Tribute to Zinder

THE ROCKEFELLER UNIVERSITY
RESEARCH PROFILES
WINTER 1987-88

A Fine Playground

Bacteriophages — "bacteria eaters" — are tiny viruses that make their living by infecting bacteria. The late Max Delbrück, one of the pioneers of molecular biology, described bacteriophage research as "a fine playground for serious children who ask ambitious questions."

In 1952 Norton Zinder, a graduate student at the University of Wisconsin, reported in his doctoral dissertation that bacteriophages can pick up genes from one bacterium and deposit them in another. Molecular biology was in its infancy. The identification of DNA as the genetic material had been reported only eight years earlier and was still being debated. Watson and Crick had yet to build a model of the double helix structure of DNA. And the universality of the genetic code to all living beings was years from being established. "A lot of people didn't even believe bacteria had genes," Dr. Zinder says.

His faculty advisor and collaborator in this research was a young assistant professor named Joshua Lederberg (later president of The Rockefeller University). "My thesis examination," Dr. Zinder recalls, "was essentially a conversation between Josh and me. The four other professors in attendance, while expert in the traditional bacteriology of the day, were frankly baffled by what we were saying."

They were talking about a process called transduction, nature's model for what we now know as recombinant DNA technology. The development of modern molecular genetic research and genetic engineering had its origins in observations

