
Parkland Memorial
Hospital
GRAND ROUNDS
MICROBIAL LATENCY
Philip A. Mackowiak, M.D.
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When a pathogenic microorganism attacks an animal, a struggle ensues in which the microbe's efforts to parasitize that host are actively resisted by the immunological defenses of the infected animal. If the microbe's capacity for parasitization exceeds the host's capacity for resisting such invasion, the infection progresses until either the immune defenses prevail or the host animal expires. If in this struggle, the immunologic defenses are the dominant force, not only is the pathogenic microorganism eliminated, but the host animal also enjoys enhanced resistance to future attacks by the same microorganism.

One other frequently ignored potential outcome of this struggle is that it may result in a stalemate in which the host succeeds in suppressing but not eliminating the pathogenic microbe. The consequence of such a stalemate is a persistent, yet seemingly inactive (latent) infection, in which the microbe retains the capacity to reactivate and cause acute disease - most frequently in the a face of flagging immunocompetence. Although the clinical, as well as the epidemiologic significance of such latent infections is immence - both because of their capacity for reactivation in a given host and their potential for spread to new hosts - they have received scant attention in the medical literature. There has been no systematic review of microbial latency, nor have reports on this subject appeared in the literature with sufficient frequency to warrant listing "microbial latency" as a heading in any of the medical indexes.

In the present review I will attempt to summarize current knowledge of the processes by which microorganisms consumate latency in man, as well as the mechanisms by which reactivation of such infections occur. I will examine each of the major groups of human parasites for evidence of latency in man, and will consider the relationship of such infections to the origin of human neoplasms. Finally, I will review the special problems and modest successes encountered by investigators searching for effective means of treating latent infections.

## MECHANISMS OF LATENCY

The immunological defenses are a sine qua non of microbial latency, since in their absence, uncontrolled proliferation of the pathogenic microorganisms would occur, leading invariably to death of the host animal. My purpose in this review will not be to describe the complex and varied forms in which these defenses exist, but rather to focus upon the means by which various pathogens suppress, subvert or elude these defenses in establishing latent human infections in man.

Immunosuppression: Conditions associated with suppression of the immune system predispose to microbial latency, as well as to reactivation of latent infections. Such suppression may result from genetic abnormalities [e.g. Epstein -Barr virus (EBV) - induced disease in boys with X-linked lymphoproliferative syndrome (1)], underlying diseases (e.g. lymphomas) or the use of immunosuppressive drugs. In addition, certain microorganisms may themselves induce nonspecific defects in the immune response. Microbially-induced immunosuppression has already been extensively reviewed in this forum (2), and will therefore, not be considered further in the present discussion.

Protected Sites: One of the most important means by which microorganisms succeed in establishing latent infections is to obtain access to sites within the body that are, for one reason or another, inaccessible to the immune system. Residence in such sites affords potential pathogens protection from an active immune response, and an opportunity to bide time in anticipation of a faltering of that response.

Foreign bodies are important examples of such protected sites. Whether introduced inadvertently during traumatic epidisodes, or intentionally during the course of surgery, foreign bodies such as mineral debris, sutures or prosthetic devices, offer places of refuge for pathogenic microorganisms. Because they are avascular, foreign bodies limit access of both inflammatory cells and antimicrobial agents to harbored microorganisms.

Renal stones (3), gall stones (4) and devascularized bone (5) are similar potential sites of refuge for pathogenic microorganisms. In approximately 20% of cases of urolithiasis, renal stones are formed in the presence of urea-splitting bacteria (3). Such bacteria not only participate in the process by which stones composed of struvite ($MgNH_4PO_4.6H_2O$) and carbonate apatite ($Ca_{10}[PO_4]_6CO_3$) are formed, but also profit from the formation of these stones by creating an environment conducive to persistent infection. Only if care is taken to detect and eliminate such stones in their entirety is the problem of recurrent infection common in these patients averted. Devitalized bone, such as that leading to or resulting from chronic osteomyelitis provides for a particularly resistent form of microbial latency (5). Pathogenic microorganisms residing within such diseased bone exhibit a remarkable capacity for resisting elimination by either the immune response or prolonged courses of antibiotic therapy. Other examples of microbial persistence occurring as a result of pathogenic microorganisms' finding access to sites isolated from the immune response include colonization of pulmonary cavities by Aspergillus fumigatus (6) and persistence of Treponema pallidum in the anterior chamber of the eye (7).

In a sense, microorganisms colonizing the skin and mucosal surfaces of man must be regarded as latent infections. Not only are microorganisms residing among the normal flora singularly important sources of opportunistic infections in the immunocompromised host (8-10), but they are also predominant etiologic agents in infections of the respiratory tract (11), the genitourinary tract (12) and the skin (13) of immunologically competent persons. Because of their location on body surfaces rather than within tissues, members of the normal flora avoid direct contact with the full force of man's immunological defenses. In these protected sites, most members of the normal flora maintain a saprophytic existence that degenerates into frank parasitism only during the most extreme instances of immunosuppression. Unfortunately, a variety of overtly pathogenic microorganisms coexist with the more numerous saprophytes (Table 1). Their presence among the normal human flora is a successful and pernicious form of microbial latency, that is held in tenuous control by competition from nonpathogenic microorganisms occupying the same body surfaces and by the hosts immunological defenses (31).

Perhaps the most sophisticated form of latency involving a protected site is the parasitization of the intracellular environment. Viruses are the masters of this form of latency and will be considered in depth later in this discussion. At this point, I will consider the various fungi, protozoa and bacteria that have also developed capacities for intracellular parasitism.

In many respects, the intracellular environment is a hostile one, and yet it offers an unexploited ecological niche protected both from potential microbial competitors, and a large part of the host immune defenses. In maximizing their capacity for filling this ecological niche many intracellular parasites have apparently given up much of their capacity for independent existence to become heterotrophs. Such life forms are totally dependent upon photosynthesizers belonging to the parasitized cell to reduce $CO_2$ to organic compounds required as sources of energy and synthetic intermediates (32).

Table 1

PATHOGENIC MICROORGANISMS REPRESENTED AMONG THE HUMAN NORMAL FLORA

| Pathogen | Colonization Rates* | Predominant site of Colonization | Conditions Predisposing to Colonization and/or Disease | References |
|---|---|---|---|---|
| *S. aureus* | 22-85 | Nasopharynx | Cystic fibrosis, chronic renal failure, narcotic addition | 14-18 |
| *S. pyogenes* | 5-66 | Oropharynx | Crowding, low socioeconomic status, young age | 14,19 |
| *S. pneumoniae* | 8-71 | Oropharynx | Chronic obstructive lung disease | 14,20 |
| *H. influenzae* | 3-97 | Pharynx | Chronic obstructive lung disease, crowding | 14,20,21 |
| *N. meningitidis* | 3-32 | Nasopharynx | Crowding, viral respiratory infections | 22-25 |
| *P. aeruginosa* | 11 | Intestine | Cystic fibrosis† | 16,26 |
| *Cl. tetani* | 1-35 | Intestine | Unknown | 14 |
| *L. monocytogenes* | 1-5 | Intestine | Unknown | 27 |
| *N. gonorrhoeae* | 1-8 | Genitourinary tract | Sexual promiscuity | 28,29 |
| *C. albicans* | 3-46 | Orophyarynx, vagina, intestine | Diabetes, obesity | 14 |
| *A. israelii* | 11-18 | Oropharynx | Pyorrhea | 30 |

* Reported colonization rates among the general population. In most cases incidence data not differentiated from prevalence data.

