5. *Encyclopedia of Bioethics* (Simon & Shuster and Prentice-Hall, New York, 1995), vol. 5, p. 2632.

Response

With regard to my discussion in the Viewpoint of the way the ancient Greeks and the first Christians of Rome, such as Saint Augustine, interpreted the question of the status of the human embryo, my point was intended to be a judicial one. It is common knowledge that according to the Catholic Church "life must be protected and favored from the beginning," as is stated by the "Declaration on Procured Abortion" issued by the Sacred Congregation for the Doctrine of the Faith (18 November 1974). However, in the Viewpoint, I was pointing out that in earlier times, there were various opinions on the infusion of the spiritual soul into the fetus's body. In particular, Saint Augustine and Saint Thomas d'Aquino developed the theory of successive animation based on Aristotle. Canon Law (*Decretum Gratiani,* around 1150 A.D.) thus made a distinction between abortion as a crime, that is to say *homicidium*, and abortion before animation. This distinction was rejected in another *Decretum* of Innocent XI, who firmly condemned the sentence "Licet procurare abortus ante animationem fœtus" (*1*).

Since modern discoveries in the fields of anatomy and biology, the Church's condemnation of abortion has made no official distinctions regarding the different stages of development of human embryos. Yet, it is interesting to note than even in 1983 when the Canon Code II was being written, there still continued to be discussions about prohibition (or proscription) versus excommuncation with regard to abortion. All in all, through the centuries the question of abortion and excommunication has been debated and indeed has not been without controversy (*2*).

Noëlle Lenoir

References

1. H. Reis, *Das Lebensrecht des Ungeborenen Kindes als Verfassungsproblem* [The Right of the Unborn Child as a Constitutional Problem] (Mohr, Tübingen, Germany, 1984), pp. 135–147, notes 650–671.
2. P. Valdrini, J. Durand, O. Echappé, J. Vernay, *Précis de Droit Privé* [Canon Law] (Dalloz, Paris, ed. 2, 1999), p. 393.

HIV-Associated Dementia

In her Perspective "HIV infection and dementia" (*Science*'s Compass, 28 Jan., p. 602), Suzanne Gartner presents a hypothesis that human immunodeficiency virus (HIV)–associated dementia (HAD) occurs primarily as a result of trafficking into the brain of infected or activated monocytes from the bone marrow late in the course of HIV disease. Gartner predicts that with systemic suppression of HIV in the periphery—possible with advances in highly active antiretroviral treatments (HAARTs)—HAD will not develop.

HIV can be contained in the periphery with HAART; however, predicting the eradication of HAD may be premature. Several lines of evidence about the importance of HIV infection in the brain suggest that HAD will continue to be a significant clinical concern. Specifically, HIV enters the brain early in infection and persists in the brain throughout the course of HIV disease, and the brain appears to provide a sanctuary site for the virus (*1*). A viral reservoir in the brain not only poses a threat to neurocognitive function, but also may augur a potential resurgence of systemic disease (*2*).

Far in advance of end-stage acquired immunodeficiency syndrome (AIDS), HIV infection is associated with neurocognitive deficits (*3*) and anatomic and functional brain abnormalities. Proton magnetic resonance spectroscopy (*4*) and functional magnetic resonance imaging (*5*) demonstrate altered metabolism and blood flow in neurologically asymptomatic HIV-infected individuals and in those with cognitive impairments. Viral RNA levels are well documented in the cerebrospinal fluid (CSF) in demented and nondemented AIDS patients (*6*). Furthermore, postmortem studies using sensitive and quantitative assays correlate CSF viral levels with high viral levels throughout the brain (*7*). These data indicate the importance of HIV in the brain at all stages of disease and raise questions about the effects of the presence and amount of virus or viral components on neuronal function.

There is not substantial epidemiological data indicating that HAD declines after the introduction of HAART. A preliminary study reported by Dore and colleagues (*8*) examined the incidence of HIV-associated severe cognitive and motor impairments. They concluded that "HAART has a lesser impact on [AIDS dementia complex] than other AIDS defining illnesses, with the poor [central nervous system] penetration of many antiretroviral agents a possible explanation." Because many protease inhibitors have poor penetration into the brain, even with aggressive treatment, the central nervous system may serve as a protected viral reservoir. Viral compartmentalization studies show that virus evolution can occur in protected sites, including the brain, independent from virus evolution in the periphery (*9*). There is evidence of latent HIV infection of astrocytes in autopsy studies (*10*) and in vitro (*11*). In the in vitro study, virus was reactivated upon stimulation with pro-inflammatory cytokines. A review of 390 brain autopsies of AIDS patients from 1982 to 1998 concluded that there has not been a decline in the pathological manifestations of HIV infection of the brain (*12*). Although more detailed analyses of the consequences of HAART on the neurological complications in AIDS are needed, it is important to recognize that 20 to 50% of patients fail to have durable responses to HAART (*1*).

