fied seasonal forcing pattern, in a single bifurcation diagram, which depends only on the effective value of the average transmission rate, $\langle\beta\rangle$ (Fig. 1 in their report) (*3*). In this way, they can then lay bare the otherwise bewilderingly different patterns of measles incidence seen (after the advent of vaccination) in London, Liverpool, New York, and Baltimore (*3*).

I think this does not, however, close the book on the topic. Earn *et al.* use the standard SEIR equations, with their "mass action" assumption that new cases arise in simple proportion to the product of the number of individuals who are susceptible and the number who are infectious. The social realities of family structures, housing conditions, and much else will be anecdotally familiar to anyone responsible for the staff in a large department (for example, parents with children in school are more likely to catch colds). Much relevant work remains to be done in teasing apart the social, genetic, age-related, and other complications that are smoothed out in the usual mass action assumption.

In a country such as the United Kingdom, where childhood vaccination remains voluntary, the practical questions have more to do with fundamental problems in the evolution of altruistic behavior than with the ecological dynamics so beautifully surveyed by Earn and colleagues. There may be risks—very, very tiny, but not zero—associated with vaccination. For example, the risk of meningitis/encephalitis associated with MMR (measles, mumps, and rubella) vaccination is estimated to be around 1 in 1,000,000 (*5*). The risks of infection itself are, however, much greater: from around 1 in 200 to 1 in 5000 for complications due to meningitis/encephalitis after natural infection with measles, mumps, or rubella (*5*). So, your best strategy is for everyone else's child to be vaccinated, thus eradicating the risk of infection, but for your own child to remain unvaccinated. But we are now trapped in the Prisoner's Dilemma: If too many parents "cheat" in this way, herd immunity will no longer protect their children. This is a real paradox, with no trick answer. I believe that the answer to such dilemmas, where individual and group interests ineluctably conflict, is a program of effectively compulsory immunization, backed by a clear and analytical understanding of the effects of population level or "herd" immunity, which are so admirably illustrated by the Earn study.

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PERSPECTIVES: AIDS

HIV Infection and Dementia

Suzanne Gartner

Morbidity and mortality associated with HIV infection have declined in developed countries as a result of effective antiretroviral combination therapies that include protease inhibitors. However, the inability of protease inhibitors to effectively cross the blood-brain barrier and penetrate the brain parenchyma has raised concerns that although infected individuals may live longer, they may face a consequent increased risk of developing HIV-associated dementia. This speculation is based on the assumption that initial entry of HIV into the brain, which usually occurs early in infection (*1*), establishes lifelong persistence of the virus. Hence, although therapy effectively controls HIV replication elsewhere in the body, replication could continue in the brain unabated, ultimately initiating neurological disease.

Evidence contrary to this view comes from several lines of investigation:

1) The brains of asymptomatic HIV-infected individuals usually contain very low levels of HIV DNA, or none at all (*2–5*), and tissue expression of the virus—a presumed prerequisite for intracranial spread of the infection—is seldom detected in the former group (*2, 6*).

2) With the advent of protease inhibitors, the incidence of HIV dementia has declined (*7, 8*). This suggests that controlling systemic HIV replication limits the development of dementia.

3) HIV dementia typically does not present before the onset of AIDS. Why is this, if the virus is present within the brain from early infection and if it plays a key role in development of the disease? Perhaps a threshold level is required that takes years to attain (possibly a consequence of the limited range of host cells for HIV in the brain). Alternatively, HIV replication within brain tissue may be controlled before immunodeficiency begins, and when this control is lost, virus replication and spread proceed. There again, HIV replication may require a stimulus associated with later stages of infection, immune activation being a likely candidate. These explanations necessitate that HIV remains essentially dormant within the brain for many years—a conceivable proposition, given that retroviruses can integrate into the host cell genome, and that the primary host cells (microglia and macrophages) are long-lived. Not known, however, is whether a significant portion of the HIV DNA within brains of asymptomatic individuals is integrated into the genome of host cells, which is not the case in those dying with AIDS (*5, 9, 10*).

4) The abundance of macrophages in the brain appears to be a better correlate of HIV dementia than the presence or extent of brain infection (*11*); in the simian immunodeficiency virus (SIV) animal model, the number of macrophages correlates with the severity of central nervous system (CNS) lesions (*12*).