† Predisposes to respiratory colonization by mucoid strains of *P. aeruginosa*.

To be successful the intracellular parasite must gain access to the host cell, multiply, escape from the original host cell and infect new cells -ideally while inflicting a minimum of damage on parasitized cells (32). The mechanisms by which intracellular parasites clear these hurdles are as intriging as they are varied.

Entrance into the host cell may occur either actively or passively. Chlamydia psittaci, for example, enters murine fibroblasts at no personal energy cost, because it is actively phagocytosed by the fibroblasts (33). Penetration of host cells by rickettsiae differs by being induced by the parasites and thus requiring a cooperative expenditure of energy by both the host cell and the parasite (34,35).

Once within the cell, intracellular parasites face their most formidable adversities. Macrophages are the usual host cell of such parasites, and as the principle scavenger cells of the body, possess highly developed organelles (lysosomes) for killing and degrading microorganisms. Phagocytosed microbes are normally disposed of as a result of fusion of the phagocytic vesicle, within which they are brought into the cell, with primary lysosomes, which contain

various degradative enzymes (36). Parasites such as mycobacteria (37) and Toxoplasma gondii (38) can survive within macrophages because they have evolved mechanisms to prevent fusion of lysosomes with phagocytic vesicles. Other intracellular parasites are simply resistant to the degradative effects of lysosomal enzymes (39), while still others such as Trypanosoma cruzi avoid destruction by escaping from the lysosome and taking up residence in the cytoplasm, where specialized mechanisms for killing foreign invaders do not exist (40,41). Finally, Toxoplasma gondii (42) and Salmonella typhi (43) appear to survive intracellularly, because they fail to trigger a vigorous respiratory burst in parasitized phagocytes.

Harnessing cellular energy sources for their own purposes, is an accomplishment of intracellular parasites no less impressive than that of resisting intracellular lysosomal attack. Except for those employed by viruses, little is known of the mechanisms by which intracellular pathogens succeed in this process. It is known, for example that rickettsiae and chlamydiae have evolved transport mechanisms enabling them to exploit host-generated adenosine triphosphate (ATP) and other energy-rich intermediates (34,44,45). However, the specific nature of these mechanisms has not yet been elucidated.

Antigenic engineering: In 1928, H.E. Meleney published observations on the relapse phenomenon in borreliosis (46). His report described experiments in which splenectomized squirrels inoculated with a single antigenic strain of Borrelia recurrentis produced six antigenically distinct strains of the organism during successive relapses. These observations established that the mechanism responsible for the relapsing febrile course of borreliosis involves continued sequential production of new antigenic variants, followed by specific antibodies directed against these successive variants (Figure 1) (47). This was one of the first recognized examples of involvement of antigenic variation as a pathogenic mechanism in microbial latency.

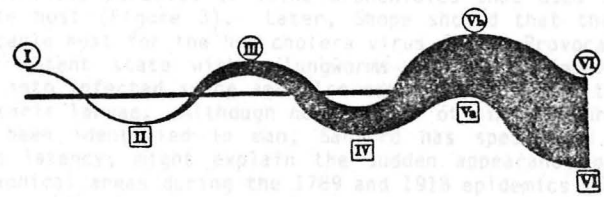


Fig. 1 The broadening zone of strain relationships in the descendants of strain I (B. recurrentis).

Trypanosomes, leishmania, plasmodia and babesia are capable of similar antigenic variation (36). The actual mechanisms responsible for such variation are not fully defined. Adaptive phenotypic variation is thought to be involved in the antigenic variation of trypanosomes (36). Experimental data suggests that the parasite has a finite number of genes coding for surface antigens, and that such genes are activated and repressed in regular sequence. By contrast, leishmania appear to modulate antigen expression by shedding surface antigens in response to specific antibodies, and as a result, become refractory to the effects of immune serum and complement (48).

Schistosomes are even more inovative in their capacity to confuse the immune system through feats of antigenic engineering. These remarkable parasites actually incorporate host cell membrane antigens into their own outer membranes (36,49,50). T. cruzi has exhibited a similar capacity in recent in vitro studies (51).

Immunological Subversion. One of the more insidious achievements of parasites capable of latency is that of subverting the immune response to their own advantage. Such is apparently the case with certain viruses within the herpes group. Cytomegalovirus, herpes simplex virus and varicella-zoster virus each induces Fc receptors during the process of parasitizing host cells (52-54). Binding of immune complexes to these Fc receptors has been shown to afford protection for both the virus and the infected cell against immune injury (55,56), and in this way might be involved in maintenance of the latent state (54). Recent studies have also established the capacity of virus-induced Fc receptors to promote adherence of antibody-coated bacteria to infected cells (Figure 2) (57). These observations raise the possibility that in addition to participating in viral latency, virus-induced Fc receptors might also have a role in the high incidence of secondary infections in transplant patients undergoing primary cytomegalovirus infections (58-60).

Synergistic latency. In 1941 Shope published experimental data suggesting that the swine lungworm is both a reservoir and an intermediate host for swine influenza virus (61). In his studies, he established the capacity of the swine influenza virus to exist in masked form in the swine lungworm (Metastrongylus sp.) - a nematode parasite of swine bronchioles that uses the earthworm as an intermediate host (Figure 3). Later, Shope showed that the swine lungworm is also a suitable host for the hog cholera virus (62). Provocation of the viruses from their latent state within lungworms followed injections of Haemophilus influenzae into infected swine and also occurred as a result of pulmonic migration of ascaris larvae. Although no evidence of similar forms of masked infection have been identified in man, Sanford has speculated that this kind of synergistic latency, might explain the sudden appearance of influenza over a wide geographical areas during the 1789 and 1918 epidemics (63).

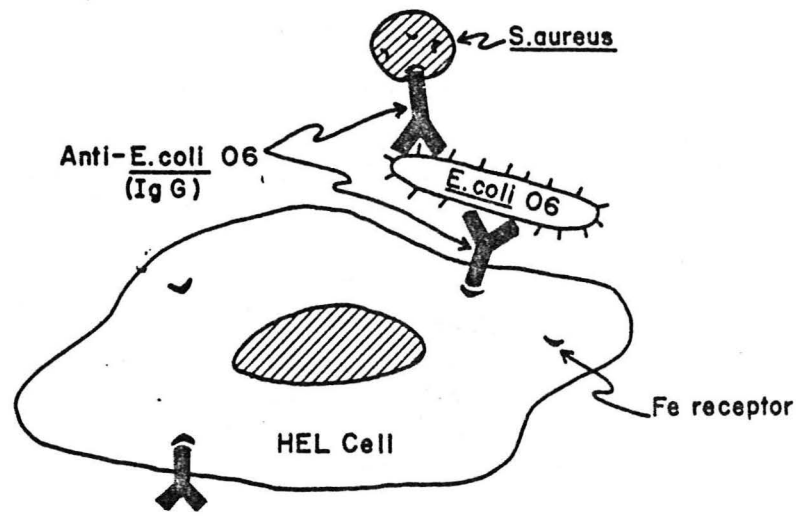


Fig. 2 Anti-E. coli O6 - mediated adherence of S. aureus to CMV-infected monolayers. Adherence is accomplished by a process of coaggregation in which the Fc regions of fixed anti-E. coli O6 IgG bind simultaneously to Fc receptors on CMV-infected HEL cells and S. aureus.

