

## LESSONS FROM PEOPLE WITH NONPROGRESSIVE HIV INFECTION

INFECTIOUS diseases can be extremely variable in their manifestations, but human immunodeficiency virus (HIV) infection is notorious for its protean manifestations. One of these, the absence of any apparent progression of disease over a decade or more, is particularly intriguing. The average time from HIV infection to death is 10 years, but clinical and immunologic decline is generally evident much earlier. About 5 percent of infected people are characterized as having nonprogressive infection because they remain healthy and do not have the declining CD4<sup>+</sup> lymphocyte counts that are evident in people with progressive disease.<sup>1</sup> Although we remain uncertain of their eventual fate, people with long-term nonprogressive infection nonetheless have especially favorable outcomes of an otherwise fatal disease. From these patients we may be able to learn important lessons that could improve the treatment of those with progressive disease. In this issue of the *Journal* there are three reports<sup>2-4</sup> of investigations into the possibility that people with long-term nonprogressive infection represent some special circumstance of the virus–host interaction.

Earlier descriptions of HIV infection suggested that it has three distinct phases: an early (acute) phase with marked viremia, a second (latent) phase with very low viral replication, and a final phase of frank AIDS, again with substantial viremia. Recent work has modified that perspective, because it has become evident that the latent period, although characterized by few clinical symptoms, involves extensive viral replication. It has even been suggested that after the end of the acute phase the rate of viral production changes little.<sup>5</sup> Virus-infected cells in the body appear to die within a few days after they begin producing virus. Therefore, to maintain the pool of infected cells in the body, there must be continual new infection of CD4<sup>+</sup> cells.<sup>6,7</sup>

Why one phase of HIV infection differs from another remains poorly understood. There appears to be initial activation of a very effective immune response. This is followed much later by a waning of the host response, reflecting the erosion of the infected immune system. The infected person's health declines when the immune system can no longer cope with the constant barrage of virus. Then the virus gets the upper hand. This could involve exhausting the replicative potential of CD4<sup>+</sup> cells. As CD4<sup>+</sup> cells are killed by infection, they are probably replaced mainly by multiplication of uninfected CD4<sup>+</sup> cells rather than by differentiation in the thymus, and it is possible that the clones of mature cells have a limited capacity to renew themselves. This implies a proportionality between the rate of virus production and the length of time before the number of CD4<sup>+</sup> cells begins to decline.

People with nonprogressive infection are probably a heterogeneous group, with some likely to have nonprogressive infection for a long time, perhaps for their lifetime, and others whose immune systems will decline

more rapidly. The latter could represent the tail of the distribution of normal responses to HIV infection, whereas the former could represent a host–virus relation that differs from that of the vast majority of others infected by the virus. Even these people with “true” nonprogressive infection are likely to be heterogeneous, with some harboring a genetically unique virus and others enjoying an unusually effective immune response to an ordinary strain of HIV. Either way, understanding the cause of the nonprogression would be illuminating.

The picture we get from the two recent studies of people with nonprogressive infection is quite consistent.<sup>2,3</sup> Most of those studied had been infected for more than 10 years, and some for 15 years. They all had robust immune responses to their infections, and Pantaleo et al. showed that their lymph nodes retained an architecture indicative of a healthy response to infection.<sup>2</sup> By contrast, during the later stages of their infections, those with progressive disease have eroded lymph nodes and generally poor immune responses. Likely though it seems, we cannot conclude that the immune reactions of the people with nonprogressive infections are the cause of their special status, because those healthy immune responses could merely reflect the lack of progression. After the acute early phase of infection has subsided, most infected people have strong immune responses, and those with nonprogressive infections may have simply retained that status. If there is anything special about their immune response to explain the nonprogression of their disease, it remains to be found. Their strong immune responses to HIV do, however, indicate that they are continually exposed to viral antigens, a finding that attests to the continued replication of the virus over the many years since the acute infection.

Attempts to isolate infectious virus from the plasma of the people with nonprogressive infection were uniformly negative, but in some cases virus was cultured from peripheral-blood cells, and in one study<sup>2</sup> it was consistently recovered from lymph-node cells. Cao et al.<sup>3</sup> studied the recovered virus in detail and found that some strains grew particularly poorly. Other strains replicated well, however, and the viruses from asymptomatic people generally replicate less well than those from patients with late-stage disease, making it impossible to conclude that the absence of disease progression is a consequence of a defect in the virus.

