

HERD IMMUNITY
AND
THE HIV EPIDEMIC

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INTRODUCTION

Herd Immunity describes the collective immunocompetence of a population and its ability to resist disease. The diseases of Mycobacteria, Salmonella, Hepatitis A, Cryptosporidia, Syphilis, Measles, Influenza, and numerous others recently have been seen in epidemic proportions in the United States. An association between these superimposed secondary infections and the Human Immunodeficiency Virus (HIV) Epidemic can be made since the HIV's imposition on individual immunity has ramifications on a population level through a decline in Herd Immunity. Exploring these epidemic phenomena as consequential to a reduction in Herd Immunity can provide a unifying hypothesis to explain existing and predict future infectious disease epidemic dynamics. The benefits of acting upon these implications has advantages for both the HIV infected as well as the uninfected.

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HERD IMMUNITY AND THE HIV EPIDEMIC

by
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Coincident with the advent of "The AIDS Era," the medical community has also borne witness to an increase in the incidence and prevalence of numerous previously controlled infectious diseases. The relationship between these two simultaneous phenomena bears a larger associative epidemiological significance than mere coincidence can explain. One would expect to see multiple infectious diseases increasing only when paralleling the presence of natural disasters, novel population contacts, or unique

population exposures. Cause/effect relationships in those environments are readily substantiated and rarely disputed such as in the case of cholera after major flooding or smallpox decimating the Western American Indian populations subsequent to the introduction of Caucasians. However, in the last decade, no events of such magnitude have occurred in the United States except for the entrance of the Human Immunodeficiency Virus (HIV) into the epidemiological equation.

Although attempts have been made to individually and in an isolated sense explain some of these infectious disease epidemic occurrences, an alternative hypothesis can be advanced that would serve as a unifying theory capable of explaining the majority of recent epidemic developments in a logical and rational manner. The explanation advanced herein, by no means all-inclusive, rests on the HIV-mediated destruction of a population's Herd Immunity.

HERD IMMUNITY

Herd Immunity is considered to be the collective immunity of a given population or "herd" that imparts to that group a protection against destruction by epidemics. It is formally defined as a group immunity that confers a resistance or relative resistance to infectious disease because of the immunity of a large proportion of the members and the consequent lessening of the likelihood of an infectious individual coming into contact with a susceptible individual.

Unarguably, people with HIV infections and especially Acquired Immune Deficiency Syndrome lose immune competence. More often than not, this new virus renders them incapable of eradicating from their bodies in a timely and efficient manner nearly every infectious disease known to cause morbidity and mortality in humans. As a result, they retain, are infectious for, and die from a host of Superimposed Secondary Infections (SSI's). Consequently, they are also more likely to transmit these communicable diseases to other persons because they remain infectious for longer periods of time, creating increased absolute numbers, preferentially supporting the growth of, and serving as reservoirs and vectors of contagious organisms.

Just as a human body with some defect in the cellular units that confer protection against disease suffers by becoming diseased, so, too, when a society's individual units have immune defects, the entire society can be seen to suffer a morbid consequence. When immune competence fails at this population or societal level, it can be interpreted as the direct result of a deterioration of Herd Immunity.

TUBERCULOSIS

A direct causal association between HIV and another infectious disease's incidence is exemplified in the well-documented epidemic of Tuberculosis (TB) observed in this decade. Since 1953, when uniform national reporting became implemented, the incidence of Tuberculosis had been decreasing by approximately 6% per year¹. Even with the heavy influx of infected Southeast Asians as a result of the Vietnam War (during the late 1970's and early 80's), from 1963 to 1985, the incidence of TB had decreased steadily by 5.9% annually. The first substantial increase, of 2.6%,² was observed in 1986. In New York City, reported TB cases increased by 36% from 1984 to 1986, the increase being causally related by the U.S. Public Health Service to HIV³.

In certain confined subpopulations with relatively high AIDS rates such as prisons (during 1988, the estimate aggregate reported incidence of AIDS in the U.S. population was 13.7/100,000 whereas in state and federal correctional systems was 75/100,000⁴), this is of no minor consideration. One review of AIDS cases among inmates in selected New York correctional facilities found TB in 6.9% of 319 persons with AIDS.⁵ The incidence of TB in prisons increased 400% in the period 1976-86⁶. This experience cannot be viewed as an isolated phenomenon since prisons are microcosms of any dense human population. Despite physical separation, in an infectious disease consideration, they are still "attached" to the general population and present a problem for the communities into which the prisoners are

released. They also can reflect conditions otherwise not observed in subpopulations of society where the prisoners originate and can function as harbingers for the entire population's potential fate without intervention.

Without question, Tuberculosis is routinely transmitted by the aerosol route when maintaining close contact with the infectious. The increase in HIV related carriage combined with a 6% rise in drug-resistant strains of tuberculosis since the mid-1970's⁷ makes the situation especially threatening to the remainder of the population. (Since the original writing of this paper, events have revealed that in the New York prison system, during 1991, twelve inmates were infected and killed by a new TB strain that is resistant to antibiotics. This organism was transmitted from an HIV-infected inmate to a corrections officer who presumably did not have an HIV infection. It killed the officer as well.⁸ Also, investigators at the Centers for Disease Control in Atlanta revealed on or around March 1991 that a single AIDS patient had infected up to 31 patients with a drug resistant form of Tuberculosis at a drug treatment center in Muskegon County, Michigan over a one month period.⁹)

Although the national and worldwide TB epidemic has been directly attributed to HIV, it is important to note that the increased acquisition of TB is not limited to those with AIDS or HIV-related conditions. There is an almost equivalent percentage of persons newly diagnosed with Tuberculosis but without HIV infection, suggesting that the HIV infected are transmitting the Tuberculosis to the HIV-uninfected. According to Centers for Disease Control statistics, 53% of 58 males ages 25-44 without AIDS but confirmed to have *M. tuberculosis* were found to be HIV seropositive¹⁰, leaving 47% to have disease independent of HIV infections. These TB acquisitions are contributing almost equivalently to the statistical increase in incidence. Consistent with the axiom that whenever the prevalence of an infectious organism increases in a subpopulation (regardless of the distinction drawn that defines that subpopulation) as long as it is in contact with the larger population, one can expect the incidence in the general population to rise due to the increased transmissions occasioned by an increased number of carriers.

This increased incidence may be significantly reflected in the elderly's recent increased acquisition of the disease. Stead et al¹¹ have shown lately that the elderly in group living quarters, such as nursing homes, are at substantial risk of acquiring new tuberculosis infections, conceivably due to increased numbers of HIV/TB infected patients being managed in the same chronic care facilities.

This experience with Tuberculosis cannot go unrecognized for its societal impact due to the profound implications and ramifications it holds for the future. Better than any other infectious disease, Tuberculosis can be used as a barometer to indirectly quantify a population's Herd Immunity. Historically, through times of societal stress (starvation, overcrowding, etc) the Tuberculosis rates have increased, probably as an inverse function of Herd Immunity being compromised by environmental factors. Now, the reduction of Herd Immunity due to a reduction in the individual immunity of the herd's members can be seen as the precipitating factor and the consequence is a predictable increase in the incidence and prevalence of infectious disease mortality.