Numerous investigators have reported a peculiar association between schistosomiasis and salmonellosis in man (64,65). Experimental evidence suggests that in at least some cases, this association exists because of a propensity of salmonellae for parasitizing schistosomes. Equally intriguing are the numerous clinical reports of simultaneous pneumocystis and cytomegalovirus infections (66). After observing cytomegalovirus-like bodies within Pneumocystis carinii cells in two patients with combined pneumocystis/cytomegalovirus pneumonia, Wang and associates (67) suggested that a possible explanation for their frequent clinical association might be that parasitized P. carinii cells occasionally function as vectors for cytomegalovirus.

Spontaneous infections involving Toxoplasma gondii and cytomegalovirus also occur with surprising frequency among patients with disseminated cancer (68,69) and may reflect a symbiotic relationship. Gelderman and his co-workers (70) showed that these two organisms occasionally occupy the same cells in patients with dual infections. Furthermore, their rosettes tend to form rings around

cytomegalovirus inclusion bodies, suggesting that mitochondria also concentrated around the cytomegalovirus inclusion bodies might provide an energy source for T. gondii.

Risk factors. Peculiarities of the host, like those of the invading microorganism may be crucial in determining the frequency with which latency is the outcome of infection, as well as the likelihood of reactivation of latent infections. A variety of such risk factors have been identified (Table 2), including: age at the time of infection, sex, genetic background, immune status, dose of infectious agent received, route of infection, pregnancy and occupation. The relative importance of each of these factors to the latent state varies from one parasite to another, and will be addressed in the discussion of individual classes of parasites in later sections.

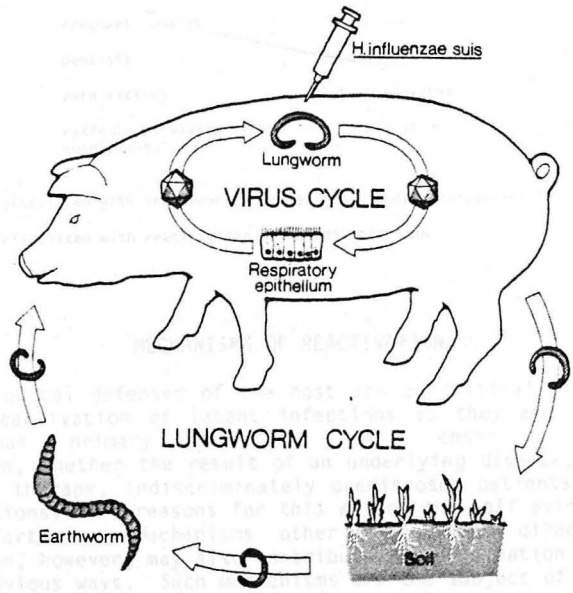


Fig. 3 The Shope hypothesis of swine influenza virus latency.

Table 2

EXAMPLES OF RISK FACTORS PREDISPOSING TO THE LATENT STATE AND/OR REACTIVATION OF LATENT INFECTIONS

| Risk Factor | Particular Persons at Risk | Agent | Effect* | Ref. No. |
|---|---|---|---|---|
| Age | Neonates | Hepatitis B virus | A | 71 |
| Sex | Males | Hepatitis B virus | A | 71 |
| Genetics | Downs syndrome | Hepatitis B virus | A | 72 |
| Immune status | X-linked lymphoproliferative syndrome | Epstein-Barr virus | A | 1 |
| Infectious dose | Persons with low worm load | Hookworm | A | 73 |
| Fertility | Pregnant females | *C. albicans* | B | 74 |
| Occupation | Dentists | Hepatitis B virus | A | 75 |
| Trauma | Burn victims | Cytomegalovirus | B | 76 |
| Nutrition | Patients receiving iron supplements | *E. histolytica* | B | 77 |

* A: Risk factor associated with the chronic carrier state and/or inapparent infection.

B: Risk factor associated with reactivation of latent infection.

## MECHANISMS OF REACTIVATION

The immunological defenses of the host are as critical in determining the likelihood of reactivation of latent infections as they are in dictating the probability that primary infections will enter a latent phase. Immunosuppression, whether the result of an underlying disease, systemic infection or medical therapy, indiscriminately predisposes patients to reactivation of latent infections. The reasons for this effect are self evident and will not be addressed further. Mechanisms other than those directly related to immunosuppression, however, may also contribute to reactivation of latent infections in less obvious ways. Such mechanisms are the subject of this section.

Disruption of anatomical barriers. Although the human body is heavily colonized by numerous and diverse microorganisms, an intricate system of anatomical barriers ensures that the actual sites colonized by these microorganisms are restricted primarily to the skin and various mucosal surfaces. The tissues themselves are carefully protected from all but the most transient and isolated contacts with representatives of the normal flora. However, when these barriers are disrupted, either as a result of trauma, disease or surgical intervention, opportunities arise for large numbers of indigenous microorganisms to enter tissues, and assume an overtly parasitic state. Colonic perforations, esophageal tears and burn injuries are but of few obvious examples of disrupted anatomical barriers predisposing to acute infections by indigenous microorganisms.

Anatomic barriers may also be disrupted or circumvented in more subtle ways. Mucosal defects may be small rather than large. Colonic ulcers resulting from chemotherapy (78), strongyloidiasis (79) or shigellosis (80) are examples of such defects, each of which predisposes to bloodstream invasion by indigenous colonic bacteria. Occasionally, intact anatomical barriers are bypassed by representatives of the normal flora. Aspiration pneumonia and honeymoon cystitis are examples of infections resulting when indigenous microorganisms bypass anatomical barriers to parasitize normally sterile tissues.

Pathogenic microorganisms, like saphrophytes within the normal flora may be held in check, largely as a result of effective anatomic barriers. The tuberculous granuloma is a classic example of such a "walled off" infection. Baum and Amberson (81) have shown that anotomic barriers holding these pathogens in check are no more inviolable than those designed to confine the normal flora. They showed that when a pyogenic pulmonary infection occupies the same lobe as a tuberculous granuloma, reactivation tuberculosis is a potential consequence, presumably because of disruption of the granuloma by the pyogenic infection.

In its most subtle form, traumatic reactivation of latent infections may involve a local disruption of anatomical integrity so minor as to defy detection. The capacity of such subtle trauma to lead to reactivation of latent infections (locus minoris resistantiae) has long been a subject of interest and speculation. One of the more colorful clinical descriptions of the phenomenon appeared in Paris Medical in 1918 (82). This report described a striking predisposition of luetic moslems for developing gummas of the forehead. The authors concluded that repeated tapping of forehead to the ground during daily prayers was in some way responsible for the peculiar localization of the tertiary lesions. Similar observations have been made in experimental extrapulmonary tuberculosis (83,84). It has been suggested that minor trauma may predispose to localization of such infections by attracting monocytes parasitized by a latent pathogens to the area of trauma (84).

