"the source is anybody's guess." He thinks it is slightly more probable that the source is in our galaxy than in the Large Magellanic Cloud. "Although I hope it is in N49, because then the energetics is so boggling that we have something really exciting to worry about."

While astronomers have found a source for the extraordinary 5 March event, no candidates have been found for any of the 100 more "normal" bursts. Typical bursts are less than 1 percent as bright as the March burst, and shine erratically for several seconds instead of flashing nearly instantaneously. Only one typical burst has been located as precisely as the March event. From its spectrum, Ramaty surmises that its source is well within our galaxy—probably closer than 200 light-years to the earth. Yet nothing can be seen in the direction of that burst, according to Fishman. Einstein's x-ray telescope is scheduled to look at the area this spring.

With no visible source for one well-located burst and the other seemingly associated with an object in another galaxy, astronomers still have more questions than answers. Many experts now suspect that there might be two types of bursts—normal ones from sources within our galaxy, and extraordinarily rare, energetic, impulsive ones from supernova remnants or something else. All in all, gamma-ray bursts are not likely to be understood until more are located and improved spectra are obtained. While more locations should be determined soon with data from the present network of satellites, no better spectra will be forthcoming until the middle 1980's, when the problem-plagued Space Shuttle is scheduled to launch the newly proposed Gamma-Ray Observatory.

—BEVERLY KARPLUS HARTLINE

AMIS Negative on Aspirin and Heart Attacks

A large clinical trial shows that aspirin does not prevent cardiac deaths in patients who have already had a heart attack. But questions remain.

In 1975, the National Heart, Lung, and Blood Institute (NHLBI) began recruiting participants for a 3-year clinical trial to determine whether aspirin can prevent heart attacks. The results* are finally in. The answer, it seems, is that aspirin does not prevent additional heart attacks in men and women who have already had at least one. Moreover, trial participants who took aspirin experienced significantly more side effects, including bleeding from the stomach and intestines, ulcerlike pains, and stomach inflammation, than those on the placebo. "On the basis of these findings," says Robert I. Levy, director of the NHLBI, "the National Heart, Lung, and Blood Institute would advise physicians not to give aspirin on a sustained basis to heart attack patients as a means of preventing another myocardial infarction [heart attack]."

The trial in question, called the Aspirin Myocardial Infarction Study (AMIS), was the outgrowth of earlier studies that had suggested that aspirin might be of some benefit as a prophylactic against heart attacks. The results were not conclusive, however, and other studies had given negative results.

The possibility that an inexpensive, widely available drug, such as aspirin, might reduce the toll from the nation's number one killer was very appealing. The NHLBI thus decided to undertake, at a total cost of $17 million, a controlled clinical trial in the hope of settling the issue once and for all. That hope has not been realized, however, despite the apparently unequivocal nature of the AMIS results. Information from some other recent studies has raised questions about the AMIS design, leaving open the possibility that aspirin may still prove to be of benefit to heart patients.

The AMIS trial is the largest test of aspirin as a heart attack preventive ever done. It included 4021 men and 503 women, who were followed for 3 years. During this time the aspirin group took 1 gram of the drug per day (about the amount in three standard aspirin tablets) and the controls received placebos. Both groups were instructed not to take any aspirin on their own and were given a substitute pain-killer (acetaminophen) for minor aches or pains. Compliance with the drug regimens, which was carefully monitored, was good.

According to the AMIS results, aspirin did not reduce mortality in heart attack patients. In fact, the total mortality in the aspirin group (10.8 percent) was somewhat higher than that in the control group (9.7 percent), with 8.7 percent of the aspirin group and 8.0 percent of the controls dying from heart attacks and related heart disease.

There were fewer nonfatal heart attacks in the patients receiving aspirin than in the controls. This decrease is difficult to reconcile with the slight increase in fatal heart attacks in the aspirin group. One possible explanation suggested in the AMIS report is that people who suffer a heart attack while taking aspirin are, for some unknown reason, more likely to die than those who are not taking the drug. Whatever the explanation, the mortality findings, together with the high incidence of gastrointestinal problems in the aspirin group, would militate against routine use of the drug for prevention of heart attacks.

"We were disappointed by the results," says Levy. "We thought we had a potential winner." The initial optimism came about both because of the encouraging results of the earlier clinical trials and because aspirin has long been recognized as an inhibitor of the clumping of the small blood cells called platelets. Platelet clumping is a necessary step in the formation of blood clots. Because researchers think that the abnormal formation of clots in the arteries carrying blood to the heart muscle is one of the causes of heart attacks, the possibility that aspirin, by inhibiting clot formation, might prevent heart attacks was the rationale for testing the drug in heart patients in the first place.

On the bright side, the AMIS results did indicate that patients taking aspirin suffered fewer strokes and transient ischemic attacks (brief dizzy spells caused by reduced blood flow to the brain) than the controls. The difference was not quite statistically significant but did tend to confirm the results of two earlier studies. Why aspirin would work in the brain but not the heart is unclear.

Even though the AMIS results would seem to lay to rest the idea that aspirin might decrease mortality from heart attacks, enough questions have been raised about the design of the trial to sug-

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gest that this is not the case. For one, critics have suggested that the dose of aspirin used was too high.

After the AMIS was already under way, investigators learned more about how aspirin affects blood clotting. They showed that aspirin blocks the formation by platelets of a chemical called thromboxane A_2 that promotes platelet clumping. This ought to inhibit blood clotting. But they also found that aspirin blocks the formation in blood vessel walls of another substance called prostacyclin (*Science*, 3 June 1977, p. 1072). Because prostacyclin's effects are just the opposite of those of thromboxane A_2, prevention of prostacyclin synthesis ought to favor clotting. What actually happens in the heart's arteries under the influence of aspirin may depend on its relative effects on the concentrations of thromboxane A_2 and prostacyclin.

