanding is the spike of 1918, the great influenza pandemic, to which we shall return.

Further improvement is on an asymptotic limb, and it has taken the second half-century to gain another decade of lifespan. Crude mortality rates have not altered very much, but we must give credit to the more advanced age of the population at risk. Heart disease has been the looming threat, accompanying affluence along with senescence. Eventually we accrue benefits from permeation of more salutogenic life styles (regard for diet, smoking, exercise; tacit medications like aspirin) bolstered by specific medical and surgical interventions.

The earlier advances rest in part on childhood immunization and other science-based medical interventions, but at least in equal measure on public health measures: protection of food and water supplies; segregation of the coughing patients; personal hygiene. Overall economic growth facilitated less crowded housing, improved working conditions and leave for stressful illness, and better nutrition, which have all played a role in setting a baseline of health expectations. Then in the 1950's we had an array of wonder drugs -- the new antibiotics: penicillin, streptomycin; chloramphenicol, and a growing list which promised to put an end to bacterial infectious disease. For viruses, we had (and have) far fewer remedies, but an array of new vaccines offered prophylaxis -- polio and the names of Jonas Salk and Albert Sabin the most indelibly inscribed on the public mind. Old vaccines like Jenner's cowpox were also mobilized in great campaigns, leading to the eradication of smallpox as an extant human disease by the end-70's.

Little wonder that by the mid 1960's, we heard a common exclamation that infection was past history; the microbes had been conquered; we should turn our attention to the constitutional scourges of heart disease, cancer and psychiatric disorder. This triumphalism was echoed in the priorities for research funding and of pharmaceutical development, e.g. as expressed in the national crusade against cancer, initiated by President Nixon in 1971 with some implied promise that cancer would also be conquered by the bicentennial celebrations of 1976. If anyone believed that then, we have come to understand that new conquests would be a long haul. The isolation, cultivation and analysis of microbes are far easier tasks than studies on humans. Studies on constitutional disorders are fraught with the material and ethical taxes levied on work on the human body. Agents that will selectively recognize and kill parasites are easier to design and test than those that must discriminate between normal versus abnormal human cells.

Although they had been for a time dethroned as objects of health-phobia, microbes nevertheless became and remain popular investigative objects for the most basic studies in molecular physiology and genetics. During the acme of microbe-hunting, say 1880 to 1940, bacteriology was almost totally divorced from general biological study. Pasteur and Koch are scarcely mentioned by the founders of cell biology and genetics like E. B. Wilson and T. H. Morgan. Bacteriology was taught as a specialty in medicine, outside the schools of basic zoology and botany; bacteriologists scarcely heard of the conceptual revolutions in genetic and evolutionary theory. Prior to the electron microscope, the bacterium's internal structure was elusive -- and lacking an organized nucleus would only be confusing. Most biologists when they mentioned bacteria at all regarded them as mysteriously pre-cellular: it was an audacious leap for Rene Dubos to entitle his 1945 monograph "The Bacterial Cell".

This segregation of instruction and thought disinformed researchers about the prospects of conducting genetic investigation with bacteria. So it is paradoxical that the pivotal discovery

of molecular genetics, that genetic information resides in the chemical sequence of DNA, arose from studies on serological types of the pneumococcus, important in tracking epidemics of pneumonia. Fred Griffith, in London, had reported in 1928 that serotypes could be interconverted with extracts of specific cell types. Oswald Avery followed up this work at the Rockefeller Institute in New York, and with Colin MacLeod and Maclyn McCarty reported in 1944 that the active substance was DNA. They and others spent much labor at further proof to exclude contaminating protein as the vehicle of biological activity. Those findings ignited a renewed interest in what was really going on in the life cycle of bacteria, and led immediately to my own work (1946) on sexual conjugation in *Escherichia coli* and the construction of chromosome maps closely emulating what had been going on in the genetics of fruitflies, maize and mice for the previous 45 years. Bacteria and bacterial viruses remained the initial testbed for most of the subsequent development of molecular genetics, and the consequent biotechnology, despite a waning interest in these microbes as etiologic agents of disease.

