FDA Puts New Heart Drug on Hold

A surprise decision by the FDA to withhold approval of TPA, a potent clot-dissolving drug, highlights a scientific debate among cardiologists

"ACTIVASE is coming," Genentech ads in medical journals proclaimed this spring. The California company was touting its version of an extraordinary clot-dissolving drug that some pharmaceutical industry analysts believe will be the first $1-billion product of the biotechnology industry. But Activase will be coming later than Genentech, cardiologists, patients, and Wall Street investors expected.

When Genentech went before an advisory panel of the Food and Drug Administration (FDA) on 29 May, it was obviously confident it would win approval to treat heart-attack victims with Activase, known generically as tissue plasminogen activator, or TPA. But to Genentech's astonishment, the advisory committee voted not to approve the drug and requested more clinical data. The decision, made on a Friday, also shocked the stock market, many FDA officials, and cardiologists too. The following Monday, Genentech stock plummeted by $11.50 to $36.75.

The decision could be a major setback for Genentech in a hotly contested race to bring TPA to market. The company is already embroiled in a legal battle with the Wellcome Company of Great Britain over patent rights to TPA, and more than a half-dozen companies in the United States alone are gearing up to enter the race. Last week, attorneys for Genentech and Wellcome presented their final arguments in the patent trial before the High Court in London. (An article about the patent trial will be published in a subsequent article.) Most observers anticipate that FDA will eventually approve TPA for treatment of heart attacks. But the FDA committee's failure to endorse the use of Activase could now blunt the edge that Genentech is widely acknowledged to hold over its rivals.

TPA is an enzyme naturally present in the body in small amounts. With the aid of recombinant DNA techniques, molecular biologists have cloned and expressed the TPA gene and coaxed mammalian cells to produce the drug in quantity.

The medical and commercial excitement over TPA is not surprising. Indeed, so dramatic is TPA's ability to relieve blockage of coronary arteries that a clinical trial sponsored by the National Heart, Lung, and Blood Institute was halted in 1985 when it became clear that TPA is greatly superior to an alternative drug in breaking up blood clots. The investigators believed that it would have been unethical to withhold the drug from patients in the trial who were not receiving it. A week later, a report appeared that an independent group of researchers in Europe had confirmed the heart institute's findings. So far, more than 4000 heart patients around the world have been tested with Genentech's product. According to Genentech, 750,000 heart patients in the United States alone could benefit from TPA.

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In view of the medical excitement generated by these test results, many cardiologists were startled by the FDA panel's decision. Although the panel based its decision on gaps in Genentech's data gathered so far and said it wanted more information on mortality or heart function, underlying the ruling was a debate over whether dissolving blood clots actually increases a patient's chances of surviving a heart attack. Compounding the surprise over the decision was the fact that at the same meeting, the panel approved wider use of another clot-dissolving drug, streptokinase, that is demonstrably less potent than TPA in lysing clots. But unlike TPA, streptokinase was shown to improve patients' health in other ways.

It was clear almost from the start of the recent FDA meeting on TPA that Genentech was headed for trouble, according to those who were present. Some say that Genentech was the victim of a turf battle between two regulatory units at FDA. But FDA officials defend the advisory panel and say it made a reasonable scientific judgment based on the data presented by Genentech. Most everyone agrees that Genentech hurt itself by giving a confusing presentation of its clinical data.

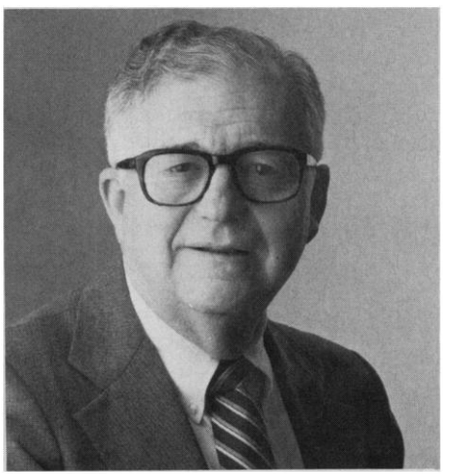
The committee had three principal questions: does TPA actually improve heart function; does TPA improve the chances of survival; and what are the appropriate dosage levels for future patients?