The principal cells responsible for neuronal dysfunction are infected, activated macrophages and microglia, which secrete cytokines and other soluble factors toxic to neurons (*13*). Trafficking of monocytes into the brain further adds to a cascade of neurotoxic events. The physiologic and pathologic role of chemokines and their receptors in this process has yet to be fully elucidated. Evidence supports a key role for the virus. Neurological dysfunction correlates with elevated levels of virus in the CSF (*6, 14*). High viral load does not necessarily correlate with dementia, but monocytes or macrophages (which are derived from monocytes) also may be required (*15*). Thus, considerable evidence supports a necessary role for the virus in directly or indirectly mediating central nervous system disease.

Preventing HIV from entering the central nervous system is critical in managing severe neurological consequences of HIV. When HAART therapy reduces systemic viral load, it usually, but not always, results in decreased CSF viral load. This is the best surrogate marker for viral load in the central nervous system. Confidence that the central nervous system will be protected by peripheral viral control is premature. The potential for HIV to enter the central nervous system during all disease stages, the latent presence of HIV within protected reservoirs in the periphery and in the central nervous system, and the ability of HIV to initiate inflammatory processes in the brain suggest that HAART may not eradicate HAD.

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References

1. W. C. Powderly, *J. Neurovirol.*, in press.
2. M. C. Zink *et al., Am. J. Pathol.* **151**, 793 (1997).
3. R. K. Heaton *et al., J. Int. Neuropsychol. Soc.* **1**, 231 (1995).
4. B. A. Navia *et al.,* 51st Annual Meeting of the American Academy of Neurology, 17 to 24 April 1999, Toronto, Ontario, abstr. 31.004; B. A. Navia and R. G. Gonzalez, *Neuroimag. Clin. N. Am.* **7**, 431 (1997).
5. I. Tracey *et al., Neurology* **50**, 821 (1998).
6. R. J. Ellis *et al., Ann. Neurol.* **42**, 679 (1997).
7. C. A. Wiley *et al., Brain Pathol.* **8**, 277 (1998).
8. G. Dore *et al., AIDS* **13**, 1249 (1999).
9. A. B. van't Wout *et al., J. Virol.* **72**, 488 (1998); J. K. Wong *et al., J. Virol.* **71**, 2059 (1997); B. T. Korber *et*

al., J. Virol. 68, 7467 (1995).
10. K. Takahashi et al., Ann. Neurol. 39, 705 (1995).
11. C. Tornatore et al., J. Virol. 65, 6094 (1991).
12. E. Masliah et al., AIDS 14, 69 (2000).
13. L. G. Epstein and H. E. Gendelman, Ann. Neurol. 33, 429 (1993).
14. B. J. Brew et al., J. Infect. Dis. 175, 963 (1997); C. Marra, Sixth Conference on Retroviruses and Opportunistic Infections, Chicago, IL, 31 January to 4 February 1999 (Foundation for Retrovirology and Human Health, Alexandria, VA, 1999), abstr. 408.
15. J. D. Glass et al., Ann. Neurol. 38, 755 (1995); L. Pulliam et al., Lancet 349, 692 (1997).

Response

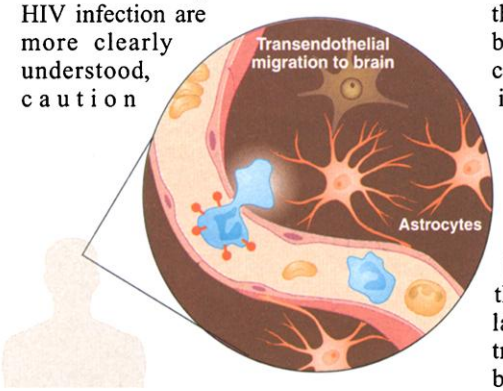
The concerns raised highlight several of the unresolved issues that remain key to a fuller understanding of HIV neuropathogenesis. These include (i) the extent of HIV infection within the brain parenchyma during the asymptomatic stage, before the onset of AIDS; (ii) the source of the HIV particles present within the CSF and, with respect to HIV infection, the relation between the CSF and brain parenchymal compartments; and (iii) the relative contributions of the macrophage, versus those of HIV itself, to the development of neurological disease. Although imaging techniques now permit detection of HIV-associated changes within the brain relatively early with respect to neurological disease, questions relating directly to HIV infection and expression within the parenchyma must usually be addressed postmortem. For this reason, our knowledge of HIV-related events occurring within the brain during the pre-AIDS stage is greatly overshadowed by our knowledge and thinking about the post-AIDS brain. Also, because of the obvious difficulties inherent with studying the brain, the practice has been to study CSF and assume that the findings accurately reflect events ongoing within the brain parenchyma.