Disruption of ecological barriers. Studies of the effect of antibiotics on indigenous microorganisms indicate that a delicate ecological balance exists between different members of the normal microbial flora. When this balance is altered in favor of a particular segment of these microbial populations, associated increases in the concentration of favored species may result in a variety of disorders loosely classified together as "overgrowth syndromes". Examples of these syndromes, the responsible microorganisms and predisposing conditions are presented in Table 3.

Table 3

SYNDROMES RESULTING FROM OVERGROWTH OF VARIOUS MEMBERS OF THE NORMAL FLORA

| Syndrome | Etiologic Agent(s) | Inciting Event | Ref. No. |
|---|---|---|---|
| Thrush | *C. albicans* | Broad spectrum antibiotics | 31 |
| Blind loop | Anaerobic bacteria | Intestinal surgery | 85 |
| Pseudomembranous colitis | *C. difficile* | Broad spectrum antibiotics | 86 |
| Toxic shock | *S. aureus* | Prolonged tampon use | 87 |

Synergisim. Occasionally, latent infections reactivate because of the cooperative efforts of a secondary pathogen (2). Reactivation of a latent infection by one microorganism may, for example, result from immunosuppression or physical perturbations caused by another microorganism. This kind of synergisim is common during epidemics of respiratory viral infections such as influenza A, during which secondary pulmonary infections are common. Organisms causing these secondary infections (i.e. S. aureus, H. influenzae and S. pneumoniae) originate in the pharyngeal flora, and appear to succeed in parasitizing the lungs of influenza patients because of virus-induced immunological and physical abnormalities (2).

A more direct mechanism by which viruses convert latent residents of the normal flora to troublesome pathogens, is through the process of lysogeny. Diphtheria provides a classic example of this phenomenon, in that production of toxin by C. diphtheriae (the key property of virulent strains) is a bacteriophage-mediated phenomenon (88-90). In short, an avirulent strain of C. diphtheria can be converted to a virulent strain by an appropriate bacteriophage. There is also evidence that production of scarletinal toxin by S. pyogenes (91), and the toxin responsible for toxic shock syndrome by S. aureus (92) may be bacteriophage-mediated. However, the relevance of the latter examples of lysogeny to the pathogenesis of human disease is not yet known.

Occasionally, the normal flora is the source rather than the recipient of virulence factors. For example, germfree animals are highly resistant to Entamoeba histolytica, which normally exists as a commensal in the large intestine of its host, feeding on resident bacteria and superficial mucosal cells. Rarely, E. histolytica becomes highly invasive, attacking the colonic wall, liver and other organs of its host. Observations in experimental animals suggest that these rare episodes of enhanced pathogenicity could result from virulence factors obtained from intestinal bacteria (93).

An even clearer example of a latent infection profiding virulence factors required by an exogenous pathogen is illustrated by the relationship between the hepatitis B virus and the delta ($\delta$) agent. All available evidence indicates that $\delta$ agent can replicate only in the presence of the hepatitis B virus (94,95). Furthermore, it is the chronic (assymptomatic) carriers of hepatitis B virus who are most susceptible to $\delta$ agent-induced disease. Interestingly, this defective virus inhibits the synthesis of hepatitis B virus products (95) and is thus a dual parasite, causing disease in both its human host and in the pathogenic microbe on which its existence depends. Although adeno-associated viruses are another example of viruses whose replication depends on support provided by a helper virus (in this case adenovirus), these defective viruses have not been shown to cause human disease (96).

## VIRUSES

Virtually every group of viruses has the capacity to cause a continuous spectum of diseases varying from acute and lethal to chronic persistent (97). The capacity for the latter form of disease is more highly developed in viruses than perhaps any other class of microorganisms because of an unique ability to incorporate their own genetic material into host genomes. Surprisingly little is known of the mechanisms involved in the transition of viruses between the replicative (cytotoxic) phase and the chronic noncytotoxic phase.

In vitro, experiments have provided considerable evidence that defective interfering particles are involved in initiation of the carrier state (98). These are non-infectious virons produced by most of the known viruses, particularly when these viruses are passaged in tissue culture at a high multiplicity of infection. They require helper function from homologous complete virus to multiply, since they possess only part of the functional viral gerome (99). Interestingly, although these particles depend on helper viruses to replicate, they interfere with the replication of helper viruses during the process of their own replication (99). Mechanisms involved in this interference are not known (100). However, the process does not appear to be mediated by interferon (99), or through stimulation of other immune mechanisms (101), and is most active against the homologous virus from which the defective interfering particles are derived. Although animal studies have established the capacity of both homologous and heterologous defective interfering particles to protect against lethal viral infections (102), their clinical significance is still uncertain. One putative role for such particles, is that of participation in the carrier state (103).

Herpesviruses. Herpes simplex virus has been estimated to infect 80-90% of persons and to cause recurrent infection in 50-60% of those so infected (104). As such, types 1 and 2 herpes simplex virus are two of the most prevalent and most troublesome of man's latent infections. These viruses most likely persist indefinitely in the nervous systems (primarily in dorsal root ganglia) of all persons exposed to the agent (105). In spite of extensive research into the mechanisms involved in herpes simplex virus latency, most of our current concepts must continue to be regarded as hypothetical (Figure 4) (106). Insight

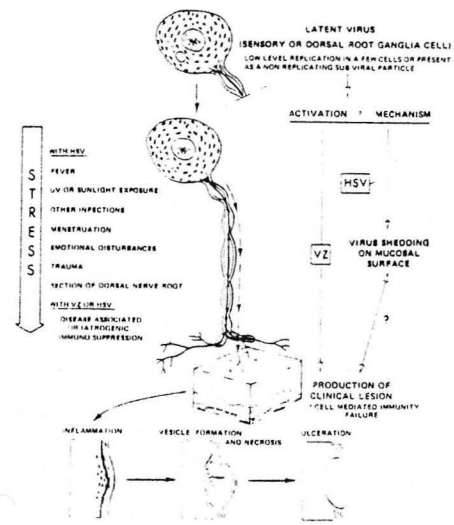


Figure 4. Mechanisms of Reactivation of Certain Cutaneous Herpes Viruses.
HSV represents herpes simplex virus, and VZ varicella-zoster virus.

into the molecular mechanisms by which the latent state is maintained has been particularly slow to develop. Recent work by Clough, Kunkel and Davidson (107) suggests that methylation of cytosine residues contained within viral DNA might be a critical event in the repression of viral replication within infected cells. However, the means by which such methylation might be altered by factors known to reactivate latent herpes virus infection (Table 4) is unknown. Nor is it clear exactly how the immune system participates in the process of establishing or maintaining latency (105). Persons who develop recurrent herpes virus infections have been reported to have elevated levels of circulating specific anti-herpes virus antibodies (109). Measurement of local antibodies has failed to show a correlation between secretory antibodies and recurrent infection (110). Increased, decreased and fluctuating blast transformation responses have each been observed in patients with recurrent disease (104). Thus, although both our clinical and experimental experience with these viruses has been extensive, our understanding of their latent processes remains rudimentary.

