

## A PATHOLOGIST'S LOOK AT INFECTIOUS DISEASES: SELECTION BY AIDS AND OTHER INFECTIONS, CLINICAL TYPES OF IMMUNITIES AND VACCINE EXPECTATIONS\*

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Thank you, Bill [Reeves], for your generous introduction. I also thank all members of the Society for the confidence you placed in me, and to those for whom I had the pleasure to work with, for your collaboration. The addresses of several of my predecessors dealt with the issues of our Society and specialty. Bill Reeves in 1972 drew attention to the fact that our war against infectious diseases can be lost.<sup>1</sup> Karl Johnson assessed the Society's recent past, and its needs for the future.<sup>2</sup> Phil Russell stressed that excellence in research was not enough and that the development of practical applications and political involvement were necessary to implement the results of research.<sup>3</sup> Franz von Lichtenberg analyzed the diverse demographics of our Society.<sup>4</sup> Bill Scherer considered the dwindling supply of medical research scientists and suggested remedies;<sup>5</sup> and Joe Cook discussed the challenge of tropical infectious disease problems in the developing world and in this country and whether we were able to meet it.<sup>6</sup> This challenge had been addressed also by the Report of the Board of Science and Technology for International Development (BOSTID) of the Institute of Medicine and the National Academy of Sciences.<sup>7</sup> Recently, this BOSTID report was unanimously endorsed by the council of this Society. The ideas presented by my predecessors received positive response from many of us. Therefore, the time was right to work towards implementing some of the ideas proposed. To do this we need financial and human resources. During the business meeting to follow, we will review the Council's efforts to improve the financial position of the Society, to provide the basis for a larger journal, to enhance continuity of the Society's functions

by means of an executive secretary, and to develop means for training and acquiring experience in tropical medicine as well as vector biology during peace time, in order to maintain and improve the United States' capacity to address tropical disease problems.

For my presidential address I first considered the theme, "A Parasitologist Looks at Government." After some consideration, however, I felt that I might not be able to present this serious subject with sufficient humor and without risk of offending at least some Washingtonians whose hospitality we enjoy.

What I propose to discuss today is the role that natural selection plays in shaping the world's population to withstand infectious diseases. I will also analyze the nature of immunity developed against individual infections, and consider what we can expect from vaccines.

During my professional career, the most provocative scientific event was the appearance of the acquired immunodeficiency syndrome, AIDS. During the last 8 years, society has been deeply affected by the AIDS phenomenon, and has changed to such a degree that some have wondered what we used to talk about before AIDS.

Although of tropical origin and involving both medicine and hygiene, AIDS differs vastly from the usual tropical and parasitic infections we have studied. We find ourselves confronted with novel phenomena and new challenges. To enumerate:

1. While severe immunodeficiency was known from congenital defects and as a consequence of tumor therapy, loss of the normally expected immunity to trivial infections was now produced by a communicable agent.

2. While a mild and temporary immunosuppression was known from several infections, an infection which progressively destroys the cell-mediated immunity over a period of years was unheard of until AIDS was recognized.

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\* Presidential Address given before the 37th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Washington, DC, 5 December 1988.

3. The infection is communicable during an unusually long incubation period, and during which time the etiologic retrovirus is integrated into the genome of the infected cells. Its epidemiologic investigation presents serious problems because we must look for a single blood or sexual exposure years ago.

4. Although specific antibodies to the virus have been serologically identified in stored human blood collected in Zaire in 1959,<sup>8,9</sup> evidence suggested that we were dealing with a new disease that became pandemic in man for the first time.<sup>10</sup>

5. The mysterious origin of the infection and all the reasons for its world-wide dissemination are not yet clear. The infection which may have originated in African monkeys has infected rural human beings sporadically.<sup>11</sup> It was endemic, but controlled by social customs and geography. Tom Weller<sup>12</sup> reviewed the effect of migration of rural African populations to the cities and the creations of large slums with a precarious social organization. There, the prevalence of heterosexually transmitted human immunodeficiency virus (HIV) infection, as measured serologically is high.<sup>13</sup> The rapid world-wide spread of the infection was aided by frequent jet set travel, homosexual lifestyle in Europe and the Americas, widespread drug abuse, and blood transfusions, all modern phenomena compared to age-old sex. Hence the pandemic of AIDS is more a consequence of over- rather than under-development, and of technology breaking natural and social barriers.