Using the polymerase chain reaction to measure viral nucleic acids, both studies found that as compared with people with progressive disease, those with nonprogressive infections had low levels of circulating viral particles as well as low levels of viral DNA and RNA in their peripheral-blood mononuclear cells. Cao et al.<sup>3</sup> found much lower levels than Pantaleo et al.,<sup>2</sup> presumably a reflection of the different populations studied.

The third report in this issue,<sup>4</sup> by Kirchhoff et al., documents a study of viral sequences isolated from one person with long-term nonprogressive infection. Segments of integrated HIV DNA isolated from samples

banked over an 11-year period all showed a clear defect, a deletion of portions of the critical *nef* gene of HIV. Monkeys infected with simian immunodeficiency virus (SIV) harboring *nef* deletions also have nonprogressive infection, suggesting that in this one case, the cause of the nonprogression may have been found. Advance reports of this observation have been circulating for some time, and many investigators have sought evidence of *nef* deletions in the virus from others with nonprogressive infection, but to no avail so far. Thus, the finding in this patient appears to be very rare. It raises the possibility, however, that other lesions will be found in other viral strains from patients with nonprogressive infections and that a low level of replication due to debilitating mutations may sometimes be responsible for HIV infection without disease progression.

An interesting corollary of nonprogressive infection is that if viral mutations are responsible in some cases, those hosts must be immune to a second infection. For instance, the person harboring the strain with *nef* deletions has hemophilia and probably had multiple exposures to HIV. Others are homosexual men who probably had multiple opportunities to be infected. In fact, it is well documented that people infected with HIV virtually never show signs of having more than one circulating strain of virus. Although the sequences of viral RNA molecules isolated from a given infected subject vary continually, they are closely related, and the variation appears to arise from mutation rather than from infection by a second virus.

It is an irony of this awful disease that an infected person's immune reaction can be effective enough to prevent secondary infections, but not effective enough to eliminate the primary infection. Thus, the virus with

*nef* deletions may act as a type of attenuated-virus vaccine. SIV with *nef* deletions has been shown to act as a vaccine in monkeys.<sup>8</sup> There has been discussion of the possibility of producing a human attenuated-virus vaccine in this way, but recent evidence that neonatal monkeys get AIDS from a virus with deletions of this type has dampened the enthusiasm.<sup>9</sup> The evident safety of vaccines made entirely of viral proteins makes such vaccines more attractive, but they have not yet proved effective. Therefore, continued study of an attenuated-virus vaccine is reasonable.

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## POST-REMISSION TREATMENT OF ACUTE MYELOGENOUS LEUKEMIA

ACUTE myelogenous leukemia (AML) is characterized by both an increase in the number of white cells and arrest of their normal maturation and function, which causes anemia, granulocytopenia, and thrombocytopenia. The goal of treatment is to eliminate all neoplastic hematopoietic cells in the marrow, peripheral blood, and elsewhere. This goal can be accomplished in some but not all adult patients with AML through the use of two distinct, consecutive phases of treatment. The combination chemotherapy administered during the first phase in a patient with newly diagnosed AML is intended to induce a complete remission, a condition in which leukemic cells can no longer be identified by cytologic, immunologic, or cytogenetic methods and the patient's peripheral-blood counts have become normal. The second phase of treatment (post-remission treatment) is designed to eradicate any residual leukemic

cells anywhere. Thus, post-remission treatment should prevent relapse and improve survival. The development of better post-remission therapies in recent years has received much attention.

During the 1970s and early 1980s all patients received post-remission treatment in the form of maintenance chemotherapy for one to three years after they had entered remission. These chemotherapy regimens gradually increased in intensity, so that the average rates of survival and disease-free survival were approximately 20 percent at four years, although late relapses occurred. During the past 10 years, considerably more aggressive post-remission regimens have been introduced in the hope of improving this rather dismal outcome. These new regimens include allogeneic bone marrow transplantation, autologous bone marrow transplantation, and dose-intensified chemotherapy.

Allogeneic bone marrow transplantation in which marrow from HLA-matched relatives is used in patients in a first complete remission results in disease-

free survival in approximately 50 percent of patients.<sup>1</sup> The patient first receives high-dose cytotoxic therapy to eliminate marrow function entirely, followed by transplantation of bone marrow from an HLA-matched relative. This regimen is currently the most effective anti-leukemic therapy available, because of the low risk of relapse (about 20 percent), but its toxicity is comparatively high. Wide application of allogeneic bone marrow transplantation in patients with AML in a first complete remission has not been possible because patients who are 50 years of age or older generally benefit little and therefore are not considered eligible for the procedure. In addition, HLA-matched related donors are unavailable for many patients. Thus, allogeneic bone marrow transplantation has remained a treatment of exclusivity, available mostly to young patients and those for whom a suitable donor can be found.

