EDITORIAL CORRESPONDENCE:
BIO/TECHNOLOGY, 65 Bleecker St., New York, NY 10012. Telephone: (212) 477-9600. Telex: 668497UW.
BIO/TECHNOLOGY, 4 Little Essex Street, London WC2R 3LF. Telephone: (01) 836 6633. Telex: 262024.

To supplement coverage of Japanese developments, BIO/TECHNOLOGY has an editorial liaison with the editorial staff of Japan Chemical Daily, Ltd. and Japan Chemical Week.

THE FIRST WORD

EVERY SIX MINUTES

At the end of May, the U.S. Food and Drug Administration's advisory committee on cardio-renal medicine issued its recommendations on streptokinase and tissue-type plasminogen activator (t-PA)—clot-dissolving agents for emergency treatment of acute myocardial infarction. The headline on this month's news story sums it up: "Streptokinase, Yes; Genentech's t-PA, No."

No, we don't understand it either. The FDA advisory panel cited the absence of evidence on t-PA's effects on overall patient mortality—in contrast to the streptokinase data, which include a multi-year, multi-center Italian study showing that streptokinase treatment reduced patient mortality by 18 percent. Other information, however, strongly suggests that t-PA is the better drug.

Just this April, F. H. Sheehan, Eugene Braunwald, and their co-authors published "The effect of intravenous thrombolytic therapy on left ventricular function: A report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI phase I) trial" (*Circulation* **75**(4):817–829, 1987). This followed earlier reports (*New England Journal of Medicine*, **312**(14):932–936, 1985) that the TIMI researchers had stopped giving streptokinase in comparative trials because t-PA's overwhelming superiority made it unethical to subject patients to the greater risk.

As the TIMI papers report, quick treatment with t-PA doubled a patient's chances of reperfusion—of regaining blood flow to the heart. About two-thirds of the patients receiving t-PA achieve reperfusion; only about one-third of streptokinase-treated patients enjoy similar results.

The news is not completely rosy, of course. Restored heart function is not synonymous with reperfusion, though the faster the thrombolytic treatment the greater the likelihood regaining some use of the affected areas.

The Italian study, cited by the FDA panel, found that 21-day mortality rates in patients treated with streptokinase were 10.7 percent, compared with 13 percent in the control group—an 18 percent relative reduction (Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI), *The Lancet*, (8478):397–402, 1986). In a much smaller, uncontrolled U.S. study (*Annals of Emergency Medicine* **16**(3):243–247, 1987), D. G. Walsh and co-workers found that immediate t-PA treatment substantially reduced heart clots in 76 percent of their 105 emergency-room patients. The overall 30-day survival rate was 94 percent—a 6 percent mortality rate. That scarcely indicates a grave, lurking danger against which America's heart-attack sufferers must be protected.

Not that either of the fibrinolytic agents is without risks. Treatment can lower the overall levels of plasma fibrinogen and produce hemorrhages. Patients treated with t-PA commonly develop hematomas, and about a quarter need transfusions. In the judgment of those conducting the TIMI trials, t-PA and streptokinase present similar risks to the patient. Indeed, according to Herman Gold (Harvard Medical School), streptokinase is, if anything, riskier than t-PA. Streptokinase is antigenic, pyrogenic, and can, he says, sometimes cause systemic lytic complications. Moreover, new preparations of t-PA promise even fewer side-effects and higher success rates—reperfusion in up to 86% of patients, according to Gold and fellow researchers at Massachusetts General Hospital (H. J. Garabedian, H. K. Gold, et al., *J. Am. Coll. Cardiol*, **9**(3):599–607, 1987).

By the time this note sees print, the FDA—habitually, in its dealings with the biotechnologies, the most enlightened federal agency—may already have overridden the advice of its advisors. If it does, it will undoubtedly be criticized for knuckling under to industry pressure. But there are more pressing reasons for ignoring bad counsel: While we wait for more information, the meter is still ticking. Ischemic heart disease kills about half-a-million Americans each year. Most of these die of acute myocardial infarction. Some back-of-the-envelope extrapolation of the mortality rates in the GISSI and Walsh studies (conducted, admittedly, on very different numbers of patients in very different areas) shows that we pay a grim price for delay: In the U.S. alone, every three to six minutes, death claims one more heart-attack victim that t-PA might have saved.

—Douglas McCormick