ATYPICAL MYCOBACTERIA

Epidemic increases in Mycobacterial disease are not limited to *Mycobacterium Tuberculosis*. Other, non-tuberculous mycobacterium have been recently receiving increased scrutiny due to their increased significance in relation to the AIDS epidemic. Up to fifty-three percent of AIDS patients on autopsy have non-tuberculous bacterial infections categorized as *Mycobacterium Avium Complex (MAC)*¹². In deference to the belief that these infections are only opportunistic, healthy young people with no evidence of impaired cellular immunity can and do acquire this disease¹³ and, contrary to those who would look upon these organisms' transmissions as largely environmental, numerous reports suggest person-to-person transmissions, intrafamilial spread, and acquisition by health care workers.¹⁴ One outbreak in 1987 resulted in *Mycobacterium Chelonae* infecting 17 persons as a result of contaminated ENT instruments.¹⁵

Some would argue that patients with HIV disease and concomitant MAC infections pose no

additional risk to their contacts since the organisms are so widely distributed in the environment; however, culture analysis has shown that isolates of mycobacteria in sputum of patients with associated pulmonary disease usually were different from those of the patient's environmental strains,¹⁶ leading one to conclude that the organisms responsible for their disease were less likely to have been environmental in origin, leaving person-to-person transmissions a more likely source of infection. Too, serotype analysis indicated that certain serotypes of *M. intracellulare* were associated with the production of disease and these differed from the serotypes found in the environment, indicating that certain serotypes had higher pathogenicity and the human body probably served as a selective media.¹⁷

The pessimistic conclusions drawn as logical extrapolations on these lines of evidence could be ignored if everyone in the population were ideally immuno-competent and could be expected to mount an effective immunological defensive response upon every inoculation with micro-organisms whose pathogenicity seems to be inversely related to the immunocompetence of the host.

When considering the total universe of potential disease causing organisms, immunocompetence exists more as a spectrum of varying degree rather than a qualitative distinction. Depending upon variable genetic, environmental and pathogenic influences, a given individual or population can become more or less susceptible to disease caused by organisms that in other circumstances would not be pathogenic. It cannot be ignored that large segments of the population have pre-existing pulmonary disease or are immuno-suppressed for a wide variety of reasons exclusive of HIV infections. Especially at risk are the very young, the elderly, those with chronic pulmonary disease, and anyone else immunocompromised for any number of reasons, since it is these populations who have been characterized in the past as particularly susceptible to those atypical mycobacterium and organisms with lower relative pathogenicities.

Notwithstanding individual genetic or acquired immunity, a rudimentary understanding of infectious disease epidemiology leads one to conclude that the successful transmission and, therefore, resultant acquisition of a given disease is largely a function of the exposure frequency. If a person is never exposed to an organism, the likelihood of disease is zero. However, if a source for repeated exposures exists in any given environment or set of contacts, then persons sharing those environments as contacts (especially those with pre-existing respiratory diseases and the immunosuppressed) are at higher risk of acquiring that disease due to the increased concentrations of micro-organisms and likelihood that a successful inoculation will occur.

If a given individual is surrounded by a "herd" containing numerous individuals lacking immune competence and producing high concentrations of pathogenic organisms the probability of successful transmissions occurring resulting in disease is likewise, logically increased.

The propensity for the HIV infected to effect the transmission of disease for even those pulmonary pathogens generally accepted to be exclusively opportunistic has been shown in relation to *Pneumocystis carinii* pneumonia. In a Texas cancer center, a nearly dose-related infection acquisition response was observed in their cancer patients that increased with the number of AIDS admissions and declined equivalently when the number of AIDS registrations fell.¹⁸

This concept when applied to the relationship between *Mycobacterium Avium Complex* (MAC) and AIDS can be argued to explain the increasing prevalence of MAC in the United States¹⁹ possibly due to the consequence of an increasing prevalence of MAC hosts serving as sources of infection because of their HIV disease. Particularly disconcerting is that non-tuberculous disease is also being seen in increased incidence in areas considered previously to have relatively low isolation rates (Philadelphia) and in elderly females without predisposing conditions.²⁰ Of not minor significance is the clinical observation that these infections are frequently fatal despite multiple drug regimens even in persons without underlying predisposing conditions²¹; and, in those with severe immune deficits, therapy is rarely successful²². Non-tuberculous mycobacterium remain viable for long periods in the environment²³, are assumed to be spread by the air-borne route and have been shown to have contaminated the water supplies of hospitals where AIDS patients are in high prevalence²⁴ indicating a potential for increasing nosocomial spread. If Mycobacterial diseases were the only infectious diseases to be considered, the population consequences of

a declining Herd Immunity might be limited to a degree commensurate with society's ability to reduce efficient, prolonged, or frequent exposures to select marginally pathogenic organisms. However, Mycobacteria are not the only infectious organisms that the HIV infected can be expected or demonstrated to preferentially harbor or transmit. They just may serve as a currently quantifiable herald for the human population's future interaction with all infectious diseases-an interaction that is, again, best explored from a perspective incorporating the concept of Herd Immunity.

Herd Immunity is more explicitly defined as the immune status of a population as a whole determined by the ratio of resistant to susceptible members and their distribution. Assuming a constant distribution, each susceptible individual added to or contained within the population reduces the quality and quantity of Herd Immunity. Mathematically, even so much as the single addition of an individual with impaired immunity to a population will undeniably, reduce the group's immunity, the magnitude of which being a function of the severity of that individual's immune deficiency which, in turn, also reflects the efficiency with which that individual transmits disease.

SALMONELLA

The notorious case of Typhoid Mary Mallon offers an excellent historical example of the consequences of a single person incapable of eradicating an infectious agent (*Salmonella Typhi*) from her body. Even with a rudimentary knowledge of communicability, this was recognized in the latter 19th Century, and she was prevented from unintentionally inflicting morbidity by effective public health isolation measures that reduced her random access to the population. In retrospect, it can be assumed that she had a relative immune deficiency allowing her to harbor *Salmonella typhi* organisms that usually would have been eradicated by a more competent immune system.

In light of human populations' ability to modify access of infectious members to the remainder of the population, the preceding definition of Herd Immunity must, understandably, be qualified by a distribution consideration. Should the components of society lacking immunity be prevented from being distributed, the Herd Immunity can be maintained even in the face of a high numerical presence. If a particular individual has the opportunity to effect the disease destiny of a wide distribution of others, the injury inflicted upon the herd can be disproportionately severe. In Ms. Mallon's case, her distribution was prevented by restricting her access to the "herd."

Unfortunately, *Salmonella* epidemics have persisted in the intervening century so equivalent transmission dynamics still apply and require exploration. Although often considered benign, self-limited conditions, they still pose a threat to the human population especially since they have recently been linked to a post-dysenteric reactive arthritis.²⁵ Concern for their increasing incidence paralleling the AIDS Era is evidenced by its recently being experienced in epidemic proportions in the U.S.,^{26, 27, 28} In New England and the Mid-Atlantic States the period 1976-88 saw approximately an 8 to 9 fold increased isolation rate for *Salmonella Enteritidis*.²⁹ The incidence of Typhoid Fever in the United States increased in 1989 to a cumulative case rate 25% greater than the median levels for 1984-88.³⁰

Several recent *Salmonella* outbreaks in New York City, an area considered endemic for HIV, such as that at Mount Vernon Hospital (involving 15 patients, two nurses, and a physician) as well as at Coler Memorial Hospital in New York City (that claimed 175 victims and three lives)³¹ and a Typhoid Fever outbreak in the San Francisco area³² appear to bear a geographical and associative relationship to the HIV epidemic since AIDS patients are twenty times more likely than the general population to be carriers and most have persistent infections or recurrences despite appropriate antimicrobial therapy.³³

Although no causal relationship with HIV has been previously elaborated epidemiologically with *Salmonella*, the existing evidence warrants investigation of this phenomenon before the current associations with the chicken processing facilities, pasteurized milk³⁴ or Grade A eggs³⁵ are accepted as solely responsible in the absence of stool culturing combined with HIV testing of food service workers as potential sources of outbreaks. There is little reason to assume that the food service industry has changed significantly the commodities and processes for decades; and it would be difficult to find a food product that is not associated with the ubiquitous Grade A eggs or pasteurized milk whose predominate association

may be that they simply offer excellent food product based culture media for Salmonella.