That complacency was shattered by the emerging recognition of AIDS starting in 1981. The chronically spreading pandemic has overtaken one continent after another, at terrible cost, and rapidly disillusioned our confidence about mastery over the microbes. It is coincident with the looming breakdown of efficacy of antibiotics as the evolutionary process takes hold in the microbial world, its counterattack with the emergence of resistance. HIV, the AIDS-virus, falls in the category of retroviruses, which had also been laboratory curiosities since the initial discovery of the (Peyton) Rous Sarcoma Virus in 1911. Serendipitously, the RSV had been under intensive study for years as a model for cancer, and the interchange of oncogenes by a viral vector. This greatly accelerated the characterization of HIV as a retrovirus, and assisted our first feeble steps at generating medications that mitigate the pace of HIV infection. This simplest of viruses still frustrates the most concentrated regime of focussed biomedical research ever mobilized. Perhaps our zeal to extirpate the virus has clouded less ambitious aims of learning to live with it, through nurturing the immune system eventually eroded by HIV in the human. Natural history points to analogous infections in simians that have long since evolved to a mutually tolerable equilibrium.

This costly experience has provoked widespread re-examination of the terms of our cohabitation of the planet. With more enthusiastic monitoring came a realization of an unbroken stream of outbreaks of exotic diseases: some new imports, some the belated recognition of older parasites, some newly evolved organisms (Fig. 3). Cholera (in the Southern Hemisphere), *Legionella*, antibiotic resistant pneumonias would be typical examples, respectively. New roles for infectious agents were revealed from closer study of gastric ulcer and the revelation of a *Helicobacter* for a disease that had been attributed almost entirely to psychosomatics. In like fashion, stress is now competing for etiological attention with *Chlamydia* infection as a cause of atherosclerosis and coronary disease. Four million Americans are now estimated to have been infected with Hepatitis C (mainly by transfusion or other contaminated blood products). This population is at significant risk of liver cancer, and must be warned to avoid hepatotoxins like alcohol -- as well as to be cautioned about donating blood. Smaller, but lethal outbreaks of Ebola virus in Africa, and hantavirus with pulmonary syndrome in the Southwest U.S. attracted popular attention disproportionate to their immediate public health significance, but not to their potential if they were to mutate to more diffusible forms, or other ecological factors favor their spread. We had to reconsider

the likelihood of a recurrence of a lethal influenza, like the "Spanish flu" of 1918, which had killed at least 20 million people worldwide, a match for the belligerent casualties of World War I. The genetic processes of gene reassortment in flu viruses, poorly confined to their canonical hosts -- birds, swine and people -- go on relentlessly and are surely bound to regenerate human-lethal variants. Those thoughts were very much in mind during the progression of an avian flu, H5N1, into a score of Hong Kong citizens during 1997 - with a third of the cases lethal. We have no idea why only these few humans succumbed; but we certainly owe a great debt of gratitude to the Hong Kong health authorities for their resolute actions, including the immolation of 2 million chickens, which in the event did stem that outbreak and avert the possibility of a worldwide spread of H5N1 -- though wildfowl may yet have the last word. We had a similar scare in New York with the unprecedented appearance of bird- and mosquito-borne West Nile Encephalitis, though happily with a very low mortality ratio. Will we see it again next Spring? On a much larger scale, Malaysia was afflicted with a new entity, the Nipah virus, with up to a hundred human fatalities, and a million livestock to be sacrificed.

In more quantitative terms, the US mortality index (annual deaths per 100,000) attributable to infection crept up from about 30 in 1982 to 60 in 1994. It had been steady for the prior 30 years. In relative terms, the rekindling is still modest compared to the 500 of the year 1900, or 850 at the 1918 spike. About half the recent uptick matches the AIDS pandemic; for the rest, respiratory disease, antibiotic resistance, and nosocomial infection play a significant role.