5) The cells expressing HIV in AIDS patients' brains, particularly the multinucleated giant cells, are frequently perivascular in location (that is, they are found in the space between the brain parenchyma and blood vessels) (*13*). The perivascular infiltrates in these brains are frequently composed primarily of macrophages (*14*). Also, neuroinvasion by SIV coincides with an increase in the number of perivascular macrophages (*15*), and these cells appear to be a major target cell for SIV in the brain not only during acute infection (*16–18*), but also later, when encephalitis is present (*18*).

6) SIV-associated neurological disease is more readily produced by intravenous, rather than intracranial, inoculation (*19*).

Together, these findings suggest that in late-stage HIV infection, an increase in trafficking of monocytes (the precursors of macrophages) to the brain may be associated with the development of HIV neurological disease (see the figure). This interpretation is further strengthened by results from a recent case study in our laboratory. We found that sequences of the gp160 gene (which encodes the highly variable HIV envelope protein) from the deep white matter of brain were more closely related to those from bone marrow than to those from other tissues. In fact, they were most closely related to sequences recovered from blood monocytes taken 5 months earlier (*20*).

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What could account for an increase in monocyte trafficking into brain tissue? It has been postulated that HIV replication within the brain precipitates neuroimmune activation, including activation of brain macrophages, which then leads to alterations in chemokine expression by brain parenchymal cells (*21–23*), as well as up-regulation of adhesion molecules on brain endothelial cells (*24, 25*). These alterations, in turn, result in increased binding and transmigration of blood monocytes. Such enhanced recruitment is plausible, particularly once the process is well established, but is there sufficient HIV replication in brain tissue to initiate it? When does this replication begin, and are latently infected cells the seed source? An alternative hypothesis is that in late-stage infection, blood monocytes are circulating in an activated state, so that when they meet brain microvascular endothelium, they themselves can initiate the changes that lead to transmigration. This would mean that critical events initiating the development of dementia occur outside of the brain.

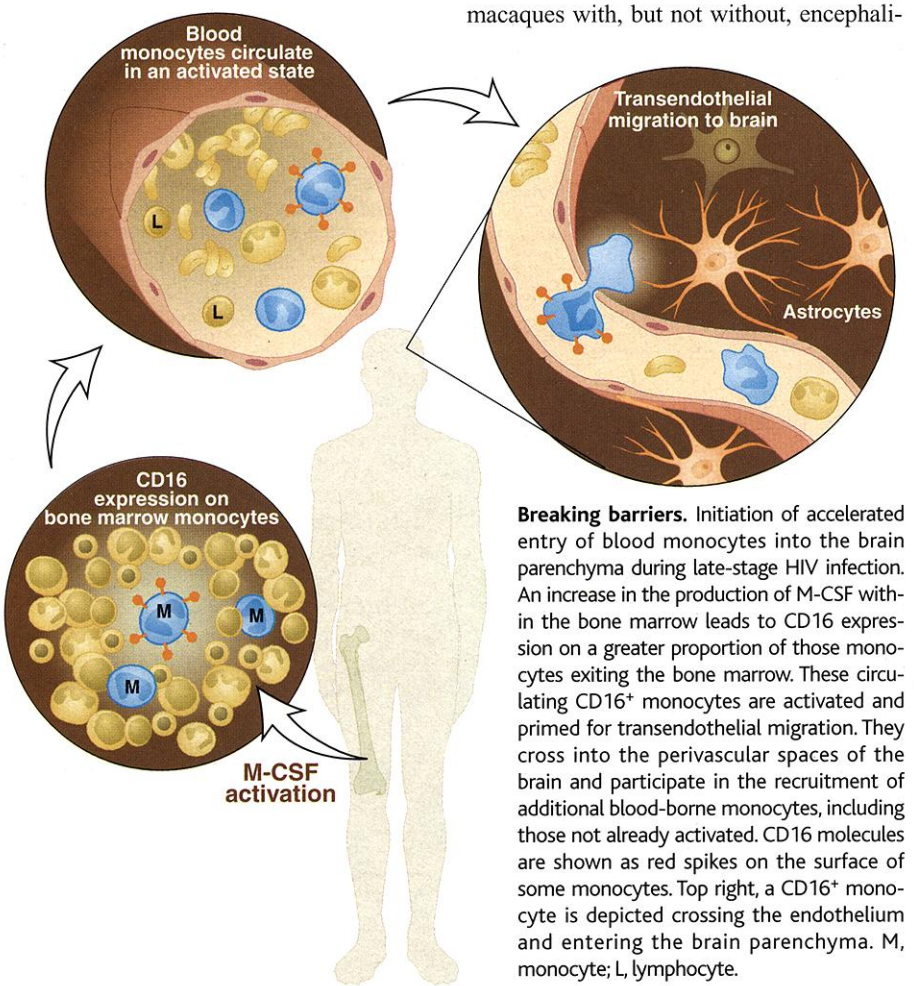
Evidence from the SIV model suggests that the relationship between virus infection within the brain and alterations in the expression of chemokines and adhesion molecules may be less clear than imagined. For example, Sasseville and colleagues detected elevated expression of the chemokines monocyte chemotactic protein–3 (MCP-3), macrophage inflammatory proteins 1α and 1β (MIP-1α and -1β), and RANTES within the brains of SIV-infected macaques with, but not without, encephalitis (*26*). However, they also observed this pattern in macaques with experimental allergic encephalomyelitis (an animal model of multiple sclerosis characterized by inflammation of the CNS), which led them to conclude that it more likely reflects a general phenomenon associated with inflammation in the brain, rather than SIV infection specifically. In addition, whereas abundant expression of vascular cell adhesion molecule–1 (VCAM-1), but not expression of other adhesion molecules, has been observed in encephalitic SIV brains, it appears insufficient for the recruitment of leukocytes into the brain parenchyma (*27*).