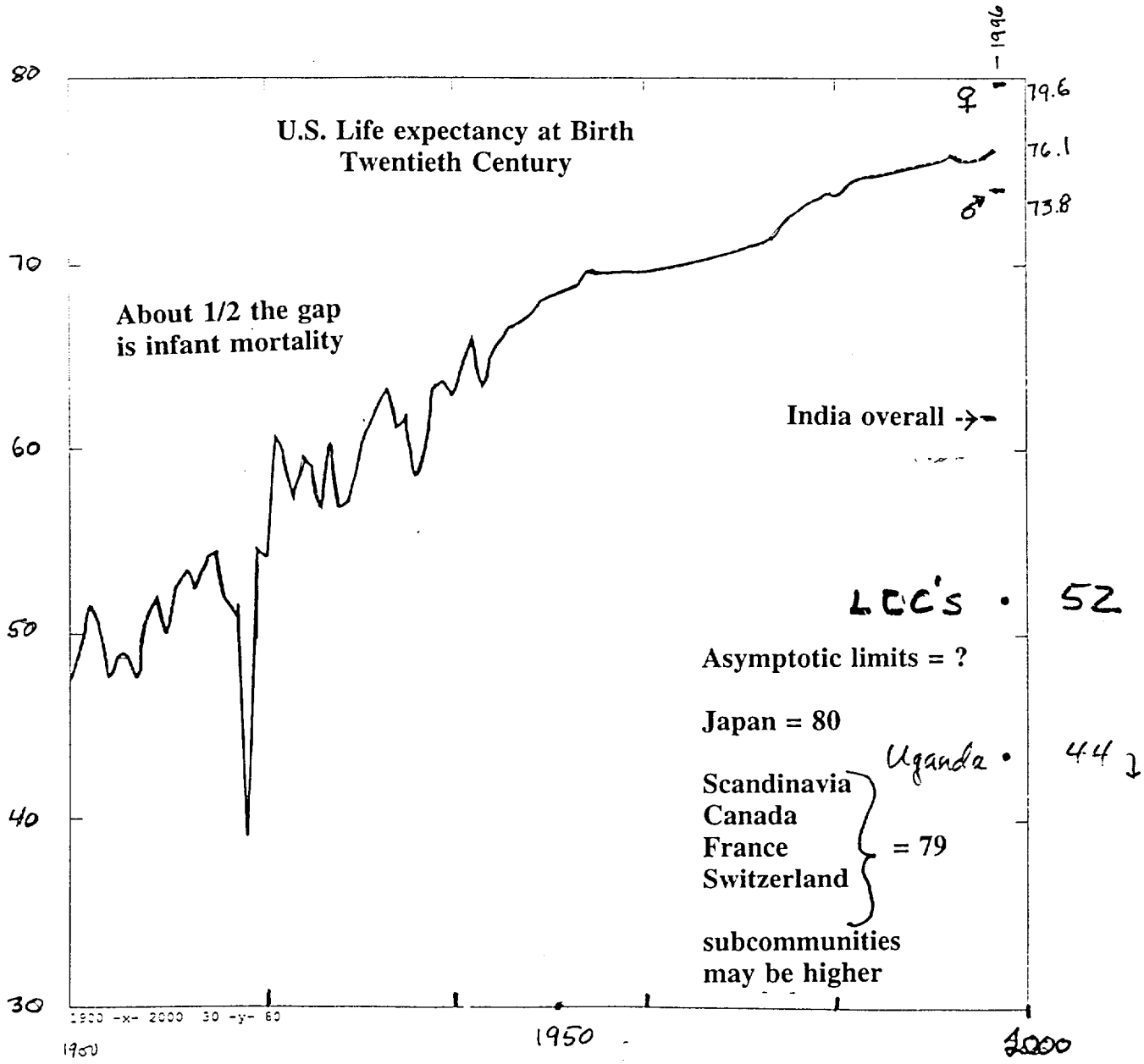
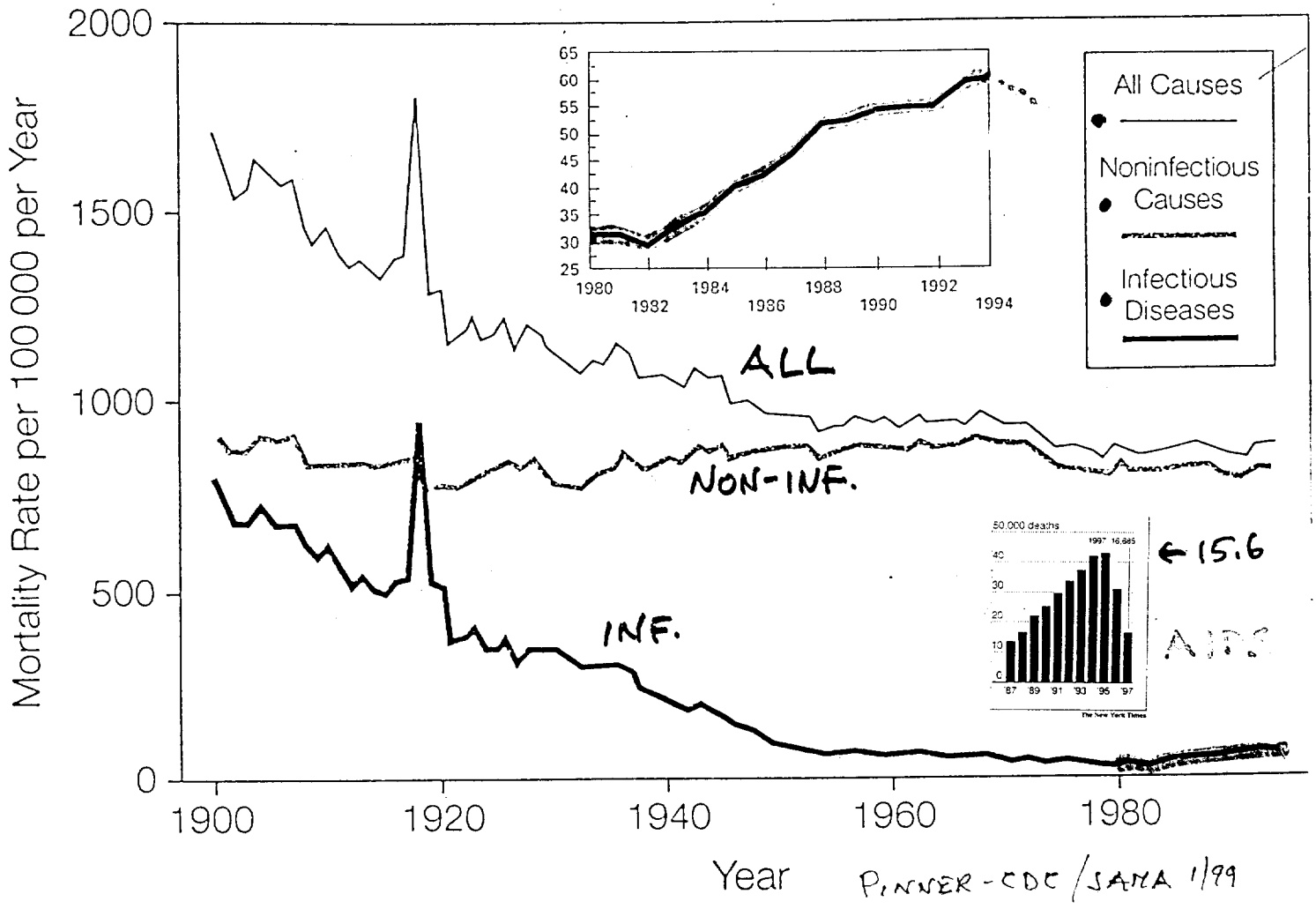

U.S. Life expectancy at Birth
Twentieth Century
- 1996
♀ - 79.6
76.1
♂ - 73.8
About 1/2 the gap
is infant mortality
India overall ->
LDC's • 52
Asymptotic limits = ?
Japan = 80
Uganda • 44
Scandinavia
Canada
France
Switzerland
= 79
subcommunities
may be higher
80
70
60
50
40
30
1900 -x- 2000 30 -y- 80
1950
1950
2000