6. We have only a 7 year experience with the disease and 10 years of serologic data to draw from. For a while it seemed that perhaps only one-third of those infected might die. Recent evidence, however, indicates this view was optimistic and that a mortality rate of close to 100% over a period of years appears possible.<sup>14</sup> Morbidity data of seropositive men in San Francisco indicated that 48% developed AIDS during a period of 10 years.<sup>15</sup> Also when classifying HIV seropositive men by laboratory findings or the severity of clinical symptoms, Redfield and Burke found that 50–90% progressed from 1 stage to the next over a period of 36 months.<sup>16</sup> When attempting to extrapolate into the future, different curve fitting techniques “predicted” that 71, 83, or even 100% of HIV infected men were to develop AIDS in 15 years.<sup>17</sup> However, mathematical projections do not take into account pathogenic mechanisms that differ in the first

decade of infection and thereafter, a population that is genetically heterogeneous, and that an absolute immunity may develop in a fraction of the population. Hence, we cannot predict. In fact, in a group of British homosexuals followed by Eales and colleagues<sup>18,19</sup> at St. Mary's Hospital in London, similar group specific components or GSC phenotypes were found in AIDS patients, and in seropositive men without disease, whereas different GSC types were found in seronegative men exposed by unprotected sexual contact with known AIDS patients. These data suggest possible resistance to infection and to expression of disease, perhaps because viral multiplication remains controlled, and because lymphocyte production remains adequate. Some of the forms of treatment, used and tried at present, may help. However, intercurrent infections may trigger expression of the integrated HIV genome in activated CD4 lymphocytes at any time.<sup>20</sup>

7. The spread of HIV infection to many communities and its generally fatal course suggest that among highly infected and reproductive heterosexual populations, some will be selected for resistance to the human immunodeficiency virus. As just mentioned, what percentage of humans can resist infection or maintain an effective immunity is entirely uncertain.

The idea that humans can be selected for resistance to disease has become strange to us in the Western world, and even asocial. The technologic control of excesses of heat and cold, flood and drought, the widespread control of infectious diseases, the medical management of formerly fatal diseases, such as diabetes and pernicious anemia, and the role of government in providing a safety net, led us to surmise that man was no longer subject to natural selection. However, we now recognize that modern air travel forges a bond between all parts of the world, providing ready contact with exotic infections, which can disseminate if ecologic circumstances are right. Rapid modern air travel, sexual promiscuity, and the drug culture were the ecologic preconditions of the AIDS pandemic.

More traditional ecologic factors in the transmission of infection are well known and have been studied by members of our Society. Without the specific mosquito vector, malaria is not endemic; however, transplacental infection with *Plasmodium malariae* and *Trypanosoma cruzi* may occur in immigrants from countries where infection is endemic. Formerly rare transmission

mechanisms can assume major importance when technology substitutes for absent insect vectors; and hepatitis B and sometimes malaria used to be transmitted by contaminated needles used for anti-syphilitic therapy, by serum additives as in the original yellow fever vaccine, by banked blood, or by homeopathic transfusions (from sharing of needles and syringes) amongst members of the IV drug culture. On the other hand, the intelligent use of technology has made our blood supply reasonably safe.

We have seen how HIV, an exotic infectious agent, has spread in the U.S. and we can speculate what other infections can disseminate here. We have acquired foci of *Aedes albopictus*, the "tiger mosquito," introduced with old tires from Asia in 16 major U.S. cities and 17 states, an example of world commerce spreading the means of infection, setting up base-line ecologic conditions for the transmission of a number of viruses, such as La Crosse, dengue, Rift Valley fever, yellow fever, and others. This new vector complements the presence of *Ae. aegypti* along the Atlantic coast from the Virginias to Mexico. In the absence of the perfectionism of Fred Soper in his efforts to control mosquitoes, so vividly described by Tom Weller in his Soper lecture,<sup>21</sup> we may be in for the surprises that Bill Reeves alluded to in his 1972 presidential address.<sup>1</sup>

As a pathologist interested in infectious diseases, I often ask myself, why does infection lead to illness, and what are the illness-producing factors in host and the microbe? Most of us are familiar with microbial factors of pathogenesis. However, the hosts, whether selected or unselected are of similar interest.

