be invited to
What a privilege it is to join in celebration of one of this century's great virus-hunters. I have never worked in the field; my own laboratory research has been on model systems for virus- host relationships in bacteria; and these indeed have been very revealing for insight into the genetics and evolution of human pathogens. But I really do look up to you workers in the trenches as real heroes in the human encounter, ~~with predatory microbes~~. Let me step back a bit from the battlefront and see if we can get any clarity about our fate as a species. "Hominid" was in my title, just to dramatize, as an only one of many species.

- Certainly I am preaching to the choir here about emerging infections. Most of you would say "What's new?" - they're always emerging, and of course that's just right. What is new is that we are emerging from a zone of complacency, born of the wonderful successes of medical technology on through the vaccines, antibiotics, the eradication of smallpox (and soon polio); only to be brought up short by the HIV pandemic. And there are still too many folks who fail to see that as a lesson, that there is an infinite reservoir of hazard of that ilk or worse; we need to wake up and see if there are not some precautions that can save us from self-inflicted surprise in future. There are some ways in which the world has evolved into a uniquely new kind of habitat: instantaneous jet travel (well over a million international air boardings every day) -- linking incredibly dense and socially stratified human populations. You all understand very well the implications of that structure for the ecology of transmissible pathogens. Nothing is more important than the surveilling watchposts, often shoestring operations, that many of you mount overseas. So you are all familiar with these extracts from the CISET report --

SLIDE CISET COVER
SLIDE EMERGING
SLIDE RE-EMERGING

and could add many more entries: drug-resistant plague, tuberculosis; vancomycin-resistant staph, resurgent meningitis and monkeypox, and every bulletin from WHO's WER.

You are also well aware of the unique facility of microbial genomes for rapid evolution and reshuffling.

SLIDE MICROBIAL EVOLUTION

--- so I am not going to dwell on those much further. I thought I would take a moment to reflect on the paradoxes of our co-evolution with the bugs, how ill we understand the divergence between the short and long run advantages.

SLIDE HOST-PARASITE CO-EVOLUTION.

Of course, I fully support efforts to impart some evolutionary understanding of how things came to be as they are -- a necessary precondition for any sort of foresight about the future. But my main conclusion is that we are poised in a state of ecological instability, and are very poorly equipped to detail the outcome of any specific encounter, or of the overall struggle. Where will AIDS be 10, 15 years from now? What were we saying 15 years ago?

NOTES TO CHART. Host/par co-evolution

========== Let me turn now to contingency planning for worst case scenarios: you have lived through any number of tactical exercises, and no one is better equipped. I mean this for a discussion of research and public health planning: the media have already done a sufficient job of arousing public awareness (not enough on the concrete measures needed for defense: those cost money.)

My imagination about these problems is informed by daily happenings in my own laboratory, going back to 45 years ago and the discovery that E. coli harbored a lysogenic virus, lambda. This is integrated in its genome very much as HIV or other retroviruses are in mammalian cells. It is a small burden to its host; in other settings like diphtheria or cholera, comparable prophages confer important toxigenic or virulence advantages to the host. Lambda prophage also normally confers immunity to lytic attack by exogenous lambda. The prophage is occasionally mobilized by DNA damage or inactivation of the repressor protein: that cell may then yield a productive infection; but it will not spread further to the immune cells in the culture.

Sporadically, the lambda mutates to a virulent form (repressor-indifferent) which can then override the immunity conferred by the lysogen in neighboring cells. In an hour or two, a culture of 10^9 bacterial cells can be cleared, leaving only a few survivors: these have a defective OMP (outer-membrane-protein), thus lack the receptor for binding the lambda. This is a rare event in E. coli; many freshly isolated staphylococci exhibit self-plaquing incessantly, and almost any lysogen has this pootentiality.

At a level of basic biological principle, this could be a model for the human population. Of course there are differences: we live somewhat less closely packed; we do have immune systems; we do have the possibility of social intelligence. These are quantitative mitigators; they do not alter the basic premises, and that vaunted intelligence will do us little good unless we learn to apply it on a global basis.

Nothing quite like that has happened to our own species -- but close enough.

Strain X is a hypothetical microbe - probably a virus, unless we are particularly somnolent about developing new antibacterials. Imagine a case fatality rate of 20% (as for yellow fever) and an attack rate of 50% (as in some influenza outbreaks). This

probably presumes aerosol transmission from person to person; it may not require an animal reservoir. With a survival of 80%, and continued infectivity during prodromal or convalescent stages, human morbidity is a minor impediment to transmission. What do we do to anticipate such happenings, minimize them starting, contain them before they reach global proportions? MALTHUS redux. He was "wrong"; but...

4 SLIDE : New strains

How could this arise? You can apply your own imagination to your own favorite bugs. It need not be a genetic innovation, but the breakout of an existing virus to a new niche. For decades, there have been many warnings of the possible spread of yellow fever to the Indian subcontinent, already burdened with competent mosquito vectors -- and the alarm already rung with hemorrhagic dengue. I have a friend in Delhi who barely survived the latter who cannot recall having seen a mosquito during the period of presumed incubation: are there other media for flaviviruses? And we have been remarkably nonchalant about Aedes albopictus eradication in the U. S. having abandoned a concerted program almost 30 years ago.