Surprisingly, the cardiology community has debated for years whether blood clots in coronary arteries are a cause of heart attacks, says Eugene Braunwald, chief of medicine at Harvard's Beth Israel and Brigham and Women's hospitals and chairman of the heart institute's TPA study. Heart specialists believed that other possible causes included a buildup of fatty deposits in the arteries, a rupture of a blood vessel near these fatty deposits, an increased demand in oxygen, or a coronary spasm, Braunwald says.

But during the past few years, the use of arteriography to monitor blood vessels soon after the onset of a heart attack and the successes of TPA and other clot-dissolving drugs have converted some leading cardiologists. "Restoring blood flow to the deprived portion of the heart in the early stages of a heart attack is the name of the game," says Braunwald.

But not all cardiologists are persuaded. Members of the FDA advisory committee did not dispute that TPA effectively dissolves blood clots. (Braunwald is not a committee member.) But many were skeptical that clots actually cause heart attacks or that dissolving clots with TPA prevents such attacks because Genentech has not conducted clinical trials to look specifically at these relationships. The main clinical trials so far have examined, with the use of arteriography, only whether TPA clears blockage by clots.

Proponents of TPA speculated that some of the panel members did not understand the scientific issues even though 9 of the 11 members are board-certified cardiologists. They suggest that, because cardiology is highly specialized, an expert in one subspecialty may not be up to speed in another. But Robert Temple, director of FDA's Office of Drug Research and Review, says,



Eugene Braunwald. *Chairman of a major TPA study sponsored by the National Heart, Lung, and Blood Institute backs TPA.*

"My position is that the committee was thoughtful and understood the issues. There is plenty of room for debate."

Temple said in an interview that Braunwald himself, as recently as 1983, wrote in a cardiology textbook he co-authored that it is unclear whether clot lysis helps prevent heart attacks. "That clot lysis is good is an open question," Temple asserts.

Braunwald remarks that his views have changed about the relationship between clot lysis and a reduction in heart attack since his 1983 textbook was published and that FDA should respond to current data. Braunwald says that since writing the textbook, "many papers clearly show that streptokinase when given early will improve ventricular function." Braunwald notes that in the *Textbook on Medicine* published last year, he wrote that clot-dissolving agents reduce the severity of heart attacks.

A transcript of the committee's proceedings indicates that most members were not convinced that TPA improves a patient's health, particularly in light of data presented early in the day on another clot-lysing drug, streptokinase. Those proceedings clearly complicated Genentech's case. Hoechst-Roussel Pharmaceuticals, Inc., and Kabi Vitrum, A.B., of Sweden, sought and won approval from the advisory committee for a new use of streptokinase, which is an enzyme derived from bacteria. Currently approved for injection directly into the heart to dissolve clots, the drug will also be approved for intravenous use if FDA follows the committee's advice.

The committee was particularly impressed with the findings that streptokinase reduces the risk of dying from heart attacks by 20 percent. The findings were based on two studies involving a total of 24,000 patients. Streptokinase manufacturers also suggested that their drug dissolves clots by thinning the blood, although the data were far from conclusive. The panel would later ask Genentech to identify the mechanism by which TPA lysed clots, but the company did not have any data on this point.

So Genentech had a tough act to follow when the committee reconvened after lunch. The company presented clinical data that demonstrated TPA's clot-dissolving power, but, unlike the streptokinase manufacturers, did not have data to show that TPA actually reduces a heart patient's chance of dying. And it could offer only preliminary information from an ongoing study by Johns Hopkins researchers that the drug helps ventricular function. As a result, the committee centered much of its attention on whether TPA's ability to get rid of clots could be used as a basis to predict its impact on survival or on heart function.

Committee member Jeremy Ruskin, who is a cardiologist at Massachusetts General Hospital, remarked that "clot lysis is clearly a desirable goal. [I]t probably is the mechanism by which these drugs are effective. We don't know that. Those data are not available. TPA is very clearly an effective thrombolytic and my gut feeling is it is an exciting drug with a great deal of promise, but with regard to any proven clinical benefit, I think the data are not there. There is suggestive data about [ventricular] function, but there is precious little of it, and the only controlled mortality data that we have show no difference between TPA and placebo. So I am left with a major concern about equating thrombolysis with clinical benefit."