The encouraging results of allogeneic transplantation have stimulated investigators to exploit the same high-dose cytotoxic treatment, except that the patient receives autologous marrow instead of donor marrow. The autologous bone marrow is collected while the patient is in remission, and temporarily stored in liquid nitrogen. Accumulating experience indicates that autologous bone marrow transplantation in adults with AML in a first complete remission results in a disease-free survival of approximately 40 to 50 percent at four years.<sup>2,3</sup> Obviously, the stumbling block of finding a suitable donor is avoided in autologous transplantation. It is less toxic than allogeneic transplantation and is currently used in patients up to 60 years of age. Thus, autologous transplantation has become available to many patients who are not eligible for allogeneic transplantation and has yielded results not much different from those of allogeneic transplantation. However, the distribution of causes of death after autologous transplantation does differ from that after allogeneic transplantation. Among patients who receive autologous bone marrow, the most important causes of death are relapse of AML and complications of the transplantation procedures.

A third type of post-remission treatment that has emerged is the use of dose-intensified chemotherapy outside the context of bone marrow rescue. In a recent prospective, comparative study of a dose-escalation regimen, high doses of cytarabine resulted in a significantly better outcome than low doses in adults younger than 60 years of age who had AML<sup>4</sup>; the disease-free survival at four years was 44 percent for the high-dose schedule.

The study by Zittoun et al.<sup>5</sup> reported in this issue of the *Journal* provides an important prospective analysis of the value of autologous bone marrow transplantation as post-remission therapy. It is the first direct comparison of autologous transplantation and chemotherapy in a large series of patients. When the results were analyzed according to the intention-to-treat method, the outcome for patients assigned to autologous transplan-

tation was better than for those assigned to chemotherapy (four-year disease-free survival, 48 percent vs. 30 percent). Does the study provide a definite answer to the question of the comparative value of autologous bone marrow transplantation and modern intensive chemotherapy? It probably does not. The study patients were considerably younger than most adults with AML. Most centers participating in the study enrolled only patients less than 45 years of age, so that the mean age of the study patients was less than 35 years. More important, the post-remission chemotherapy regimen, when considered in retrospect, may have been less than optimal. One cycle of chemotherapy was compared with autologous transplantation; under these conditions autologous transplantation appeared superior. In another study of sequential cycles of intensive chemotherapy in somewhat older patients,<sup>4</sup> the results (disease-free survival, 44 percent) were not at all inferior to those reported by Zittoun et al. after autologous transplantation. In addition, in a recent prospective, controlled study of autologous transplantation and high-dose chemotherapy, the results of the two treatments were similar.<sup>6</sup>

Autologous bone marrow transplantation after marrow-ablative cytotoxic treatment allows dose-intensified and time-concentrated anti-leukemic treatment. However, for patients with AML it represents an example of a halfway technology that is still associated with many constraints. Among patients who have complete responses after induction chemotherapy and are thus the prospective candidates for autologous bone marrow transplantation, only a minority ultimately undergo transplantation. There are many reasons why in clinical practice eligible patients do not undergo autologous transplantation. They include intercurrent relapse of AML, collection of marrow of insufficient quality, and the presence of coexisting high-risk conditions. In the study by Zittoun et al.,<sup>5</sup> among 393 patients in remission and without an HLA-matched sibling, only 95 underwent autologous bone marrow transplantation and 104 received intensive chemotherapy. Thus, less than 50 percent of the patients in complete remission underwent autologous transplantation and completed their treatment according to the protocol despite their comparative youth. The dropout rate was also high in other studies, confirming that frequent withdrawal is an important problem.<sup>3,6</sup>

A second serious drawback of autologous bone marrow transplantation is that hematopoietic regeneration is notoriously slow in patients with AML.<sup>2,3</sup> As a direct consequence of the prolonged marrow hypoplasia after autologous transplantation, the patients remain at high risk of infection and bleeding for a long time, remain dependent on transfusion support, and must be hospitalized for prolonged periods. In the study by Zittoun et al.,<sup>5</sup> for instance, the median length of time for the platelet count to recover fully was more than 20 weeks.<sup>5</sup> For autologous transplantation to be established as a generally useful therapy, it must be simplified. It is

conceivable that the use of hematopoietic growth factors or peripheral-blood cells as transplants may make autologous stem-cell transplantation a more practical procedure.

