spasm on its own, but Schroeder has devised a test that can pick up the problem more readily. It requires the administration of a drug called ergonovine maleate, a known vasoconstrictor, to patients who are undergoing coronary angiography. This drug induces spasms in coronary arteries that are susceptible to them. Although the test sounds dangerous, Schroeder says that the spasms are easily relieved by nitroglycerin and that coronary angiography with ergonovine maleate administration is no more dangerous than the angiography without it. He concludes that it is a safe test for coronary spasms in patients whose symptoms cannot be explained by atherosclerotic blockage of their coronary arteries.

The calcium antagonists may be useful for treating other heart problems in addition to coronary artery spasms. Researchers, including Robert Jennings of the Duke University Medical School, have shown that one of the earliest changes produced during ischemic damage of the heart is accumulation of calcium ions by the cells of the affected region. This has prompted suggestions that the calcium antagonists may be valuable for limiting the damage caused by a heart attack. Henry and his colleagues have shown that nifedipine prevents calcium accumulation in isolated rabbit hearts subjected to oxygen deprivation and also prevents the rigid contraction that usually occurs in such oxygen-deprived hearts.

Rigid contraction is one of the hallmarks of a condition called stone heart that sometimes occurs in patients who have been put on a heart-lung machine for cardiac surgery. The surgeon occasionally finds that the heart, which is in this state as a result of oxygen deprivation, does not beat properly, if it beats at all, when it is reconnected to the body's circulatory system. Henry has shown that nifedipine prevents this form of heart failure in dogs put on cardiopulmonary bypass for 2 hours—enough time to kill the control dogs who were not treated with the drug. The Washington University group is now testing the drug for prevention of stone heart in human patients.

Another way in which the calcium antagonists may help to limit damage to heart muscle is by dilating, and thus increasing the flow of blood through whatever vessels remain open after a heart attack. Schwartz, with Ronald Millard, who is also at Cincinnati, showed that diltiazem has this effect on both pigs and dogs in which they induced artificial heart attacks. Henry found a similar effect of nifedipine in dogs.

Currently, then, the calcium antagonists are being tested as therapies for coronary artery spasms, cardiac arrhythmias, stone heart, and heart attacks. If they continue to work out, cardiologists will have a potent new weapon for combating a wide range of coronary problems.—JEAN L. MARX

FDA Says No to Anturane

Controversial study of Anturane fails to show that the drug prevents "sudden death," FDA says

Each year, 1 million people suffer heart attacks and of them 400,000 survive. But the survivors are still at a high risk of dying—one out of eight will succumb within the year, many from "sudden death," a somewhat poorly defined term meant to connote a death caused by abnormal heart rhythms.

Since sudden deaths in the first year after a heart attack are such a formidable public health problem, the medical community was elated by reports that Anturane, a drug widely used for the treatment of gout, might prevent them. The evidence was from a clinical trial funded and designed by Ciba-Geigy (which makes Anturane) but conducted by independent members of the medical community.

In January, the final report from the trial was released. Anturane, it said, reduced the sudden death rate by 74 percent from the second through the seventh month following a heart attack. The total mortality rate was also reduced, but by an amount just short of statistical significance. Interest in the report was great and it received much favorable publicity.

On the basis of the reports from the Anturane study, an advisory committee to the Food and Drug Administration (FDA) recommended that the agency approve Anturane for the prevention of sudden death. But on 25 April, the FDA said no on the grounds that the case for Anturane is not persuasive.

Ciba-Geigy disagrees with the FDA and in a prepared statement says it "is confident that in cooperation with the FDA the differences will be resolved and Anturane will be found to be useful in preventing sudden death following a heart attack."

Ironically, the Anturane trial was never expected to show that the drug prevents sudden death, and there are no good explanations for how it may do so. The working hypothesis was that the drug might prevent heart attacks in patients who had already survived one. A heart attack is caused by an obstruction in a coronary artery that, by preventing the heart from getting an adequate supply of blood, actually causes the death of a portion of heart muscle. Usually it is accompanied by chest pains and characteristic electrocardiogram tracings. One of the possible causes of a heart attack is the formation of blood clots in the coronary arteries. Anturane inhibits blood clot formation by stopping platelets from clumping. So, the theory went, Anturane might prevent heart attacks.

While Ciba-Geigy was testing Anturane, the National Heart, Lung, and Blood Institute (NHLBI) was also testing the hypothesis that drugs that inhibit clotting could prevent subsequent heart attacks in patients who already had survived one. The heart institute's trial compared aspirin (well known for its effects on platelets) and a placebo. The NHLBI trial showed no effect of aspirin in decreasing the mortality rate of heart attack victims, but most of the study participants began taking aspirin at least 6 months after their heart attacks. It remains possible that the drug might be effective if given earlier.

The Anturane study and the NHLBI study were concluded at about the same time and the Anturane results were released just before those of the NHLBI. But despite the apparently dramatic decrease in the sudden death rate among Anturane users, there was some feeling

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in the research community that the Anturane results were questionable. This feeling, which was a result of a long-standing controversy about the design and analysis of the Anturane trial, surfaced at a workshop held just after the results of the two trials were reported.

