tive criteria to define an "archeologist." SOPA has addressed itself to this matter by setting minimal standards of education and experience for professional archeologists, standards for report writing, and a code of ethics.

Contract archeology calls for a "new kind of archeologist," says Cleland, one who knows about contracts and negotiations and who is prepared to do directed research as opposed to investigating a broad theoretical problem.

"Archeologists are used to flying by the seat of their pants," says Thomas F. King of the Park Service. He explains that the federal laws come at a time when there has occurred a basic shift in the discipline away from "particularistic" investigations toward looking at a particular site as part of a broader settlement system. This type of research calls for a good deal more advance planning, and selective sampling of sites rather than wholesale excavations. In the old days, says McGimsey, an archeologist conducted a survey, then dug. Now, more selectivity is called for, decisions have to be made about what level of archeology is appropriate, whether testing or complete excavation is called for, and what the significance of a site is. The trend in archeology, as in surgery, is toward more thinking and less digging, and this, says King, is just the kind of archeology the historic preservation program needs.

Park Service archeologists are still trying to formulate regulations that will bring all the relevant laws in synchrony with each other, and are having a hard time getting federal construction and land management agencies to do things the way they recommend. The Soil Conservation Service, for example, doesn't think the Moss-Bennett law applies to the SCS because "we don't own the land." SCS's Gerald Lanman complains that projects are held up because "If there's any indication an Indian has been there they [the Park Service] say the site's important." The Army Corps of Engineers, on the other hand, has jumped on the bandwagon and has hired 30 archeologists over the past few years. Larry Banks of the Dallas office says the corps alone has spent $5 million for salvage in the past 15 months.

If the government had all the money it needed to keep pace with all the land disturbance going on it wouldn't be able to find anywhere near enough qualified archeologists. Even now, with the modest increments in funding, qualified professionals are in short supply. But archeologists are scrambling to shape up for the new opportunities. While some may consider that doing work on contract, on a site not of their choosing, may be tedious, unromantic, and riddled with paperwork. McGimsey finds the whole field "challenging and exciting." He predicts "the majority of archeology will be done on contract in the next 10 years if we do it right," and "most of the major advances" in the field will occur under contracts.—CONSTANCE HOLDEN

RESEARCH NEWS

Blood Clotting: The Role of the Prostaglandins

The discovery late last year of a new prostaglandin that appears to prevent formation of blood clots has begun a new chapter in the story of these potent regulatory chemicals. The recent discovery complements an earlier finding of a thromboxane (thromboxanes are close chemical relatives of the prostaglandins) that is extremely effective in causing blood platelets to clump and arteries to constrict, both effects that should promote blood clotting. Since the new prostaglandin has exactly opposing effects, the emerging picture is that the balance between the activities of the two agents may determine whether or not a clot will form.

The findings are of potentially great clinical significance because heart attacks and strokes are often caused by abnormal clot formation. Investigators hope that a better understanding of how the prostaglandins affect clot formation will lead to the development of new drugs that prevent clots. For example, the structure of the prostaglandin has been determined, and it may be possible to synthesize a stable analog that mimics its action. Aspirin, an old drug that is now known to block prostaglandin synthesis, is already being tested in a clinical study sponsored by the National Heart, Lung, and Blood Institute (NHLBI) to see whether it can protect against heart attacks (see box, p. 1075).

Investigators have known for some time that the prostaglandins affect the aggregation of platelets in the test tube. Platelet clumping in response to blood vessel injury is one of the first steps of clot formation. However, investigators found it difficult to work out the exact role played by the prostaglandins in the living animal. The body makes several prostaglandins, and some of them promote platelet aggregation, whereas others inhibit it. Investigators simply did not know enough about where and how the agents were synthesized and what controls the synthesis to determine which are physiologically important in regulating blood clotting.

A development that helped to clarify the situation—and that of prostaglandin biochemistry in general—was the discovery a few years ago of the prostaglandin endoperoxides. Then, in 1975, Mats Hamberg, Bengt Samuelsson, and their colleagues at the Karolinska Institutet in Stockholm identified the thromboxanes (*Science*, 21 November 1975). Both the endoperoxides and the thromboxanes were hard to find and are still hard to study because they are very unstable.