Regarding changes in the incidence of HAD, we have observed, in association with the introduction of HAART, a 52% decline in the incidence of dementia among participants in the Multicenter AIDS Cohort study, a large cohort of homosexual and bisexual men, which has high rates of antiretroviral usage and adherence (*1*). We have also observed a 43% decline in the incidence among individuals seen by the Johns Hopkins AIDS Service; this group has a high proportion of injection drug users (*2*). We agree that an accurate assessment of the impact of HAART on HAD requires more epidemiological data, especially because, with improved survival of individuals with advanced HIV disease, we can anticipate a rising prevalence of HAD.

Perhaps some of the controversy associated with the aforementioned three issues results from using the detection of HIV RNA, particularly within CSF, as an indicator of HIV infection within the brain parenchyma. Examination of CSF in HIV-infected individuals has provided critical information, but many questions remain. We believe that HIV RNA levels in CSF can be useful in specific clinical settings (for example, to document the efficacy of a particular antiretroviral therapy regime for virologic suppression), but that CSF levels are not a surrogate marker of levels of HIV RNA in brain. In a study of 10 individuals, Wiley and colleagues showed a correlation between CSF and brain HIV RNA levels, but only for individuals with high viral levels (*3*). In a larger study, we observed only a very weak correlation between antemortem HIV RNA levels in CSF and postmortem levels in the brain (*4*). Price and Staprans introduced the terms "transitory" and "autonomous" to describe the differential contributions of trafficking cells compared with sustained productive parenchymal central nervous system infection (*5*).

Regarding the source of HIV particles in CSF, evidence from our studies, as well as that from others (*3*, *6*), supports the concept that HIV RNA in CSF is potentially

derived from multiple sources including trafficking cells, meningeal or choroid plexus macrophages, and T lymphocytes, as well as brain parenchyma. It is probable that different sources predominate during the different stages of the infection. It is important to keep in mind, however, that tissue macrophages and microglia are long-lived cells, and consequently they can produce HIV within the brain for extended periods of time. Thus, until the relations between the CSF and parenchymal compartments at all stages of HIV infection are more clearly understood, caution should be exercised when extrapolating from one to the other. We propose that detection of viral DNA be performed in parallel on brain tissue specimens. This could help clarify the sources of viral RNA and also provide key information regarding HIV replication in macrophages.



An activated monocyte (blue cell with red spikes) migrates from a blood vessel into brain parenchyma.

As mentioned in the Perspective, the perivascular macrophage, which likely originates from a blood-derived monocyte, may be a primary host for HIV infection within the brain. These cells have been shown to express HIV, and given their anatomical location, it seems probable that, particularly when present in considerable numbers (as in demented individuals), they could contribute significantly to the cell-free HIV present within the CSF. These cells could also represent a continually replenished seed source of HIV. That is, during the earlier stages of infection, small numbers of infected monocytes could cross the endothelium and become perivascular macrophages. [Low-level monocyte trafficking into brain has been shown to be a normal occurrence in humans (*7*).] As argued earlier, this process could be accelerated during AIDS, when generalized immune activation is present, including activation of circulating monocytes. Thus, the idea that the perivascular macrophage is a primary host cell for HIV within the brain is compatible with existing knowledge, including the observations referred to by Major and colleagues, and moreover, it can help to explain some of the seemingly contradictory observations.

The hypothesis proposed, which provides a new explanation for how HAD begins, is consistent with existing observations, although at odds with certain interpretations of these observations. The definitive picture awaits further investigation.

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References

1. N. Sacktor *et al.*, paper presented at the 6th Conference on Retroviruses and Opportunistic Infections, Chicago, IL, 31 January to 4 February 1999.
2. R. Moore *et al.*, paper presented at the 12th World AIDS Conference, 28 June to 3 July 1998, Geneva, Switzerland.
3. C. Wiley *et al.*, *Brain Pathol.* **8**, 227 (1998).
4. J. McArthur *et al.*, *Ann. Neurol.* **42**, 689 (1997).
5. R. Price and S. Staprans, *Ann. Neurol.* **42**, 675 (1997).
6. R. Ellis *et al.*, *Neurology* **54**, 927 (2000).
7. E. Unger *et al.*, *J. Neuropathol. Exp. Neurol.* **52**, 460 (1993).