

Early Germinative Ideas on the Origins of Infectious Disease

In his Pathways of Discovery essay "Infectious history" (14 Apr., p. 287), Joshua Lederberg presents a perceptive and insightful overview of the historical background and progress in our understanding of infectious diseases that affect humans and animals. However, in view of the importance of infectious diseases that affect the major food and fiber crops worldwide, it would have been valuable if Lederberg had mentioned the important contributions to the germ theory of disease made by plant scientists long before the classic contributions of Robert Koch and Louis Pasteur. For example, in 1807 Isaac Benedict Prevost, a Swiss scientist working in Montauban, France, was the first to provide definitive evidence that the bunt disease of wheat is caused by a microorganism, smut fungus (1). He completed detailed experiments on the germination of bunt spores and demonstrated by direct inoculation that they could infect wheat. In 1853 Heinrich deBary, a German physician who became interested in plant diseases, published a comprehensive paper that clearly implicated smut and rust fungi as causal organisms of diseases affecting cereal crops

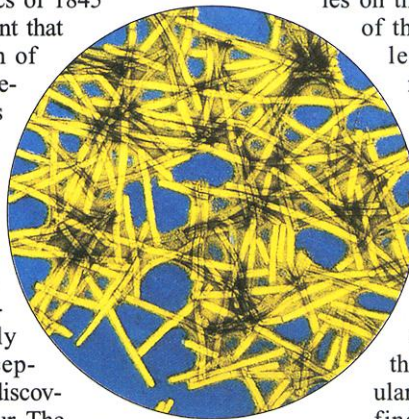
(2). In subsequent research, he determined that a fungus was responsible for the late blight disease of potatoes (1, 2). This disease caused extensive starvation and mass migration of the population of Ireland after the devastating epidemics of 1845 and 1846. It is significant that deBary published much of his work two decades before Koch published his classical studies on anthrax disease of cattle.

These and several other examples of the early pioneering work on plant diseases that supported the germ theory of disease likely paved the way for acceptance of the landmark discoveries of Koch and Pasteur. The late blight epidemics undoubtedly also served as a major incentive for research on microbial diseases that affected humans directly. It is perhaps ironic that evidence that bacteria could cause disease in plants was hotly contested in Germany, and this led to a bitter controversy between Alfred Fischer, a distinguished German scientist, and Erwin

F. Smith, an American microbiologist (3). Smith completed seminal studies on bacterial plant diseases including crown gall disease, which causes cancerlike tumors on many plants (3). In recent years, basic studies on the tumor-inducing factor of the crown gall bacterium led to the discovery of methods for genetic transformation of crop plants (4).

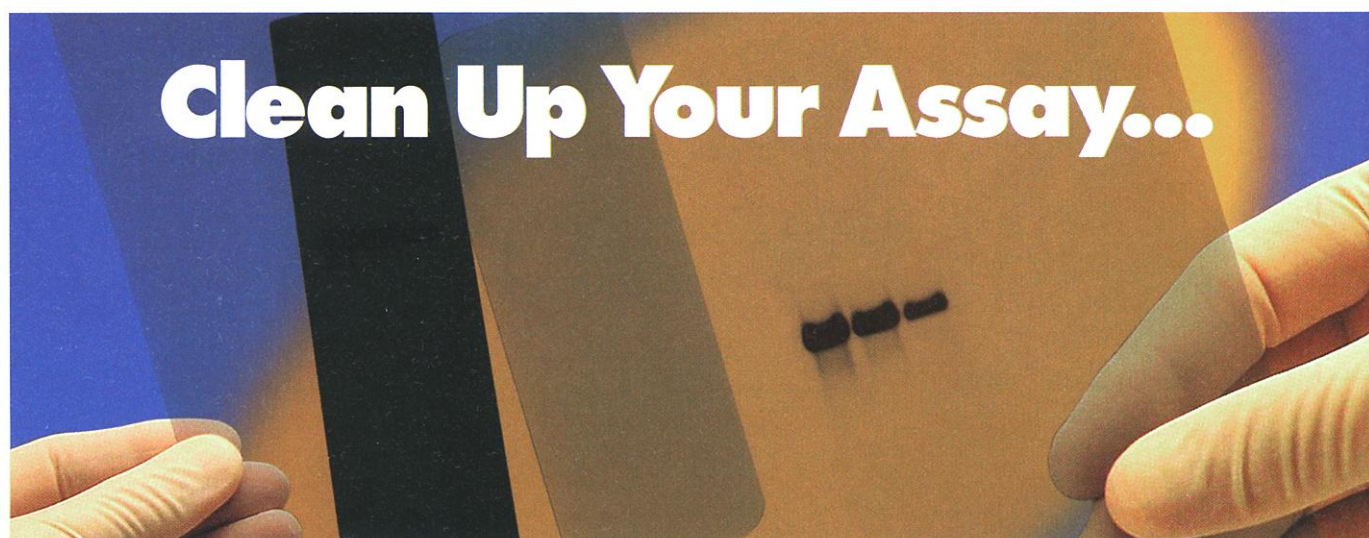
The discovery that the tobacco mosaic disease is caused by a virus (TMV) likely had a greater impact on subsequent research on human diseases and the development of molecular biology than any other finding in the field of microbiology. Lederberg notes the early work on TMV, but does not emphasize the full