The endoperoxides, now designated PGG_2 and PGH_2, are key intermediates in the synthesis of several prostaglandins and the thromboxanes (Fig. 1). They are formed by the enzyme cyclooxygenase from arachidonic acid, a common fatty acid present in fats and other lipids. The enzyme is inhibited by aspirin and related compounds such as indomethacin, which thereby block the synthesis of all the prostaglandins and thromboxanes formed from PGG_2 and PGH_2.

Although platelets clump when they are exposed to endoperoxides, the Karolinska group thinks that much, and possibly all, of this effect can be attributed to the fact that endoperoxides serve as a source of the thromboxane called TXA_2. Samuelsson and Hamberg have shown that TXA_2 is an extremely potent aggregator of platelets. In addition, the investigators have evidence that the agent is identical with "rabbit aorta contracting substance" originally described by John Vane and Priscilla Piper, then at the Royal College of Surgeons in London. Both materials contract rabbit aortas, have similar half-lives, and are formed in platelets from endoperoxides.

The enzyme that synthesizes TXA_2 (thromboxane synthetase) has been iden-

tified in platelets by investigators from Vane's laboratory at Wellcome Research Laboratories in England, working in collaboration with Hamberg and Samuelsson. The Wellcome group included Philip Needleman, who was then on sabbatical from Washington University Medical School, and Salvador Moncado. The enzyme is located in the platelet microsomes, small granules composed of fragments of interior cell membranes.

While examining other types of tissues to see if they too contain the enzyme, Moncada and Vane found that microsomes prepared from pig and rabbit aortas do not form TXA_2; instead, they contain an enzyme that converts the endoperoxides to a previously unknown, highly unstable prostaglandin that prevents or reverses platelet aggregation and relaxes several kinds of blood vessels. The investigators at first named this material prostaglandin X. The name was changed to prostacyclin after determination of the agent's structure showed that it contains a ring not found in other prostaglandins (Fig. 2).

The structure was determined last fall by a group of investigators at the Upjohn Company under the direction of Roy Johnson. They proved the structure of the new prostaglandin by synthesizing it, the classic means by which chemists establish the structure of a compound. The Upjohn group, in collaboration with Moncada and Vane, then showed that the properties of the synthetic material were the same as those of natural prostacyclin. The full chemical name of the material is (5Z)-9-deoxy-6,9α-epoxy-Δ^5-prostaglandin $F_{1\alpha}$. Most recently, the compound has been designated PGI_2, following the alphabetical nomenclature scheme applied to previously described prostaglandins.

The investigators could predict the structure of prostacyclin because those of its immediate precursor, PGG_2, and of its breakdown product, 6-keto-prostaglandin $F_{1\alpha}$, were known. The latter substance was discovered about 6 years ago in stomach tissue by Cecil Pace-Asciak of the Hospital for Sick Children in Toronto, who postulated at that time that the compound now called PGI_2 was an intermediate in the synthesis of the stable keto derivative.

Moncada and Vane have shown that PGI_2 is synthesized in human arteries and veins and in bovine coronary arteries in addition to pig and rabbit aortas. They say that the enzyme that generates PGI_2 is located in the innermost lining of the blood vessels. According to these investigators, PGI_2 is the predominant product formed from the endoperoxides in blood vessel linings, whereas in platelets the endoperoxides are converted into TXA_2 and other prostaglandins but not into PGI_2.

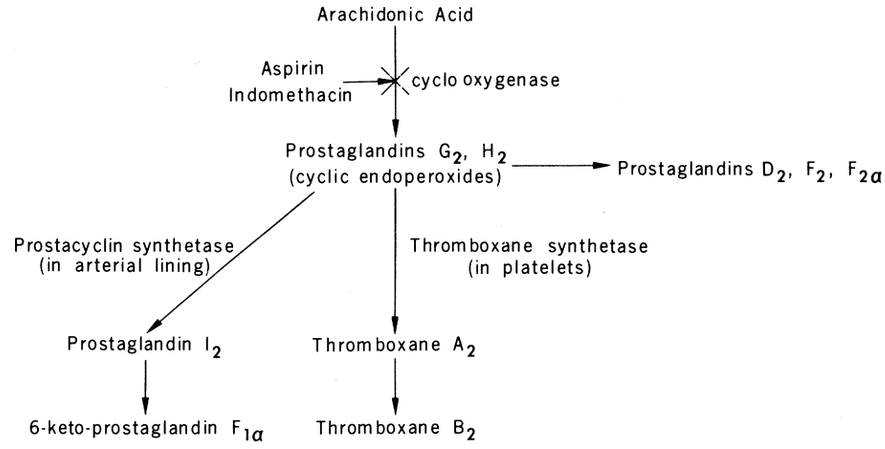

Fig. 1. Scheme showing the major steps in the conversion of arachidonic acid to the prostaglandins and thromboxanes. Prostaglandin I_2, which inhibits platelet clumping and arterial constriction, is formed by an enzyme in blood vessel linings. The enzyme that synthesizes thromboxane A_2, which has the opposite effects, is located in platelets. The breakdown products, 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2, have little or no biological activity.