To ignore the ramifications of a reduction in any population's immunocompetence as it relates to food-borne illnesses can result in missed opportunities to prevent disease and death especially in the very young (even healthy children can die from Salmonella)³⁶, pregnant, and aged who are at increased risk of significant morbidity due to Salmonella. (In 1991, a resurgence of Cholera was seen in epidemic proportions for the first time in the Western Hemisphere in over 100 years and investigations of Salmonella epidemics have found the contamination to have originated in melons grown in Texas. Both of these phenomena can be attributed to the increased carriage of these bacteria in the bowels of Latin American peoples and this fecal contamination subsequently finding its way into orally ingested food or water.)

HEPATITIS A

The consequences of a reduction in Herd Immunity secondary to HIV related risk sources appear to also have associative significance with respect to Hepatitis A. A valid contributing factor for the most prolonged Hepatitis A outbreak in the history of the Centers for Disease Control is probably that the source case(s) had immunosuppression induced by Human Immunodeficiency Virus infection. Two of the pantry worker source cases in a study of 103 cases of Hepatitis A in a Florida restaurant³⁷ were described as male homosexuals, promiscuous, and practitioners of anal intercourse. One had anal intercourse 3-4 times per month and shortly afterward acquired Hepatitis B. Although all of these activities were recognized risk factors for infection by the HIV, they were unfortunately not tested for HIV; however, according to the study's author "could reasonably be assumed to have been infected by HIV."³⁸

This phenomenon with respect to Hepatitis A is not limited to isolated nor rare events and gives cause to implicate the Human Immunodeficiency Virus Epidemic as contributory. A large outbreak in Texas at a salad-bar restaurant³⁹ and two other food borne outbreaks in Alaska were traced to homosexual male source-cases⁴⁰. In the past 10 years, nearly 50% of source cases associated with food borne Hepatitis A outbreaks in California have been homosexual men⁴¹.

However, homosexuality is not the only HIV related risk factor linked to an increase in Hepatitis A in the immediate past. Intravenous drug users have been only recently identified as sources of Type A Hepatitis in New York state and Northern California.⁴² Previously it had been held that Hepatitis A outbreaks were not sustained by blood borne routes due to the short duration of the viremia. However, in persons with immunodeficiency, it is reasonable to assume that the viremia would be prolonged enough to sustain such outbreaks and, thus, provide an explanation for this new association.

Prior to the advent of the HIV epidemic, Hepatitis A had only been associated with crowding, poor personal hygiene, improper sanitation, and (less commonly) contamination of food or water; and the recognized risk factors of intimate contact with infected persons, day-care and travel to developing countries. Most recently, an outbreak has been identified among at least 80 students and staff at the University of Southern California in Los Angeles,⁴³ which is not a characteristic environment to sustain an epidemic requiring the previously cited conditions if they are considered environmental requisites.

Nationally, there has been a 25% increase in the incidence of reported Hepatitis A infections through 1989⁴⁴. Were this country undergoing a major deterioration in the standard of living, sanitation, or Public Health Department activity, alternative explanations could be strongly supported; however, the increased prevalence of persons with deficient immune systems that allow the Hepatitis A infections to be prolonged or inefficiently neutralized by protective antibody seems to be an especially intriguing explanation since the elaboration of these previously unrecognized risk groups have an equally common association being that they are both likely to be associated with HIV infection. This association is strengthened by a geographical correlation since California and New York are the states of highest AIDS incidence. Thus, the finding of temporal, risk group, and geographical associations makes the relationship between HIV epidemics and Hepatitis A Epidemics certainly worthy of further Public Health Department scrutiny and probably will be shown in the future to play a major role in Hepatitis A epidemiology especially as it relates to subsequent transmissions within the food service industry and as an enteric

pathogen.

If these associations are confirmed, consideration may be given for routine HIV testing of those persons in the food service industry implicated in outbreaks of any food borne pathogen. Public health departments may then include in their preventative function subsequent laboratory monitoring of HIV infected food service employees so that they could be removed from food service employment until it can be demonstrated that they no longer pose a risk for contagion.

CRYPTOSPORIDIOSIS

Cryptosporidiosis epidemics, too, can be seen as a consequence of the AIDS epidemic's influence on Herd Immunity. Seemingly, the immunity of the American "herd" had been sufficient enough in the past to keep this disease at such a low incidence as to not be observed by the medical community. So much so, it went unreported as a human pathogen in the United States until 1976.⁴⁵ Prior to the advent of the AIDS epidemic it was not recognized as a disease entity of concern outside of animal populations in the U.S. Only recently has this enteric pathogen been identified as one of the more common causes of intractable diarrhea in AIDS victims--being seen in as much as 15%⁴⁶ to 20%⁴⁷ of those with chronic diarrhea, but, retrospectively, can be assumed to have been contributing to the late 1970's phenomenon known as "Gay Bowel Syndrome."

In the period 1976-81, the first seven cases of human cryptosporidiosis were reported and in five out of the seven cases the patients were immunocompromised.⁴⁸ Since then, it has been linked to daycare centers in San Francisco⁴⁹ and elsewhere^{50, 51} and has infected nearly 13,000 people in Western Georgia after it contaminated a water supply⁵². There is no effective treatment for the disease. It is highly infectious,⁵³ can kill children⁵⁴, can be transmitted when the spores dry out and are carried through the air;⁵⁵ and person-to-person spread has been documented.⁵⁶

It would appear that this organism's appearance as a human pathogen in the U.S. was relatively recent. Its association with the immunocompromised may have allowed it to gain sufficient concentrations in human hosts to increase its prevalence, thereby, allowing for the epidemic transmission to immunocompetent hosts. It is reasonable to conclude that without the increased incidence of immunocompromised persons and consequent decline in Herd Immunity, it would not have been able to establish itself as a pathogen in the United States' population. For without the maintenance of a population of immuno-incompetent individuals, it would not have had a reservoir. Therefore, it can be logically argued that the advent of Cryptosporidiosis demonstrates a declination in Herd Immunity and without this decline in Herd Immunity the Cryptosporidiosis prevalence could not be perpetuated.

The increased incidence of these and countless other communicable diseases is the predictable ramification of an increase in the carrier state of those diseases. Simply put, the longer a person carries any given disease in a population, the greater chance the disease will be spread to others. It is also an epidemiological constant that as the number of persons with disease in a given population increases, the greater chance they will have of infecting other uninfected people. Therefore, the probability that they will spread the disease increases even for diseases with less efficient modes of transmission.

SYPHILIS

The changing Syphilis epidemiology also offers an opportunity to explore the consequences of a loss in Herd Immunity especially as it relates to medical technology's potential inability to benefit by the serologic manifestation of Herd Immunity in disease identification.

