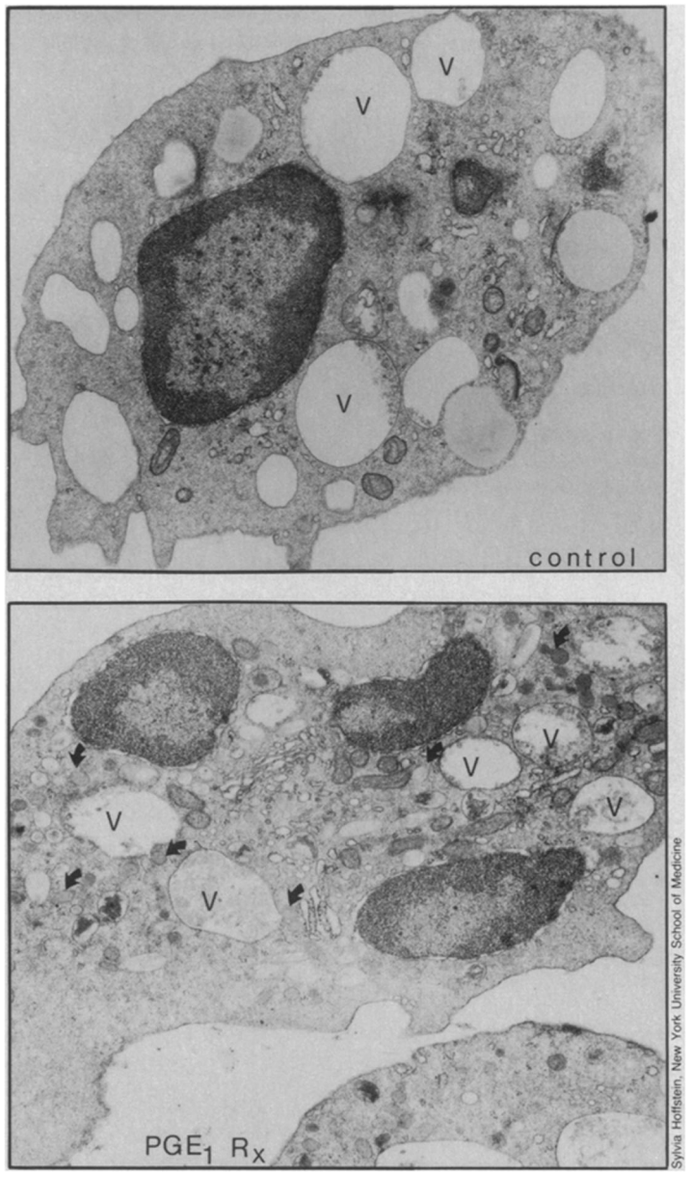
# Where Are All Those Prostaglandin Drugs?

**Here, coming or sidetracked. The optimists still believe that the drug potential of prostaglandins has scarcely been tapped.**

BY JOAN AREHART-TREICHEL




*Prostaglandins appear to both help and hinder arthritis, hence delaying the development of an effective prostaglandin drug against arthritis. Microscopic evidence underscores prostaglandins' ability to counter arthritis. Upper photo: A white blood cell from infllamed joint tissue. It contains few lysosomes, suggesting that the lysosomes have been extruded and have released enzymes that trigger inflammation. Lower photo: A white blood cell from inflamed joint tissue that has been treated with a prostaglandin. It retains many lysosomes (see arrows), suggesting that the prostaglandin prevented the release of inflammation-causing enzymes.*

In 1970, the first international meeting on prostaglandins was held at the New York Academy of Sciences. Many scientists prophesied then that these local hormone-like messengers which do an incredible number of things in the body would become the miracle drugs of the 1970's, just as steroid hormones were the drug finds of the 1950's and 1960's (SN: 10/10/70, p. 306).

Now, five years later, where are all those lustily heralded drugs?

Here, coming or still hovering on the horizon, according to leading prostaglandin investigators. If the last five years of prostaglandin research have revealed anything, it's that the field is full of surprises. Some of the uses that looked hot in 1970 have not panned out as expected, whereas some dark horses have slipped over the finish line and are already benefitting society. What's more, as the numerous actions of prostaglandins and their precursor chemicals in the body become increasingly deciphered, the challenge of bringing prostaglandin drugs to market has probably become more complex rather than less so. Nonetheless, the optimists are still convinced that the prostaglandins haven't even begun to meet their pharmacological potential.