As we are living in a sea of microbes with about  $10^{12}$  organisms per gram of feces and about  $10^{15}$  in the gut and on the skin of an average human, it is intuitively apparent that we evolved a capacity to manage both the number and diversity of organisms and that those genetically unable to do so have perished. We may ask, is there still evidence of natural selection by infectious diseases, as I have postulated for AIDS?

Suggestive and perhaps metaphoric evidence comes from the asymptomatic occurrences of common microbes, such as *Leptospira ballum* in mice and rats. However, in an unnatural host, Golden hamsters, an acute generalized disease develops, with hepatitis and hemolysis, or destruction of the kidneys with uremia.<sup>22</sup> In humans, severe epidemics of measles, malaria, and

influenza in isolated areas are sometimes cited as evidence of a lack of selection. In Hawaii, the bird population has been decimated by introduced bird malaria and bird pox and the mosquitoes which transmit them.<sup>23</sup>

It is difficult to prove the selection process from anecdotal evidence; we need controls or quantitative data, as provided by the prevalence of certain genetic traits in different human populations.

In a study of malarious populations, Allison proposed that the increased frequency of the sickle cell trait indicated natural selection.<sup>24</sup> *P. falciparum* does not utilize hemoglobin-S (HbS) as readily as the normal HbAA. In 1-year-old children with similar infection rates, the mortality in the HbS carriers is lower than in the homozygous HbAA. Clinical attacks are shorter in 1-5-year-old children with HbSA than in those with HbAA. The selective advantage of heterozygous HbS carriers is shown by their increasing percentage in the population, from about 8% in infants to over 20% in adulthood in areas where falciparum malaria is endemic. It appears that the gene frequency of HbS heterozygotes will increase until counterbalanced by the disadvantage of the homozygous sickle cell disease state.<sup>25</sup>

It struck me as curious that neotropical monkeys and Australian marsupials in zoos often die of toxoplasmosis.<sup>26, 27</sup> Because cats are essential for the occurrence of toxoplasmosis,<sup>28</sup> it was reasonable to assume that the Australian marsupials had not been selected for resistance, because they evolved in the absence of cats. Cats were introduced to Australia only about 200 years ago (B. L. Munday, Mt. Pleasant Laboratories, Dept. of Agriculture, Tasmania, personal communication). Consulting Darlington's Zoogeography,<sup>29</sup> I learned that cats had also been absent from Madagascar; and there are indeed several reports from zoos of fatal toxoplasmosis among Madagascan lemurs.<sup>30</sup>

That neotropical monkeys were so prone to develop fatal toxoplasmosis also suggested a lack of exposure to cats and selection. We found that although about half of various ground-feeding animals in Panama had antibody to *Toxoplasma*, only 1 of 50 monkeys did.<sup>31</sup> In nature, the ground-feeders are exposed to *Toxoplasma* oocysts shed in the feces of cats, while the arboreal monkeys are not. As shown both in zoo epidemics and experimental studies, these South American monkeys do not readily develop im-

munity and hence die from toxoplasmosis in zoos.<sup>26</sup> Even after exposure to a low pathogenic live vaccine, marmosets and Aotus monkeys have difficulty resisting challenge. This suggests a lack of evolutionary experience with *Toxoplasma* and lack of natural selection for being able to develop a strong immunity.<sup>32</sup>

We recently had the opportunity to study the sera of some 40 arboreal African green monkeys, in which only 5% had *Toxoplasma* antibody, whereas in a group of 50 terrestrial Chinese rhesus monkeys, 40% had antibody. As yet we have no data concerning the immune potential of these 2 groups.

How quickly can genetically pleomorphic hosts be selected and consequently develop resistance to a microbe not previously encountered? Because hosts are selected by *Toxoplasma* mainly in zoos, and because these infections are sporadic and do not transmit further, we have no opportunity to learn from such happenings. And whatever selection occurred during the 200 years of feline exposure in Australia has not been studied. One might consider toxoplasmosis in kangaroos living in close contact with cats near cities, in comparison with relatively isolated populations, such as in the central Australian desert. Such studies might give us some information on the speed with which kangaroos are selected by *Toxoplasma*.

