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LETTERS

Embryo Research Guidelines

I would like to clarify two points for readers of Eliot Marshall's article of 19 August, "Rules on embryo research due out" (News & Comment, p. 1024). First, the report of the National Institutes of Health (NIH) Human Embryo Research Panel, a group of outside experts, is still under development. Therefore, an accurate and complete picture of the panel's findings and conclusions cannot now be drawn.

The panel's work, moreover, is one step in a larger policy development process. The process involves a review of the panel report by the Advisory Committee to the Director (ACD) of NIH. This review will continue into the fall and winter. On 1 December, the ACD will deliberate the report in a public session. Only after receiving the advisory committee's recommendations about the panel report will the NIH make any decisions about which areas of research are acceptable for federal funding and what guidelines (not rules, as the article indicates) will be formulated to govern that research.

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Primates and New Viruses

In a ScienceScope item, "Mystery virus fells donor baboons" (10 June, p. 1523), it is reported that a new, uncharacterized virus triggered an outbreak of encephalitis in baboons and was threatening the colony at the Southwest Foundation for Biomedical Research (SFBR), a primate facility that houses close to 3000 baboons. In fact, only a few animals have developed an encephalitis-like disease, making it unlikely that the implicated virus is highly virulent in baboons. Moreover, the infectious agent responsible for this outbreak has probably been around for some time, even if it has only recently caught the attention of scientists.

What is of greater concern is that a virus that infects baboons could also be hazardous to humans under the right circumstances. In the past 2 years, two baboon-to-human liver transplants have been conducted (*1*). The identification of a previously unknown virus in nonhuman primates illustrates the possibility of doing more harm than good through xenograft transplantation: any pathogen carried by a baboon donor would be introduced to the human recipient along with the baboon organ. Most new pandemics arise through inadvertent transmission of viruses from another species (which functions as a natural reservoir) to humans. Surgeons and infectious-disease experts have made good-faith efforts to identify and exclude as organ donors baboons carrying known pathogens such as simian immunodeficiency virus (SIV) and simian T cell leukemia virus; however, it does not follow that the chosen baboons are therefore free from all infectious agents. Baboons carry an abundance of pathogens that are potentially dangerous to humans, including both herpesviruses and retroviruses, which can remain dormant for long periods. Identifying and excluding animals that harbor any number of viruses (some unknown) from transplant studies is virtually impossible.

So far the baboon-to-human liver transplants have been experimental and the human recipients have been terminally ill before transplantation therapy was attempted, but success in any form will likely lead to more investigations and testing until patients begin to recover. It is most disturbing that the public health implications of these studies have not been adequately discussed. One suggestion is to convene virologists, infectious-disease experts, transplant surgeons, and public-policy officials under the guise of the National Institutes of Health (NIH) and the Centers for Disease Control to begin openly discussing the overall risks to the human population. Any panel should be independent of the committees previously constructed by transplantation groups.

At the very least, national guidelines for medical surveillance of transplant recipients and their relatives should be considered: recipients could be quarantined in biosafety conditions for at least 60 days, and all health care personnel could follow accepted NIH guidelines for working with unknown human pathogens. At SFBR, we consider nonhuman primates and their tissues and body fluids to be biohazards and use standard biosafety procedures similar to those required for working with AIDS. Employees of SFBR wear fully protective clothing, including masks and latex gloves, when working with animals or their tissues. We sell these same animals to medical centers, where their tissues may be placed directly into humans along with a cocktail of immunosuppressive drugs. Scientists do not

have the luxury of a crystal ball for predicting the outcomes of these experiments. What we do have is AIDS as a reference point.

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The Sobering D_2 Story

The article "A cautionary genetic tale: The sobering story of D_2" by Constance Holden (News, 17 June, p. 1696) sends the wrong message to the field and creates embarrassment for scientists who are pioneering at the forefront of research in the genetics of addictive-compulsive disorders.

The article states that "attempts to replicate [our] finding [about the A1 allele of the D_2 receptor gene] have been largely unsuccessful." A meta-analysis (*1*) of nine independent studies of a total of 491 heterogeneous alcoholics (severe and less-severe) and 495 heterogeneous control subjects (assessed and unassessed for alcohol abuse) found a statistical association between the D_2 A1 allele and alcoholism that was highly significant: the value of P was 10^{-7}. When attention was focused on six studies dealing only with a homogenous sample of 158 severe alcoholics, the association was found to be even more striking: the value of P was 10^{-8}.

The article states that "even those whose research appears to confirm it can't come up with a mechanism for the gene's presumed effects. . . ." In fact, the finding of a genetic marker is only the first step in what may be a long and involved process of continuing research. As in the case of Huntington's chorea, a chromosomal marker first discovered in 1983, adequately marks vulnerability to a disease without knowledge of the gene responsible for its expression. The actual gene was discovered 10 years later. The DRD_2 variants appear to adequately mark vulnerability to addictive-compulsive behaviors, but the mechanism for the specific genetic defect may not be discovered for the next decade. The causative factor may even involve closely linked microsatellites at the DRD_2 locus or possibly distant genes that are in linkage disequilibrium with the DRD_2 gene.

The article quotes psychiatric geneticist Elliot Gershon and his colleagues as saying that, in a study of alcoholics and schizophrenics (whose disorder also involves dopamine transmission) examining the gene instead of the marker, they "found several coding variants," but "the frequency was pretty much the same in the subjects and the controls." In fact, we were also coauthors of that report (*2*), and the findings were not unexpected. Gershon was referring to exonal anomalies that might alter the structure of the D_2 receptor and hence its ability to bind to its ligand. Our finding (*3*) suggests an anomaly in the transcriptional process that affects the number of receptors. Gershon's study did not examine anomalies around the 5′ promotor region, introns, and the 3′ untranslated region, all of which have been shown in a number of other disorders to have mutations that alter transcriptional or translational processes.

The article states that [David Goldman's group] "could find no significant difference between alcoholics and nonalcoholics in the frequency of the suspect allele. . . ." In fact, Goldman's sample (*4*) excluded severe alcoholic subjects having medical complications. Moreover, the nonalcoholics were not assessed for the presence or absence of alcohol or drug abuse. In contrast, our sample (*5*) of severe alcoholics had died from alcohol-related pathology. Furthermore, our nonalcoholic control subjects were assessed for the presence of alcohol and drug abuse. Goldman's study, therefore, was not a replication of our first study and has little bearing on it.

Joel Gelertner's group is indirectly quoted as saying that "there is little reason to accept Blum and Noble's conclusion." In fact, in the Gelertner study (*6*), as in Goldman's, any alcoholic subject showing liver enzyme abnormalities, let alone significant medical problems, was excluded. This is a clear indication that Gelertner's group was excluding severe alcoholics. Furthermore, their paper included no assessment of the control subjects. By excluding the severe alcoholic phenotype, the group was studying the more "environmental" rather than the more "genetic" type of alcoholism.

Holden's article refers to preliminary work by Robert Cloninger and says it "appeared to support the A1 connection, at least with regard to severe alcoholism." Holden then says that "when the group expanded its sample, it found . . . that the association between the D_2 receptor and alcoholism faded out." In their first study (*7*), Cloninger's group found that 60% of the severe alcoholics in the sample had the D_2 A1 allele, a prevalence that was significantly higher than the nonalcoholic controls. But careful scrutiny of their follow-up paper (*8*) revealed that the sample of alcoholics in the second study was heterogeneous, including both severe and less severe alcoholics. The inclusion of less severe alcoholics diluted the sample. Moreover, although the group found that the homozy-