The Coming Competition Among Clot-Busting Drugs

The advent of TPA and other thrombolytic drugs is transforming care of heart attack victims and sparking competition among pharmaceutical companies

FOR THE PAST YEAR, Genentech's TPA has been heralded as the wonder drug for heart attack victims because of its extraordinary ability to dissolve blood clots. It made pharmaceutical history by racking up $93 million in sales at $2200 a treatment in the first 4 months after hitting the market in November.

But TPA's preeminence may be seriously challenged in the next few years by two new clot-busting therapies produced by other companies. This spring, researchers have presented findings showing that streptokinase and a third drug, known as APSAC, are also very effective in heart attack treatment. Streptokinase is of particular interest because, at $200 a treatment, it is less than one-tenth the price of Genentech's TPA, whose brand name is Activase.

The new findings have excited cardiologists, given Genentech investors the jitters, and caused insurers to think twice about covering the added expense of TPA. They have also prompted a debate among clinicians over which is the best and most cost-effective treatment to use. At present, however, the clinical data cannot provide a clear answer because the drugs have not been tested against one another.

One clear conclusion from the data, however, is that all three thrombolytic drugs represent a major advance in the clinical care of heart attack victims. "The good news is that thrombolytics, when given early enough, help people a lot," says Eugene Braunwald, chief of medicine at Harvard's Beth Israel and Brigham and Women's hospitals, in an interview in his Boston office.

This year, about 1.5 million Americans will suffer heart attacks, according to the American Heart Association. Roughly a quarter of them will die immediately and another quarter are unaware that they have had an attack. Of the remaining half, thrombolytics may eventually be able to cut the mortality rate in half if victims can be treated within a few hours of onset, Braunwald and other heart experts predict. The drugs are all easily administered intravenously, which should facilitate rapid and broad adoption by physicians. Thrombolytics are quickly becoming standard therapy, Braunwald says.

Not since the 1960s, when coronary care units were introduced has a single technology improved a heart attack victim's chances of survival so dramatically as thrombolytics, according to Braunwald and other experts.

In the past, when a person suffered a heart attack, physicians sought to relieve chest pain and minimize the risk of other problems, such as congestive heart failure and arrhythmia. But they could not actually interrupt the process of most heart attacks. Braunwald says that coronary bypass operations and angioplasty, in which a small balloon is inserted into an artery to open up the blood vessel, are performed primarily to relieve chronic chest pain, "but there is no evidence that these procedures have dropped mortality from heart attacks."

Eugene Braunwald. *"I maintain that TPA is at this time the agent of choice but I don't think this is the last word."*

In contrast, thrombolytics represent a remarkable transformation in treatment in which "we are improving survival and really doing something for patients," says Salim Yusuf, scientific project officer at the heart institute. Says Eugene Passamani, director of the division of heart and vascular diseases at the National Heart, Lung, and Blood Institute, "Thrombolytics have been the Holy Grail among cardiologists."

Most heart researchers agree that TPA, which stands for tissue plasminogen activator, is superior to streptokinase at dissolving clots. But Yusuf and others say that a better test of a thrombolytic's true effectiveness is whether the drug can reduce the risk of dying and to what extent. Superiority in clot-busting power might not necessarily equate with superiority in reducing mortality because a thrombolytic that acts by a different mechanism may have important peripheral effects that also reduce a patient's chances of dying, Yusuf and others explain. TPA, streptokinase, and APSAC, which is a modified streptokinase, each dissolve clots by different biochemical mechanisms.

"Dissolving clots is important, but to say no other mechanism is important might be shortsighted," Yusuf remarks.

What has caused all the excitement in the past few months is that mortality studies testing streptokinase in combination with ordinary aspirin and APSAC have indicated that the drugs can substantially reduce the risk of dying among heart attack victims. The streptokinase results are considered especially reliable because the studies are large.

But no large mortality study has yet been completed for TPA. Cardiologists do not doubt that TPA will reduce mortality, but they do question whether it is actually better than streptokinase and APSAC in lowering the risk of dying.

A large mortality study of TPA is currently under way at the University of Nottingham, but the results are not expected to be presented until late summer, says Genentech spokeswoman Debra Bannister. And they will not be published before fall, she adds.