Decreasing Syphilis rates from the 1940's to the 1950's were largely due to a combination of serologic testing, public health measures, and the availability of a cure. Seemingly, with the described successes in educational efforts to reduce sexual behaviors that put person's at high risk for sexually transmitted diseases, especially HIV, one would assume that Syphilis rates should still be declining;

however, the opposite is true. The previous downward trends were reversed in 1987 when this nation experienced at least a 25% increase over the previous year.⁵⁷ Geographically, this increase has predominately occurred in areas of high HIV prevalence. Eighty-three percent (83%) of the national increase and 57% of all cases occurred in New York City, California, and Florida.⁵⁸ This epidemic continues to date with a 9.7% increase in 1989, the 1989 total representing a 52% increase over the median incidence for 1984-88.⁵⁹

Numerous explanations have been advanced including sexual promiscuity related to drug use, use of spectinomycin (which does not cure incubating syphilis), and decreased public health resources.⁶⁰ Neglected in these explanations are the influences consequent to Herd Immunity decline due to the prevalence of HIV. Paralleling a decrease in a population's Herd Immunity comes the commensurate decrease in that population's sensitivity of serologic assays that require competent immune functions. Hicks et. al. have described in a case report⁶¹ a phenomenon that probably is occurring on a much larger yet unquantified level. HIV infected patients' faulty immune systems can fail to produce sufficient antibody against Treponemal antigens to allow for seropositivity to be recognized on the standard tests (VDRL and FTA-ABS) that rely upon these antibodies for proper function. The ramification of this reality is that screening programs relying upon these standard screening procedures can be expected to miss significant numbers of infectious persons. Hence an increased ability of Treponema Palladium to exist and spread without detection.

Too, high therapeutic failure rates occur in patients infected with both HIV and Syphilis even when recommended levels of antibiotics are administered⁶² leading to the conclusion that spirochetes sequestered in the CNS and elsewhere can serve as sources for re-infection.

Others have recognized an association between genital ulcer disease and HIV.^{63, 64} On the basis of this association, some would conclude that behavioral considerations and/or the presence of blood contact with the syphilitic ulcer predisposed the acquisition of HIV. An equally plausible explanation could be that the disease causing the ulcer was present largely due to the HIV induced loss of immunity in either the transmitter or the recipient of disease. Attempts to determine which condition preceded the other so that a cause effect relationship can be substantiated is as difficult to prove as the argument asking: Which came first, the chicken or the egg? However, it cannot be denied that Syphilis's association with HIV exists; and when applied to populations the consequence of a loss in Herd Immunity as contributory cannot be neglected in any explanation of the phenomena.

The complex interactions and natural consequence of these immune capacity failures combined indicates that, without the intervention of an as yet undefined variable, as the prevalence of HIV infection increases, society can also expect to see a commensurate and continuing increase in Syphilis incidence rates. Therefore, this set of circumstances must also be added to the list of reasons that explain the increasing rates of syphilis seen only since the advent of the HIV epidemic.

Unfortunately, a substantial number of other currently used serologic screening tests and skin tests rely upon humoral and cell mediated immunocompetence for proper function. As a population's immunocompetence is lost, even if difficult to quantify, so to is lost modern medicine's ability to cheaply and efficiently screen for the presence of or assume the absence of disease. Especially problematic is the impact HIV infection will have on the ability of clinicians to rule out diseases that have been in the past excluded by the absence of specific serologic markers or cell-mediated immune responses. In the case of Tuberculosis, anergy to skin testing is seen in up to 29% of AIDS patients⁶⁵ and the absence of cavitations on chest x-ray cannot be relied upon since this is a cell-mediated response and distinctly uncommon in AIDS⁶⁶.

By any measure, as Herd Immunity declines, so declines the serologic manifestations of this competence that have been capitalized upon by modern medical diagnostics. Ultimately, the ramifications of this loss can only be seen to result in further damage to the populations wherein it resides since a substantial quantity of disease will go undetected for longer periods giving rise to both prolonged carrier states and increased frequencies of infectious transmissions.

The effort to improve Herd Immunity has long been evoked as a justification for mandatory immunization programs that require children to be vaccinated against diseases before allowing them to

enter schools. Acting upon that logic was demonstrated to be successful. By surrounding school children only with other children who have immunity to a particular disease causing entity, the chances that a given epidemic will flourish are greatly reduced because each contact made by the infectious person is more likely to be with someone who is already protected (immune) and therefore, an epidemic that would have otherwise occurred is not sustained.

MEASLES

The current Measles epidemic (during 1989 a 430% increase in cases were reported over the same period in 1988⁶⁷) and mumps epidemic (during the period 1985-87 the annual incidence rate rose almost five-fold⁶⁸ and 1989 saw a 15% increase over the previous year⁶⁹) serve as theoretical and probably real examples demonstrating the consequences of a reduction in Herd Immunity that had been previously established as a result of intensive prior vaccination programs. If, indeed, an induced heightened level of Herd Immunity was to be credited for the precipitous decline in incidence seen immediately after the initiation of wide-spread vaccination programs, then a resurgence of disease could only be a reflection of a decline in the previous level of population immunity.

For the years 1962-83, the Measles vaccination programs have been effective in steadily and markedly reducing the occurrence of this disease. However, novel in and coincident with the AIDS era, the period 1983 through the present has seen an overall increase in Measles incidence continuing with substantial increases being seen in 1989.⁷⁰ In 1988, 68.9% of reported cases occurred among school-aged children who had been previously vaccinated and most vaccine failures occurred in persons 12-19 years of age⁷¹ who earlier were believed to be sufficiently protected. So, the larger part of this epidemic occurrence cannot be explained on the basis of an increasing failure to have children immunized.

Again, Measles outbreaks have been observed in areas with relatively high HIV seroprevalence such as Los Angeles⁷² and Dade County Florida.⁷³ Indicating (in the absence of a more virulent organism) a loss in Herd Immunity to Measles demographically associated with relatively high HIV prevalence.

In deference to claims that a primary vaccine performance failure may be responsible⁷⁴, it is reasonable to assume that a stable rate of individual vaccine performance failures had been present throughout the history of Measles immunization programs yet a failure had not been observed because the prevalence of the Measles virus was kept low enough by national vaccine performance (induced Herd Immunity) to prevent the percentage of poor vaccine responders from being seen epidemiologically. However, when higher numbers of Measles carriers exist in the population, the statistical probability of an inadequately immunized individual (either from a primary vaccine failure or a waning of vaccine-induced immunity) being exposed, infected, and becoming infectious correspondingly increases. Almost by definition, this event can only occur in the presence of a reduction in Herd Immunity. It can be concluded that an increase in infections in previously immunized persons would not have been observed if the Herd Immunity had remained constant or increased.

The presence of HIV infected Measles carriers and their increased Measles transmissions with insufficiently immunized contacts qualifies with equal if not greater weight as any other explanation. Since the HIV infected individual is less likely to clear the infectious organism from his or her body in a timely and efficient manner due to the incompetent immune system, they can be seen to serve as a probably more infectious source of transmissions for a longer period of time. HIV infected children with Measles do not necessarily demonstrate the typical, diagnostic rash.⁷⁵ Therefore, these children can serve as a more efficient source of outbreaks for longer periods of time because the absence of typical clinical symptoms precludes diagnosis, thereby delaying or preventing initiation of treatment, outbreak control measures, or appropriate isolation procedures.⁷⁶ It is likely that a substantial number of HIV infected individuals harbor Measles from exposures and clinical disease that cannot be eradicated or is present due to a failure of humoral immunity occasioned by HIV infections.

There is also good reason to believe that AIDS victims are repeatedly susceptible to most of those diseases that ordinarily are not re-acquired by, persist in active states in, or result in disseminated disease

in persons who have previously acquired immunity. This phenomenon has been described in a previously immunized 14 yr. old who had been immunized with live-attenuated Measles vaccine at 15 months and again at 9 years of age yet still developed serologically confirmed Measles.⁷⁷ This recurrence of disease also has been described in Hepatitis B⁷⁸, Herpes Simplex⁷⁹, and Varicella Zoster⁸⁰. Therefore, the HIV infected are at increased risk of repeatedly serving as sources of infectious transmissions of any other diseases that would otherwise have been arrested in the presence of a competent immune system.