Should a patient with AML who is 60 years old or younger receive a bone marrow transplant or intensive chemotherapy? In general, in such patients intensive chemotherapy results in rates of disease-free and overall survival that are similar to those with bone marrow transplantation. Thus, the choice of treatment remains an open question. Are there variables that might suggest that a patient is more or less suitable for one of these options? The presence of cytogenetic abnormalities has a strong impact on outcome in patients with AML and may identify those with a good or a poor prognosis. There is accumulating evidence to suggest that patients with unfavorable cytogenetic features benefit little from aggressive chemotherapy or transplantation and still have a poor outcome.<sup>7,8</sup> The use of prognostic factors in therapeutic decision making for patients with AML is still in its infancy.

Will allogeneic transplantation, autologous transplantation, and intensive chemotherapy continue to be used in parallel? Will one of these become the first choice in distinct subgroups of patients? When should

treatment be carried out? Future studies will need to answer all these questions.

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## SOUNDING BOARD

### INSTITUTIONAL CONFLICT OF INTEREST

FINANCIAL conflicts of interest in a research setting can adversely affect patient care, teaching, and research. Discussions of these conflicts ordinarily focus on issues that arise when individual physicians and biomedical scientists conduct research in which they have a financial interest.<sup>1-18</sup> Less attention has been paid to the conflicts of interest that arise when health care institutions have a financial stake in the research conducted in their laboratories and clinics.<sup>19,20</sup> This relative inattention persists despite the increased pressure on health care institutions to seek new sources of revenue to fund their activities and the government's encouragement of the commercialization of federally financed discoveries.<sup>20-23</sup>

In this article we analyze the ethical issues related to institutional conflicts of interest, focusing our analysis by presenting a case that arose at a Harvard-affiliated hospital. All the details provided are the actual facts of the case, although the names of the hospital, biotechnology company, drug, and diseases involved in the case are omitted. Our inquiry is limited to situations involving clinical research and a financial interest in the form of a licensing agreement, but the analysis can be extended to include institutional conflicts of interest that involve basic scientific research and situations in

which an institution has equity in a company that is developing a compound, process, or therapy.<sup>19</sup>

### A CASE OF INSTITUTIONAL CONFLICT OF INTEREST

In collaboration with scientists at a biotechnology company, two employees in a division of a Harvard-affiliated hospital developed a new drug. The employees subsequently left the hospital. The hospital granted the biotechnology company exclusive worldwide rights to the hospital's portion of the drug patent in return for royalties on sales and other payments. If the drug is found to be clinically beneficial, annual sales could total millions of dollars, and the hospital could receive substantial royalties. According to an agreement between the hospital and the employees who developed the drug, each employee receives 12.5 percent of the hospital's proceeds, 50 percent is allocated to the hospital's general-research fund, 12.5 percent goes to the department in which the drug was developed, and 12.5 percent goes to the division.

Investigators at the hospital propose two phase 1-2 clinical trials of the drug. In one trial, the drug would be given to patients with an exceedingly rare, universally fatal disease in which certain normal biologic products are lacking. The hospital is a national referral center for the treatment of patients with this rare disease and for research on it. The second trial would be a multicenter study in which the drug would be used to treat patients with a more common medical disorder.

The hospital would probably enroll 20 of the 150 patients in the study.

Neither the proposed principal investigator for both trials nor any of her nearest relatives have any financial interest in the biotechnology company or derive a personal financial benefit from the drug patent. The principal investigator's department and division at the hospital receive proceeds from the drug's royalties. Also, a senior physician at the hospital is a member of the biotechnology company's scientific board and a consultant to the company. Payments for his services to the company go directly to his department, not to him personally.\*

### DISTINGUISHING BETWEEN INDIVIDUAL AND INSTITUTIONAL CONFLICTS OF INTEREST

An institutional conflict of interest arises principally when an institution has equity in a company and investigators employed by the institution conduct research that could affect the value of the equity interest, or when an institution holds a patent on a compound, process, or therapy that it licenses to companies and investigators employed by the institution conduct research on that compound, process, or therapy. Institutional and individual conflicts of interest differ in three ways. First, when an investigator at an institution has a financial stake in a company and is conducting research sponsored by that company, the institution receives the company's payment for the research and monitors the work, but the size of the payment is not linked to the success of the research. Thus, neither the short-term nor the long-term financial interests of the institution are linked to the outcome of the research.