But I will concentrate on the tougher case of a new emergent, tougher as there will be delays in recognition, identification and any possibility of vaccine development.

Please criticize my premises; and if you don't disagree, help think through what we should be planning on

5 SLIDE

T/66. johnson
12/8/97

New mutant and recombinant strains
Endogenous and exogenous viruses

Ecological settings:
- Inter-species encounters
  - Forest margins (includes suburbia)
  - Megaprojects and climate change -- vector scrambling
  - Mixing bowls: pigs (and fowl), domestic pets
    - lessons from sheep scrapie and mad cows
  - xenotransplants: wild baboon tissues!
  - laboratory experimentation (minor compared to biosphere)
- Co-morbidity and immune deficiency
  - HIV (as already seen for TB)
  - immunosuppression
- Urban gardens
  - megacity slums

Genetic facilitators
- Physical and Chemical mutagens (and recombinogens)
- Mutator genotypes
- Relaxed constraints on genetic (inter)change
  - mutS - abrogation of mismatch repair
  - antibiotic and other stress: - downregulate DNA restriction

e.g. mutagenic or recombinogenic hosts or "helpers". for rec-RNA.

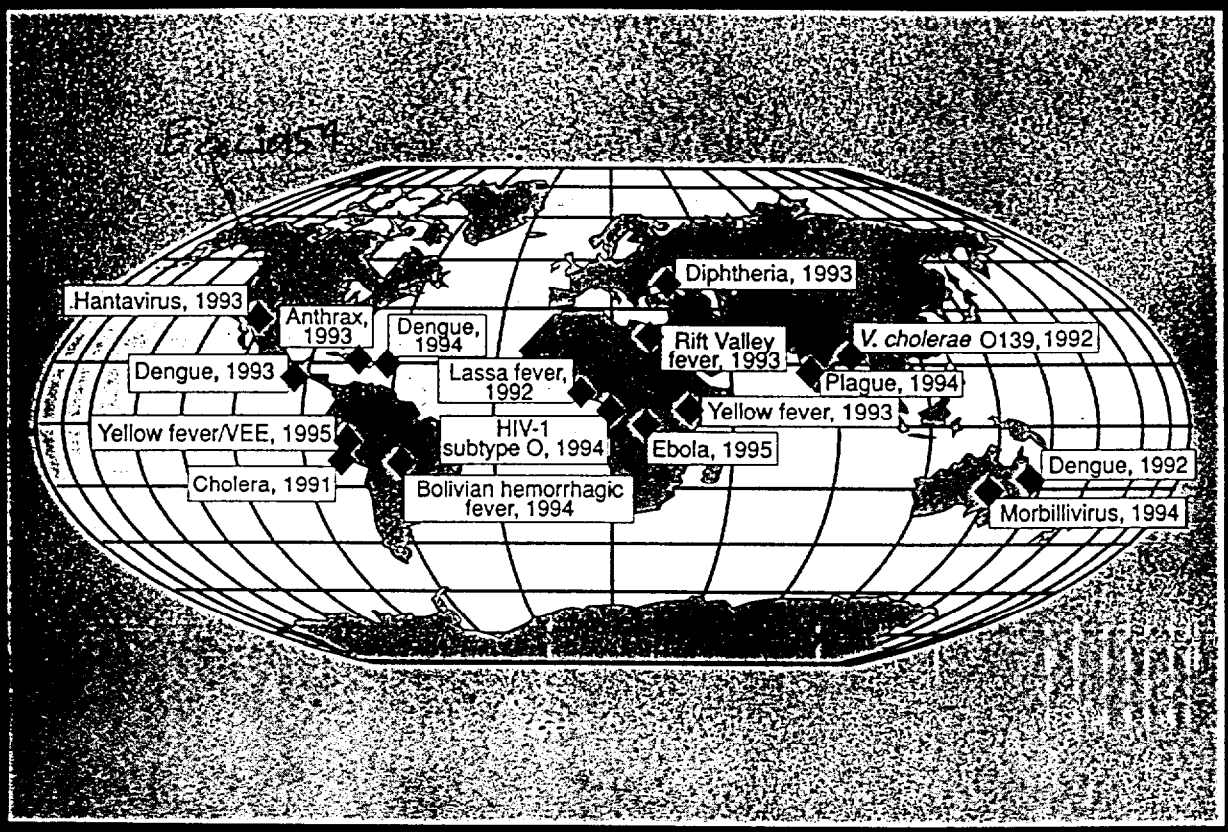
With few exceptions, little we can do to prevent emergence without a much stronger investigative base: laboratory and field research.

Prospects for reactive measures

intelligence (surveillance, reporting, integration)
QRF's
nimble remedial development: vaccines
new antivirals: combinatorial chemistry

Disaster management.
How oversee infection control measures for a continent.
(Preview: plague in India sans antibiotic?)

