tested for their action on blood clotting. According to one rumor, Upjohn chemists have already made 200 or so compounds, and numerous other investigators are doing the same.

One problem that they will all have to face is that most prostaglandins act on more than one system. This makes it difficult to design an agent to affect only the desired target and have no unwanted side effects. For example, PGI_2 reduces blood pressure. And, since the agent is being found in tissues other than blood vessels, it may have additional unknown effects. Nevertheless, the high stakes make inevitable a large research effort to find a specific inhibitor of blood clotting.—JEAN L. MARX

The AMIS Trial: Can Aspirin Prevent Heart Attacks?

Aspirin has been used to relieve pain, inflammation, and fever since 1899. The question now being asked is: Can the drug save lives by preventing heart attacks? To answer the question the NHLBI is sponsoring a large clinical trial, including 4524 patients who have already suffered at least one heart attack. The trial is called "AMIS" for the Aspirin Myocardial Infarction Study. It will cost a total of $17 million by the time it is completed.

Initial hopes for the outcome of the trial were high. Aspirin is an inexpensive drug and is relatively safe, at least compared to other agents that may be used to treat heart attack victims. And the demonstration that it could prevent potentially fatal heart attacks would be of great benefit. However, the discovery late last year that PGI_2 inhibits blood clotting and arterial contraction has led some investigators to question whether taking aspirin would prevent heart attacks.

The problem is that aspirin inhibits the first step of prostaglandin synthesis from arachidonic acid (see Fig. 1 on page 1072) and thus blocks the formation both of PGI_2 and that of TXA_2, a thromboxane that is a potent promoter of blood clotting and arterial constriction. Most investigators agree that if, as seems likely, it is the balance between the activities of PGI_2 and TXA_2 that determines whether or not clotting will occur, the information is not adequate to predict the effects of aspirin on the process.

The results of a half-dozen or so already completed studies have been mixed. Some indicated that aspirin might protect against heart attack. For example, some participants in the Coronary Drug Project, which was sponsored by the NHLBI and completed in 1975, took 1 gram of aspirin (the equivalent of about three standard aspirin tablets) every day. These patients appeared to have fewer heart attacks than the controls. Other studies, however, gave negative results. John Vane has suggested that the fact that aspirin inhibits both PGI_2 and TXA_2 synthesis may account for the lack of dramatic results. In any event, the anticlotting prostaglandin was discovered only after the completion of these trials and after recruitment for AMIS was completed in August 1976.

According to William Friedewald of the NHLBI, the institute decided to undertake AMIS because the inconclusive results of the earlier studies suggested the need for a trial that was well-designed, prospective, and double-blind (neither the patient nor the physician know who is getting aspirin and who placebo). He says that the discovery that aspirin inhibits TXA_2 synthesis, although not the rationale for the NHLBI study, did lend credence to the suggestion that aspirin might protect against heart attacks.

The participants in AMIS have been randomly divided into control and experimental groups. Those receiving aspirin take 1 gram of the drug every day. Friedewald says that the patients will be carefully watched for possible aspirin side effects, such as gastrointestinal bleeding and liver and kidney damage. The experimental phase of AMIS will be over in August 1979.

One criticism directed at AMIS—and at other large clinical trials being conducted by the NHLBI (*Science*, 21 November 1975)—is that such studies are very expensive; critics think that they drain off money that might be better spent on basic research. For example, Peter Ramwell suggests that putting the money into a search for a specific inhibitor of the enzyme that synthesizes TXA_2 or for a stable compound that mimics the effects of PGI_2 might be more valuable in the long run. At the moment, however, no such agent is available. And as long as 10 years may be required to get Food and Drug Administration approval for use of a new drug in humans, whereas aspirin is already available as an over-the-counter drug.

Another argument that can be made in favor of a study to determine whether aspirin prevents heart attacks is that local effects in diseased coronary arteries may be different from those in normal blood vessels. John Oates agrees that PGI_2 production may prevent clot formation in the latter but he points out that diseased coronary arteries that have severe atherosclerotic lesions may have few lining cells capable of producing the prostaglandin. Here the effects of TXA_2 release by platelets may well predominate and contribute to heart attacks and angina pectoris. Thus, inhibiting synthesis of the thromboxane might help persons with diseased arteries. Oates is beginning a trial to determine whether aspirin can benefit patients with unstable angina, a severe form of the condition in which individuals experience chest pain due to inadequate blood flow to the heart even when at rest.

A final question that has been raised about the AMIS trial concerns the dose used. Philip Majerus of Washington University Medical School says that recent results from his laboratory suggest that it may be too high. He and his colleagues have found that platelet cyclooxygenase is extremely sensitive to the drug; much less aspirin is needed to inhibit the platelet enzyme than the one from sheep seminal vesicles. When the investigators gave aspirin to human volunteers they found that a daily dose of as little as 180 milligrams produces 99 percent inhibition of the platelet enzyme. This is far less than the amount needed to achieve anti-inflammatory and analgesic effects. It is equivalent to about one-half of a standard aspirin tablet—or about one-sixth of the quantity taken by AMIS participants.

Majerus says that the results suggest that if the dose used in the aspirin trial is excessively high, it may at best be associated with more side effects than would be found with a low dose; at worst, it may inhibit cyclooxygenase in vessel linings in addition to that in platelets and thus prove ineffective. Majerus thinks that there may well be a role for aspirin in heart attack prevention but points out that "it would be irritating if we had to do the whole trial over again with a lower dose."—J.L.M.