We may turn now from a historical to a contemporary and future-oriented one.

What are the zones of risk? What precautions can and should we be taking? Are we more or less vulnerable today than 20 or 50 years ago? Can we get a deeper understanding of the roots and origins of pathogenesis, and how can this inform our strategies?

The instabilities of cohabitation arise from two main sources, loosely definable as ecological and evolutionary.

Ecological comprises the ways in which we alter the physical and biological environment, microbial, animal and our own habitats, and our intersections with the parasites' *modus vivendi*. These includes all of hygienic and therapeutic interventions, "Our wits versus their genes", which have gained us added longevity and softened the pall of infant mortality -- thereby irrevocably changing our own human ecology. As side effect, together with economic (especially agricultural) productivity these have been the substratum of the population explosion. That spread is also the main source of new vulnerability: crowding of humans, with slums cheek by jowl with the jetsetters' residences; incursions into the forests for agriculture or suburbiana, with closer contact with rodents and ticks; unmitigated travel. It is a new historic experience that round-the-world travel is consummated in less than 80 hours (much less than the 80 days of Jules Verne's fantasy.) And this has become an everyday experience: well over a million passengers board aircraft every day for international destinations. International commerce by ground, sea and air -- for example in foodstuffs -- does but add to the traffic of potential pathogens and vectors. The transit times are short compared to the incubation times of disease, reducing health quarantine to a near absurdity. Our systems for monitoring and diagnosis of exotic disease have nowhere nearly kept pace

with this qualitative transformation of global human and material exchange. In contrast to 1918, a new flu could transit the world and pop up simultaneously in a dozen new locations with limited hope of even identifying the primary focus of this metastasis. This cauldron will then redistribute people, their culture, their prior immunities, their inherited predispositions, with pathogens that may have been quiescent at other locales for centuries. The most evident precedent is the European conquest of America, attended - even enabled - by pandemics of smallpox and measles; and the payback to Europe of syphilis' *Treponema*.

New technology is part of the ecological armamentarium which may go a long way to reinforcing our defenses; and it may be said that this obligation is beginning to be understood by high national policy. It should also bolster our commitment to international organizations like WHO for global health improvement. AIDS in America and Europe may be regarded as penance for near obliviousness to the frightful health conditions in Africa, which remain far behind the celebration of millennial ascent depicted in Fig. 1. At least some cutting-edge internet communications technology has been harnessed for prompt global alerts of emerging diseases: see <http://osi.oracle.com:8080/promed/>.

On the evolutionary side, we may ponder intrinsic changes in genotype, both in the human host and in the world of germs. Charles Darwin was well aware of Pasteur and Koch's contributions, and optimistic about their contribution to human welfare. Koch's mentor, Ferdinand Cohn, was a frequent guest in Darwin's home. It is the more remarkable then that infection is all but totally ignored as a factor of natural selection in Darwin's writings. For my own discussion, I must concede how difficult it is to corroborate an evolutionary narrative, and we must regard this one as a provocation to experiment rather than a settled account. Darwin, had he been so inclined, was not yet able to recite a concrete example of hereditary adaptation to disease. This had to await J.B.S. Haldane's speculation in 1949 that the prevalence of hemoglobin disorders in Mediterranean peoples might be a defense against malaria. This did precede, if not necessarily inspire, A. C. Allison's report of the protective effect of heterozygous hemoglobinopathy against falciparum malaria in Africa. The side effects of this bit of genetic engineering on Nature's part are well-known: the heavy burden of sickle cell disease when this polymorphism is driven to higher gene frequencies, and the morbid homozygotes become more prevalent. Since then, a handful of similar examples have been deciphered, the majority connected with malaria. Why so? Malaria and tuberculosis are the two scourges so prevalent that ameliorative predispositions will be both strongly selected and obvious for ascertainment. In a similar vein, we have news that a *ccr5* (chemokine receptor) deletion offers some protection against AIDS, but not yet any clarity as to what may have driven that polymorphism in earlier human history.

