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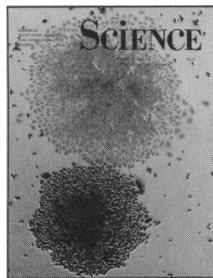
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COVER Fragile X-bearing somatic cell hybrids cultured under positive selection for hypoxanthine guanine phosphoribosyl transferase (HGPRT) followed by in situ histochemical staining for glucose-6-phosphate dehydrogenase (G6PD) activity. The G6PD⁺ (blue) and G6PD⁻ (yellow) colonies indicate segregation of the HGPRT and G6PD genes, suggesting chromosome breakage at the fragile X site. See page 420. [Photo by S. T. Warren, Emory University School of Medicine, Atlanta, GA 30322]

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TPA and PDQ

When a circus clown steps on his toes and falls on his face, it is a cause for laughter. When a regulatory agency that licenses drugs for heart attacks stumbles, it may have not only egg on its face but blood on its hands. Complex questions seen in an oversimplified way, however, can make good intentions look like bureaucratic bungling. The recent decision by the Food and Drug Administration (FDA), or lack thereof, in the tissue plasminogen activator (TPA) controversy is an interesting case in point.

The questions surrounding the controversy involve science, turf battles, money, ethics, public health, and historical complexities. The science starts with the attempt by Genentech, Inc., to get approval for what many consider a major wonder drug for dissolving blood clots. The company approached the FDA, was told what it needed to do, and proceeded to do so. The apparent turf battle arose when at the last moment a second committee of the FDA requested that Genentech satisfy a new set of criteria that would delay approval by months. The FDA's advisory committee was quoted as saying that Genentech had failed so far to demonstrate that dissolving a clot would prolong the life of the patient, a seemingly absurd charge. A closer look, however, indicated that the committee was pointing out that tests on dose levels of the drug were incomplete. The money issue was highlighted by the fact that other companies were pushing their own versions of TPA, and any delay to the front-runner had enormous financial implications. The ethical issue arose when a committee of cardiologists judged TPA to be so effective that the ethics of continuing to give placebos to a control group came into question. The historical complexity was caused by recent approval of a similar but probably less effective drug for clot removal, streptokinase. Should discoverers of new drugs be required to repeat all the trials of previously approved drugs, or may they use earlier results to buttress approval?

Aside from matters of procedure, there are interesting scientific and intellectual questions illustrated by this case. When a new drug appears on the market in 1987, it inevitably incorporates proven information accumulated over the years. A drug that dissolves blood clots should no longer have to answer whether such an action prolongs life. The new drug must not have unforeseen side effects, and its balance between dissolving clots and preventing bleeding must be shown. Since there are 750,000 heart attack victims per year in the United States alone, any appreciable delay in approving a drug widely considered to be a drug of choice is not simply a bureaucratic minutiae—it is a matter of life or death to many patients. It is therefore incumbent on an agency to ask truly scientific questions and not simply go through pro forma experiments that were appropriate in 1967 but not in 1987.

There is an apparent irony in the delay on the TPA drug, since the same agency was recently criticized for failing to put azidothymidine (AZT), a drug for AIDS, on the market more rapidly. Like AIDS, the drug AZT itself is not well understood, far less than is blood clotting. Therefore, it could be argued that approving AZT and denying license to TPA is inconsistent. Yet the agency is legitimately more cautious in the TPA case because an alternative, streptokinase, does exist. In the case of AZT there is no comparable drug, and the disease is also fatal.

The question of money also inevitably enters but cannot and should not be determining in such decisions. If an agency delays a front-runner, it unavoidably helps the followers. A pattern of bureaucratic timidity would surely deter companies from investing in basic research, since it is far cheaper to be a follower. Front-runners always will want decisions PDQ (pretty damn quick), whereas followers will delight in a glacial approach to certainty. Haste has dangers of commission; excessive caution, dangers of omission.

In the TPA case, a final decision had not been made by the FDA commissioners as of this writing. And they are allowed to consider additional evidence accumulated since the time of the advisory committee recommendation. Turf battles, money, and excessive publicity will hopefully be eliminated at this Olympian level. To the second-guessers of the world, accreditation of new drugs will continue to offer fertile ground for controversy. The controversy in this case has served a useful purpose, for it highlights the fact that delay is a decision in itself that can be as damaging as excessive speed. Scientists should continue to exert pressure for maximum efficiency and maximum fairness in the licensing of new drugs. TPA is only one case, but PDQ will arise in every case.—DANIEL E. KOSHLAND, JR.

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