Second, when the institution has a direct financial interest, the institutional conflict of interest is mediated through individual investigators employed by the institution. A physician, nurse, or biomedical researcher actually performs the patient care or research activities. Yet because of pressure or their institutional roles, such investigators may be unwilling to object to the institution's practices.

Finally, when individual investigators pursue their own financial gain, there is no doubt that this constitutes self-interested behavior, and their personal motives may undermine their patient care, teaching, or research activities. Conversely, society recognizes that health care institutions need to obtain funds to carry

out their missions and sanctions institutional pursuit of such funding. Society may not view this as self-interested behavior and consequently may erroneously be more tolerant of circumstances in which an institution's financial interests may compromise the integrity of its missions than of similar situations involving individual conflict of interest.

### A FRAMEWORK FOR ANALYZING INSTITUTIONAL CONFLICTS OF INTEREST

Institutional conflicts of interest must be evaluated in the light of four factors: the relation between an institution's primary missions and its financial interest, the size of the financial interest, the degree of discretion involved in achieving the primary missions, and the seriousness of the harms that might result from the institutional conflict of interest.

#### Conflict of Interest and Primary Missions

Health care institutions have three primary missions that are pursued for the benefit of the public: patient care, teaching, and biomedical research.<sup>1-3,5,8,10-12,16-19,24</sup> There can be conflicts among these missions when one institution pursues them.<sup>8,10-12,24-26</sup> It is well recognized, for example, that clinical research can conflict with patient care. Our society has developed procedures, such as reviews of clinical trials by institutional review boards, to prevent or mediate these conflicts.<sup>25,26</sup>

Health care institutions also have other goals and interests, including raising funds to support their missions and gaining recognition for their accomplishments. Institutional conflicts of interest are conflicts between the primary missions of a health care institution and its other interests.<sup>1,2,8,10-12,16-19</sup> Although securing financial resources is important, it is only a means — albeit a very important one — to support and further the institution's missions. Consequently, the institution's legitimate interest in obtaining funds to support its activities must be considered secondary to its primary missions. Any conflict between secondary interests and primary missions needs to be examined to ensure that the primary missions neither are compromised nor appear to be compromised.<sup>1,2,8,10-12,16-19</sup>

#### The Size of the Financial Interest

In the case of individual conflicts of interest, the amount of the financial interest is an important factor in determining whether the conflict is prohibited. Financial interests that are small are unlikely to have, or to appear to have, an influence on decisions about patient care, teaching, or clinical research.<sup>1,8,10-12</sup> A similar view should prevail with regard to institutional conflicts of interest.<sup>1,19</sup> There is, however, no absolute standard for what constitutes a *de minimis* (minimal) financial interest. Factors that should be considered in establishing a dollar figure for a *de minimis* interest include the value of the present and potential payments to the institution, the nature of the events that trigger

\*Officials of the Harvard-affiliated hospital involved in this case requested that we examine the underlying ethical issues, although there was no requirement or request to do so by any official body of the hospital or Harvard University. Neither of us and none of the members of our immediate families are or have ever been employed by or served as consultants to the hospital or the biotechnology company, although Ropes & Gray, a law firm with which one of us is affiliated, does legal work for the hospital. Neither of us and none of the members of our immediate families have a financial interest in the biotechnology company. We have been affiliated with Harvard University for many years and are currently members of its faculty. We received no compensation from the hospital or the biotechnology company for this report and have not received grants, contracts, consultancies, or other benefits as a result of it.

the payments, and the size of the institution's research, discretionary, and operating budgets.

### **Professional Discretion in Patient Care and Biomedical Research**

Both patient care and biomedical research, the basic elements of clinical trials, entail a high degree of professional discretion — for example, in determining whether a symptom is an adverse reaction and whether an adverse reaction is severe enough to discontinue the therapy and in establishing relevant end points for a trial. We should try to minimize, if not eliminate, circumstances in which financial interests may influence or even distort any of these judgments.<sup>1-3,10-12,16-19</sup> It is also inevitable that professional judgments will appear to be affected by institutional conflicts of interest. Because any discretionary decision can be influenced by many factors, it may be impossible for external observers to determine what factors influenced a particular decision. Indeed, it may even be difficult for decision makers to be certain about their own motives and what factors influenced a particular decision. Thus, reasonable people may wonder whether financial motives have influenced decisions.