TABLE 4. FACTORS REPORTED TO BE ASSOCIATED WITH RECURRENCES OF HERPES SIMPLEX INFECTIONS (ADAPTED FROM CHANEY, REF. NO 108)

| | |
|---|---|
| Febrile illnesses* | Emotional stress |
| Mestruation | Sunlight |
| Corticosteroid therapy | Nerve trauma |
| Foreign protein injections | |

* Includes infections such as malaria, pneumococcal pneummonia, and meningococcal meningitis, but not febrile illnesses due to staphylococci, streptococci, Gram-negative bacilli, richettsia or other viruses.

Cytomegalovirus, varicella-zoster virus and Epstein-Barr virus are the other clinically important viruses within the herpes group noted for their latent infections. With each, reactivation from the latent state is seen primarily in association with immune abnormalities such as those occurring in transplant recipients or cancer patients who receive immunosuppressive drugs (111). As with the herpes simplex viruses, little is known of the mechanisms that govern the latent state. During latent infections it appears that only a few genes within the viral genomes of these viruses are expressed (112). However, the means by which suppression of the remaining genes occurs or those by which reactivation is achieved are not known.

Varicella-zoster virus, like the herpes simplex viruses, appears to reside in the dorsal root ganglia during the latent state (108). Although with cytomegalovirus, evidence for latency in humans is largely circumstantial (113), at least one group of investigators has succeeded in activating latent cytomegalovirus in human leukocytes acquired from seropositive blood (114). Other cells or tissues strongly implicated as sites of latent cytomegalovirus infection in

man include the kidney, colon, and heart (115). Epstein-Barr virus, for its part, is the only human herpes virus that is lymphotropic (116). It is an extremely successful parasite that appears to infect the majority of the people of the world. Following infection, viral DNA circularizes and persists in infected cells as an episome, usually in multiple copies (112). A peculiar feature of latently infected cells is their capacity for sustained growth in tissue culture (112). This property of the Epstein-Barr virus, and the association of this and other herpesviruses with a variety of malignant neoplasms has led many investigators to postulate a role of latent herpesvirus infections in human carcinogenesis (see below).

Hepatitis B virus. It has been estimated that as many as 400,000 people in the United States and 175,000,000 people world-wide are chronic carriers of hepatitis B virus (71). Almost nothing is known of the specific mechanisms responsible for latent infections with this virus. Nevertheless, a great deal is known of the risk factors influencing viral persistence after a primary infection. Age is one of the most important risk factors in this regard (71). The earlier in life hepatitis B virus is acquired, the higher the rate of viral persistence. Immunologic status is important in that when immune systems are impaired, viral elimination is inhibited (117,118). Male sex (71), a mild primary infection (119), and a small viral inoculum (120) have each been reported to increase the likelihood of viral persistence. Finally, Down's syndrome, for unknown reasons, is associated with a marked predisposition for progressing to the chronic carrier state after infection with hepatitis B virus (72).

As with the herpesviruses, latent hepatitis B virus infections have been associated with malignant neoplasms in man (see below). These latent infections are also important in the pathogenesis of periarteritis nodosa, and appear to have an etiologic role in a disturbingly high percentage of such cases through the induction of antigen-antibody complexes (121). As mentioned earlier, the chronic carrier state has potentially ominous implications for the host, out of proportion with the Hepatitis B virus' own potential for direct harm, because it provides necessary ingredients for successful invasion by the $\delta$ agent.

Adenoviruses. Adenoviruses have been known to cause persistent infections in humans, since 1953 when Rowe and colleagues reported isolation of a cytopathic agent from human adenoids undergoing spontaneous degeneration in tissue culture (122). Neither tonsils nor adenoids yield infectious virus when homogenized and tested in standard cell cultures. However fragments of approximately 85% of normal tonisils and adenoids show characteristic cytopathic changes and yield infectious virus after a variable period of time in tissue culture (123). These viruses establish persistent infections in humans at an early age and remain latent in lymphoid tissues thereafter. Their clinical significance in the latent state has never been fully elucidated. Although, as mentioned earlier, adenoviruses are essential to the replication of a group of defective viruses known as adeno-associated viruses, these are not known to cause disease in man.

Slow viruses. Infections with viruses such as those responsible for Kuru and Jakob-Creutzfeldt disease do not conform to the classic concept of latency, because rather than being acute infections that become latent and retain the potential for reactivation, they are simply infections with unusually long incubation periods. Therefore, these viruses will not be addressed in the present review. Rather, I will consider a group of viral disorders associated with

debilitating neurological sequellae that follow a latent period of many years after a symptomic primary infection.

Subacute sclerosing pemencephalitis is one such disorder. This progressive neurological disorder of children is caused by a virus that is antigenically indistinguishable from measle virus and shares regions in its genome that are at least 70% homologous with the measles virus (98). Furthermore, greater than 50% of children developing subacute sclerosing pemencephalitis have histories of measles prior to two years of age. It has ben hypothesized that persistence of maternal antibody, the status of immunologic maturation, and the ability of measles infection itself to depress cell-mediated immunity might have a role in the evolution of this disorder (98). However the precise mechanisms responsible for expression of the disease two to ten years after the primary infection are not known.

Progressive panencephalitis is a disorder of adolescent children that bears some similarities to subacute sclerosing panencephalitis. This progressive disorder of children with congenital rubella, like subacute sclerosing panencephalitis, occurs years after the primary infection (124). Unfortunately, the similarity with subacute sclerosing panencephalitis extends to our knowledge of the mechanisms responsible for the disorder. These too are unknown (125).

## BACTERIA

Because of their success in colonizing the body surfaces of man, bacteria are no less important than viruses in terms of their potential for producing latent infections. The normal bacteria flora of the skin and mucosal surfaces, is the source of many of the acute bacterial infections affecting both the normal and immunosuppressed host. These microbes may eschew their latent condition to attack man directly, or may have an indirect adverse role on human infections by providing resistance factors or virulence factors to nonindigenous pathogens (31). It is also possible that latent infections involving Gram-negative bacilli contribute to the pathogenesis of ulcerative colitis and chronic pyelonephritis. At least a mechanism for such an association has been advanced in a report demonstrating antigenic cross-reactivity between enterobacterial common antigen and various human tissues (126).

Most of what is known of how bacteria establish latent infections under "natural conditions has been reviewed under" Mechanisms of Latency. However, two additional mechanisms may be important when bacterial latency is a response to pressure from antibiotic therapy. Some bacteria transform into antibiotic-resistant L-form variants in response to such pressure (130). Although experimental data show that normal human sera contains factors that are lethal for these forms, an increasing number of reports have implicated L-forms in the pathogenesis or persistence of human infections (130,131). The salmonellae profit from somewhat different mechanisms in their efforts to avoid antibiotic destruction (132). It has been suggested that the failure of these bacteria to respond *in vivo* to some of the antibiotic agents to which they are sensitive *in vitro* relates to their ability to inhibit phagosome-lysosome fusion (see earlier section). As a result, antibiotics such as the aminoglycosides, which are effective *in vitro* but are concentrated intracellularly within lysosomes, are infective *in vivo* because they fail to reach intraphagosomal salmonellae.