Streptokinase, an enzyme extracted from bacteria, has been marketed for several years to dissolve clots related to heart attacks, but it has never been a popular heart therapy because the standard way of administering the drug was by catheter directly into the clot. Only about a fifth of the hospitals in the United States are equipped with catheterization labs, says Sol Sherry, dean of the medical school at Temple University and a pioneer in thrombolytic therapy.

In the past 2 years, however, researchers have switched to intravenous delivery of streptokinase with striking results. Italian researchers reported last year that the drug saved a significant number of lives when it was administered early to heart attack patients.* It was this study that prompted a Food and Drug Administration advisory committee a year ago to urge the agency to grant approval to Kabi Vitrum and Hoechst-Roussel to market the drug for intravenous use. In a highly controversial

*The findings were later published in the 17 October 1987 issue of *Lancet*.

decision at the same meeting, the committee voted not to recommend TPA for approval in part because Genentech lacked mortality data, but the two drugs were subsequently approved by the agency within a few weeks of each other last fall.

But the talk of the cardiology community now is another mortality study of streptokinase that went beyond the Italian clinical trial by testing streptokinase in combination with aspirin. The massive study, rich in unexpected and promising results, evaluated 17,000 randomized heart attack patients treated in 400 hospitals located in more than a dozen Western countries, including the United States. The lead investigators were Oxford University scientists Rory Collins, Peter Sleight, and Richard Peto, who presented the findings in March at a meeting in Atlanta of the American College of Cardiology and submitted them for publication.

The study showed that when streptokinase was given intravenously within 4 hours of a heart attack, the mortality rate dropped 37% compared to the placebo group, confirming the Italian study's results.

But the scientists also discovered that a drug regimen with streptokinase and aspirin had an additive effect of dropping the mortality rate 50% compared to the placebo group when they were administered within 4 hours of a heart attack. "Streptokinase dissolves the clots and aspirin prevents the clots from forming," Collins said in a telephone interview from Oxford.

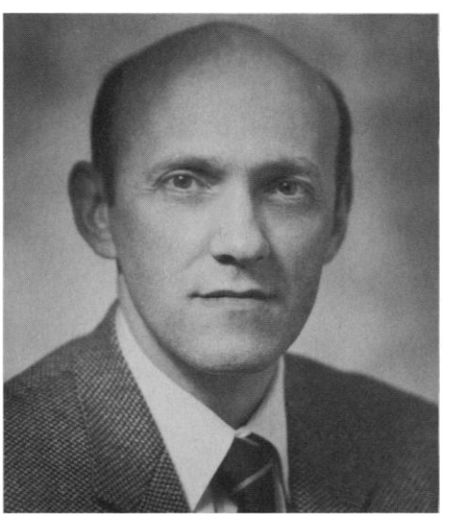
In addition, the study findings suggested that streptokinase with or without aspirin reduced mortality even when treatment was started 6 to 24 hours after a heart attack occurred, a benefit that has not been clearly shown in previous studies. The finding, if confirmed by additional research, would be important since many patients are not treated until several hours after a heart attack.

The study also showed that aspirin alone, given immediately after a heart attack for 5 weeks, reduced mortality by 21%, lowered the incidence of a second heart attack by blocking platelet aggregation, and cut the incidence of stroke by 30%, Collins said. Patients received half of a standard 325-milligram tablet for 5 weeks.

Heart attack patients are already commonly advised to take aspirin as part of long-term follow-up therapy, but the drug previously has not been administered so early—almost immediately after a heart attack occurs. Collins notes, "Aspirin is a very simple, cheap treatment" that in and of itself could save tens of thousands of lives every year. Yusuf, who was an adviser to the study, says that aspirin may do what angioplasty is supposed to: prevent reocclusion. But "aspirin is certainly more cost-effective than angioplasty," he notes.

Braunwald remarks that the Oxford study "is important for its size. It shows that the ability to reduce mortality exists in a wide variety of institutions. You don't have to be a specially equipped facility [to reduce fatal heart attacks]. And because of this study's findings, aspirin administration will probably become routine."

The third thrombolytic, APSAC, might eventually prove to be a strong competitor of TPA and streptokinase. APSAC alone lowered the number of fatal heart attacks by 48% in a 1000-patient study, British researchers reported in the 12 March issue of *Lancet*. The drug is manufactured by Beecham Inc. under the brand name Eminase. It is still experimental in most countries and is not expected to be approved for use in the United States for another 1 to 2 years. The study was led by D. A. Chamberlain of the Royal Sussex County Hospital. In other studies, APSAC demonstrated prolonged clot-dissolving power, showed it could prevent arteries from becoming blocked again, and lowered patients' blood pressure, according to a Beecham official.



