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LETTERS

Minnesota Drug Sales

Christopher Anderson's article "Scandal scars Minnesota medical school" (News & Comment, 17 Dec., p. 1812) reports that some do not understand why the Food and Drug Administration (FDA) put a clinical hold on the investigational drug Minnesota antilymphocyte globulin (MALG). The FDA acted because of the sponsor's failure to obtain informed consent, to properly monitor clinical trials, and to report adverse reactions (including deaths). These are serious violations of the Food, Drug, and Cosmetic Act.

Contrary to observations in the article, the FDA has successfully licensed 12 university facilities—five of them before the introduction of MALG in 1971—for the production of biological products and vaccines. In addition, two state health departments have been licensed for production of vaccines and other biological products.

Despite repeated requests to the MALG investigators, data establishing the drug's safety and efficacy have not been submitted to the FDA. Alternative therapies that have been shown to be safe and effective were available to patients at the time the FDA took action.

Kathryn C. Zoon
Director, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD 20857

I am writing to add my perspective to the 17 December article about the University of Minnesota Medical School and the antilymphocyte globulin (ALG) program in its Department of Surgery.

First, it should be pointed out that it was *not* the university's General Counsel who temporarily withdrew a National Institutes of Health (NIH) grant renewal application from the ALG program that is under federal investigation. That action was taken by the appropriate university officer, the vice president for research and dean of the graduate school.

From my perspective, I am also concerned about the characterization that "after reviewing the grant with the researchers, university administrators resubmitted the application with only minor changes." As president, I find it difficult to characterize any information that federal agency regulations require as "minor." The regulations have the force of law. It's that simple.

By law and by contract, principal investigators and their staff members are obligated to know and comply with regulations, regardless of their opinions of the regulations and regardless of the sponsoring agency's oversight and enforcement behavior. As Minnesota's recent problems should be reminding researchers and administrators alike, persistent noncompliance with federal regulations is wrong, and it is trouble.

By common sense and institutional policy, researchers should be obliged to inform departmental, collegiate, and central administrators of problems with sponsoring agencies and steps being taken to solve them. Looking back, early and forthright notification of the appropriate medical school and central administrators could have—would have—avoided this entire controversy.

Looking back, we found what we regard to be compelling evidence of persistent noncompliance, research misconduct, and malfeasance in the ALG program, and we have taken appropriate action within the university's academic misconduct and tenure code provisions. We have also determined that there was inadequate oversight, including institutional policies that were not up to today's more demanding standards. With strong leadership from medical school faculty, we have strengthened the policies and developed a new management-oversight and administrative support structure that will meet modern standards, enhance competitiveness in the health care marketplace, and allow our highly talented medical faculty to concentrate on their teaching, research, and clinical contributions that continue to earn international respect. Those contributions are made every day, and it is a terrible price we pay when much less prevalent, but far better publicized problems divert public attention from that good work. But the price will go higher yet if the public loses confidence that institutions will own up to mistakes and correct them.

Nils Hasselmo
President, University of Minnesota, Minneapolis, MN 55455–0110

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Heavy Ion Drivers

I write to add a footnote to Gary Taubes' interesting article about laser fusion of 3 December (News & Comment, p. 1504).

My first involvement in reviewing this program was in 1978 when John Deutch, then director of energy research at the Department of Energy (DOE), set up a review panel chaired by John Foster to go over the entire DOE fusion program (magnetic and inertial). In three phases (known in the community as "Jaws One, Two, and Three"), the entire program was reviewed; inertial confinement fusion was identified as a serious potential competitor for power plant applications; and heavy ion drivers were identified as the most promising technology to ignite a fusion pellet, whether the applications be civilian or military. Many other suggestions with respect to the program were also made, most of which were eventually carried out. The report was classified and remains locked in a filing cabinet at DOE.

Since that time, many other reviews of the inertial fusion program have been made, and all have come to the same general conclusion as the Foster panel with respect to drivers. I personally reached the point in the mid-1980s when I refused to serve on any more review panels, because no matter what one said, the most promising approach, heavy ion drivers, continued to be starved and virtually ignored.

It is interesting to note in Taubes' article that heavy ion accelerators are still regarded as "the best bet for drivers." What is not said is that nearly 16 years after the first Foster panel report, the heavy ion program is still starved for funds, and we have made very little progress on "the best bet."

I learned one other lesson from my service on the Foster panel—never agree to serve on a classified panel that will not, at the very least, have an unclassified executive summary.

Burton Richter
Director, Stanford Linear Accelerator Center, Stanford, CA 94309

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ApoE, Amyloid, and Alzheimer's Disease

The amyloid cascade hypothesis for Alzheimer's disease (*1*) undoubtedly has some holes in it; thus, the distinctive distribution of lesions in the disease remains unexplained (*2*), as does the precise mechanism of neuronal death. Furthermore, the results emanating from Allen Roses' group at Duke University relating the presence of the E4 allele of apolipoprotein E (ApoE) to the occurrence of Alzheimer's disease (J. Travis, Research News, 13 Aug., p. 828) (*3*) are undoubtedly important—possibly the most important ever presented in the study of the epidemiology of the disease. However, while some may now appear to wish to jettison the amyloid cascade hypothesis (J. Marx, Research News, 19 Nov., p. 1210), I suggest that this would be throwing out the baby with the bathwater.

The original identification of ApoE as a risk factor for disease (*3*, *4*) was made because the Duke group was searching for β-amyloid binding proteins. In other words, they were implicitly working within the framework of the amyloid cascade hypothesis and came up with an important finding based on their version of this hypothesis. Not only have they demonstrated isoform-specific effects of ApoE4 (compared with those of ApoE3) in its binding to β-amyloid (*5*), they have also demonstrated that individuals who are homozygous for ApoE4 have a greater amyloid burden than those who are homozygous for E3 (*6*); in addition, we have demonstrated that in Alzheimer's patients with amyloid precursor protein (APP) mutations, the ApoE genotype modulates the onset age (*7*). These findings strongly support the notion that there is a biochemical relationship between β-amyloid and ApoE and, together with the occurrence of Alzheimer's in individuals with Down syndrome (*8*) and in those with pathogenic mutations in APP (*9*), they provide strong evidence for the validity of the general framework for the amyloid cascade hypothesis.

It is difficult to judge the hypothesis by the Duke group that ApoE4 is not itself a risk factor for disease, but rather that ApoE3 (or ApoE2) is necessary for normal neuronal function and resistance to neurofibrillary change. However, because ApoE4 appears to be the ancestral allele in related animal species, because a high proportion of people with typical Alzheimer's pathology are homozygous for ApoE3, and because persons with APP mutations develop Alzheimer's disease whatever their ApoE genotype, it seems unlikely that this new hypothesis will endure. It is more likely that the binding of ApoE to amyloid is somehow closely related to the transition between diffuse, apparently benign, β-amyloid deposition and neuritic, damaging deposits (*10*).

John Hardy
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