CYTOMEGALOVIRUS

Any decline in Herd Immunity can be predicted to result in a detrimental tipping of the dynamic balance of those highly infectious viruses, such as Cytomegalovirus (CMV), Respiratory Syncytial Virus, Rhinoviruses (Common Cold), Adenoviruses (Tonsillitis), and Rotaviruses ("Stomach Flu") which have previously established delicate, long-standing, commensal relationships with human populations. The incidence and prevalence of these diseases is best exemplified by Cytomegalovirus infections which can reasonably be expected to increase due to their strong association with acquired immunodeficiency and serve as a source of increased morbidity in HIV bearing populations. Although the epidemiological impact on the general population is and will be difficult to assess due to their highly variable sero-prevalence being a function of age, socio-economical status, geographical location, and often subclinical presentation, an increased concern related to Cytomegalovirus infections in those children exposed to contacts in day care has been raised for the acquisition of CMV by susceptible day care workers and mothers who carry a risk for fetal infection⁸¹ as well as for those increasing numbers of patients iatrogenically (exposed by a healthcare procedure) or etiologically immunosuppressed in whom transfusion related or nosocomial (hospital acquired) transmission⁸² is likely. If these concerns are valid for those persons preferentially exposed to a higher probability of contact, infection, and potential morbidity then the same concern should be directed towards the entire population whose increased exposure will logically be the result of an increasing number of viremic contacts who have become so as a consequence of concurrent HIV infections.

An increased population threat can be envisioned and attributed to the HIV mediated deterioration of Herd Immunity as it pertains to AIDS and CMV since up to 97 percent of AIDS patients carry, actively secrete, and are infectious for Cytomegalovirus.⁸³ On autopsy, 93% of AIDS patients have evidence of disseminated CMV disease.⁸⁴

It has long been understood that CMV can cripple, blind, mentally retard, or kill fetuses and newborn infants when transmitted perinatally.⁸⁵⁸⁶⁸⁷⁸⁸ Its potential for prevention often discounted due to its high prevalence (up to 45% in Albany, New York, and 82% in low-income areas of Birmingham⁸⁹), it, nevertheless, has been characterized as the leading cause of virus induced birth defects (including mental retardation) in the nation.⁹⁰ Its precise frequency and transmission in people is currently poorly understood; but there is reason to believe it is significantly infectious, being transmitted sexually,⁹¹ horizontally and vertically⁹², and can infect newborns perinatally⁹³⁹⁴ or as a consequence of fomite spread⁹⁵.

Although CMV infection in the normal or otherwise healthy person may be asymptomatic, it can produce a febrile illness resulting in a clinical picture similar to infectious mononucleosis or complications including Guillain-Barre syndrome, meningoencephalitis, myocarditis, hemolytic anemia, granulomatous hepatitis, pneumonia, thrombocytopenia, and retinitis.⁹⁶ In the immunosuppressed or transplant recipients the problem is by no means trivial and accounts for significantly increased recipient mortality.⁹⁷

Recently, it has been shown that day-care workers have annual seroconversion rates as high as 11%⁹⁸ and concern has been voiced for child-bearing-aged women from areas of low prevalence who are being exposed to a higher risk for primary Cytomegalovirus infection due to their daycare childrens' contact with other children infectious for Cytomegalovirus⁹⁹. Logically, the same concern should be directed towards those populations in close contact with any person infectious for Cytomegalovirus.

Consider the consequences of a single daycare teacher with HIV related disease or AIDS who is

daily secreting any number of infectious diseases because (s)he lacks the immune competence to suppress the infections; and, therefore, is relatively both more infectious for any particular infectious agent and infectious for longer periods of time when compared with an non-HIV infected person.

Cytomegalovirus (CMV) provides an appropriate example since some studies have shown nearly 100% of AIDS patients are actively secreting CMV, and CMV is easily spread by contaminated objects (fomites) and hand contact. When a child acquires the disease the infection comes into the home of that child where, quite often, the mother is of child bearing age or pregnant (since mothers with one child in daycare have a higher probability of being still in their childbearing years, currently pregnant or with a susceptible newborn at home than other contingents of the population). CMV may be a relatively benign infection for non-pregnant, otherwise healthy and non-immunosuppressed persons, but it has been known to spread through nurseries killing neonates and it carries a 30-40% chance of being transmitted to the fetus in pregnant women who become infected.¹⁰⁰

For this reason, HIV infected persons with active Cytomegalovirus infections should be considered capable of placing at higher risk pregnant women, newborns, or the immuno-suppressed (such as other HIV infected persons, transplant recipients, cancer patients, or the elderly) with whom they are in close physical contact or when the likelihood of fomite transmission is high.

INFLUENZA

Influenza provides a model supporting the likely reality of the hypothesis that the HIV afflicted are more likely to serve as sources of infection by pathogenic organisms because their bodies do not respond like a normally immuno-competent person's with regard to protection by individually acquired immunity and vaccinations. This belief also serves to explain the currently and continuously increasing influenza activity¹⁰¹ and morbidity seen since the advent of AIDS since, not unlike the above mechanism postulated for measles, as the herd becomes increasingly peopled with immunocompetent individuals. One can reasonably conclude that the ability to induce and benefit from the Herd Immunity that has served as a basis for broad-based Influenza vaccination strategies¹⁰² also will be significantly impaired.

Centers for Disease Control data have shown that during the 1980's the number and percentage of deaths attributable to pneumonia and Influenza among persons age 25-44 more than doubled in cities with high AIDS incidence.¹⁰³ This association with AIDS and Influenza is significant enough for some authors to advocate annual immunization of the HIV-infected's household contacts.¹⁰⁴ The mortality from pneumonia and Influenza reported by vital records offices in 121 U.S. cities recorded from 1979 through 1989 have shown a progressive increase from approximately 3.5% to 5.5%.¹⁰⁵ Nationally, the number of deaths from Influenza and pneumonia during 1988 was higher than the preceding four years.

If the hypothesis put forth here is an accurate reflection of nature, one can expect a future increase in not only numbers of same serotype epidemics but the number of serologically different epidemics as well. This can be predicted because the Influenza organisms do not reproduce in the environment, they require human hosts in which to undergo the successive, successful mutations that allow for antigenic drift and shift to occur. It is reasonable to assume that a limiting factor in the rate of shift or drift is the immunity generated by individuals in the population that eradicate the organisms from the host prior to their production of a new immunologically distinct strain. Unless one holds to the archaic spontaneous generation theory or a belief that they filter down from outer space, these strains most probably originate in Influenza's hosts; and it is logical to assume that they originate in humans who are infected with the progenitor strain. If conditions are such that human hosts allow the organisms to thrive for prolonged periods of time and/or the number of human hosts increases, the statistical probability that new serotypes will develop can only be increased. HIV infections in the hosts provide precisely that environment by preventing an appropriate immune response from eradicating the organisms before they undergo sufficient mutational events to allow for the creation of novel, serologically distinct strains.

It has been shown that more than half of persons with AIDS or ARC do not produce antibodies

considered to be protective in response to four different Influenza vaccines.¹⁰⁶ It can be assumed, then, that, once infected by the initial wild-type Influenza virus, the HIV afflicted host will retain and be infectious for this organism for significantly longer periods than their immunocompetent counterparts. A consequence of this increased carrier state duration is that the immunocompromised hosts will serve as a preferential media for not only increased infectivity and transmission to their contacts but prolonged viral reproduction allowing for the higher probability of production of new serologically different strains. This HIV related phenomena probably applies to all viruses but special concern should be directed towards genetically integrative viruses whose reproduction would be otherwise limited or arrested on an individual and population level by a competent immune system. The HIV itself appears to capitalize upon its induction of immuno-incompetence combined with a prolonged duration of infection and propensity for mutagenicity to produce variant surface morphologies that allow for increased infectivity and for the creation of successive serotypes that require a specific immune response each more progressively difficult to generate in order to effect successful antibody neutralization.