The expectations of five years ago that have panned out are mostly in the area of human reproduction. In 1972, the Upjohn Company in Kalamazoo, Mich., a world leader in prostaglandin research, marketed two prostaglandin drugs in Britain for inducing labor and second-trimester abortion. These were the first prostaglandin drugs to be marketed. In 1973, Upjohn marketed one of the drugs, for abortion, in the United States. Getting these drugs to market was actually a quicker process than Upjohn scientists expected, since Upjohn has been heavily committed to prostaglandin research only since 1965, and it can easily take 10 to 15 years to get a drug marketed today.

Another area of prostaglandin drug development that was loudly proclaimed in 1970 and that is now well into clinical trials throughout the world is the use of prostaglandins to speed the healing of stomach ulcers. Success with such trials has been reported during the past several months by Sultan M.M. Karim of the University of Singapore and by Stanislaw Konturek of the Institute of Physiology in Krakow, Poland.

"The reason that prostaglandin drugs for stomach ulcers could be so valuable," explains André Robert, a gastroenterologist and Upjohn's authority on prostaglandins and ulcers, "is that they actually stop gastric secretion, which is the cause of stomach ulcers. Drugs already on the market do not do so effectively. The antacids, for example, can relieve pain, but not gastric secretion. And while the anticholinergic drugs are able to block nerves that trigger gastric secretion, they cannot be given to people in large enough amounts to do so without causing serious side effects."

Even though prostaglandins continue to show an excellent profile in the treatment of stomach ulcers, Robert does not antici-

pate that they'll be licensed for marketing for several more years. "One of the most important questions that still has to be answered," he says, "is what the side effects are from chronic prostaglandin treatment."

There have also been some unexpected and valuable prostaglandin drug spinoffs since 1970. At the third international prostaglandin conference in Florence, Italy, in May, Flavio Coceani, a physician at the Hospital for Sick Children in Toronto, reported that he has used prostaglandins to save the lives of three "blue babies" (newborns with cyanotic congenital heart disease). He injected prostaglandins directly into the hearts or aortas of the babies. The treatment reversed their cyanosis and made it possible for them to undergo successful corrective surgery.

In 1972, Lars A. Carlson of the Karolinska Institute in Stockholm, whose scientists are world pioneers in prostaglandin research along with Upjohn, attempted to use prostaglandins to increase the blood supply to the legs of five elderly patients with peripheral arteriosclerosis. Their blood supply had been shut off to such a degree that they suffered excruciating pain. The prostaglandins improved the patients' conditions so much that prostaglandins for peripheral arteriosclerosis are now being evaluated on an international scale.

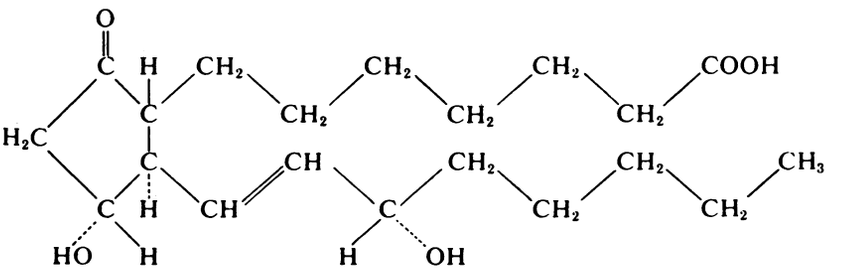
During this past year, for example, a team of surgeons at a major American medical center injected prostaglandins into the legs of patients with this condition. The patients' pain was so great that they were on the verge of being scheduled for leg amputations. The prostaglandins relieved the pain; the amputations could be canceled. What's more, the surgeons were able to demonstrate that prostaglandins actually increased blood flow to the patients' legs.

More clinical evidence has to be gathered, though, to convince cardiovascular scientists that the beneficial effects in peripheral arteriosclerosis patients really come from prostaglandins, since pain is hard to study scientifically. The treatment is also technically difficult. As William Martin, an Upjohn cardiovascular specialist working in this area, explains, "a catheter the diameter of pencil lead has to be inserted into an artery in the leg, and you can shoot blood all over the place if you don't do it right. The prostaglandins also have to be injected through the catheter in incredibly small amounts. In brief, the technique is far from ready for routine use by family physicians." It will be at least five years before a drug can be marketed to help patients with peripheral arteriosclerosis, Martin predicts.

Still another unexpected bonus of the past five years has been in the area of livestock reproduction. In fact, this application may ultimately mean more to world health than all other uses of prostaglandin drugs together. Last year, Imperial Chemical Industries marketed a prostaglandin drug in Britain and Upjohn marketed a prostaglandin drug in the United States that brings cattle and horses into heat, thus paving the way for breeding large numbers of them at one time by artificial insemination. Until now, artificial insemination has been used almost exclusively to genetically upgrade horses and livestock. So the drugs should help increase the world's supply of meat.