The small lessons to be gleaned are how fitful and sporadic human evolution is when our genetic change (measured in generations to millenia) is pitted against microbial attack. We have inherited an adaptive immune system, little changed since its early vertebrate origins 200 million years ago. In its inner workings, immunity is a Darwinian struggle, with randomly generated diversification of leukocytes to prime their duel with an unpredictable invader. But this duel is in the soma, with nothing passed on to the host genome to mark a successful encounter. It is plausible that we might inherit a predisposition for good immune responses to the pathogens most prevalent in our racial experience -- but so far this is hardly tested, even for species comparisons. A uniformitarian ideology about immunity may have

hindered more inspired searches for species-restricted innovations in defense against infection. By contrast, the germ that wins the battle does proliferate its genes for success, and can use those enhancements to go on to new hosts, at least in the short run.

"Germs" have long been recognized as living entities. Indeed there is an ambiguity in that nickname to suggest their affinity with "genes". Viruses, with some realism, were credited with being "naked genes" long before they joined the repertoire of molecular genetic investigations. Nevertheless, the idea that they might be evolving has been slow to sink into the ideology and practice of public health. At our millennial dawn, Robert Koch was obsessed that rigorous technique would support the doctrine of monomorphism: the invariance of microbial species in pure culture. Purported "variants" were more likely to be aliens that had floated into the Petri dishes from the atmosphere. Much the same might be said (and truly) about many claims of complex morphogenesis and life-cycles among common bacteria. Koch's rigor was an essential riposte to careless claims of interconvertibility, e.g. that yeasts could be converted into spirilli or cocci. Koch himself relented in time, admitting some possibility of variation, but for him and his contemporaries this was a nuisance rather than the essence of microbes' competence. The multitude of isolable species was confusing enough to the epidemic-tracker; it would be almost too much to bear to cope with new variants of altered serological specificity, host-affinity, or virulence. Even today it would be near heresy to balk at the identification of the great plague of the 14th century with today's *Yersinia pestis*; but we cannot readily account for its ready pneumonic transmission without guessing at some intrinsic adaptation to aerosol conveyance. Exhumations of ancient remains might still furnish DNA evidence to test such ideas.

The molecular genetics that began in 1944 has changed all that, and microbial systems provide our most convenient models for experimental evolution. Diverse mechanisms for genetic variation and recombination are spelled out in ponderous monographs. Assays for chemical mutagenesis are now routinely exercised on bacteria (the Ames test, with *Salmonella*), as testimony for the accessibility of bacterial DNA to environmental insult. Mutators abound, and may be switched on and off in accord with the variegation of the ambient scene. The germs are promiscuous, notably in plasmid transfer conferring resistance to antibiotics, so that innovations are not species-bound. Indeed, the microbial biosphere can be thought of as a world wide web of informational exchange, DNA transfer as the internet. That DNA, in the case of many viruses may be integrated into host genomes; then later remobilized to form active, transmissible particles: hundreds of segments of human DNA originated as integrated retroviruses from historical encounters. Most important is the vastness of population size, and the intensity of its fluctuation. Microbial populations may fluctuate by factors of  $10^{10}$  on a daily cycle, as they move between hosts, or as the host exploits antibiotics or antibodies to defeat them. If we set out to compare the pace of evolution from a priori argument, it would be conservative to give a  $10^6$  or  $10^9$  advantage to the microbe compared to the multicellular host. A year in the life of bacteria would easily match the span of mammalian evolution. We ought then be quite fearful of the outcome of the contest, barring only what we could bring to the contest by way of technical wit and social intelligence. We would still wonder, how account for the reality that, however punctuated is our history with catastrophic plague -- and evidence of sporadic species wipeouts in natural history -- we are indeed still here!