Eugene Passamani. *"Thrombolytics have been the Holy Grail among cardiologists."*

APSAC is administered much more quickly than TPA. It is delivered intravenously in less than 5 minutes whereas TPA is given over 3 hours. Yusuf and others regard the ability to deliver the drug fast as a significant advantage over TPA. Jeffrey Anderson of the University of Utah, who was an investigator in the APSAC study, points out that a heart attack victim has many clinical complications. "With APSAC, you don't have to worry about an i.v. drip. You just give it in 2 minutes and then you can deal with the other things," Anderson says.

But Eliot Grossbard of Genentech, the company's lead TPA researcher, says that, with APSAC, a clinician might lose control of treatment. For example, he says, if a patient begins to bleed too much from thrombolytic therapy, a risk that is common to all clot-dissolving drugs, or if the patient has been diagnosed improperly (a peptic ulcer, for example, can mimic some of the symptoms of a heart attack), a doctor can stop the administration of TPA, but not APSAC. He acknowledges, however, that such circumstances would be "unusual."

Grossbard and Braunwald point to a 700-patient study conducted in Europe as an indication that TPA, given with aspirin and heparin, an anticoagulant, dropped mortality by 40%. A Genentech brochure reporting the company's first quarter earnings goes even farther in characterizing the importance of the study, asserting it "showed that the Activase treatment resulted in the lowest inhospital mortality rate for heart attacks ever reported in a large clinical study."

But experts, including Yusuf and Collins, say that the study, which was originally designed to evaluate TPA's effect on heart function, not mortality, was too small to provide a reliable estimate of the degree of benefit. "To claim that the study tells you the size of the reduction is statistically naïve," Collins says.

Yusuf says, "In theory, Genentech is right that lysis should make a difference in mortality, but the data don't support [the contention]. In theory, although there is no proof yet, peripheral effects may matter in a beneficial way."

In spite of the growing wealth of clinical data, there is as yet no firm basis on which to compare the effectiveness of the three thrombolytic drugs in reducing mortality because the studies completed of APSAC and TPA were too small and patient populations were different, says Peto of Oxford and others. But future studies will compare the drugs directly against each other. The Italian researchers who conducted the streptokinase study last year recently began a study comparing streptokinase and TPA in a mortality study and plan to test at least 10,000 patients. Collins and colleagues hope to evaluate all three drugs in a clinical trial starting this fall that will involve 30,000 patients. But on 20 May, Beecham decided not to participate in the study as yet. Braunwald says, "It would be highly desirable for Beecham to reconsider. The situation is confusing enough that when people want to do a comparison, it ought to be encouraged."

If these trials produce a clear winner, the results could have a major impact on the thrombolytic market. Last year, analysts predicted that TPA would be the first billion-dollar drug of the biotechnology industry.

But in view of the Oxford findings on streptokinase, physicians and health insurers are already adopting a cautious attitude about TPA because of its expense. The reason for the vast price difference between streptokinase and TPA is that the patent on streptokinase expired decades ago. Meanwhile, Genentech is trying to recoup the $220 million it invested to develop TPA and make a profit, too, Bannister says.

Analysts say that the results have put Genentech on the defensive, pressuring it to drop TPA's price. As yet, however, the company is holding the line on the charge

Last month, it was widely reported that Medicare officials had decided not to cover the expense of TPA at all. In fact, the agency said that the cost of TPA can be reimbursed under current limits of reimbursement for overall heart attack treatment, but decided that it would not make a special adjustment to cover TPA's high price alone, says William Winkenwerder, of the Health Care Financing Administration.

Winkenwerder points out that the net costs of treating a heart attack patient might be the same or less if, for example, TPA cuts the length of a patient's hospital stay. But it is too soon to tell, he says. A study by University of Michigan researchers suggests that TPA does lower medical costs by shortening patients' hospital stays, but the researchers themselves say that the findings are only preliminary.