Figure 2. Crude Mortality Rates for All Causes, Noninfectious Causes, and Infectious Diseases



U.S. population now 270 MM
annually 2 MM deaths
3 MM births

AIDS peaked at 15.6 now ~5.0, or 0.5% of mortality.
Another flu would enhance mortality by 50% ~ heart disease, 2x cancer

Selected Emerging and Re-emerging Diseases (1995-1996)

WHO/EMC

CISET

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

Influenza serotypes
V. vulnificus

April 21, 2000

CDC Reports U.S. Meningitis Cases

WASHINGTON (AP) -- The first U.S. cases in an apparent worldwide outbreak of a rare strain of meningitis have been reported. Government health officials said Thursday that at least three New Yorkers have come down with the type of the disease that's been linked to this year's Muslim pilgrimage to Mecca. Health officials warn that anyone else who returned from the annual pilgrimage last month, or who has had close contact with a participant, should see a doctor if they suffer meningitis symptoms.

Bacterial meningitis is a serious and often deadly infection of the fluid and membranes covering the brain and spinal cord. It is spread through coughing, kissing and other close contact.

The U.S. Centers for Disease Control and Prevention warned all returning pilgrims and their close contacts to contact a doctor or go to the nearest emergency room if they experience fever, intense headache, stiff neck or neck pain, pain when looking at bright lights, nausea or vomiting.

The World Health Organization said Thursday it had recorded 250 cases of meningitis linked to the pilgrimage, including 55 deaths. The reports began about a week ago when Britain and France diagnosed meningitis in people returned from the pilgrimage.

http://www.promedmail.org

Date: Fri, 28 Apr 2000 23:40:58 -0400 (EDT)
From: ProMED-mail <promed@promed.isid.harvard.edu>
Subject: PRO/AH/EDR> Monkeypox - Congo, Dem. Rep. (Mbuji-Mayi): 1999

MONKEYPOX - CONGO, DEMOCRATIC REPUBLIC (MBUJI-MAYI): 1999

****

From: Pierre Bigras <pbigras@netrover.com>
Source: IRIN-CEA Bulletin 911, Thu 26 Apr 2000 [in French]
<http://www.reliefweb.int/w/rwb.nsf/>

According to a report from the United Nations Office for the Coordination of Humanitarian Assistance, there were 315 deaths from monkeypox in the diamond mining town of Mbuji-Mayi in 1999.

[The case fatality rate for monkeypox in children ranges from 1-14%, so taking an average of 7% there may have been 2000 cases. From 1970-94 only 400 cases were reported from Africa, most of them from the DRC; most were found during a 5-year period of active surveillance by WHO from 1981-86. In 1996 there were 70 suspect cases with 6 deaths, and the virus was isolated. Smallpox vaccine protects against monkeypox, but vaccination was stopped in the DRC in 1982 and WHO does not recommend restarting it. (Chin, J. (ed.) Control of Communicable Diseases Manual 2000, 17th edn., p.458). So the virus may be emerging. - Mod.JW]

Why we have a problem in competing with microbial evolution!

Human: limited population size 10 ^10
each organism large and costly
generation time (3-4 per century)
intolerance for violent fluctuations
buffering of genetic system vs. mutations
diploid gene set: deferred expression

Microbial:
huge populations 10 ^15 ....
tiny organisms, dispensable
rapid reproduction, 20 mins or less
high exposure to mutagenesis
mechanisms of gene transfer

Why are we still here?

Microbes have some shared interests in the survival of their hosts

ARE WE TOO HOST-CENTERED?

towards a germ's eye view.

Some Eschatology: Dust unto Dust

- **The ultimate sink of (organic) carbon is CO2**
  by combustion; else by (microbial) metabolism
- **The ultimate competition is between**
  saprophytes and parasites
  (with us as the prey)
- **Bacteria preceded us by 3 Billion years**
  will probably be our successors

-------"SO WHAT?"--------

- **The tempo of microbial evolution >>> multicellulars.**
  ergo the equilibria we observe are governed by the microbes
- **investigate how parasites moderate their attack**
  How *chronic* infection is sustained
  How host immunity is exploited
  the brunt of research is on hypervirulence
- **investigate how parasites (commensals) protect us**
  against *their* competitors
  (Normal flora ecology is notoriously neglected)
- **Beware of eradication**
  at least be prepared to treat future outbreaks
  and unexpected secondary consequences
- **Toxins are *hormones***
- **Hygiene may sometimes be too much of a good thing.**
- **Bacteriophobia has historically impeded basic enquiry.**

-------The difference BW makes---------

- **Artificially selected pathogens may be hard to devise**
  but not subject to these constraints of natural selection

Science 4-14-00