Infectious Disease -- A Global Health Threat



14th C. Plague — Asia → Europe
16th C. Syphilis — New World → Europe
Smallpox, measles ←
19th C. Yellow Fever — South → North
1918 Influenza — ?? N. America → world
1980's HIV — Africa → world
1990's MDR

Table 2 Examples of pathogenic microbes and infectious diseases recognized since 1973

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

CISET

Table 3 Re-emerging infections during the last two decades and factors contributing to their re-emergence

EVOLUTIONARY CHANGE ALWAYS A CONTINGENCY

Disease or Agent	Factors in Re-emergence
Viral	
Rabies	Breakdown in public health measures; changes in land use; travel
Dengue/dengue hemorrhagic fever	Transportation, travel and migration; urbanization
Yellow Fever	Favorable conditions for mosquito vector
Parasitic	
Malaria	Drug and insecticide resistance; civil strife; lack of economic resources
Schistosomiasis	Dam construction, improved irrigation, and ecologi cal changes favoring the snail host
Neurocysticercosis	Immigration
Acanthamebiasis	Introduction of soft contact lenses
Visceral leishmaniasis	War, population displacement, immigration, habitat changes favorable to the insect vector, an increase in immunocompromised human hosts
Toxoplasmosis	Increase in immunocompromised human hosts
Giardiasis	Increased use of child-care facilities ; water contam.
Echinococcosis	Ecological changes that affect the habitats of the intermediate (animal) hosts
Bacterial	
Group A Streptococcus	Uncertain
Trench fever	Breakdown of public health measures
Plague	Economic development; land use
Diphtheria	Interruption of immunization program due to political changes
Tuberculosis	Human demographics and behavior; industry and technology; international commerce and travel; breakdown of public health measures; microbial adaptation
Pertussis	Refusal to vaccinate in some parts of the world because of the belief that injections or vaccines are not safe
Salmonella	Industry and technology; human demographics and behavior; microbial adaptation; food changes
Pneumococcus	Human demographics; microbial adaptation; international travel and commerce; misuse and overuse of antibiotics
Cholera	Travel: a new strain (O139) apparently introduced to South America from Asia by ship, with spread facilitated by reduced water chlorination and also food

GENETIC EVOLUTION

Microbes (bacteria, viruses, fungi, protozoa).

Rapid and incessant

Huge population sizes 10^14+ and generation times in minutes vs years

Intraclonal:

DNA replication -- may be error-prone -- in sea of mutagens
sunlight; unshielded chemicals, incl. natural products

RNA replication -- intrinsically uneditted, > 10^-3.
swarm species

haploid: immediate manifestation; but partial recessives not accumulated
contra multicopy plasmids

site-directed inversions and transpositions: phase variation
compiling treasures of past learning : repressed enzymes

amplification

?? Other specifically evolved mechanisms
genome quadrant duplication; silencing

• mutators – pheno: and geno. stress-regulated?

Interclonal

Promiscuous recombination -- not all mechanisms are known.

Conjugation -- dozens of species

Viral transduction & lysogenic integration: universal
Classical: phage borne toxins in C. diphtheriae

Plasmid interchange (by any of above) and integration ; cassettes, integrons
Toxins of B. anthracis ; pathogenicity islands
Pasteur: heat attenuation: plasmid loss; chemically induced

RNA viral reassortment; ?? and recombination?

Transgressive -- across all boundaries
Artificial gene splicing
Bacteria and viruses have picked up host genes
(antigenic masking?)
Interkingdom: P. tumefaciens and plants
E. coli and yeast
Tobacco and immunocytes
Shigella; phage; -- and human cells
Vegetable and mineral! oligonucleotides and yeast.

HOST-PARASITE CO-EVOLUTION

Co-adaptation to mutualism *vs.* accentuation of virulence?
Jury is still out. (Efforts at theory: May and Anderson; Ewald).
Probably divergent phenomena
Short term flareups and Pyrrhic victories
Long term trend to co-adaptation

The parasites' dilemma:

- proliferate rapidly - kills host as byproduct
  winning strategy if transmission is easy, e.g vectors
  anarchic rogues may subvert optimum strategy for the swarm
- proliferate slowly - host defenses win (Darwinian struggle in host)
  try stealth, molecular mimicry, subvert immune system

Vectors: rarely symptomatic; exception: mad dogs

Symptoms are they parasite tricks; host defenses; spandrels ??
Fever; Cough; Diarrhea; Hemorrhage; Malaise; Headache; Anorexia
Death: when is it to parasite's advantage?

Zoonotic transfers notorious (recall debate on Martian bugs)
Most don't take at all, or for closely related hosts, neutral.
These are unremarked
Some are especially vicious (Ebola, Hantavirus)
host sees aliens, has no evolved defenses
naive re maternal immunity

Mitochondria and chloroplasts as ultimate symbionts
Who serves whom?
Integration of viruses into genome: λ/ E. coli; retroviruses
Plasmids in bacteria: enhance virulence; sexual transmission; infatuation

ECOLOGICAL INSTABILITY