Other prostaglandin drug ideas touted five years ago still have potential, but they're not reaching the market as fast as hoped. One is to use prostaglandins to treat nasal congestion. Another is to use prostaglandins to treat asthma. Although aerosol inhalation of prostaglandins relaxes the bronchiole muscles of asthmatics, it produces a cough as a side effect, Upjohn's Gordon White reported at the 1974 meeting of the Federation of American Societies for Experimental Biology. A prostaglandin drug to treat rheumatoid arthritis is not progressing very fast because scientists are still not sure whether

## Prostaglandins in Perspective




**1935:** U.S. von Euler of the Karolinska Institute in Stockholm discovered that human semen and prostate glands contained material that could contract smooth muscles and reduce blood pressure when injected into animals. He named the material "prostaglandin," believing it to be a single chemical entity. Subsequent research has shown that there are many related compounds in the body, and that they do a welter of different things.

**1945:** Sune Bergström of the Karolinska Institute joined von Euler and started working on the purification of the three grams of prostaglandin that von Euler had saved during the War.

**1957:** Thanks to the arrival of mass spectrometry and gas chromatography, Bergström and his colleagues were able to isolate two prostaglandins. They would isolate more during the next four years. The Upjohn Company started to help finance the Swedish prostaglandin research and also started prostaglandin research of its own.

**1962:** Bergström and his team delineated the structure of four prostaglandins and thereafter several more.

**1965:** The problem of obtaining large amounts of natural prostaglandins to study was partly solved when investigators at Upjohn, the Karolinska Institute and Uniliver Research Laboratories in The Netherlands independently developed biosynthetic techniques that produced prostaglandins enzymatically by incubating essential fatty acid precursors with sheep vesicular glands.

**1966:** Bengt Samuelsson and Mats Hamberg of the Karolinska Institute isolated eight more prostaglandins and determined their structures. Elias J. Corey of Harvard University and Upjohn chemists reported synthesis of some prostaglandins from commercially available materials. Synthesis of more followed in the next several years. Upjohn started providing free samples of prostaglandins to researchers around the world, stepping up prostaglandin research immensely.

**1972:** Two prostaglandin drugs were marketed by Upjohn in Britain for labor induction and second-trimester abortion.

**1973:** One of these drugs was marketed by Upjohn in the United States for abortion.

**1974:** Imperial Chemical Industries marketed a prostaglandin drug in Britain, and Upjohn marketed a prostaglandin drug in the United States, to induce ovulation in cattle and horses.

**1975:** Clinical trials are underway on prostaglandin drugs for ulcers, peripheral arteriosclerosis, high blood pressure and other diseases. Prostaglandins were used to save the lives of blue babies. At least 15 different natural prostaglandins are now known, and over a thousand prostaglandin analogs are now being analyzed for their drug potential.

prostaglandins increase or lessen tissue inflammation. "So if you have rheumatoid arthritis," Robert B. Zurier of the University of Connecticut Health Center advises tongue-in-cheek, "don't throw away your aspirin or gold." (Aspirin and gold are two long-standing treatments for rheumatoid arthritis.)

Certain investigators are still optimistic about getting a prostaglandin drug on the market that lowers high blood pressure. At a Georgetown University prostaglandin symposium in May, James B. Lee of the State University of New York at Buffalo School of Medicine reported that he and his colleagues have been able to lower high blood pressure in patients by using one of the prostaglandins. The prostaglandin also tends to make patients urinate, which is good, Lee says, because antihypertensive drugs on the market tend to compromise urination. So he concludes that the prostaglandin "at least now appears to be an ideal antihypertensive agent."

Other researchers don't altogether agree with him, though. At the same meeting, Lawrence M. Slotkoff of Georgetown University Medical Center reported that he and his colleagues had also been able to lower high blood pressure in patients by using the same prostaglandin. But the prostaglandin didn't affect urination. Slotkoff thinks it's hard to determine at this point whether the prostaglandin might ever prove superior to drugs already on the market for treating hypertension.

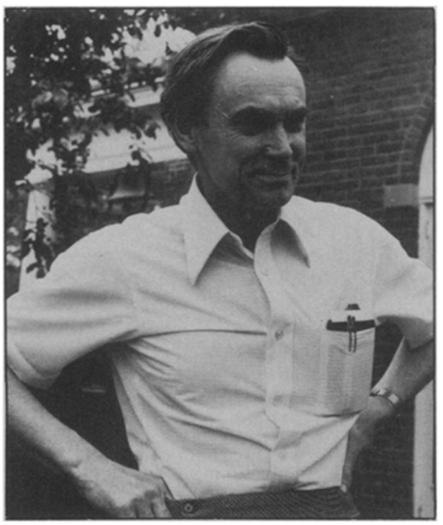
Still another reason why it may be difficult to bring a prostaglandin antihypertensive agent to market is the short-lived effect of the prostaglandin on blood pressure, John Pike, an Upjohn chemist, points out. Even analogs of the natural compound, he says, have this same problem.