Some evidence has suggested that thromboxane formation may be knocked out more readily by aspirin than that of prostacyclin, in which case a lower dose of the drug might be more effective than a higher one in preventing heart attacks. Philip Majerus of Washington University School of Medicine, one of those who raised the dosage issue, suggests that only one aspirin tablet per day, not the equivalent of three, is a sufficient dose for inhibiting platelet aggregation. A lower dose might also reduce the aspirin side effects seen in AMIS. Much of this is conjecture, however. As Majerus says, "The dose problem remains a hypothetical question."

He is now concerned about what he views as a more concrete problem in the study design. About 85 percent of the AMIS trial participants did not begin receiving aspirin or placebo until more than 6 months after their heart attacks. The death rate from heart attacks is greatest during the first 6 months, with 15 percent or so of heart patients dying during this time. In the next 6 months, the rate is only about one-quarter of what it is earlier. "By enrolling participants so late," says Majerus, "they thereby shrank the effective size of their study very dramatically." He points out that the annual death rate in AMIS was only about a quarter of what it has been in some other studies of aspirin and heart attacks. In other words, there might not have been enough cardiac deaths in AMIS to detect an aspirin effect.

According to Lawrence Friedman of the NHLBI, the relatively low number of cardiac deaths seen in AMIS did not affect the results. They might have, he says, if there had been any sign that aspirin was helping to prevent heart attacks. "In the complete absence of a trend," Friedman maintains, "I cannot accept the argument that more events would have made a difference. There was not even a hint of any aspirin benefit for mortality." He points out that the earlier studies that suggested a benefit, such as the Coronary Drug Project, did not indicate any need for early enrollment.

Another possibility is that by starting the therapy late, the researchers missed an early critical period during which aspirin might have helped. This is suggested by the results of a clinical trial with sulfinpyrazone (trade-named Anturane), another drug that inhibits platelet aggregation. (Sulfinpyrazone is currently registered by the Food and Drug Administration for the treatment of gout, but not for heart attack prevention.) This trial was sponsored by the Ciba-Geigy Corporation at a cost of $4 million, even though the corporation's patent on Anturane has expired. The results, which were reported in January by the Anturane Reinfarction Trial Research Group, showed that the drug reduces cardiac mortality, but only if given during the first 6 months after a heart attack. During this time, the total cardiac mortality of patients taking the drug was only about half that of the controls. After the first 6 months the mortality rates of the two groups were similar.

A major reason why the first 6 months after a heart attack are so dangerous is that the damaged heart muscle is very susceptible during this period to abnormal heart rhythms, which often prove fatal within minutes if they are not treated. One of the conclusions of the sulfinpyrazone study is that the drug appeared to be working by preventing the deaths due to these abnormal heart rhythms. This is surprising since sulfinpyrazone was tested because of its ability to inhibit platelet aggregation. Its potential as an antiarrhythmic agent was unexpected.

According to Levy, there was no evidence in AMIS that the patients whose aspirin therapy began within 6 months of their heart attack fared any better than those whose therapy started later. Only about 700 patients had been assigned to either the aspirin or the placebo group within that early period, however.

There is also the possibility that sulfinpyrazone's apparent ability to inhibit cardiac arrhythmias may be independent of its platelet effects and may not be shared by aspirin. If this is the case, then aspirin may just not work at all. Friedman notes that there is no reason to expect aspirin to affect arrhythmias.

Two additional clinical trials are pertinent to the question of whether aspirin needs to be given early to be effective. In one, dubbed PARIS for Persantine Aspirin Reinfarction Study, the effects of both aspirin and Persantine, another inhibitor of platelet aggregation, were tested in heart attack patients. The study, which cost around $8 million, was supported by Boehringer-Ingelheim Corporation, the manufacturer of Persantine. It included 2000 patients, who were followed for 3 years. Of these, 800 received 1 gram of aspirin per day, 800 received 1 gram of aspirin plus 225 milligrams of Persantine, and the remaining 400 served as controls.

According to Thomas Chalmers of Mount Sinai School of Medicine, chairman of the policy board for PARIS, the total mortality of the patients on both drug regimens was about 20 percent less than that of the controls. The combination of aspirin plus Persantine was slightly better than aspirin alone. Although PARIS was not designed to compare early and late initiation of drug treatment, Chalmers says, examination of the data indicated that patients who began treatment within 6 months of their heart attack did much better than those who started later.

The trouble with PARIS, as with some of the other studies suggesting that aspirin prevents heart attacks, is that the differences between the treatment and control groups were not quite statistically significant. Consequently, none of them are conclusive. Or, as Chalmers puts it, "My impression is that the question is still open."

The fourth recent clinical trial to test aspirin's effectiveness in preventing additional heart attacks was carried out by P. C. Elwood and P. M. Sweetnam of the Medical Research Council Epidemiology Unit, Cardiff, South Wales. A total of 1628 patients, 50 percent of whom were admitted to the study within 7 days of their heart attack, participated in it.

In this trial, the cardiac mortality was 22 percent lower in the aspirin group than in the controls, a difference that is again just short of statistical significance. Nevertheless, the differences found in this trial and in PARIS are large enough to fuel the suspicion that aspirin might be of some value after all, if treatment begins shortly after the heart attack.

In any event, the heart institute is sponsoring a workshop on 20 February, to thrash out the issues raised by AMIS and the other drug trials. "It is quite possible," says Levy, "that we may have to undertake another study of aspirin in the acute stages after a heart attack." He did not sound enthusiastic about the prospect.—JEAN L. MARX