The recent Oxford findings on streptokinase and press reports that Medicare had decided not to cover TPA have made Genentech investors skittish. The company's stock prices have been dropping this spring, starting from a high of about $44 at the beginning of the year, falling to around $35 in April and closed at about $26 in late May. "A whole lot of things have put pressure on the stock," says Linda Miller, an analyst with PaineWebber. "Today people can't tolerate uncertainty."

Meanwhile, Bannister says that TPA sales have not changed and that the drug is outselling streptokinase about 2 to 1. Nevertheless, stock analysts have been lowering their projections of earnings per share for 1988. M. Kathleen Behrens of Robertson, Colman & Stephens says that company officials themselves "are more cautious in its outlook."

Braunwald says, "I maintain that TPA is at this time the agent of choice but I don't think this is the last word. We'll see different thrombolytics. We're likely to end up with a cocktail of a thrombolytic and an anti-platelet–like aspirin or others. Now we're off to the races in that there are many thrombolytics. The next few years will be as exciting as the past few." ■ **MARJORIE SUN**

A Prod to Productivity

For more than a decade, economists and policy-makers have been concerned about the sluggish growth in economic productivity in the United States. The problem affects perhaps two-thirds of the nation's industries and if not reversed will pave the way for the country to become a second-rate economic power. Understanding the problem and finding a cure has been difficult. Hundreds of industries are involved and productivity is affected by their interdependencies as well by swings in foreign exchange rates, and other economic factors.

Many economists, however, have long postulated that underinvestment by industry in research and in manufacturing processes is a key cause. This view is supported by two economists at the Brookings Institution, Martin Neil Baily and Alok K. Chakrabarti, who have attempted to analyze this long-standing problem in *Innovation and the Productivity Crisis*. They conclude that federal support for applied R&D as well as for basic research must rise and federal tax credits should be continued.

Growth in productivity in the United States has been depressed to an extent by stiffer health and safety regulations and inflation. But the authors argue that to a large degree low productivity has resulted from slow innovation, missed opportunities, and poorly invested capital. For now, the country's competitive posture in overseas markets is improving, the economists note, because of declining currency values. But this reprieve, they say, will prove short-lived without improvements in productivity because foreign competitors are winning the efficiency race on many fronts.

The behavior of the business sector must change, the authors assert, if productivity is to grow at a faster pace. To do this, Baily and Chakrabarti contend that a climate must be created for expanding private investment in applied research to produce new technology. Federal assistance is needed, they say, to give industry sufficient incentive to conduct applied research that otherwise would not be done because the economic return is not readily apparent or sufficient for a private company to undertake alone.

The failure to realize substantial productivity gains involves not just industry, but extends to the white-collar service sector. While the United States has had steady productivity improvements in the manufacturing of computers, the computerization of the American workplace has not yielded similar results, the authors say. There may be multiple explanations for this "productivity paradox": difficulty in measuring gains; a delayed response related to learning how to utilize the equipment efficiently; or findings that staffing cannot be reduced because equipment is not readily substitutable for labor in the information sector.

A fundamental weakness affecting much of American industry, according to Baily and Chakrabarti, is the failure to diffuse new knowledge quickly and to refine existing technology. The slowdown in productivity in the United States, they say, occurred because we "failed to incorporate new technology effectively into production. . . . " The blame must be shared by the technical community for failing to make their innovations widely known and by industry executives who chose not to employ available technology that would have raised productivity.

In the machine tool industry, for example, innovation slowed between 1970 and 1977—long enough to allow foreign competitors to close the technology gap. As a result, Japanese, German, and Italian firms were able to take market share from the U.S. manufacturers in overseas and domestic markets

Although a collapse in demand for machine tools and an overvalued dollar had adverse effects on the U.S. machine tool manufacturers, the authors say, "exports could have been sustained more effectively if [they] had retained their technological edge." The U.S. textile industry, Baily and Chakrabarti note, was able to remain competitive because it retooled and it also closed inefficient plants.

Industry must increase its spending on research and utilize its capital more wisely. Costly marketing campaigns often yield only transitory results in what are finite markets. Companies might have been better off, the authors suggest, to have funded more research to enable them to produce superior products at lower costs.

Even with reforms, Baily and Chakrabarti emphasize that additional federal support for R&D will be required to increase productivity. This research, the economists say, should be conducted by private companies that provide more than 50% in matching funds. Unless the nation makes a greater effort to improve productivity, they say, America's standard of living will continue to erode. ■ **MARK CRAWFORD**