Informative studies of myxoma virus infection in rabbits are often cited. This virus is indigenous to the Americas where it produces a benign fibroma in *Sylvilagus*. However, when infecting European rabbits (*Oryctolagus cuniculus*) either in Australia or in Europe, an almost uniformly fatal disease developed.<sup>33</sup> Surprisingly, after only 2 years, a few immune surviving rabbits were found. During the succeeding 30 years, the mortality rate varied between 90% in rabbits never exposed, and about 30% in rabbits from populations exposed to several prior epidemics.<sup>33</sup>

Because of their much longer generation time, humans are selected more slowly than other animals. Tuberculosis is still a more serious disease in American Indians first exposed in the 16th century than in Europeans and their descendants who were probably selected by the infection for a much longer period of time. I would also expect a higher morbidity rate with toxoplasmosis in Australian aborigines than in other human populations, however I know of no data concerning this.

Recognizing that the genetic endowment to develop immunity is so important, let us now turn our attention to the type of immunity that can be achieved by the human host. It is axiomatic that obligate parasitic microbes have developed a way to persist in the population. Microbes persist in immune hosts as chronic infection, or in vector such as mosquitoes, ticks, or other arthropods, or in another host, such as monkeys for yellow fever and rodents for plague. Alternatively, microbes sustain themselves as "childhood diseases" or cyclic epidemics involving the susceptible fraction of the population. This "strategy" is usually seen when sterile immunity is achieved.

In Table 1, I have categorized the types of immunity seen with severe infections. I have never seen such a classification. Perhaps it will be of interest to you and I hope it will stimulate disagreement and refinement of these clinicoimmunologic concepts.

Myxoma is either fatal in rabbits between 13 and about 50 days, or a sterile immunity develops and the virus disappears. Smallpox in humans behaved similarly; it was fatal to some, but if immunity developed the virus disappeared. This was one of the reasons that smallpox was eradicated.<sup>34</sup>

However, in tuberculosis, toxoplasmosis, and CMV infection, immunity is partial, and is associated with chronic infection. Such infection-immunity, concomitant immunity, or premunition<sup>35,36</sup> is the result of long co-evolution of host and microbe. Chronicity is essential for these obligate parasites to persist. Between the extremes of sterile immunity and infection-immunity, there is measles which gives rise to sterile immunity in most humans, except in an instructive few who develop subacute sclerosing panencephalitis. Varicella produces sterile immunity in some and infection-immunity in others, who may develop zoster as a recurrent infection.<sup>37</sup>

Let us now consider the infections regularly followed by infection-immunity. In group 1, immunity is generally acquired promptly, it is good, although immunosuppression may precipitate a relapse; examples are toxoplasmosis, pneumocystosis, herpes simplex, histoplasmosis, and epidemic typhus. In group 2, immunity is acquired more slowly and it appears more vulnerable to immunosuppression as exemplified by tuberculosis, hepatitis, and cytomegalovirus infection.

TABLE I  
Nature of clinical immunity observed against various infections\*

	No chronic infection		Chronic infection							
	Sterile immunity	Sometimes	1 Good	2 Slowly acquired	3 Labile, microbe variable	4 Locally defective in	5 Incomplete			
Always	Usually					CNS	Adrenal	Skin	In some	In most/all
Myxoma (Rabbit)	Measles	Histo-plasmosis	Histo-plasmosis	Tuberculosis	Malaria	Crypto-coccosis	Tuberculosis	Dermal leish-	Hepati-tis B	Human immuno-
Smallpox	Varicella			Hepatitis B		Trypano-somiasis	Histoplasmosis	leish-maniasis		deficiency virus
Polio-myelitis	Crypto-coccosis		Herpes hominis	Cytomegalo-virus (CMV) infection	Relapsing fever		Coccidio-mycosis	Leprosy		infection
Yellow fever			Toxo-plasmosis		Trypano-soma brucei (live-stock)		CMV infection	Blasto-mycosis		
Rocky Mountain Spotted Fever			Pneumo-cystosis				Cryptococcosis			
Western equine encephalitis			Epidemic typhus							

\* Infection in humans unless noted.