Among individual species of bacteria, *M. tuberulosis* reigns supreme as a pathogen capable of latency in man. It has an almost unequaled capacity for

remaining viable but metabolically dormant. Reactivation of these dormant foci may occur at any time after the primary infection, and have historically been one of the most important infections of immunosuppressed patients. The aforementioned ability of tubicle bacilli to inhibit phagosome-lysosome fusion appears to be critical to its ability to establish latency. The fact that dead mycobacteria, or those coated with antibody lack this ability suggests that viable bacilli may actively produce substances that inhibit such fusion (127). Lowrie and associates (128) have shown that M. microti protects itself from intracellular destruction by releasing cyclic AMP into phagosomes. In addition, virulent tubercle bacilli contain high molecular weight glycolipid sulfates, which on accumulating in lysosomes-even in very low concentrations - render the lysosomes almost incompetent of fusing with phagosomes (129).

The mechanisms involved in reactivation of latent tuberculosis are only partially understood. One not considered earlier in this review concerns the peculiar association between silicosis and active tuberculosis. The apparent mechanism underlying this recognized clinical relationship relates to an adverse effect of silica particles on macrophage integrity (133). These particles, it seems, have a poorly understood toxic effect on phagosomal membranes, that results in rupture of phagosomes, concommittant release of lysosomal enzymes, and death of macrophages ingesting such particles. As a result of repeated cycles of this process, sublethal doses of silica can have a deleterious effect on the ability of macrophages to inhibit growth of tuberile bacilli, and in this way predispose to progressive infections by M. tuberculosis.

Syphilis is another bacterial pathogen well recognized for its capacity for latency. The little that is known of the mechanisms by which treponemes avoid immunological destruction has been reviewed in an earlier section.

Latent S. typhosa infections, like those involving M. tuberculosis and T. pallidum, have historically been some of the most important latent bacterial infections. An estimated 1-5% of persons developing typhoid fever become chronic carriers of S. typhosa following recovery from the acute illness (4,134). The gallbladder is the site of persistent infection in most carriers. The likelihood of developing the carrier state increases with age, is more common in women than men, and is most often associated with gallstones or gallbladder dysfunction. Although reactivation of the carrier state to acute typhoid fever is not normally seen in such carriers, there is evidence that the carrier state might predispose patients to hepatobiliary neoplasms (135).

Recent experience with veterans of the Vietnam conflict have reminded clinicians of the capacity of Pseudomonas pseudomallei to persist in a latent state for long periods, only to reactivate many years later, causing acute melioidosis in patients long removed from an endemic area (136). The frequency with which listeria, nocardia and legionella cause opportunistic infections in immunosuppressed hosts suggest that these bacteria might also be important causes of latent infections in man. The prevalence of L. monocytogenes in the normal intestinal flora in man (see Table 1) and an isolated report of reactivation of latent legionellosis in two immunosuppressed patients (137) illustrate the capacity for these two pathogens to establish latent infections in man. N. asteroides, however, appears to originate primarily as an exegenous pathogen (138).

## FUNGI

As stated earlier, Candida albicans commonly exists on man in a latent state, hidden among the normal flora of the oropharynx, intestine and vagina. Its capacity for reactivating into an overtly parasitic state, causing local as well as systemic disease in certain patient groups is well known to clinicians. Cryptococcus neoformans has a predilection for assymptomatic colonization of the upper airways of patients with chronic obstructive pulmonary disease (139), and as such may also cause reactivation disease under appropriate circumstances.

Outside of these two important examples, systemic reinfection by endogenous fungal pathogens is probably rare. Although reinfections by both Histoplasma capsulatum and Coccidiodes immitus are known to occur, the weight of available epidemiologic evidence suggests that the majority of these episodes represent exogenous reinfections rather than reactivation of latent (endogenous) foci (140). Clearly, both agents have been far less important that M. tuberculosis as opportunistic invaders of immunosuppressed patients, in spite of skin test surveys showing contact of large segments of the population with these agents. Furthermore, because tissue forms of these dimorphic fungi are not communicable, latent infections by these fungi are not epidemoilogically important as reservoirs for these mycoses.

## RICKETTSIA

Persistence of rickettsiae in nature as latent infections of a wide variety of arthropods and small mammals, has long been recognized as a key element in the epidemiology of the rickettsioses (141). In 1955, Price proved Zinsser's hypothesis - that man is also a potential interpidemic reservoir for rickettsiae - by isolating R. prowazeki from two healthy patients with prior histories of epidemic typhus, under conditions which precluded any possible environmental source of the isolations (142). As a result of these observations and the work of others, it is now clear that persisting infections in humans are a major reservoir for interepidemic survival of both the agents of louse-borne typhus (R. prowazeki) and trench fever (Rochalimeae quintana) (143). Viable R. rickettsii and R. tsutsugamushi have also been shown to persist in lymphatic tissues after recovery from Rocky Mountain spotted fever (144) and scrub typhus (145) respectively. However, the significance of such persistance in human tissues to the overall epidemiology of these diseases is in all likelihood small.

## PROTOZOA

Throughout history, man has been plagued continuously by malaria. The capacity of plasmodial species for establishing latent infections punctuated by intermittent acute exacerbations and remissions is equalled only by the herpesviruses. The extraordinary success of these parasites in establishing latent human infections can be attributed to a variety of mechanisms by which resistance to immune defenses is conferred. As mentioned in the foregoing discussion, antigenic variation is one such mechanism. In addition, plasmodial infections characteristically induce two nonspecific perturbations in immune rsponsiveness - polyclonal B cell activation and immunosuppression, and defects in macrophage function (146). These immunological abnormalities and an accompanying iron-overload state could contribute to the high incidence of secondary bacterial infections in children with chronic malaria (147), as well as to plasmodial persistence in man. Finally, the parasitic life cycle may itself

represent an important mechanism of confusing the immunological defenses (Figure 5). Each developmental stage has unique antigenic determinants (148). As a consequence, merozoites coming directly for the liver might be unaffected by an immune response that has developed against circulating trophozoites or gameotocytes (149).

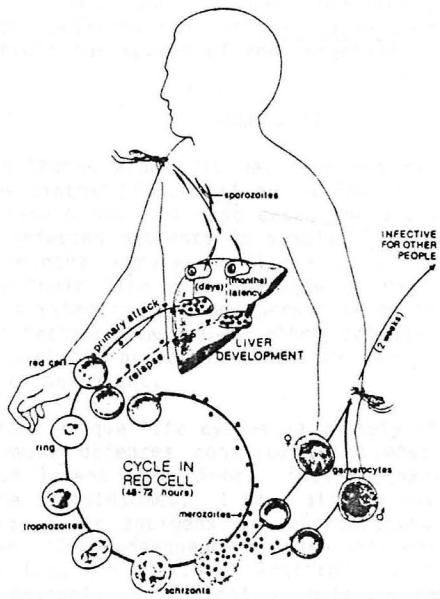


Figure 5. The life cycle of malaria.