The controversy was over the possible introduction of bias into the study by the exclusion of certain patients from the analysis. For example, patients who, for whatever reason, had failed to take their assigned therapy for a period of 7 days were excluded and their deaths referred to as "nonanalyzable."

Paul Meier, a statistician at the University of Chicago, is among those who object to the idea of nonanalyzable deaths. "I find that an outrageous term for perfectly analyzable deaths," he says. "If someone is not taking a drug when he dies, his death may be related to the side effects of the drug and the side effects may have caused him to stop taking the drug." The idea of nonanalyzable deaths, Meier says, "is an innovation in the analysis of clinical trials that we can do without." Most other trials, and all NHLBI trials, do not exclude patients who fail to comply with their assigned treatment.

Another source of controversy is the exclusion of patients from the Anturane study because they were subsequently found to be ineligible. These patients were sometimes excluded months after the trial began—some were excluded only after they had died. William Friedewald of the NHLBI explains that if the criteria for eligibility were absolutely clear such exclusions would not be too controversial. But eligibility often involves medical judgments: Did the patient really have congestive heart failure, a condition that would make him ineligible for the trial? Did he have cancer or some other serious disease before randomization? In addition, Meier explains that even if the same number of patients were excluded from each group, the study would end up with smaller groups than anticipated. The differences in the proportion of deaths between the groups could thus be magnified. And, in fact, Meier says, in this case the differences were magnified.

Sol Sherry of Temple University, who is chairman of the Anturane study's policy committee, explains that the study was designed to avoid diluting the results with data on patients who did not take the drug or who were not really eligible for the study. Since neither the investigators nor the patients knew who was taking the drug and who was taking a placebo, there should have been no bias introduced when patients were dropped. Sherry says that if the Anturane investigators had run the trial "as conservative biometricians would have wanted us to," they would have had inconclusive results. In that event they might have retrospectively eliminated from the analysis ineligible patients and those who did not comply with therapy. In the end, they would have had a positive result. But a retrospective analysis, Sherry remarks, "is a lot less convincing than a prospective one."

The purely scientific arguments over how the trial should have been designed and analyzed have been muddied by charges that the NHLBI really did not want to see the Anturane trial succeed. There is no evidence that this is so, but at least two eminent investigators have suggested it. Sherry indicated at a workshop in February that he thinks the NHLBI and Ciba-Geigy are in competition. Other participants felt that the implication of Sherry's charge is that the NHLBI, whose trial showed no evidence that aspirin prevents heart attacks, was then anxious to discredit the seemingly positive Ciba-Geigy results and to poison the air for a favorable recommendation by the FDA. Sherry says, "You can draw your own conclusions."

Similar insinuations were made by Eugene Braunwald of Peter Bent Brigham Hospital, chairman of an NHLBI panel convened in September 1978 to review the preliminary results of the Anturane study, which had just been released. The review was to enable NHLBI to decide whether it should stop its aspirin study or make any statement to the medical community about the usefulness of Anturane. Lawrence Friedman of the NHLBI sent Braunwald a draft he had written of the panel's conclusion in which he said the panel questioned the exclusions of patients from the analysis of the Anturane study. Braunwald wrote back to Friedman expressing concern that the draft was too negative, saying that the patient exclusions were appropriate and writing, "the report emanates from the staff of the clinical trials branch [of the NHLBI] and seems to support the position held by the clinical trials branch before the review." Braunwald sent copies of his letter to a number of members of the medical community.

Friedman says that after receiving Braunwald's letter he elicited comments from the rest of the panel, wrote a final summary, which was not different in substance from the original but was slightly less negative in tone, and had the final version approved by all the panel members, including Braunwald. The panel's recommendation was that the heart institute should take no action until the final report of the Anturane study was published.

Friedman denies that the clinical trials branch was biased against the Anturane study, saying it selected its panel, including Braunwald, who was strongly in favor of the study, on the basis of their expertise in the field of cardiovascular diseases and platelet-active drugs.

The controversy was over the possible introduction of bias into the study by the exclusion of certain patients from the analysis.

The final report of the Anturane study appeared in the *New England Journal of Medicine* on 31 January of this year. It said that Anturane reduced the sudden death rate in heart attack patients by 74 percent from the second through the seventh month after their attacks. The report was accompanied by an editorial, written by Braunwald, calling the study's conclusions one of four major advances made in the past 10 years in the treatment of heart attack patients. The report, as would be expected, was picked up by the popular press and stories about the Anturane study appeared on the front pages of the *New York Times*, the Washington *Post*, and other newspapers.

Yet because of the controversy over the study's design and analysis, many members of the medical community had serious reservations about the report and were upset by the publicity and by the charges that the study's critics did not want to see the study succeed. One prominent epidemiologist says the *New England Journal* report of the study "was orchestrated [by Ciba-Geigy] for presentation in the scientific and public arena so as to create an impression that there was an unequivocable, clear-cut, dramatic result. What happened was almost a con job." Meier says, "It was an

interesting but not a convincingly positive result. It was made into a breakthrough by PR."