Apparently, there is a micromolecular natural selection process occurring wherein viral clones preferentially reproduce through a selection advantage imparted by variant envelope protein structures. The envelope proteins that bind more efficiently to human cells or more successfully evade the existing antibodies impart a more competent capacity to both survive and reproduce. The HIV infected host, over time, creates multiple clones each increasingly capable of infecting and inflicting cytotoxicity on T-Cells or other cell types, resulting in progressive damage to the immune system. The result is morbidity ultimately terminating in host death.

This hypothesis is supported by the findings that in an individual presumably infected with a singular viral isolate, cumulative changes develop in immunologically relevant regions of the HIV-1 envelope,¹⁰⁷ the development of AIDS in seropositive individuals is correlated with the emergence of HIV isolates that were more cytopathic¹⁰⁸ and were more replication efficient in a variety of human cells,¹⁰⁹ and most of the HIV isolates from asymptomatic individuals do not infect T-Cell lines yet isolates from those persons with AIDS do.¹¹⁰

This prolonged period of virus presence that predisposes an increased opportunity for viral mutagenicity and variant clone creation has been previously described in relation to a continuous Varicella-Zoster infection (Chicken-Pox/Shingles) in a child with AIDS who developed an Acyclovir resistance during the course of her treatment,¹¹¹ acyclovir-resistant herpes simplex in AIDS patients,¹¹² and ganciclovir resistant cytomegalovirus in AIDS patients.¹¹³ These findings not only confirm the reality of the above described hyperclonic phenomenon occasioned by viruses in the presence of HIV induced immunocompetence but raises the specter of yet another threat to the ability of a population to avoid associated disease occasioned by the HIV epidemic--the increasing frequency and rapid development of anti-microbial resistance both in viruses¹¹⁴ and bacteria¹¹⁵.

Persons concerned with the future consequences of HIV on Herd Immunity must view Herd Immunity in an all-encompassing perspective that incorporates all aspects of a population's ability to resist the damage inflicted by pathogenic organisms over time. An increase in the rapidity, incidence and prevalence of drug resistance development by all types of pathogenic microorganisms can be predicted for society or the herd that includes all of the human population because these microbes will be allowed to persist and replicate in HIV infected hosts that lack sufficient immunocompetence to completely eradicate the residual colonies that reside in body areas and tissues where inhibitory concentrations of chemotherapeutic agents cannot be attained and a reliance upon the intrinsic capability of the immune system is essential for the microbe's eradication from the host.

Although this scenario has used viruses as an example, the same concepts hold for every infectious organism capable of causing disease in humans. The more persons lacking immunity in any given population, the greater chance that epidemics will occur and the greater chance any given uninfected individual has for acquiring disease as a result.

In this way, it can be seen that when components of a population with faulty immune systems are increasingly distributed throughout a population, it comes at the expense of Herd Immunity. The ultimate consequence of a societal failure to act upon the known ramifications of a reduction in Herd

Immunity is difficult to accurately quantify; however, one thing is certain--the "herd" can be assured of an increased incidence and prevalence of disease. To what degree this will impact the society, especially in densely populated areas where the necessary contact to allow for a transmission of disease is more likely to occur, remains to be seen; yet, no single factor better serves to explain the multiple epidemic increases being seen in the United States that have occurred since the advent of the HIV era than HIV itself.

Out of necessity, the HIV epidemic causes us to re-evaluate the relationships individuals have with their society in the context of infectious disease. The belief that our society had evolved beyond the catastrophic consequences of infectious diseases has had to be abandoned in light of the Human Immunodeficiency Virus's entry into the grand equation of life and death. These considerations argue strongly for Public Health Department identification and monitoring for Human Immunodeficiency Virus with especially focused surveillance for the AIDS-Related Superimposed Secondary Infections by preferential screening programs. Most certainly, the infected individuals would benefit by being afforded the opportunity for early diagnosis and treatment. Without question, society would benefit since the transmission of technologically preventable disease would be significantly reduced.

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1. CDC, Use of BCG Vaccines in the Control of Tuberculosis: MMWR, 1988; 37:663-664, 669-675.
2. CDC, Tuberculosis, Final Data--United States, 1986, Morbidity and Mortality Weekly Report, 1988;36:817-819.
3. Tuberculosis and Acquired Immunodeficiency Syndrome--New York City, Morbidity and Mortality Weekly Report, (CDC) 1987; 36:48 785-95.

4. CDC, Prevention and control of Tuberculosis in Correctional institutions: Recommendations of the Advisory Committee for the Elimination of Tuberculosis, Morbidity and Mortality Weekly Report, 1989,38;18:313-19.
5. Braun MM, Truman BI, Morse DL, Maguire B, Broaddus R. Tuberculosis and the acquired immunodeficiency syndrome in prisoners (Letter). Journal of the American Medical Association, 1987;257:1471-2.
6. Snider DE, Hutton MD, Tuberculosis in Correctional Institutions, Journal of the American Medical Association, 1989, 261;3:436-437.
7. Iseman MD, Drug-resistant Tuberculosis--New threats from an old disease, Postgraduate Medicine, 1989;86:2:109-114.
8. Anon, TB Deaths Reported in N.Y. Prison System, San Francisco Chronicle, 11/16/91, p. A6.
9. Carpi J, Faivelson S, AIDS workers face high incidence of tuberculosis, Medical Tribune, 3/21/91.
10. Centers for Disease Control, Tuberculosis and Acquired Immunodeficiency Syndrome--New York City, Morbidity and Mortality Weekly Report, 1987, 36;48:785-795.
11. Stead WW, Lofgren JP, Warren E, et al: Tuberculosis as an epidemic and nosocomial infection among the elderly in nursing homes, The New England Journal of Medicine, 1985; 312: 1483-1487.
12. Hawkins CC, Gold JMW, Whimbey E, et al: Mycobacterium avium complex infections in patients with acquired immunodeficiency syndrome. Annals of Internal Medicine, 1986;105:184-188.
13. Wolinsky E, Nontuberculous Mycobacteria and Associated Diseases, American Review of Respiratory Disease. 1979;119:107-159.
14. Ibid. p.126.
15. Lowry PW, Jarvis WR, Oberle AD, et al: Mycobacterium Chelonae causing otitis media in an ear-nose-and-throat practice, The New England Journal of Medicine, 1988;319:978-82.
16. Tsukamura M, Mizuno S, et. al., A comparative study of mycobacteria from patients' room dusts and from sputa of tuberculous patients: Source of pathogenic mycobacteria occurring in the sputa of tuberculous patients as casual isolates, Jap Journal of Microbiology, 1974;18:271.
17. Ibid.