### **Potential Harm from Conflicts of Interest**

#### *Patient Care*

In the process of obtaining informed consent from patients for participation in a clinical trial, physicians might fail to provide information of interest to the patients, such as the nature or magnitude of the institution's financial interest in the results of the trial. If the patients gave consent without this information, their right to informed consent might be violated, and their consent might be invalid.<sup>25-28</sup> An institutional conflict of interest could also influence the investigators to ignore or minimize symptoms indicating adverse reactions, which in turn might endanger the health of the patients in the trial. Furthermore, the positive results of a clinical trial in which adverse reactions were ignored or altered could lead to the approval of a therapy with unreported adverse effects that could endanger the health of patients throughout the United States.

#### *Teaching*

A student, postdoctoral fellow, or other trainee might be encouraged to conduct research in which the institution had a financial interest even if that research was not the most beneficial to the person's education or career development. However, teaching is not likely to be seriously threatened by institutional conflicts of interest involving clinical research.

#### *Biomedical Research*

Investigators conducting a clinical trial of a compound, process, or therapy in which the institution had a financial interest could compromise the trial by using a poor or biased study design or by introducing bias into the data-collection methods, statistical analyses, or

reporting and interpretation of the data. In addition, the conflict of interest could distort research priorities by affecting the distribution of essential research-related resources, including space and discretionary funds. Subtle pressure might induce clinical staff to encourage patients to participate in a clinical trial in which the institution had a financial interest, reducing enrollment in other clinical trials with similar eligibility requirements. Finally, the appointment or promotion of faculty members associated with the clinical trial in which the institution had a financial interest could compromise the integrity of the appointment-and-promotion process. Even though particular decisions, such as those concerning space allocation or promotion, might not actually be influenced by financial motives, they might be perceived by other investigators in the institution as reflecting a bias in favor of the clinical trial in which the institution had a financial interest, thereby undermining morale.

Institutional conflicts of interest also threaten the overall biomedical-research enterprise in the United States. If the public becomes aware that a substantial proportion of clinical research is performed in institutions with conflicts of interest, its confidence in and support of biomedical research may be eroded. Although a financial conflict of interest on the part of one health care institution will not alter the public's perception of the integrity of biomedical research in general, there is a cumulative effect. Moreover, the nation's leading health care institutions have a critical role in defining the norms for appropriate practices. Public confidence is most likely to be maintained if it is the exception rather than the rule for health care institutions to have financial interests in the clinical research conducted under their auspices.

These are not just potential threats. The primary missions of health care institutions have been compromised by individual investigators with conflicts of interest.<sup>3,13,29</sup> The most notorious example may be the Tseng case, in which an ophthalmologist at Massachusetts Eye and Ear Infirmary conducted a study of an ointment for the treatment of "dry eyes" while he owned 530,000 shares in the company that would have marketed the medication if the trial had been successful. There were many irregularities in the clinical trial, as well as manipulation of the release of data.<sup>30</sup>

### **PRIMA FACIE CLAIM TO AVOID INSTITUTIONAL CONFLICT OF INTEREST**

In the light of these considerations — the importance of preserving the integrity of the primary missions of health care institutions, the role of discretionary judgments in clinical trials, and the potential harms from conflicts of interest — there arises a prima facie claim that such a conflict should be avoided and that a clinical trial should not be conducted in an institution that has a financial interest in the outcome unless that interest is de minimis.

Some might argue that these ethical problems could

be overcome by prohibiting commercial links between health care institutions and companies. This position ignores three points: federal encouragement of health care institutions to commercialize their discoveries,<sup>20-22</sup> the lack of alternative avenues for developing biomedical advances into safe and effective products,<sup>20</sup> and the increasing financial pressures on health care institutions. Prohibiting commercial links between health care institutions and companies would require substantial changes in federal law and the economic system for supporting the development of biomedical products. The possibility of such extensive changes seems remote.

Others might argue for an absolute prohibition on conducting clinical research at institutions with a financial interest in a product under study. Just as no rights are absolute, no prohibitions should be absolute. The ultimate objective of health care institutions is to advance the primary missions of patient care, teaching, and biomedical research for the public good. The purpose of regulating institutional conflicts of interest is to protect the integrity of these missions. However, in the unusual circumstance that a primary mission could best be realized at an institution with a conflict of interest, the prohibition imposed by the *prima facie* claim could actually have the paradoxical effect of preventing the realization of the mission. In this case, the public interest would be better served if the *prima facie* claim were overcome. For example, an institution with a conflict of interest might be the only appropriate site for a clinical trial because of particular facilities or expertise that could not be found elsewhere. But even if the *prima facie* claim were overcome, the threat posed by the financial interest would remain and therefore necessitate appropriate safeguards.