There was also considerable confusion about the right dosage levels. Genentech scientist Eliot Grossbard, who heads the company's clinical trials of TPA, asserted that the appropriate TPA dose is 100 milligrams. But in the course of trying to prove the safety and effectiveness of this dose, he mentioned that some patients had received doses of 150 mg. That particularly bothered committee member Peter Kowey, a cardiologist at the Medical College of Pennsylvania in Philadelphia, who said to Grossbard, "You made a fairly firm statement that the dose ceiling was 100 mg, and yet we are being presented with efficacy trials in which a higher dosage of the drug was used, and I am having a difficult time figuring out how to interpret that. . . . It is getting progressively confusing to follow this [discussion]."

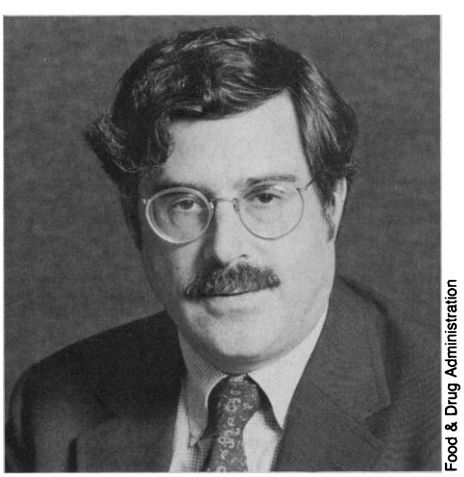
Grossbard also noted that some of the patients were tested with TPA made by a different cell culture method. This raised questions about the comparability of the data. Then there were questions about serious bleeding in the brain in some patients. At the end of the day, eight committee members voted not to recommend approval, one voted for approval, and two abstained.

Braunwald and other cardiologists who have tested TPA argue that the FDA and the committee focused on the wrong questions. Braunwald says that FDA asked the committee to decide whether a study that assesses TPA's ability to dissolve clots "is a surrogate for a mortality study. The answer is no, but that doesn't mean that clot lysis isn't an important endpoint." Bert Sobel, who is chief cardiologist at Washington University Medical Center and is a consultant to Genentech, agrees and says, "The failure to establish a decrease in mortality doesn't mean there is none."

Braunwald, Sobel, and others say that TPA's successes got lost in the discussion. TPA's potency as a clot-dissolver was dramatically demonstrated in the 1985 heart institute study. The 300-patient trial showed that TPA was twice as effective in breaking up clots than streptokinase. The investigators reported in the 4 April 1985 issue of *The New England Journal of Medicine* that the trial had been stopped early because of the "substantial, statistically significant differences" between the two drugs' effectiveness.

Now the institute is sponsoring a clinical trial to test whether a heart patient treated with TPA can benefit even more with the addition of angioplasty, a procedure in which a tiny balloon is inserted into an artery to widen the blood vessel. The study will involve 4000 patients, all of whom will receive 100 mg of TPA. About half the patients have been tested so far; investigators anticipate that it will take another year to begin testing the remaining subjects.

Braunwald, who is deeply disappointed by the FDA committee's decision not to approve TPA, says, "We're past questions



Food & Drug Administration

Robert Temple. *Director of FDA's Office of Drug Research and Review says caution is justified.*

about whether to give TPA to patients. We're asking what do we do after we give TPA."

Eugene Passamani, associate director of the heart institute and director of its TPA trials, and Braunwald each say that a mortality study involving TPA would be difficult to conduct because it would require thousands of patients. In their opinion, the mortality studies involving streptokinase should be sufficient evidence that a clot-lysing drug helps patients. A mortality study comparing TPA against a placebo would now be "unethical," Braunwald adds. European researchers have conducted a study comparing TPA and a placebo and reported no difference in mortality. But Braunwald says that the study, which involved about 120 patients, was far too small to measure a difference.

FDA officials concede that the agency never specifically requested mortality data from Genentech until shortly before the meeting. By then it was clearly too late to generate that kind of data. In fact, in 1984, an advisory panel to the Office of Biologics Research and Review said that mortality studies would be "so experimentally demanding that they would not yield useful data in the near future." Peter Drake, an analyst at Kidder Peabody, says, "FDA changed the rules and the playing field in the eighth inning."

The rules might have been changed because a regulatory turf battle between two branches of FDA broke out, Drake and others assert. But the reasons could stem simply from bureaucratic inefficiency as well. Since 1984, FDA's Office of Biologics Research and Review has informally discussed with Genentech the clinical data that the company should consider providing before it actually submits an application for product approval. This is not an uncommon practice because human studies can take a long time to design and conduct.