In group 3, we see chronic infection with labile immunity because of microbial variation, such as in the malarial, spirochetal relapsing fever, and *T. brucei* infections. The trypanosome infections are of interest because they produce mild infections in native animals, but give rise to severe infection in domestic ruminants, especially in recently introduced stock, suggesting co-evolution of trypanosomes and native hosts.<sup>25</sup>

Group 4 consists of chronic infections with a fair degree of immunity in most tissues, but with an immune defect in one body compartment. So we find that while antibody lyses cryptococcal capsules in the lung, the portal of entry, infection progresses in the brain, probably because of the low IgG diffusion. African trypanosomes are cleared from most of the body except the brain, where the Rhodesian variant is especially progressive. In another subgroup, immunity is corticoid-labile; so that after adrenal localization, there is progressive multiplication of tubercle bacilli, *Histoplasma*, or cytomegalovirus. This can lead to the development of Addison's disease if adrenocortical regeneration is insufficient.<sup>38</sup> Generalized immunity is also sensitive to hypercorticism induced for a variety of therapeutic purposes in this group, as in groups 1 and 2. Another subgroup shows localization of the infection in the skin such as with dermal leishmaniasis, leprosy and a few cases of blastomycosis. It is my impression that this resulted from defects of expressing immunity in the cooler parts of the body.

Group 5 consists of infections in which immunity is clearly incomplete. In a small percentage of people, hepatitis B infection remains chronically active, leading to progressive damage of the liver and polyarteritis nodosum and glomerulonephritis with persistent infection. Immunity to HIV is defective in many or most humans, with persistent proviral DNA in the host genome. After a period of seeming immunity, there follows progressive destruction of lymphoid tissues, especially the T-4 subset of lymphocytes, which, possibly together with human herpes type 6 and other viruses, leads to immunosuppression, a compromised host. This permits infection with a variety of organisms; these are either endogenous agents of chronic infections, such as CMV, herpes, *Toxoplasma*, and *Pneumocystis*; or they are exogenous microbes, such as *Histoplasma*, *Aspergillus*, *Entamoeba*, *Cryptosporidium*, or *Mycobacte-*

*rium avium-intracellulare*. These exogenous agents can be either first infections or re-infections.

Classifying infection by the type and degree of immunity developed is useful in predicting clinical behavior. We may ask, can it predict eradicability and vaccine responses? I believe yes, when qualified answers are given. All infections with a sterile immunity can be eradicated provided that man is the only host, immunity is effective in all body compartments, and all susceptibles can be reached and immunized. Smallpox has thus been eradicated and it is hoped that measles will soon follow. The slow human reproductive rate permitted time for vaccination, and the presence of an immune population, herd immunity, prevented further spread. Myxoma in rabbits, although similar in many respects, infects a host that is so prolific that immunologically naive hosts are born several times each year, permitting the virus to persist. What would happen if all rabbits were benevolently immunized soon after birth? The infection would probably die out. As shown with ectromelia by Topley,<sup>39</sup> the effect of herd immunity would be sufficient to protect the group, allowing for even a few conscientious objectors to vaccination.<sup>39a</sup>

One might suspect that poliovirus could be eliminated; however intestinal immunity does not appear good enough to curb viral proliferation to the degree seen in smallpox. Therefore while the disease of the central nervous system can be prevented, poliovirus infection persists in the population after exposure to killed vaccine. Even though there is humoral immunity, the intestine is still susceptible. However, oral vaccination with live vaccine appears to immunize the vaccine and the vaccine strains replace the wild poliovirus strains in the intestine.<sup>40</sup>

Although producing a sterile immunity, yellow fever, western equine encephalitis, and Rocky Mountain spotted fever have animal hosts which are impractical to either immunize completely or to eradicate, and therefore endemicity will persist. Cryptococcosis cannot be eradicated because the fungus grows in the environment. Measles appears eradicable by adequate immunization and the few who develop subacute sclerosing panencephalitis do not have communicable infections. However, with varicella, the population pool with chronic infection may be sufficiently large, so that those who develop zoster maintain the virus in the human population. This im-

munologic hypothesis can be tested in near future when varicella vaccine will be licensed in the United States.