significance of this discovery, omitting mention of the description by Myron Brakke (5) in 1951 of density gradient centrifugation, a now widely used method for the isolation and purification of viruses. This innovative procedure is generally



The discovery of TMV was a cornerstone for molecular biology (7).

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recognized as "one of the most influential developments in virology and molecular biology" (6, p. 5).

In view of the growing body of evidence that many animal and plant pathogens use similar mechanisms for pathogenesis, it is important that medical scientists concerned with infectious diseases be aware of the important contributions that are being made today, as well as in the past, in research on infectious diseases of plants.

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7. The image is a false-color transmission electron micrograph taken at a magnification of x34,000.

In an otherwise brilliant essay, Lederberg writes, "Four million Americans are estimated to be infected with hepatitis C, mainly by transfusion of contaminated blood products." However, many epidemiological studies of hepatitis C have documented that transfusion of contaminated blood accounts for no more than 3 to 10% of the 4 million people infected in the United States (1).

The leading cause of the silent epidemic of hepatitis C, far and away, is intravenous drug abuse, followed by "unknown" routes of transmission. Transfusion of contaminated blood is near the bottom of the list, along with tattoos and sexual/household contact (each of the latter cause less than 5% of the cases).

As a transfusion medicine specialist who frequently interacts with a public somewhat unduly concerned about blood safety (a residue from the HIV epidemic of the early 1980s, before the implementation of highly sensitive screening assays for infectious disease markers), I want people to be able to make appropriate

transfusion decisions on the basis of accurate data. Although there is no question that the risk of exposure to the hepatitis C virus from a transfusion was high (as high as 5% in the late 1970s before the cloning of the virus in 1989 and the subsequent development of a screening assay in 1990), it is also true that more than 90% of those people who comprise the silent hepatitis C epidemic did not acquire the virus through a blood transfusion.

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Response

I am more than happy to accept the amendment by Kelman, Sequeira, and Nester. My own institution, the Rockefeller Institute, re-sounds with names like Wendell Stanley, L. H. Kunkel, and Armin Braun, who made important contributions to our understanding of pathogenesis through their study of

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plant disease. I could add that the first discoveries of host gene polymorphisms affecting disease outcome ensued from the earliest applications of mendelian analysis to wheat (1). In a brief essay, it was impossible to do justice to every worthy milestone.

I would indeed be sorry if, as pointed out by Silvergleid, my remarks about hepatitis C might leave some confusion about the safety of the blood supply. At least since 1992, the advent of improved screening methods has essentially erased that threat. According to the Center for Disease Control and Prevention, the incidence of hepatitis C infection has fallen from 230,000 to 36,000 per year since the advent of that screening (2), and as Silvergleid notes, intravenous self-inoculation accounts for most new cases today.