Entamoeba histolytica is a highly effective protozoan parasite of man. Most persons infected by E. histolytica are assymptomatic carriers of the microorganism. The ratio of assymptomatic carriers to patients with invasive amebiasis varies from one population to another. However, it has been estimated that in Mexico only one in 4-5 infected persons has clinical evidence of invasive disease (150). E. histolytic may evade immunological systems, because of its location in superficial mucosal layers, and because it appears to constantly shed antigen-antibody complexes that protect it from immune destruction (151). Although as mentioned earlier, experimental evidence indicates that E. histolytica can obtain virulence factors from intestinal bacteria, the association with bacteria does not appear to be an absolute requirement for tissue invasion by amebae (77). Nevertheless, the association may benefit E. histolytica in intestinal colonization by lowering oxidation-reduction potential, by promoting adherence of the protozoan parasite to intestinal mucosa and by providing a source of nutrients.

Toxoplasma gondii has been shown experimentally to cause assymptomatic parasitemia as long as one year after inoculation into apparently healthy mice,

guinea pigs and rabbits despite the presence of high levels of neutralizing antibodies (152). The mechanisms by which such latent infections might be established have been discussed in an earlier section. Similar latent parasitemia has been demonstrated in man, and in at least one instance been shown to result in congenital transmission of the infection.

It has been assumed that Pneumocystis carinii also establishes latent infections in healthy adults (66). This hypothesis is supported by a report of high complement fixation titers for P. carinii among personnel caring for affected patients. There are also data indicating that parents and healthy siblings of affected patients can carry P. carinii for many years, constituting an important reservoir for spread of the infection to other susceptible persons (66).

## HELMINTHS

In the United States alone, it has been estimated that 54 million persons are infected by helminths (73). All but a few of these persons are perfectly healthy and will remain so. In most cases the explanation for the absence of symptomatology in infected patients is simple. Unlike viruses, bacteria, fungi and protozoa, helminths rarely replicate directly in man. Instead they generally complete their life cycle outside of the human host. Consequently, the number of worms infecting any one person tends to be low when compared with numbers seen in infections caused by other pathogenic microorganisms. Since symptomatology is directly proportional to the worm load of such patients, most infestations tend to be latent.

Aside from their unique life cycles, a variety of mechanisms concerned with evasion of the immune defenses constitute the most effective means by which helminths establish latent infections. These mechanisms are particularly well developed among the schistosomes. I have already reviewed the ability of these worms to camouflage their antigens by incorporating host antigens into their outer lipid bilayer. The consequence of such antigenic remodeling is to obscure it immunologically from the host. In addition, suppressor mechanisms appear to exist in infected patients which limit or modulate responsiveness to schistosomal antigens. These include serum factors (153,154), esterase-positive adherent mononuclear cells (155) and suppressor T cells (156).

The chlamydiae have a wide range of animal hosts and cause substantial latent infections in these hosts (157). This property of chlamydial parasites is particularly striking in psittacosis, where apparently healthy birds may shed chlamydiae in their feces for prolonged periods. Whether such chronic latency ever occurs in man is unclear. Nevertheless, the agent of lymphogranuloma venereum can persist in human subjects, with acute sequellae sometimes occurring many years after the initial infection (158). Furthermore, persons removed from areas endemic for trachoma as children, have been observed to develop reactivation trachoma 40 to 50 years later (159). Unlike some of the other latent infections already discussed, those caused by chlamydiae appear to involve continuous low levels of parasitic multiplication held in check by host defenses, rather than a persistence of the parasite in a non replicative form (157).

## MALIGNANT NEOPLASMS

There is no convincing evidence to date that latent microbial infections are at the root of human cancer. Nevertheless, a number of microorganisms have

been shown to be intimately associated with certain malignant neoplasms, and largely through guilt-by-association, have come to be regarded as probable participants in the oncogenesis of these tumors. The most compelling evidence in this regard has incriminated a group of viruses collectively referred to as retroviruses, as well as hepatitis B virus and the herpesviruses. These viruses, although diverse as a group, each shows some defect in the replicative cycle during chronic infections that can be traced to deletions in viral nucleic acid sequences or restrictions of the host that limit certain viral functions (97).

Retroviruses are enveloped viruses containing a dimeric RNA genome, which is copied into DNA by a viral reverse transcriptase (160). The DNA copy is integrated into the host cell genome as an obligatory life cycle intermediate called the provirus. The provirus inserts itself into the chromosomal DNA of the host, where it codes for viral RNA. Transmission of virus from cell-to-cell is accomplished in two different ways (Figure 6) - one involving horizontal

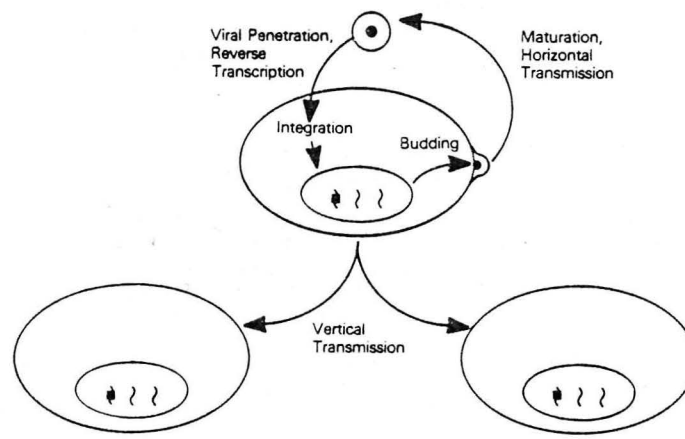


**Figure 6.** Modes of transmission of exogenous and endogenous retroviruses. The former replicate by cell-to-cell transmission, whereas the latter replicate passively via host cell replication.

transmission, and the other in which passive replication occurs with proliferation of the host cell itself. The former mode of transmission appears to be the predominant one where animal tumors are concerned, and involves assembly of viral RNA and proteins at the cell surface, where these exit by budding into mature viral particles (161). This process can apparently occur continuously, apparently without adversly effecting the host cell. Although retroviruses have been known to be casual agents of naturally occurring leukemia in various animal species for some time (162), only recently has definitive evidence been reported of involvement of a retrovirus in human cancer (160). The mechanisms by which these viruses induce neoplasia have not been fully elucidated. However, activation and/or facilitated dissemination of onc genes are two such mechanisms incriminated in retroviral-induction of animal tumors (162).

The herpesvirus are the other major viral group that has been epidemiologically linked to human cancer. In man, Epstein-Barr virus has been consistently

linked with Burkitt's lymphoma and with nasopharyngeal carcinoma, while types 1 and 2 herpes simplex viruses have long been associated with squamous cell carcinoma of the lip and cancer of the cervix, respectively (163). There is also some indirect evidence that a similar association exists between cytomegalovirus and Kaposi's sarcoma (164). The role of these viruses in the origin of the respective malignant neoplasms has not yet been determined. Clearly, such latent viral infections are neither absolutely necessary nor sufficient for malignant transformation of infected tissues (112). If they do have a causal role in such transformation they could fulfill this role by promoting cell growth, and in so doing indirectly increase the likelihood of occurrence of a low probability transforming event. They might also act as cocarcinogens or render infected malignant cells less subject to immune surveillance. Finally, they might activate the oncogenic process directly. The rarity with which experimentally or therapeutically induced immunosuppression gives rise to these tumors in latently infected subjects suggest that virus-induced immunosuppression is not the primary oncogenic mechanism.