### SAFEGUARDS AGAINST HARM FROM INSTITUTIONAL CONFLICTS OF INTEREST

#### Disclosure

Any patient considering whether to participate in a clinical trial should be told about the conflict of interest, and the conflict must be stated on the informed-consent form. In addition, the institutional conflict of interest should be disclosed to others, including the institutional review board, collaborators and coinvestigators at other institutions, other funders that have supported the clinical research, readers of articles and abstracts that report the research results, and audiences at oral presentations of the research results. Other safeguards adopted by the institution should also be disclosed to the patient.

In theory, disclosure to the patient might be unnecessary if the people involved in the care of the patient or the research were unaware of the institution's financial interest. Because it is both highly unlikely that these people would not know of the licensing arrangement and impossible to document who knows about the financial interest during the research, disclosure should

be required in all cases. We recognize that disclosure of institutional conflicts of interest is not standard practice in informed-consent procedures and may be controversial,<sup>27,28</sup> but it is consistent with the ruling in one well-publicized case.<sup>31,32</sup> Moreover, disclosure of commercial relations is necessary for scientists to evaluate critically the merit of biomedical research.<sup>33</sup> Similarly, for patients to decide whether participation in a trial is in their interests, they must be able to evaluate the information they are provided, which necessitates the disclosure of institutional conflicts of interest.

Although disclosure has been the safeguard recommended most frequently, it is necessary but insufficient for several reasons.<sup>1,10-12,14</sup> First, disclosure "only reveals a problem, without providing any guidance for resolving it."<sup>1</sup> Second, those who receive the information, especially patients, may not know how to evaluate it; in fact, the disclosure may only increase their anxiety during an already stressful period. Finally, health care institutions lack monitoring systems that can act on the basis of a disclosure of a conflict of interest. Universities, medical schools, and hospitals have begun to establish committees to monitor individual conflicts of interest,<sup>3,11,12</sup> but there have been few efforts to establish similar committees for institutional conflicts of interest.<sup>19</sup> Institutional review boards, collaborators, funding agencies, and journal readers are not organized to monitor or respond to disclosures of conflict of interest.

#### Internal Monitoring

Because internal reviews of patient care and research have been used to monitor individual conflicts of interest, a similar approach might seem appropriate for institutional conflicts of interest. Internal monitoring could be performed when an institutional review board, ad hoc committee, or chief of service reviewed the patient care and research data and analysis associated with a clinical trial.

Such an internal review seems insufficient. Because of their responsibility for the financial condition of the institution, officials may not be disinterested in their judgment. Furthermore, money is fungible; every administrator, chief of service, and investigator could therefore benefit from the institution's proceeds from a commercial license, even if they or their departments did not receive the funds directly. To maintain public confidence, monitoring must operate independently of those who have responsibility for the institution's financial condition or who, in their professional roles, could benefit from increased revenues.

The institutional review board, which does not have primary responsibility for the financial condition of the hospital, has members from outside the institution, and has a mandate to review research protocols, might appear to be more independent. Yet, some members of the board might work for the department that stood to benefit financially from the clinical research, and others might benefit indirectly from the institution's royal-

ties. Finally, the public perceives these boards as internal rather than external bodies. Just as citizens may be suspicious of the thoroughness of a government agency's review of its own behavior, there may be little confidence in an institutional review board's judgment when the institution has a financial interest in the research.

### External Monitoring

External monitoring offers a final safeguard against the potential harm due to an institutional conflict of interest. If a trial is to be conducted at several centers, and none of the other institutions have a conflict of interest, then these institutions could provide a monitoring function that would be internal with respect to the trial but external to the institution with the financial interest. In one of the studies conducted by John Darsee, the multi-institutional aspect of the study resulted in the discovery of a fabrication of research results.<sup>34,35</sup> However, the very possibility of a multicenter trial means that there are institutions qualified to perform the clinical research other than the institution with a financial interest, which in turn means that there is no compelling reason to overcome the prima facie claim and have the trial conducted at the institution with the conflict of interest.<sup>1,10-12</sup>