Can the naturally acquired immunity also predict the immunity achievable by immunization? Agents that are followed by sterile immunity should, after vaccination with a good antigenic cocktail, also develop sterile immunity, and even after challenge, be followed again by sterile immunity.

For infections leading to premunition, vaccination is aimed at protecting against illness, not infection. The non-persistent *Toxoplasma* vaccine candidate ts-4 is a good example; it produces good immunity in laboratory animals, and we learned from it that immunity to *Toxoplasma* is not dependent on chronic infection. It protects against illness from challenge.<sup>41-43</sup> However, challenge is followed by persistence of the challenge organism. The vaccine for cats inhibits oocyst shedding and thereby reduces dissemination.<sup>44</sup> The 2 vaccines might be used together for a local toxoplasmosis control program. We hope to test this in Panama. The clinical efficacy of various vaccines against normally persistent organisms, the malarias, leishmaniasis, Chagas' disease, and several helminthic infections remain to be demonstrated.

The outlook for protection by vaccines for infections usually accompanied by premunition is not good. However, we have at least one example, feline leukemia, where the normally persistent infection can be prevented by vaccine. Protective and immunosuppressive antigens were identified and after separating these, vaccination with the protective antigens produced satisfactory immunity.<sup>45</sup>

This prolonged virus infection of cats, similar to HTLV-1 infection of man, gives rise to leukemia. In this interesting feline model, the virus is also commonly incorporated into the genome of infected cells. However, immunization with the protective antigens inhibits viral multiplication to such a degree that opportunities for incorporation and development of leukemia were practically precluded. This successful subunit vaccine suggests testing for immunosuppressive qualities all of the many non-protective antigens of other infectious agents which give rise to premunition. If such are found, they could be excluded from the antigenic cocktail used as vaccine. This could lead to the preparation of a more highly protective vaccine, and hopefully, sterile

immunity rather than infection-immunity will follow. We would also learn more about the determinants of infection-immunity.

We must also consider that most of the infections accompanied by infection-immunity are controlled more by cellular immunity than by antibody-related effects. It would be important therefore to identify putative protective antigens not only by antibody responses. Testing for the production of protective lymphokines, specific as well as non-specific, could lead to a better selection of antigens for a vaccine.<sup>46</sup>

I have reviewed some aspects of the novel pathogenesis of HIV infection, and the probability that man is selected by it. I have also presented a classification of the clinical types of immunity produced, and speculated on the immunity achievable by vaccines. The tropical infectious disease problems are quite diverse and staggering where they exist. I have not discussed selection of microbes such as of falciparum malaria for drug resistance—which is always ongoing, and so far dwarfs AIDS in importance. Certainly, modern travel tends to expose the U.S. population to foreign microbes more frequently. The AIDS outbreak is only the first major introduction of an exotic infection. Dengue, yellow fever, Rift Valley fever may be waiting, and the vector mosquitoes are here already.

We have an exciting future for the study and problem solving problems ahead of us. Because preventing the spread of infections requires sustained efforts and because eradication can only be achieved for some infections and regionally, a reservoir of competent experts is required to achieve and maintain these goals. The political initiative proposed by the Society is to assure the adequate training and experience of a critical mass of medical and vector biology specialists as a national resource. To be successful, individuals of this Society need to maintain commitment and leadership, responsibility in argument, and crosscultural teaching of the electorate and its representatives. The 2 culture phenomenon of C. P. Snow<sup>47</sup> is still with us. Field study, shoe leather epidemiology, ecologic biology, and common sense born by experience are still necessary in an age of molecular biology and immunology, a 3 trillion dollar deficit, nuclear deterrence, and star war fantasies.

But in a sense we cannot lose and the future of tropical medicine is bright. We will either be controlling infections, or be diagnosing and treat-

ing them. In the interest of potential victims, I hope that this Society, through its political efforts, can become more effective in the control, prevention, and even eradication of infectious diseases worldwide. But if we must continue to fight imported epidemics, and spreading epidemics elsewhere, we may join the group of ultimate growth industries: garbage disposal and government bureaucracy. And then, the sun never sets on tropical medicine.

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