That may be taking a too Manichean view: "us good, them evil". Yes, at the top of the food chain, the human species shares the summit only with micropredators. We also know our eventual fate, if not by fire, then our remains will be restored to the geosphere by some form of microbial combustion. The real contest is between the greedy parasites and the ubiquitous saprophytes in ensuring the ultimate triumph of entropy. Why are we still here?" In fact the parasites have a shared interest in our survival: the death of the host is a dead end for every invader, bar a few bottom-feeders. To domesticate the host is a preferred outcome for the longer run. This has no more persuasive example than the most successful of all microbes: the mitochondria. These have invaded every eukaryote (embracing yeast, protozoa, and all multicellulars), and provide the machinery of oxidative metabolism. Other bacteria have evolved into the chloroplasts: these are the primary captors of solar energy, emitting both oxygen and the fixed carbon that nourishes the biosphere. Who has domesticated whom? Every animal builds its existence around the recapture of that food, including the relentless burden of heavy breathing to sustain the respiration, to stoke the mitochondrial furnaces.

These ideas have been voiced over many years, sometimes too emphatically as if the parasite has an active intelligence to guide its symbiotic restraint. In the short run, the infected host is at metastable equilibrium: think of it as a superorganism, with the respective genomes yoked in a form of chimera. The host's immune response may be excessive, with autoimmune injury (not least from cytokines) a byproduct. On the microbes' part, as with rogue cancer cells, exuberant deviant cells may overtake the soma, with their own demise and that of the parent population the outcome. In a broader reach, it is as important for parasites to moderate their virulence once established, as it is for them to have aggressive means of entering the body surfaces and radiating some local toxicity to counter the hosts' defenses. Lacking to date has been any systematic study of that optimization. We are so focussed on hypervirulence as a research paradigm that we neglect the physiology of homeostatic balance in the infected host qua superorganism.

That the burden of mutualistic adaptation must fall largely on the parasite is a corollary of the evolutionary pace: at odds with the more popular teachings of co-evolution, where host and parasite genomes negotiate their coexistence. When a parasite enters another species, what we then call a zoonosis, the outcomes may be divergent. In many cases, there will be no infection at all -- we ignore that. In others, the host environment is not greatly altered, and we may have similar infection, as with many enteritides. Exceptionally, the parasite is maladapted to the new host, through lack of prior experience, and the restraints fail: we call that a virulent zoonosis, with such examples as psittacosis, Q-fever, rickettsioses, or hantavirus. Human infections play a small part in the life cycle of these zoonoses, so that selection for moderation is inoperative. From this perspective, the ill-adapted pathogen is the one that has not surveilled the host genome and not parlayed its own genome to optimize its position on the scale of virulence. Host genomes will also adjust themselves, but on an incommensurably slower time scale. Almost by definition, most of our experimental models of infection are zoonoses, alien hosts to simulate human disease. The operational ideal is the mouse succumbing overnight to inoculation of a few cells. This is superb for "in vivo" testing of an antibiotic, but bears little relationship to the dynamics of everyday human disease.

In its dominant role the parasite may go so far as to manipulate the immune system of the

host to its own advantage. I'd suggest that a parasite will tend to display just those epitopes as will a) moderate but not extinguish the primary infection, and b) will inhibit superinfection by competing strains, of the same or even of other species. According to this doctrine, the symptoms of influenza are evolved in part to help ward off other viral infections. This is purely speculative, but the doctrine does have substantial support in tuberculosis and in schistosomiasis. The HIV fails in the end when opportunistic infections supervene to kill the host as a byproduct of the virus' protracted duel with the host's cellular immune system. We need generally to look more closely at earlier stages of chronic infection for cross- protective factors. Helicobacter has been found to secrete antibacterial peptides that inhibit other enterics, and HIV and other lentiviral envelopes also do make antimicrobials -- their significance for natural history of disease as yet unknown.