18. Haron E, Bodey GP, Luna MA, et al., Has the incidence of Pneumocystis carinii pneumonia in cancer patients increased with the AIDS epidemic?, The Lancet, 1988, Oct. 15:904-5.
19. O'Brien RJ, Geiter LJ, Snider DE Jr. The epidemiology of nontuberculous mycobacterial diseases in the United States; results from a national survey. American Review of Respiratory Disease, 1987; 135:1007-14.
20. Prince DS, Peterson DD, Steiner RM, et al., Infection with Mycobacterium Avium Complex in Patients without Predisposing Conditions, The New England Journal of Medicine, 1989; 321:863-8.
21. Ibid. p. 867.
22. Lynch JP, Managing pulmonary infiltrates in immunocompromised patients, The Journal of Respiratory Diseases, 1988;9:11:p. 11-28.
23. Wolinsky, op. cit., p. 127.
24. Stine TM, Harris AA, et al., A Pseudoepidemic due to Atypical Mycobacteria in a Hospital Water Supply, Journal of the American Medical Association, 1987;258:6:809-811.
25. Inman RD, et al, Post dysenteric Reactive Arthritis: A Clinical and Immunogenetic Study Following an Outbreak of Salmonellosis, Arthritis Rheum, 1988;31:1377-1383.
26. Ryan CA, Nickels MK, et. al., Massive Outbreak of Antimicrobial-Resistant Salmonellosis Traced to Pasteurized Milk, Journal of the American Medical Association, 1987;258:22:3269-3274.
27. St. Louis ME, Morse DL, Potter ME, et. al., The Emergence of Grade A Eggs as a Major Source of Salmonella enteritidis Infections, Journal of the American Medical Association, 1988;259:2103-2107.
28. CDC, Increasing Rate of Salmonella Enteritidis Infections in the Northeastern United States, Morbidity and Mortality Weekly Report, 1987; 36:1:10-11.
29. CDC, Update: Salmonella enteritidis Infections and Grade A Shell Eggs--United States, 1989, Morbidity and Mortality Weekly Report, 38;51&52:877-80.
30. CDC, Summary--cases of specified notifiable diseases, United States, Morbidity and Mortality Weekly Report, 1990;38;52:891.
31. Editor, Third Patient Dies of Salmonella Poisoning, American Medical News, Sept. 4, 1987. p. 63.

32. Bodovitz K, East Bay Officials Seek Source of Typhoid Cases, San Francisco Chronicle, August 26, 1988.
33. Laurence J, Gastrointestinal Infections in AIDS Patients, Infections in Medicine, 1986, October:318-326.
34. Ryan, op. cit., p. 3269.
35. St. Louis, op. cit., p. 2103.
36. Taylor DN, Bopp CA, Birkness K, Cohen ML. An outbreak of Salmonella associated with a fatality in a healthy child: a large dose and severe illness. American Journal of Epidemiology, 1984;119:907-12.
37. Lowry PW, Levine R, et al., Hepatitis A outbreak on a floating restaurant in Florida, 1986, American Journal of Epidemiology, 1989, 129;1:155-64.
38. Lowry PW, Personal Communication, November 21, 1989.
39. Centers for Disease Control. Food-borne hepatitis A--Oklahoma, Texas. MMWR, 1983; 32:652-9.
40. Kosatsky T, Middaugh JP, Linked outbreaks of Hepatitis A in homosexual men and in food service patrons and employees. West J Med 1986; 144:307-10.
41. Lowry PW, Levine R, et al., Hepatitis A outbreak on a floating restaurant in Florida, 1986, American Journal of Epidemiology, 1989, 129;1:163. (quoting personal conversation with Dr. R Roberto, Calif. Dept. of Health Serv., 1987).
42. Hepatitis A Among Drug Abusers, MMWR, 1988; 37:297-300,305.
43. Los Angeles Daily News, Hepatitis A Outbreak in Los Angeles, 12/28/1989, quoting Donnell Ewert of LA County Health Dept.
44. CDC, Summary--Cases of Notifiable Diseases, United States, Morbidity and Mortality Weekly Report, 1990;38;51&52:891.
45. Nime FA, Burek JD, Page DL, et al., Acute enterocolitis in a human being infected with the protozoan *Cryptosporidium*, Gastroenterology, 1976; 70:592-8.
46. Smith PD, Lane HC, Gill VJ, et al: Intestinal Infections in Patients with the Acquired Immunodeficiency Syndrome (AIDS), Annals of Internal Medicine, 1988;108:328-333.
47. Nelson JA, Reynolds-Kohler C, Margaretten W, et al: Human Immunodeficiency Virus detected in bowel epithelium from patients

with gastrointestinal symptoms. Lancet, 1988;1:259-262.

48. Soave R, Armstrong D. Cryptosporidium and Cryptosporidiosis, Reviews of Infectious Diseases, 1986, 8;6:1012-23.

49. Infectious Disease Section California State Dept. of Health Services, Cryptosporidiosis: A newly recognized cause of diarrheal illness in day care centers, California Morbidity Weekly Report, 1984;41;October 19:1.

50. Alpert G, et al., Outbreak of Cryptosporidiosis in a Day Care Center, Pediatrics, 1986; 77:152-7.

51. Gallaher M, Cryptosporidiosis Outbreak Linked to Day-Care Center, American Journal of Public Health, 1988; 79:39-42.

52. Hayes EB, Matte TD, O'Brien TR, et. al., Large Community Outbreak of Cryptosporidiosis due to contamination of a filtered public water supply, The New England Journal of Medicine, 1989;320:1372-6.

53. Soave, Op. cit. p. 1015.

54. Peck P, Animal Rights: Terrorists Strike Medicine, Physician's Management, 1989, June;49-68.

55. Ibid.

56. Koch KL, Phillips DJ, Aber RC, Cryptosporidiosis in hospital personnel; evidence for person-to-person transmission, Ann Internal Med, 1985; 102:593-6.

57. CDC, Syphilis and Congenital Syphilis--United States 1985-1988, Morbidity and Mortality Weekly Report, 1988, 37:486.

58. CDC, Continuing Increase in Infectious Syphilis--United States, Journal of the American Medical Association, 1988, 259;7:975-7.

59. CDC, Summary--cases of specified notifiable diseases, United States, Morbidity and Mortality Weekly Report, 1990;38;52:891.

60. CDC, Continuing Increase in Infectious Syphilis--United States, Journal of the American Medical Association, 1988, 259;7:975-7.

61. Hicks CB, Benson PM, Lupton GP, et. al., Seronegative Secondary Syphilis in a Patient Infected with the Human Immunodeficiency Virus (HIV) with Kaposi Sarcoma, Annals of Internal Medicine, 1987; 107:492-495.

62. McGuire R, Neurosyphilis: Menacing AIDS Companion, Medical Tribune, 1989, January 19: p. 3-18.

63. Simonsen JN, Cameron DW, Gakinya MN, et al, Human immunodeficiency virus infection among men with sexually transmitted disease: Experience from a center in Africa. The New England Journal of Medicine, 1988, 319:274.
64. Stamm WE, Handsfield HH, Rompalo AM, et al, The association between genital ulcer disease and acquisition of HIV infection in homosexual men. Journal of the American Medical Association, 260: 1429, 1988.
65. Mann J, Snider DE, Francis H, et al., Association Between HTLV-III/LAV infection and Tuberculosis in Zaire, Journal of the American Medical Association, 1986;256;3:346.
66. Anon, TB Making a Comeback as AIDS-Related Pathogen, Medical World News, 1986;July 28:61. (Quoting Dr. Philip Hopewell, Univ. of California, San Francisco)
67. CDC, Summary--cases of specified notifiable diseases, United States, Morbidity and Mortality Weekly Report, 1990;38;52:891.
68. CDC, Mumps Prevention, Morbidity and Mortality Weekly Report, 1989, 38;22:388-400.
69. CDC, Summary--cases of specified notifiable diseases, United States, Morbidity and Mortality Weekly Report, 1990;38;52:891.
70. CDC, Measles--United States, 1988, Morbidity and Mortality Weekly Report, 1989, 38;35:601-605.
71. Ibid. p. 603.
72. CDC, Measles--Los Angeles County, California, 1988, Morbidity and Mortality Weekly Report, 1989, 38;4:49-57.
73. CDC, Measles--Dade County Florida. Morbidity and Mortality Weekly Report, 1987; 36:45-8.
74. Markowitz LE, Preblud SR, Fine PEM, Orenstein WA, Duration of live measles vaccine-induced immunity. Pediatr Infect Disease J (in press). From CDC, Measles--United States, First 26 Weeks, 1989, Morbidity and Mortality Weekly Report, 1989; 38:863-872.
75. Krasinski K, Holzman RS, Lacouture R, et al. Nosocomial measles: are current vaccination guidelines for staff adequate? (Abstract). In: Program and abstracts of the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, October 4-7, 1987. Described in: CDC, Measles in HIV-Infected Children, United States, Morbidity and Mortality Weekly Report, 1988; 37/Nos. 11, 12 (Obtained from Journal of the American Medical Association, Leads from the MMWR, 1988, 259;16:2352-57.