The onset of AIDS has been reported to be associated with an extension of HIV infection beyond the lymphoid organs into nonlymphoid tissues such as brain (*3*). How this is accomplished is unclear, but infected cells are likely participants. Because HIV expression in brain (even within perivascular infiltrates) has been detected almost exclusively in macrophages, it is probable that this redistribution (at least with respect to brain) is the result of increased entry of infected monocytes. Substantial infection of nonlymphoid tissues has also been seen in end-stage SIV infection, and in this case, the viral genome is present primarily as unintegrated DNA within macrophages (*28*). For neurological disease, the entry of uninfected monocytes into brain is probably also important because these cells could serve as additional targets for HIV infection, as well as contributing to the pool of potentially neurotoxic macrophage products.

Increased numbers of blood monocytes expressing FcγRIII receptors (CD16) have been seen in patients with late-stage HIV infection (*29*), particularly those with opportunistic infections. A correlation between HIV dementia and increased levels of circulating monocytes expressing CD16 and CD69 (molecules expressed when the cells are activated) has been reported (*30*). Macrophage colony-stimulating factor (M-CSF) has been shown to induce CD16 expression on monocytes (*31–33*) and has been detected in the cerebrospinal fluid of HIV-infected individuals, with the highest levels found in people with HIV encephalitis or opportunistic infections (*34*). Recently, we have found elevated M-CSF levels in the serum of patients with HIV-associated cognitive impairment (*35*).

Although the induction of CD16 expression on monocytes might occur in blood, it is likely that the primary site is bone marrow, where monocytes are produced and mature, with M-CSF playing a pivotal role. Surprisingly, little is known about the effects of local or systemic HIV replication on bone marrow. Of relevance here are the findings of increased numbers of monocytes and resident macrophages in the bone marrow of AIDS patients (*36–38*) and the presence of HIV infection and expression (*39*). Also, SIV typically infects the bone marrow during acute infection, the primary target cells being monocytes and macrophages (*40*). This infection is also a feature of the later stages of disease, where it is associated with pathological changes in marrow and hematological abnormalities such as anemia; moreover, it correlates with disease progression as defined by lymph node depletion (*41*).

Perhaps, then, bone marrow is the site of the first steps leading to HIV dementia. The events of late-stage infection, HIV replication in marrow, and/or the



Breaking barriers. Initiation of accelerated entry of blood monocytes into the brain parenchyma during late-stage HIV infection. An increase in the production of M-CSF within the bone marrow leads to CD16 expression on a greater proportion of those monocytes exiting the bone marrow. These circulating CD16$^+$ monocytes are activated and primed for transendothelial migration. They cross into the perivascular spaces of the brain and participate in the recruitment of additional blood-borne monocytes, including those not already activated. CD16 molecules are shown as red spikes on the surface of some monocytes. Top right, a CD16$^+$ monocyte is depicted crossing the endothelium and entering the brain parenchyma. M, monocyte; L, lymphocyte.