Parasite dominance may also account for some paradoxes: many of the most successful pathogens are slow-growing and nutritionally fastidious. Invasive bacteria do not produce the most potent toxins -- these are left to the clostridia (botulinum, tetanus) which are mainly carrion-feeders and soil inhabitants, for whom people are the most incidental hosts. We may think of sexually transmitted disease as incidental to our erotic proclivities. However, it is not a facetious suggestion that parasites invented sex, e.g. the apparatus of bacterial conjugation, as their method of moving from one host to another, is today exemplified by many plasmids which have encoded the transfer apparatus in their own genomes.

Within the past decade, the complete genomes of many microbes have been displayed, but they are far from unravelled. Most observers have been impressed by their complexity, diversity and novelty, at the same time as they see evidence for the web of interchange permeating the evolutionary charts. Innumerable genes have yet to have their functions explored -- a marvelous opportunity for the definition of therapeutic targets. Together with wiser insight about the groundrules of pathogenic evolution, we have a platform for new generations of success in responding to the challenges of infectious disease: certainly many new vaccines, antibiotics and immune modulators. The lesson of HIV and other emerging infections has also begun to take hold in government and as a market opportunity for an invigorated biotechnology industry. If we do the hard work, and take no success for granted, we may be able to fend off recurrences of 1918 (influenza) and 1981 (HIV) in the further history of this millenium.

The executive summary of this discussion is a plea for a more ecologically informed research program in infectious disease, a germ's eye view, if you like. Besides the morbidic colonizers of our skin, gut and mucous membranes we are host to a poorly catalogued ensemble of symbionts to which we pay scant attention. Yet they are equally part of the "superorganism" genome with which we confront the rest of the biosphere. Their protective role is already attested to by the superinfections that often attend specific antibiotic therapy. Intermicrobial competition in the soil was recognized for decades before its exploitation by Dubos and Waksman in seeking the early antibiotics. The microbial ecology of our own bodies is overdue for yielding similar fruit. Another corollary is a caveat about the eradication of pathogens (like smallpox, and soon polio) absent a strategy for sustaining some level of immunity, guarding against a possible recrudescence. This might be achieved by our domestication of commensals to bear relevant cross-reacting epitopes, or alternatively to implant these into food additives. At a cruder level, a super-hygienic environment might be



to our disadvantage if we fail to understand what we then lack by way of immunogenic stimulation. If we dare not return to random filth, biosynthetic dirt may be the recipe.

CODA The moderately optimistic note of the foregoing discussion is premised on the rational investment in technology and social systems needed to understand infection and moderate its impact. There is a darker side to that microbiological engineering: its prospective use for biological warfare (BW). As often remarked, BW may become the poor man's atomic bomb; if not now there is the prospect of eventual development of etiological agents and systems to deliver them that would justify such nightmares. Future technology is likely to favor the offensive; technical defenses are unlikely to meet all of the threats that can be collected today or designed tomorrow. As a measure of social intelligence, it would be a positive mark if there could be a consolidated consensus to internalize and enforce the 1975 BW disarmament convention. The moral basis of that is a global crusade to enhance and apply scientific knowledge to counter infectious disease everywhere. =====

Fig. 1 Life expectancy

Fig. 2 Infectious disease mortality

Fig. 3 Table, examples of emerging infections.

Fig. 4 Timeline.

==== Fig. 3 Table, examples of emerging infections.

Examples of pathogenic microbes and infectious diseases recognized since 1973  
from CISET report 1995

Year	Microbe	Type	Disease
1973	Rotavirus	Virus	Major cause of infantile diarrhea worldwide
			1975 Parvovirus B19 Virus Aplastic crisis in chronic
			hemolytic anemia 1976 Cryptosporidium parvum Parasite
			Acute and chronic diarrhea
1977	Ebola virus	Virus	Ebola hemorrhagic fever
1977	Legionella pneumophila	Bacteria	Legionnaires' disease
1977	Hantaan virus	Virus	Hemorrhagic fever with renal syndrome (HRFS)
			1977 Campylobacter jejuni Bacteria
			Enteric pathogens distributed globally 1980 Human T-lymphotropic