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Still Havens for Coral Reefs

In her Letter "Confounding factors in coral reef recovery" (21 July, p. 391), Caroline S. Rogers says that "the recovery of coral

reefs from hurricanes is almost invariably confounded by anthropogenic stresses, most notably fishing... Humans have now degraded tropical marine ecosystems to the point where our ability to evaluate ecological theories about succession and effects of disturbance has been compromised."

Although true for many locales, this statement should not be overgeneralized. The Great Barrier Reef of Australia comprises almost one-third of global reef and lagoon area. Fishing pressure is very low, and other anthropogenic effects are negligible. The total fishing catch of reef species is less than that of Florida, which has a reef area less than 1% that of the Great Barrier Reef. Elsewhere in the Pacific and Indian oceans, numerous oceanic reefs remain relatively pristine, with little or no noticeable anthropogenic stress.

A realistic estimate of negatively impacted reefs would probably be about 50%. They are, of course, where there are the most people and hence receive the most attention, but there is still ample opportunity "to evaluate ecological theories about succession and effects of disturbance" where there is little or no anthropogenic stress.

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CORRECTIONS AND CLARIFICATIONS

News Focus: "Will Livermore laser ever burn brightly?" by Charles Seife and David Malakoff (18 Aug., p. 1126). Information about the work-sites of two scientists was incorrect. Steve Haan works at Lawrence Livermore National Laboratory, not at the Los Alamos National Laboratory. In addition, Bedros Afeyan works at Polymath Research Inc. in Pleasanton, California.

Policy Forum: "China's forest policy for the 21st century" by R. Zhang *et al.* (23 June, p. 2135). On the map of China, two provinces were labeled "Jiangxi." The more northern province should have been labeled "Jiangsu."

Pathways of Discovery: "Cloning: Pathways to a pluripotent future" by Anne McLaren (9 June, p. 1775). The lamb at the bottom of the figure on page 1780 should have been dark to indicate the origin of its genetic material.

News Focus: Sidebar piece "Decoding a mouse name" by David Malakoff (14 Apr., p. 250). The acronym used by the Charles River Laboratories for the mice they breed is CrI, not Cr as stated in the article. And 1297/SvEvBrd-Hprt^{b-m2} mice have a white-bellied agouti coat color, not a steel-colored coat. [E. M. Simpson *et al.*, *Nature Genet.* 16, 19 (1997)].

Program Announcement

Cystic Fibrosis National Bioinformatics Center

Cystic Fibrosis Foundation Therapeutics, Inc., an affiliate of the Cystic Fibrosis Foundation, in cooperation with InforMax, Inc. and the University of North Carolina-Chapel Hill announces the creation of a Cystic Fibrosis National Bioinformatics Center.

In its effort to apply cutting edge technology to cystic fibrosis research, Cystic Fibrosis Foundation Therapeutics, Inc. has licensed the GenoMax enterprise bioinformatics software from InforMax, Inc., and will provide this powerful gene analysis software tool free of charge to a limited number of CF researchers. In addition, Cystic Fibrosis Foundation Therapeutics, Inc. has established a contract with University of North Carolina-Chapel Hill's Center for Bioinformatics to house and support the use of the software by participating CF researchers. The software will be accessible to researchers via the internet, in particular for analysis of data generated during gene expression studies using microarray platforms. Participating researchers will be asked to contribute their data to a centralized database that will also be housed and maintained at the University of North Carolina-Chapel Hill, so that results from many laboratories can be mined together by the participants.

This centralized informatics solution for CF investigators, made possible by an unprecedented relationship among academia, industry and a non-profit voluntary health organization, is another measure of the Cystic Fibrosis Foundation's continuing commitment to assure the progress of cystic fibrosis research.

By providing this informatics solution to members of the cystic fibrosis research community, the Cystic Fibrosis Foundation hopes that scientists will use the tools of functional genomics to identify new and novel targets for future CF drug development.

Scientists wishing to use this resource to address important cystic fibrosis-related questions are invited to visit the Cystic Fibrosis Foundation web site (www.cff.org) or contact Dr. Christopher Penland, Director of Research at the Cystic Fibrosis Foundation, at (301) 907-2520 for more information about the program and application forms.



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