About a year ago, Genentech applied for approval from the biologics office. In December, director of the biologics office Elaine Esber asked the Office of Drug Research and Review, headed by Temple, to examine the application, a move which ultimately led to the advisory committee's review of the drug in May. Temple's branch is responsible for the review of synthetic pharmaceuticals, including heart drugs. Shortly afterwards, officials from that branch fired off a long list of questions to Genentech. Then the cardio-renal advisory committee, which reports to Temple's branch, was requested to review the application. When asked why Temple's office was not brought in formally earlier in the process, officials in the biologics branch say that Genentech made its application a year ago, which they consider a short time ago. And they add that informal discussion about the application has been held in the hallway. A former FDA official involved in TPA's review, who criticizes the way FDA handled the Genentech application, said, "Intelligent people can disagree from day one, but not late in the game."

FDA is not bound by the committee's recommendation, but it would be highly unusual if the agency went against it. Data from the current Johns Hopkins trial that is testing TPA's effect on heart function and from the heart institute's ongoing study may be enough to satisfy the agency's concerns. Since the committee meeting, Genentech officials have met once with FDA staff and once with FDA commissioner Frank Young, who has tried to accelerate the approval process for drugs. Analysts are betting that TPA won't be approved for another 6 to 18 months.

Braunwald says, "There are so many interests in TPA, in turf, dollars, and principle. But the most important concern is the patient. What I'd like to see is some meeting of the minds. I'm not saying TPA is the only way to achieve it [clot lysis], but it's a terrific way to do it." ■ MARJORIE SUN

U.S. Policy on Exchanges with the Soviets Called a "Shambles"

"In my view, the process by which decisions are made that affect broad policy, detailed negotiations, and eventual implementation of agreements for scientific and technical exchanges with the Soviet Union is a shambles, marked by indifference, incompetence, and parochialism." That's the opinion of Richard Perle, former assistant secretary of defense and currently resident scholar at the American Enterprise Institute. Perle was the lead-off witness for 2 days of hearings on U.S.–Soviet scientific exchanges, held by the new House subcommittee on international scientific cooperation.

Never one to mince words, Perle accused the State Department's Bureau of Oceans, International Environmental and Scientific Affairs of succumbing to "reckless abandon . . . whenever it encounters a Soviet scientist with a pen in his hand" ready to sign a scientific agreement. Perle, who spent a lot of time when he was in the government arguing against broadening scientific contacts with the Soviets, said that the Soviet Union routinely gains the lion's share of benefits from exchanges, and he expressed astonishment that U.S. government agencies would advocate extending and initiating exchanges with the Soviet Academy of Sciences, "an organization known to be part of the Soviet intelligence establishment."

Two days later, John Negroponte, who heads the State Department's scientific bureau, delivered himself of a measured review of U.S.–Soviet exchanges over the years, ticking off a list of benefits. "It would be short-sighted of us not to recognize that it is in our national interest to seek to expand scientific cooperation with the Soviet Union. We have gained much from this relationship already," he said.

Perle and Negroponte clearly reflected opposite poles of a debate that has been going on within the Administration for the past 6 years. Their appearances provided good theater, but little more, however.

Perle, for example, said "the unhappy fact is that we have no policy, no deliberate sense of gains and losses, no orderly interagency process for evaluating risks and benefits. We have been operating on a chaotic, case-by-case adhockery that reflects the careless indifference with which policy levels in the executive branch have treated the whole subject."

"I simply cannot agree," countered Negroponte, who pointed out that the State Department produces an annual report, called "Science, Technology, and American Diplomacy," which includes a "systematic evaluation" of science and technology agreements.

The hearings were held in part to probe into two recent incidents in which the Defense Department was instrumental in blocking agreements involving the Soviets. These were a decision by the National Security Council (NSC) to instruct the National Science Foundation not to fund a grant to the International Institute for Applied Systems Analysis, an East-West think tank based in Austria, and a second NSC directive to disinvite the Soviets from joining the international Ocean Drilling Program. In both cases, Perle's office had objected, but the reasons have never been spelled out in public.

The hearings shed little new light on the incidents, however. Perle, it seems, had simply won another round in the political battles between Defense and State. ■

COLIN NORMAN