Moncada and Vane postulate that the formation in platelets and blood vessel linings of agents with opposing effects provides a mechanism for the normal control of blood clotting and suggests an explanation for the genesis of atherosclerotic plaques. (Such plaques are thought to contribute to the deaths of some 900,000 heart attack and stroke victims in the United States every year.) Normally, platelets do not stick to the inner linings of arteries and veins even though they are known to adhere easily to many other kinds of surfaces. The investigators think that when platelets come in contact with the linings, they release endoperoxides that are then converted to PGI_2, which prevents the platelets from aggregating and forming a clot, by the enzyme in blood vessel linings. However, where blood vessels are damaged there would be a lack of the PGI_2-synthesizing enzyme (prostacyclin synthetase) and clot formation could occur.

Many investigators think that destruction of the inner lining of arteries is one of the initial steps in the formation of atherosclerotic plaques. Moreover, platelets are present in the plaques and possibly promote formation of the lesions. Thus, in the view of Moncada and Vane, loss of the cells containing prostacyclin synthetase may be a major contributor to the atherosclerotic process. Furthermore, the lesion sites would themselves lack the enzyme, a situation that would encourage further clot formation and increase the danger that the artery would become blocked. The investigators have also shown that a lipid hydroperoxide effectively inhibits the activity of prostacyclin synthetase. Moncada and Vane speculate that the presence of lipid peroxides in atherosclerotic plaques might help explain the increased clotting problems of patients with atherosclerosis.

Although blockage of a coronary or cerebral artery by atherosclerotic plaques of a blood clot may cause a heart attack or stroke, respectively, arterial constriction can also reduce the flow of blood and deprive tissue of needed oxygen, at least temporarily. The effects of TXA_2 on the contraction of arterial smooth muscle could make an additional contribution to the disease process, whereas the opposing effect of PGI_2 may help to protect against restriction of blood flow.

John Oates, Earl Ellis, and their colleagues at Vanderbilt University have demonstrated that when human platelets aggregate in the presence of thrombin (a natural promoter of clotting), they release a labile substance that causes the contraction of porcine coronary arteries. They identified the substance as TXA_2 and hypothesized that platelets aggregating in regions where the lining of the coronary arteries is damaged could release the agent. Consequent constriction of the arteries could then play a causative role in heart attacks and angina pectoris (a condition in which transient restriction of blood flow to the heart muscle causes chest pain but does not actually kill the muscle as true heart attacks do).

In contrast, Needleman and his colleagues have evidence that coronary arteries release a substance that relaxes arterial smooth muscle. The investigators at first thought that it was PGE_1, a known relaxer of smooth muscle. Further studies ruled out that possibility. They showed that arachidonic acid,

which is not converted to PGE_1, relaxes preparations of coronary arteries. Indomethacin added with the arachidonic acid not only blocked the relaxing effect but also caused the arteries to contract. Needleman says that this result suggests that arachidonic acid was not active itself but had to be continuously converted to an unstable prostaglandin that causes the relaxation.

Although the investigators subsequently showed that the endoperoxide PGH_2 relaxes coronary artery muscle, they have evidence that the endoperoxide is converted to another labile compound that is much more potent. This material has all the characteristics of PGI_2. For example, Needleman and his colleagues find that bovine coronary arteries incubated with labeled arachidonic acid convert it to 6-keto-prostaglandin $F_{1\alpha}$, the stable breakdown product of PGI_2.

Needleman says that the coronary blood vessels produce PGI_2 when the heart is stimulated by the hormone bradykinin or when it is made oxygen-deficient by temporarily obstructing the coronary arteries. He thinks that by promoting dilation of the coronary arteries and increasing blood flow, the compound may help to protect the heart muscle when the demand for oxygen is great, as in times of stress, or when blood flow to the organ is restricted.