Finally, two other prostaglandin drugs that looked highly promising five years ago but now have run into snags are a prostaglandin once-a-month birth control pill and a prostaglandin drug that women could use to bring on ovulation, thus clearing the way for sexual intercourse without fear of pregnancy.

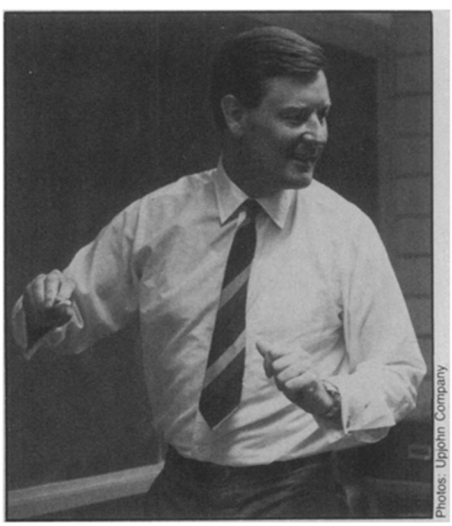
Prostaglandin injections, scientists know, can cause regression of the corpus luteum in female subprimates, and this regression leads to follicle growth and ovulation. That is why prostaglandins can now be used to bring groups of horses and livestock into synchronized heat. In contrast, regression of the corpus luteum in female primates and women is known to lead to menstruation. That is why investigators hoped prostaglandins might cause corpus luteum regression and bring on menstruation in women if they miss a period through pregnancy. This hope was dashed, however, when researchers found that the natural prostaglandins do not cause corpus luteum regression in women.

As for using prostaglandins to induce ovulation, investigators have known that prostaglandins are essential for rupture of the follicle to release an egg from the ovaries, at least in female subprimates. So they hoped that prostaglandins might be used in women to induce ovulation at a predictable time. However, the exact time during the human menstrual cycle at which the follicle matures to a state where it is ready to ovulate is highly variable. "So giving prostaglandins to an individual woman at the right time to cause ovulation would be difficult," says John Wilks, an Upjohn biologist working in this area.

*Robert with dog that assists ulcer tests.*



*Bergström: A prostaglandin pioneer.*



Photos: Upjohn Company

*Pike: A pro on prostaglandin chemistry.*

Prostaglandin investigators haven't given up altogether on a prostaglandin once-a-month pill and a prostaglandin ovulation inducer, though. As Wilks points out, prostaglandin analogs might do the job that the natural compounds appear incapable of doing.

Meanwhile, some thousand prostaglandin investigators throughout the world continue to learn more and more about the manufacture of prostaglandins in the body and prostaglandins' incredibly diverse and often contradictory actions in various tissues and organs. This wealth of new scientific knowledge will probably lead to more prostaglandin drugs in the long run. Meanwhile it is undoubtedly complicating rather than easing the task of bringing such drugs to market, or at least diverting the attention of scientists from their original aims.

At the recent international prostaglandin conference in Florence, for instance, Bengt Samuelsson of the Karolinska Institute reported that the body's chemical precursors of prostaglandins—the endoperoxides—can also be converted by the body into compounds known as thromboxanes rather than into prostaglandins. Intriguingly, endoperoxides and thromboxanes appear to have powerful pharmacological effects in their own right. The endoperoxides are potent bronchoconstrictors, the thromboxanes potent clotting agents. Might these natural chemicals be turned into drugs instead of, or in addition to, prostaglandins? Investigators don't rule the possibility out.

Since 1965, when the prostaglandin field really got rolling around the world, millions of dollars have been spent on learning what the prostaglandins do in the body and how they might be turned into drugs. Although these financial investments haven't begun to be returned in profits, the company that has spent the bulk of the money, Upjohn, continues to be optimistic. "The drug potential of prostaglandins hasn't even begun to be tapped," asserts John Hogg, director of experimental chemistry and biology at Upjohn and one of the key decision-makers behind Upjohn's long-range prostaglandin commitment. "I will retire from Upjohn long before we reach that peak," he predicts. "It's incredible," he says, "how the excitement about prostaglandins continues to escalate. I saw it at the meeting in Florence. We can't remain excited forever. But we can keep aglow."

Similar confidence is being echoed in university medical centers. At the Georgetown University prostaglandin conference, Peter W. Ramwell, a Georgetown University physiologist, declared: "One-third of all medicine in five years will be prostaglandin-related, including the fields of immunology and cancer control." □