Virus	T-cell lymphoma-leukemia virus I (HTLV-1)		
1981	Toxic producing strains of <i>Staphylococcus aureus</i>	Bacteria	Toxic shock syndrome (tampon use)
1982	<i>Escherichia coli</i> O157:H7	Bacteria	Hemorrhagic colitis; hemolytic uremic syndrome
1982	HTLV-II	Virus	Hairy cell leukemia
1982	<i>Borrelia burgdorferi</i>	Bacteria	Lyme disease
1983	Human immunodeficiency virus (HIV)	Virus	Acquired immunodeficiency syndrome(AIDS)
1983	<i>Helicobacter pylori</i>	Bacteria	Peptic ulcer disease
1985	<i>Enterocytozoon bieneusi</i>	Parasite	Persistent diarrhea
1986	<i>Cyclospora cayatanensis</i>	Parasite	Persistent diarrhea
1988	Human herpesvirus-6 (HHV-6)	Virus	Roseola subitum
1988	Hepatitis E	Virus	Enterically transmitted non-A, non-B hepatitis
1989	<i>Ehrlichia chafeensis</i>	Bacteria	Human ehrlichiosis
1989	Hepatitis C	Virus	Parenterally transmitted non-A, non-B liver infection
1991	Guanarito virus	Virus	Venezuelan hemorrhagic fever
1991	<i>Encephalitozoon hellem</i>	Parasite	Conjunctivitis, disseminated disease
1991	New species of <i>Babesia</i>	Parasite	Atypical babesiosis
1992	<i>Vibrio cholerae</i> O139	Bacteria	New strain associated with epidemic cholera
1992	<i>Bartonella henselae</i>	Bacteria	Cat-scratch disease; bacillary angiomatosis

1993	Sin nombre virus	Virus	Adult respiratory distress syndrome
1993	Encephalitozoon cuniculi	Parasite	Disseminated disease
1994	Sabia virus	Virus	Brazilian hemorrhagic fever
1995	HHV-8	Virus	Associated with Kaposi sarcoma in AIDS patients

Fig 4.

needs more work Timeline. Mostly derived from Nobel Prizes (\*) and the ASM poster. The prizes \* often postdate the discoveries by 10-20 years

1346 - initiation of Black Death in Europe

1492 - Columbus initiates European conquest of America

1546 - Fracastoro -- On contagion

1637 - Cinchona bark (quinine) brought to Europe for malaria

1684 - Jenner observes bacteria with new microscope

1798 - Jenner, vaccination

----- current millenium ----- 1877 - Patseur & Koch, initiate studies of anthrax

1892 Ivanowski, Dmitri: Discovers tobacco mosaic disease

1893 Smith, Theobald and F. L. Kilbourne: ticks carry Babesia microti;

1900 Reed, Walter: yellow fever is caused by mosquitoes; mosquito eradication programs were begun

1901 \* VON BEHRING, EMIL ADOLF "for his work on serum therapy, especially its application against diphtheria

1902 \* ROSS, Sir RONALD "for his work on malaria

1905 \* KOCH, ROBERT "for his investigations and discoveries in relation to tuberculosis"

1907 \* LAVERAN, CHARLES LOUIS ALPHONSE "in recognition of his work on the role

played by protozoa in causing diseases"

1908 \* METCHNIKOFF, ELIE \* EHRLICH, PAUL "in recognition of their work on immunity"

1913 \* RICHET, CHARLES ROBERT "in recognition of his work on anaphylaxis"

1915-17 Twort, Frederick, then Felix d'Herelle discover bacteriophage.