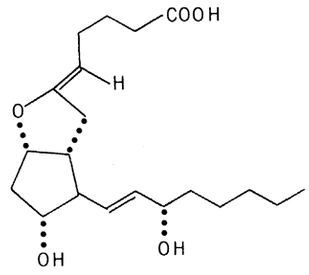

Fig. 2. The structure of PGI_2 or prostacyclin.

Although most investigations of PGI_2 activity have been carried out in vitro, investigators are beginning to look at the effects of the agent in intact animals. For example, Peter Ramwell and his colleagues at Georgetown University Medical School and the Naval Medical Research Institute have found that PGI_2 injections into dogs and rhesus monkeys markedly reduce blood pressure. They think that the agent works by relaxing the smooth muscle of blood vessel walls. In monkeys it decreases the resistance to blood flow of the systemic circulatory system, an effect usually attributed to dilation of the small arteries.

The discovery of the role of TXA_2 and PGI_2 in blood clotting may make it possible to design more effective strategies for preventing heart attacks. Investigators do not expect that PGI_2 itself will be very useful in this regard because it is unstable, although it might be of some benefit if given by continuous intravenous injection to hospitalized patients. The agent reverses aggregation of platelets as well as preventing it and could help to dissolve clots that have already formed. But clinicians would no doubt prefer longer-acting agents. Chemists are already trying to synthesize stable analogs of PGI_2; another approach to preventing blood clotting would be to develop specific inhibitors of the enzyme that synthesizes TXA_2.

E. J. Corey and his colleagues at Harvard University have synthesized PGI_2 and four analogs that have been tested in in vitro systems by Ramwell. All the analogs inhibit the aggregation of human platelets induced by incubating them with adenosine diphosphate, but none are as potent as some of the natural prostaglandins. For example, PGE_1 is 20 times more effective in preventing platelet aggregation than the most active analog.

Although the effects of these analogs are not impressive, cardiovascular disease is such an important health problem that it is a sure bet that a large number of PGI_2 analogs will be synthesized and

Speaking of Science

Drinkers Rejoice: A Little Wine May Kill Your Virus

Wine lovers can take heart from new Canadian results about the value of wine to your health. Wine connoisseurs already know that a U.S. government report has said that a goblet a day is a good tonic for lassitude, sleeplessness, old age, and other infirmities. Now, Jack Konowalchuk and Joan I. Speirs of Health and Welfare Canada have shown that wine is an effective antiviral agent.

The disinfectant properties of wine have long been recognized. Ancient Egyptian warriors invading less civilized countries mixed wine with the local water in an effort to avoid contracting what was then probably termed the Assyrian Two-Step. Up until the 19th century, it was frequently recommended that wine be used to detoxify impure water that could cause cholera. And more recently, several investigators have shown that wine is an antibacterial agent. But Konowalchuk and Speirs believe they are the first to demonstrate that it possesses antiviral properties.

Konowalchuk and Speirs are food virologists in their agency's Bureau of Microbial Hazards. Their primary responsibility is to check shellfish, vegetables, fruits, and so forth to find potential hazards from contamination. In the course of their work, they observed that some fruits, such as strawberries, raspberries, and grapes possess antiviral activity. Investigating further, they found that this activity apparently results from the presence of tannins and other naturally polymerized phenols, the same substances that endow the fruits with antibacterial activity. Since these compounds are present in grapes, they decided to check wine.

They found that poliovirus, herpes simplex virus, and various enteric viruses (which cause gastrointestinal distress) are inactivated by incubation with wine or diluted wine. Red wine is much more effective than white wine, presumably because grape skins, which contain most of the phenols, are used in fermentation of red wines but not for the whites. Plain grape juice is even more active. This last fact may be distressing to oenophiles, but it is not surprising. Various scientists have estimated the phenolic content of white wines to be about 260 mg/liter, whereas that of red wines is about 2200 mg/liter and that of Concord grape juice is 3300 mg/liter.

The two investigators do not claim to have discovered disease-curing properties for wine or grape juice. All of their experiments were conducted in the test tube and under the microscope and not with human subjects. But their findings do indicate that the fruit of the vine can inactivate viruses with which it comes in contact, suggesting that it might be of some benefit against the little beasties that wreak havoc in the stomach and intestines. Four ounces of prevention may well be better than a pound of cure.—T.J.M.

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.