Alternatively, a committee composed of people outside the institution could be formed to review the research design before the commencement of the trial and regularly review all data related to the research. This external committee should have the authority to require modifications of the research or even stop the trial. The chair and members of the committee should be sufficiently removed from the institution so as not to be subtly influenced by the interests of the institution or its members and yet sufficiently knowledgeable to review the research intelligently. To ensure that the committee members do not themselves have a conflict of interest, they should not hold stock in any company connected with the clinical trial and should receive no compensation for their monitoring activities (other than reimbursement for expenses). The membership of such a committee might include a biomedical researcher and an ethicist or lawyer, and the committee should have access to a statistician. Such an external monitoring committee, whose purpose would be analogous to that of peer review of articles submitted for publication and grant applications, would seem to provide the best safeguard.

External monitoring, however, has its own costs. For the committee members, the work would be time-consuming and professionally uncompensated, and it might put them in the awkward position of criticizing colleagues. For the investigators at the institution itself, the external review could be quite time-consuming. The monitoring process might also create an adversarial relationship between the external reviewers and the institution's investigators. Nevertheless, in those few cases where the prima facie claim is overcome and a clinical trial proceeds despite an institutional conflict

of interest, monitoring by an external committee would seem to provide the best safeguard.

### APPLICATION OF THE FRAMEWORK TO THE CASE OF THE HARVARD-AFFILIATED HOSPITAL

The Harvard-affiliated hospital involved in this case has a substantial financial interest in the outcome of the clinical research, creating a prima facie claim that it should not conduct either of the clinical trials of the drug. In the trial involving the rare disease, however, researchers at the hospital claim that it may be the most appropriate site for the trial and perhaps the only institution capable of conducting the research. We are neither experts on this particular disease nor knowledgeable about all the special skills and facilities required to conduct such a phase 1–2 trial. However, a literature search seems to corroborate the researchers' claim. In the past 10 years, 19 original articles have been published on this disease, including 15 case reports and 4 reports on treatment. The hospital's research is the most recent, involves the largest number of patients, and constitutes the only therapeutic investigation of this disease conducted by a U.S. institution. Also, fewer than 50 cases of the disease have been reported, and the hospital may be one of the few referral centers that follows a sufficient number of patients to conduct a therapeutic trial. If the hospital does not conduct the trial, the public may be deprived of an effective treatment for this rare, fatal disease. To ensure that the public's interest in continued research on the disease is served, the hospital should probably perform the study, with appropriate safeguards.

Conversely, the prima facie claim should not be overcome for the multicenter trial involving a more common medical disorder. Hospitals other than the Harvard-affiliated hospital are well qualified to conduct the trial, and the number of patients that this hospital would contribute to the trial would be comparatively small. Although the multicenter nature of this trial does provide a safeguard against some of the threats posed by the institutional conflict of interest, it does not provide complete protection. The presence of safeguards does not mean that the public interest is better served by conducting the trial at the hospital that has a financial interest in the outcome.<sup>1,9,11</sup>

### ADDITIONAL REGULATION OF INSTITUTIONAL CONFLICTS OF INTEREST

Institutional conflicts of interest clearly exist. Public policies supporting technology transfer and the growing financial needs of health care institutions make it likely that these conflicts will become more frequent.<sup>20</sup> Yet we have no valid data on the dimensions of the problem or institutional responses to it. The paucity of data suggests the need for a study to document the frequency of institutional conflicts of interest and the existence and efficacy of institutional policies regulating them. If there are problems that institutions are not addressing properly, federal guidelines on institutional conflicts of interest might be appropriate. Such con-

licts arise almost exclusively in the development and clinical testing of compounds, processes, or therapies that require the approval of the Food and Drug Administration (FDA). Thus, an effective approach might be for the FDA to designate any data from clinical trials conducted at institutions with conflicts of interest as inadmissible evidence for the approval of a drug or device, unless there was sufficient reason to overcome the prima facie claim and appropriate safeguards had been implemented. Such a policy would result in uniform rules and interpretation of exceptions to those rules, with rigorous enforcement by a regulatory authority.

We recognize that this proposal would require more stringent regulation of institutional conflicts of interest than the recently proposed FDA regulations for individual conflicts of interest.<sup>36</sup> The stricter regulation is necessary because of the essential differences between institutional and individual conflicts. Before such federal guidelines were implemented, it would be important to evaluate their benefits as well as the burdens they would impose on health care institutions.

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