1918 Epidemic of Spanish flu causes 40 million deaths in Europe (1918- 1919)

1919 \* BORDET, JULES "for his discoveries relating to immunity"

1927 \* WAGNER-JAUREGG, JULIUS therapeutic use of malaria inoculation in treatment of syphilis

1928 \* NICOLLE, CHARLES JULES HENRI "for his work on typhus"

1928 Griffith, Frederick:discovers genetic transformation phenomenon in pneumococci

1939 \* DOMAGK, GERHARD "for the discovery of the antibacterial effects of prontosil"

1941 - bacterial viruses visualized by electron microscope                      Ruska, Helmut; using microscope invented by Ernst Ruska

1944 Avery, Oswald, Colin MacLeod and Maclyn McCarty: discover that DNA is the transforming principle

1945 \* FLEMING, Sir ALEXANDER \* CHAIN, Sir ERNST BORIS \* FLOREY, Lord (HOWARD WALTER) "for the discovery of penicillin and its curative effect in various infectious diseases"

1951 \* THEILER, MAX "for his discoveries concerning yellow fever and how to combat it"

1952 \* WAKSMAN, SELMAN ABRAHAM "for his discovery of streptomycin, the first antibiotic effective against tuberculosis"

1954 \* ENDERS, JOHN FRANKLIN \* WELLER, THOMAS HUCKLE \* ROBBINS, FREDERICK CHAPMAN " cultivation of viruses in cell cultures

1958 \* BEADLE, GEORGE WELLS \* TATUM, EDWARD LAWRIE genes act by regulating definite chemical events"; \* LEDERBERG, JOSHUA genetic recombination in bacteria

1959 \* OCHOA, SEVERO \* KORNBERG, ARTHUR "enzymology of biological synthesis of RNA and DNA

1960 \* BURNET, Sir FRANK MACFARLANE \* MEDAWAR, Sir PETER BRIAN "acquired immunological tolerance"

1962 \* CRICK, FRANCIS HARRY COMPTON \* WATSON, JAMES DEWEY \* WILKINS, MAURICE HUGH FREDERICK DNA is a double helix

1965 \* JACOB, FRANCOIS \* LWOFF, ANDRI \* MONOD, JACQUES " genetic control of enzyme and virus synthesis"

1966 \* ROUS, PEYTON "discovery of tumor-inducing viruses";

1969 \* DELBRCK, MAX \* HERSHEY, ALFRED D. \* LURIA, SALVADOR E. "replication mechanism and the genetic structure of viruses"

1972 \* EDELMAN, GERALD M. \* PORTER, RODNEY R. "chemical structure of antibodies"

1973 Cohen, Stanley, Annie Chang, Robert Helling and Herbert Boyer: use of plasmids as cloning vectors in genetic engineering

1975 \* BALTIMORE, DAVID \* DULBECCO, RENATO \* TEMIN, HOWARD MARTIN "tumour viruses and the genetic material of the cell; reverse transcription"

1976 \* BLUMBERG, BARUCH S. \* GAJDUSEK, D. CARLETON hepatitis and atypical slow viruses.

1979 Smallpox eradication program of WHO completed

1980 \* BENACERRAF, BARUJ \* DAUSSET, JEAN \* SNELL, GEORGE D. antigen presentation and histocompatibility in immune response.

1981 AIDS first identified as a new infectious disease

1983 Montagnier, Luc and Robert Gallo: discover the HIV virus that is believed to cause AIDS

1984 \* JERNE, NIELS K. \* KVHLER, GEORGES J.F. \* MILSTEIN, CISAR " immune networks and monoclonal antibodies

1987 \* TONEGAWA, SUSUMU "for his discovery of the genetic principle for generation of antibody diversity"

1995 Venter, Craig, Hamilton Smith, Claire Fraser and TIGR colleagues: elucidate the first complete genome sequence of a microorganism

1996 \* DOHERTY, PETER C. \* ZINKERNAGEL, ROLF M. "for their discoveries

concerning the specificity of the cell mediated immune defence"

1997 \* PRUSINER, STANLEY B. "for his discovery of Prions \* a new biological principle of infection"