The New Mystery—Maybe

By LAWRENCE GALTON

LIKE all really difficult questions, the one posed by the young Indian pharmacologist at Makerere University in Kampala, Uganda, had the teasing element of unexplained universal experience. Why, Dr. Sultan H. M. Karim wondered, did the umbilical cord stop bleeding after childbirth?

Logic and training led him to the working hypothesis that some substance in the womb's amniotic fluid caused the bleeding artery within the cord to contract. He was still trying to identify the healing agent in his laboratory in 1966 when his reading led him, correctly, to suspect a newly identified group of hormones called prostaglandins. Within three years, he had gone far beyond the answer to his original question: He had used injections of prostaglandin to safely induce labor in a sizable number of patients—and to abort one prized but injudiciously pregnant Siamese cat.

Prostaglandin research, extensive enough five years ago to accidentally provide Karim's clue, has since undergone an explosive growth and now constitutes one of the most promising fields in the biological sciences. An estimated 500 laboratories around the world are working on prostaglandins; new scientific reports on the subject are appearing at the rate of almost two a day.

THE prostaglandins are a group of 14 compounds—there may be others not yet identified—present in human beings and all other mammals. They are classified as hormones. The well-known hormones produced by the thyroid and pituitary glands, however, are circulated through the body by the blood and act on distant target organs. In contrast, the prostaglandins are produced by virtually all tissues of the body and act on the spot, and they are involved in both pathology and normal body functioning. The 14 identified so far resemble one another in basic chemical structure: They can be classified as 20-carbon, acidic lipids, the fatty substances present in cells. Yet the minor chemical differences among them make possible greatly differing effects.

There seems little doubt that, if they live up to their early promise, the prostaglandins will provide the basis for a shelf of highly effective medicines. That day is in the indefinite future; the wide variety of drugs now being tested are all considered experimental and none are commercially available. They include some drugs capable of opening closed airways to the lungs, making them potentially useful in treating asthma and emphysema, and some which clear the clogged nasal passages familiar to common-cold sufferers. There are prostaglandins which shut off the secretion of stomach acid, indicating possible value for peptic-ulcer control. Several lower blood pressure, apparently without the undesirable side effects possessed by currently available antihypertensive medications.

It is in the field of reproduction that the prostaglandins have truly startling implications. Used in the early weeks of pregnancy, a tiny amount of prostaglandin—on the order of a tenthousandth of an ounce—has produced therapeutic abortions. Contraception once a month, after intercourse and even conception, is a distinct possibility. Trials with hundreds of women have shown that within a few hours after use of vaginal suppositories containing prostaglandin, menstruation begins whether or not conception has occurred. Some investigators think it may not even be necessary to use the suppositories as often as once a month. They speculate that a woman would need to insert them only if she was late with her period; on the average, this might be no more than three or four times a year. They regard prostaglandins as "post-conceptive contraceptives" offering women the luxury of hindsight in determining whether they wish to be pregnant.

Though considerable research remains to be done to establish not only the safety but the best method of using such contraceptives, controversy will not wait. Those engaged in population control are enthusiastic. "Prostaglandins have such new qualities and importance," says Dr. Reimert T. Ravenhold, director of the Office of Population of the U.S. Agency for International Development, "that they might mean as much in controlling the reproductive process as the introduction of penicillin meant in fighting infection." In England, Dr. Malcolm Potts, medical secretary of the International Planned Parenthood Foundation, predicts that once techniques for using prostaglandins are perfected, "they will by their availability and cheapness mean that every woman who wanted to could have the means of abortion in her own hands. We shall see a complete rethinking of our moral and social attitudes toward birth control and abortion."

Others shrink from that prospect. In a letter to Medical World News, Penni Mulvihill, a Catholic laywoman, calls "post-conceptive contraceptive" a euphemism for abortion. She adds: "As a Catholic, I am, of course, opposed to both contraception and abortion. But there are millions of non-Catholics who, while they do not object to contraception, recoil in horror at the very thought of abortion."