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condition of chronic systemic inflammation could result in the activation of greater numbers of circulating monocytes. If they are already activated, these cells would be primed for transendothelial migration. This notion is substantiated by the fact that acute SIV infection is associated with increases in both the number of circulating CD16-positive monocytes (*42*) and the number of perivascular macrophages in the brain (*17*). This hypothesis could also help to explain why the best-known predictor of HIV dementia is anemia (*43*). Most important, it suggests that with effective control of systemic HIV replication and consequent macrophage activation, HIV dementia will not develop.

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PERSPECTIVES: MATERIALS SCIENCE

Movies of the Glass Transition

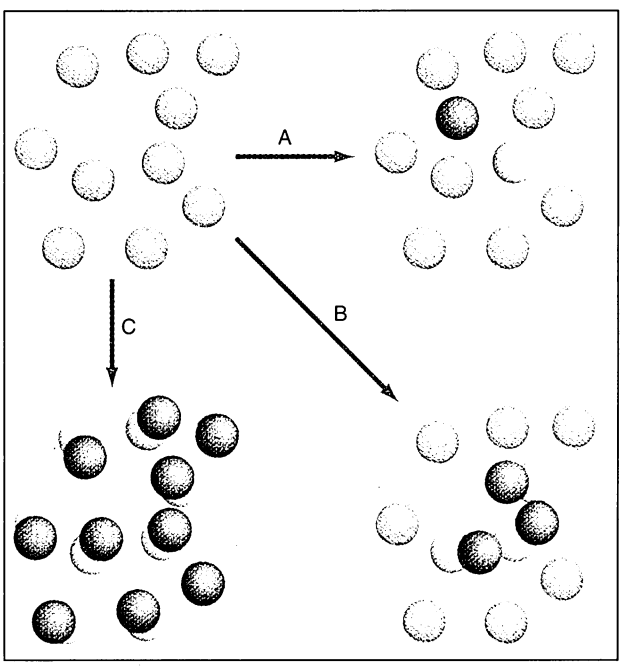
M. D. Ediger

When a liquid is cooled, it can solidify in two very different ways. The familiar route produces an ordered crystal. In this case, the change in the mechanical properties of the material from viscous liquid to elastic solid can easily be explained by the change in structure. An equally important but more subtle transformation occurs when crystallization is avoided during cooling. With decreasing temperature, the molecules in the liquid move more and more slowly. In the absence of crystallization, the viscosity of the liquid increases continuously, typically by a factor of 10^{10}. Eventually, molecular motion is frozen on the time scale of laboratory experiments, and a noncrystalline solid—a glass—forms. The structural changes that occur during this cooling are small, and we must look to molecular motion for an explanation for this transformation. Key insights into the motion responsible for the transition to the glass are provided by Weeks *et al.* on page 627 of this issue (*1*) and in a recent report by Kegel and van Blaaderen (*2*).

Understanding the nature of glass formation is an important practical issue that goes far beyond window glass. Glassy pharmaceuticals are more rapidly available to the body than crystals. Saccharide glasses are being used to preserve biological structures (tissues, cells, and enzymes) for storage and transportation. All synthetic polymers form solids that are at least partially amorphous; the properties of materials and devices made from polymers thus depend on the molecular motions responsible for the glass transition. Breakthroughs in our understanding of the glass transition may also impact related fields, including protein dynamics and the flow of granular materials.

The phenomenology of glass formation has been known for decades (*3*, *4*), but we are still far from understanding the relevant features of molecular motion. Experiments have not allowed us to directly measure how a molecule moves relative to a particular neighbor in a glass or to observe which local structures are prone to reorganization. Therefore, important questions regarding the heterogeneity and cooperativity of molecular dynamics in glasses (see the figure) have remained unanswered. Computer simulations provide the required level of detail, but can only supply limited insight because the relevant time scales are so long.

Kegel and van Blaaderen (*2*) and Weeks *et al.* (*1*) have approached this problem through uniquely powerful experiments on a model glass-forming system made of colloidal spheres suspended in a solvent (*5*). The colloidal glass transi-



How do particles move near the glass transition? For each of the three possibilities shown, the average particle moves 20% of a particle diameter between frames. New particle positions are shown in red; vacated positions are pale red. Motion is either concentrated on one particle (**A**), or distributed across some (**B**) or all particles (**C**). Colloid motion is most like (C), but occurs primarily in a subset of unusually fast particles.

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