76. Enders JF, McCarthy K, Mitus A, Cheatham WJ. Isolation of measles virus at autopsy in cases of giant-cell pneumonia without rash. The New England Journal of Medicine, 1959;261:875-81.
77. CDC, Measles in HIV-Infected Children, United States, Morbidity and Mortality Weekly Report, 1988; 37/Nos. 11, 12 (Obtained from Journal of the American Medical Association, Leads from the MMWR, 1988, 259;16:2352-57.
78. Vento S, Di Perri G, et al, Reactivation of Hepatitis B in AIDS, The Lancet, 1989, July 8:109-10.
79. Lynch JP, When opportunistic viruses infiltrate the lung, Journal of Respiratory Diseases, 1989; 10;2:25-30.
80. Reuler JB, Chang MK. Herpes zoster: epidemiology, clinical features, and management. South Med J, 1984;77(9):1149-56.
81. Pass RF, Hutto C, Reynolds DW, Hohill RB. Increased frequency of cytomegalovirus infection in children in group day care. Pediatrics, 1984;74:121.
82. Adler SP, Nosocomial Transmission of Cytomegalovirus, Pediatric Infectious Disease, 1986; 5;2:239-46.
83. Lerner CW, Tapper ML: Opportunistic infection complicating acquired immune deficiency syndrome: Clinical features of 25 cases. Medicine, 63:155-164, 1986.
84. Macher AM, Reichert CM, Straus SE, et al. Death in the AIDS patient: role of cytomegalovirus. The New England Journal of Medicine, 1983; 309:1454.
85. Stagno S: Cytomegalovirus Infection a Pediatrician's Perspective, Current Problems in Pediatrics, 1986, Year Book Medical Publishers, p. 648-9.
86. McCracken GJ, et al: Congenital cytomegalic inclusion disease: A longitudinal study of 20 patients. Am J Dis Child, 1969;117:522.
87. Medearis TN: Observations concerning human cytomegalovirus infection and disease. Bull Johns Hopk Hosp, 1964; 114:181.
88. Berenberg W, Nankervis G: Long-term follow-up of cytomegalic inclusion disease of infancy. Pediatrics, 1970; 37:403.
89. Ho M, ed. Cytomegalovirus, biology and infection, New York; Plenum, 1982; 79-104.

90. Wilson, "At the Edge of Life: An Introduction to Viruses, A Report from the National Institute of Allergy and Infectious Diseases", (1980), p. 16.
91. Noble RC, Sexually Transmitted Cytomegalovirus Infection, Medical Aspects of Human Sexuality, 1987; October: 18-27.
92. Stagno S, Cytomegalovirus Infection: a Pediatrician's Perspective, Current Problems in Pediatrics, 1986; Year Book Medical Publishers, Inc.:632-65.
93. Kumar ML, Gold E, Nankervis G, Risk of acquired cytomegalovirus infection in infants of maternal cytomegalovirus excretors. Pediatr Res, 1975; 9:342.
94. Stagno S, Reynolds DW, Pass RF, Alford CA, Breast milk and the risk of cytomegalovirus infectio, The New England Journal of Medicine, 1980; 302:1073-76.
95. Spector SA, Transmission of cytomegalovirus among infants in hospital documented by restriction-endonuclease-digestion analyses, The Lancet, 1983; February 19:378-81
96. Cohen JI, Corey GR, Cytomegalovirus infection in the normal host. Medicine, 1985; 64:100.
97. Grattan, MT, Moreno-Cabral CE, Starnes VA, et al., Cytomegalovirus Infection is Associated with Cardiac Allograft Rejection and Atherosclerosis, Journal of the American Medical Association, 1989;261;24:3561-6.
98. Adler, SP, Cytomegalovirus and child day care: evidence for an increased infection rate among day-care workers. The New England Journal of Medicine, 1989;321;(Nov 9):1290-6.
99. Murph JR, Bale JF, Murray JC, et al., Cytomegalovirus transmission in a Midwest day care center: Possible relationship to child care practices, The Journal of Pediatrics, 1986;1;109:35-39.
100. Stagno S, Pass RF, Cloud MS, Britt WJ, et al. Primary Cytomegalovirus Infection in Pregnancy, Journal of the American Medical Association, 1986;256;14:1904-1908.
101. CDC, Influenza Activity--United States, 1989, Morbidity and Mortality Weekly Report, 1989;38:863-872.
102. CDC, Prevention and Control of Influenza, Morbidity and Mortality Weekly Report, 1988;37:361-364,369-373.
103. CDC: Increase in pneumonia mortality in young adults and the HIV epidemic in New York City, United States. Morbidity and Mortality

Weekly Report, 37:593, 1988.

104. Nelson KE, Annual influenza vaccination indicated for HIV-infected patients, Medical Aspects of Human Sexuality, 1989, December:p. 8.
105. Tipple MA, Kendal AP, Influenza epidemiology: Lessons from recent outbreaks, The Journal of Respiratory Diseases: Supplement "Influenza in the 1990's: Use of Antiviral Agents in Prophylaxis and Treatment", 1989;December, p. S11.
106. Nelson KE, Clements ML, Miotti P, et al, The influence of HIV infection on antibody responses to influenza vaccines. Annals of Internal Medicine, 1988;109: 383.
107. Kong LI, Taylor, ME, Waters, D, et al., Genetic analysis of sequential HIV-1 isolates from an infected lab worker, Fifth International AIDS Conference on AIDS, Montreal, Canada 1989, T.C.O.19, p 518.
108. Tersmette M, Gruters RA, Wolf, et al: Evidence for a role of virulent human immunodeficiency virus variants in the pathogenesis of acquired immunodeficiency syndrome; Studies on sequential HIV isolates. Journal of Virology, 1989;63:2118.
109. Cheng-Mayer C, Seto D, Tateno M, et al. Biological features of HIV-I that correlate with virulence in the host. Science, 240:80,1988.
110. Gupta P, Balachandran R, Thampatty P, et al. HIV isolates from asymptomatic men are biologically and genetically different from those isolated from AIDS patients, Fifth International Conference on AIDS, Montreal, Canada, 1989, Th. C. O. 28, p. 537.
111. Pahwa S, Biron K, Lim W, et al, Continuous Varicella-Zoster Infection Associated with Acyclovir resistance in a Child with AIDS, Journal of the American Medical Association, 1988;260;19:2879-82.
112. Erlich KS, Mills JM, Chatis P, Mertz GJ, et al. Acyclovir-resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome, The New England Journal of Medicine, 1989;320;5:293-300.
113. Erice A, Chou S, Biron KK, Stanat SC, et al. Progressive disease due to ganciclovir-resistant cytomegalovirus in immunocompromised patients, The New England Journal of Medicine, 1989;320;5:289-293.
114. Erlich KS, Mills J, Chatis P, Mertz GJ, et al, Acyclovir-resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome, The New England Journal of

Medicine, 1989,320;5:293-6.

115. Handwerger S, Bacterial resistance to antibiotics seen increasing, Modern Medicine, 1989;February;57:37.