The one other virus having a close association with human malignant neoplasms is the hepatitis B virus. Both seroepidemilogical and histopathological data strongly suggest either direct or indirect involvement of this virus in the etiology of cancer of the liver (71,165). However, as with the herpesviruses, proof of a causal relationship of the virus with the tumor is incomplete.

Certain bacterial species have a similar apparent predilection for malignant neoplasms. Streptococcus bovis (166), Clostridium septicum (167), and various non-typhoidal strains of salmonella (168) are examples of such bacteria. In addition, epidemiological data show a 6-fold higher incidence of hepatobiliary cancer among chronic typhoid carriers than among matched controls (135). Production of a human choriogonadotropin-like substance by certain tumor-associated bacteria -- some of which continue to produce the substance even after having been subcultured for years -- suggests that exchange of genetic material between tumor cells and tumor-associated bacteria might take place in some cases (169). However, it is not yet known whether tumor-associated bacteria such as these are simply "innocent bystanders" or are actively involved in the carcinogenic process.

## TREATMENT

Available therapy of latent infections can be divided into modalities that attack the microorganisms directly, and those that attempt to eliminate latent microorganisms indirectly, through stimulation of immune defenses. The former mode of therapy has been most successful against latent bacterial infections. Tuberculosis, syphilis, typhoid and other dread bacterial pathogens of the past are now readily destroyed, even when present in latent seclusion, thanks to the advent of the antibiotic era. An ever widening array of antimicrobial agents has also increased our capacity in recent years for eliminating latent infections involving fungi, rickettsia, protozoa, helminths and chlamydia. Only viral latency remains a therapeutic conundrum. Even viruses, such as the herpes simplex viruses, against which effective chemotherpeutic agents are available, continue to be immune to such agents when in the latent state (170-172). The reasons for this refractoriness are still uncertain, but could relate to a failure of latent viral populations to reactivate simultaneously, so that at least part is dormant and thus protected from the action of the antiviral drugs (171). Subsequent reactivation of the dormant segments is then possible once the antiviral agent is discontinued.

Another means of direct attack against latent pathogens is by surgical removal of such infections. This approach has been particularly useful as either primary or adjunctive therapy of the latent infections associated with chronic osteomyelitis, renal calculi, and the typhoid carrier state. Surgery is also the only effective means of eliminating such diverse latent infections as aspergillomas (173) and echinococcal cysts (174).

Attempts to control latent infections by stimulating immunological defenses have been directed primarily against microorganisms for which no effective chemotherapeutic agent is available. Prevention of such infections with live attenuated and killed vaccines has been the only reasonably promising approach to controlling viral latency. Passive immunization using immune globulin directed against certain refractory pathogens is another potential means of dealing with latent infections in high risk patients. Meyers, et al (175) have shown cytomegalovirus immune globulin to be effective in preventing reactivation of latent endogenous cytomegalovirus in association with bone marrow transplantation.

Nonspecific immunopotention with agents such as BCG and C. parvum is another approach to the treatment of latent infections that has been used with some success in cancer chemotherapy (176). Several investigators have also evaluated the effect of immunization with BCG on recurrence rates among patients with type 2 herpes simplex virus infections (177,178). These studies have shown both a beneficial effect (177) and no effect (178) of BCG immunization on recurrence rates.

Recently Hoofnagle and colleagues (179) reported the case histories of two assymptomatic carriers of the hepatitis B virus who developed acute reactivation of hepatitis B while undergoing cancer chemotherapy. Following completion of their chemotherapy, both patients recovered from these episodes of acute hepatitis, and also become seronegative for hepatitis B surface antigen. These cases illustrate a highly unorthodox means of eliminating a latent infection using immune stimulation -- that is by stimulating replication of the latent microorganism during immunosuppressive therapy, and then inducing rebound potentiation of the immune response against this agent with cessation of immunosuppressive drugs. With these cases in mind, Hoofnagle and his associates have cautiously proposed that intentional reactivation of hepatitis B virus (using a short course of immunosuppressive drugs) might be one approach to treatment of the chronic carrier state.

## CONCLUSIONS

Both the potential clinical and epidemiological consequences of microbial latency are enormous (123). Aside from reactivating to cause acute disease in individual patients, they also represent potential reservoirs from which pathogens originate to infect new susceptible hosts. In the latter instance, transmission occurs horizontally, but can also occur vertically with congenital infection of a developing fetus (180). We have seen that latent infections occasionally progress to chronic progressive disorders such as subacute sclerosing panencephalitis and progressive rubella pancencephalitis. There is also increasing experimental and clinical evidence that certain latent viral infections can result in uncontrolled proliferation of cells and may be involved in the development of some human cancers. Finally, latent infections may have an indirect adverse effect on the host, by providing factors essential for invasion of that host by a secondary pathogen. The relationship between the hepatitis B virus and the $\delta$ agent exemplifies this phenomenon.

The potential adverse effects of latent infections on human health have been magnified by the advent of transplantation techniques. In some cases, problems have arisen because of latent infections within the transplanted organs or cells that are reactivated upon arrival in their new host (181,182). In other cases latent pathogens endogenous to the tranplant recipient are reactivated as a result of immunosuppressive therapy (183), graft-vs-host disease (184) or host-vs-graft disease (185). Regardless of the mechanisms of transmission and reactivation, latent infections pose a major obstacle to organ transplantation.

In many other respects these infections are a product of advances in medical technology. They are a modern day plague among dialysis patients, hemophiliacs, dentists, doctors and hospital laboratory personnel, all of whom live and work under a constant threat of acquiring hepatitis B (and to a lesser extent other latent pathogens) contained within blood products to which they are exposed.

In spite of these dangers, latent infections should not always be viewed as consummate antagonists of their host. In fact, in some situations latent infections may actually benefit their host. An example of a latent infection causing "good health" is that caused by the potato X virus (186). Potato plants infected with certain wild strains of this virus, it seems, outgrow and outyield their uninfected counterparts. The capacity of latent microorganisms within the normal flora to contribute to the nutritional requirements of their host and to the host's ability to resist exogenous microbial pathogens is well established (31). There are also preliminary data suggesting that latent colonization of the lower urinary tract by enterococci may increase resistance of patients with chronic urinary catheters to symptomatic urinary tract infections (187). Although there has been concern about persistence of vaccine viruses, such persistence is most likely important in producing long-term immunity (71). Furthermore, the first successful cancer vaccine, the one used against Marek's disease of poultry, causes a chronic assymptomatic infection associated with a 97% reduction in mortality from Marek's disease (71).

Ultimately, the most compelling conclusion to be drawn from a review of microbial latency is that our knowledge of the mechanisms involved in microbial latency is at best rudimentary. We know very little about how such infections initiate, what factors are important in sustaining microorganisms in the latent state, or what it is that triggers these infections to reactivate. Few areas of basic research hold greater promise of substantial contributions to our understanding of disease or relief of human suffering.

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