The aspects of the Anturane study that most disturbed critics like Meier were also those that disturbed the FDA and that led Robert Temple, head of the FDA's cardiorenal division, to audit the study. But the objections about the study's design only concerned the question of whether Anturane reduced the total death rate. This, of course, is "the key endpoint," says Jeremiah Stamler of Northwestern University. But most of the fuss was over sudden death, and the question of whether it reduces the mortality from sudden death turned out to hinge on the definition of sudden death, Temple explains.

Technically, a sudden death can be documented only by electrocardiogram tracings indicating abnormal heart rhythms. But most people who die suddenly are not hooked up to heart monitors, and rapidly occurring deaths are frequently referred to as sudden deaths, even though they may be caused by heart attacks, not arrhythmias. The designers of the Anturane study chose to define sudden deaths as those that occurred within 60 minutes after the onset of symptoms or those that were unobserved, unless a postmortem examination showed such evidence of a "recent" heart attack as newly damaged heart tissue. A heart attack, in contrast, was defined by characteristic changes in electrocardiograms and characteristic chest pains. Any death that did not fit either of these categories was to be defined as "other."

This distinction between sudden death and heart attack is weak, according to Temple, who says he fails to see the point of the classification. For example, many recent heart attacks do not show up on autopsies, he says, and the requirement that a heart attack be documented by an electrocardiogram means that the patient must get to a hospital before his death for it to be counted as a heart attack.

The classification of deaths also leaves a certain ambiguity, says Temple. Take a person who has chest pains for 3 hours but who dies before the ambulance arrives. Is that a sudden death or a heart attack or neither? Many cases like that were called sudden death, according to Temple, although, he remarks, "it's not clear why."

Temple audited about 50 percent of all deaths in the study. "It became apparent that a large fraction of the deaths should have been classified in other ways," he says. For example, there were patients who, on autopsy, were reported as having had recent occlusions of their coronary arteries or recent extensions of the dead area of heart tissue that resulted from their previous heart attack. Yet despite such evidence of heart attacks, these patients were said to have died of sudden death. By the time Temple finished reclassifying half of the deaths, he found that the highly significant difference favoring Anturane (26 sudden deaths in the placebo group in the first few months after their heart attacks compared to 6 in the Anturane group) was wiped out.

It is Temple's opinion that the designers of the study were unintentionally caught up by their ambiguous classification of deaths.

It is Temple's opinion that the designers of the study were unintentionally caught up by their ambiguous classification of deaths. No one anticipated before the trial began that sudden deaths would be important. That was discovered afterward in a post hoc analysis, or data dredging. The definition of sudden death, says Temple, "wasn't very well thought out. It turned out to be more crucial than anyone would have anticipated." The Anturane researchers could not have been biased by expectations that Anturane would prevent sudden death, however, because the study was double-blind. The physicians reporting causes of death did not know who was taking Anturane and who was taking placebo.

Fraser Mustard of McMaster University in Ontario, who is a member of the Anturane study's policy committee, says he is concerned that Temple could have been biased in his report since he knew which patients took Anturane and which took placebos. Temple responds by saying he has submitted a detailed report to Ciba-Geigy. The company can see for itself that its own definition of sudden death was not adhered to.

The second question Temple considered is whether Anturane affects the overall mortality of the heart attack victims. The patients given Anturane did seem to live longer, but the difference was just short of the commonly accepted definition of statistical significance. The survival data Ciba reported would have made for a tough regulatory decision, Temple says. But patients were excluded from the analysis who, the FDA thought, should have been included. Once those patients were put back in, it no longer looked as though Anturane saved lives.

Despite all the furor over the non-analyzable deaths, the results were not affected when patients excluded for this reason were put back in the study. What did make a difference were the patients excluded because they were later found to be ineligible.

Although the eligibility criteria were set up before the study began, there was no stated plan to drop patients after randomization. Temple says he was especially disturbed by those ruled ineligible and dropped only after they had died. "If you plan to do this, you must state it and defend it in your analysis," Temple explains. "Everyone in this business knows [such exclusions of dead patients] just are not done."

Despite the FDA's audit of the Anturane study, the debate over the results is by no means over. Sherry has not wavered in his support of the study, saying, "My opinion is that this trial was very well designed, very well run, and showed a marked benefit for patients taking Anturane rather than placebo." Mustard says, "I don't think the FDA's case is established yet." Braunwald says, "If the data are in dispute I can't feel the same about them but I don't know that they are in dispute."

Temple views the problems with the Anturane study as an example of what may be expected in other large-scale studies where post hoc analyses may show therapeutic effects in small subgroups. He believes it is very easy for these subgroups, such as the sudden death group, to be poorly defined. The Anturane study shows "why you must be rigorous in your definitions beforehand," he says.

At this point, Temple thinks the FDA has proved its case. He has contacted the members of the advisory panel that recommended approval of Anturane for heart attack victims, and all said that, in light of Temple's audit, they would not recommend this use of the drug. Now it is up to Ciba-Geigy to decide if it wants to try to persuade the FDA to reevaluate its decision.—GINA BARI KOLATA