There will probably be less disagreement with the practical argument advanced by Norman Applezweig, a New York biochemist, who says: "The birth-control pill isn't working satisfactorily. The majority of the people we have to reach aren't motivated enough to seek out a means of contraception. The only way to get the majority of the 450 million women of child-bearing age in the world is to get them when they've got something in their belly. The woman is motivated enough then if she doesn't want another mouth to feed. A useful abortion-inducing agent is the only answer for population control, and prostaglandins may very well be it." That many women have second—or first — thoughts about their pregnancies is both common knowledge and statistically demonstrable. In the first year after easily available abortion became legal in July, 1970, in New York State, more than 200,000 women had pregnancies terminated.

THE research will not wait for the debate, either. It is likely that every major drug company in the world is actively researching some aspect of prostaglandins. The Upjohn Company, a pioneer in the field, which has some 700 scientific investigators in its Kalamazoo, Mich., research laboratories, prefers not to divulge how many of them are involved in prostaglandin studies. But some officials note that what is going on now, not necessarily at Upjohn alone, is reminiscent of the days when cortisone and other steroid hormones first appeared—and as much as half of a pharmaceutical firm's research effort went into them. One measure of the commercial and academic effort under way is in the increased production of research papers: Of 1,200 scientific reports on prostaglandins published up to 1970, 800 appeared in 1968 and 1969.

The history of prostaglandin research has most of the familiar chapters—false starts, dedicated, dogged investigators, accidental linkups, a tantalizing shortage of natural materials and, finally, synthetic manufacture to permit multiple experiments. Prostaglandins presented an additional problem: Though omnipresent in the body, they are there in such tiny quantities that they could not be isolated and studied without relatively recent analytical techniques.

As long ago as 1930, two New York City gynecologists with an interest in fertility problems, Drs. Raphael Kurzrok and C. C. Lieb, had what seems to have been an unconsummated relationship with prostaglandins. They discovered that strips of uterine tissue from women with histories of successful pregnancies relaxed when ex-

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posed to fresh semen while that from sterile women contracted. But if Kurzrok and Lieb followed up on these promising observations, they reported nothing further.

Three years later, two investigators working independently of each other made similar discoveries but pursued their implications. In England, Dr. Maurice W. Goldblatt was studying human semen; in Sweden, Prof. Ulf S. von Euler of the Karolinska Institute was working with extracts of sheep vesicular glands, which produce semen. Both found that when they injected either material into test animals it caused smooth muscle to contract, and also lowered blood pressure; neither effect could be accounted for by any known agents. Von Euler coined the name prostaglandin for the material produced in the prostate. A misnomer (he apparently believed it was produced only in the prostate), it has stuck nevertheless.

World War II interrupted von Euler's work. After the war he concentrated on other research—the isolation and identification of a basic nervous-system compound, noradrenaline—which was to earn him a Nobel Prize. But he encouraged a younger colleague at Karolinska, Prof. Sune Bergstrom, a physician and biochemist, to try to isolate prostaglandin and determine its structure. The quiet, hard-working Bergstrom, now 55, devoted his career to prostaglandin work, and perhaps more than anybody else deserves the credit for all that is happening now in the field.

His first need was for huge quantities of sheep glands. He turned for financial help to Dr. David I. Weisblat, an American friend he had met in the early nineteen-forties when both were doing postdoctoral work at Ohio State University. Weisblat, a biochemist who is now vice president for pharmaceutical research at Upjohn, got his company to finance the purchase and refrigeration of several tons of sheep glands.

Not until 1957 did Bergstrom succeed in isolating two different prostaglandins; it took him another five years to establish their precise architecture. In the view of Dr. John A. Hogg, Upjohn's director of experimental chemistry and biology, Bergstrom's role in the field constitutes "the stuff Nobel Prizes are made of." But Bergstrom's breakthrough could not be fully exploited. Natural supplies of the compounds were meager; there were not enough available glands in the world to permit extensive biological testing.

ONLY total synthesis of prostaglandins — production from chemicals right off the shelf, cheaply and in large quantity—could provide the logistical base for the broad research and extensive clinical testing that was necessary. It came in two steps. In 1964 and 1965, investigators at three laboratories, Karolinska, Unilever in the Netherlands, and Upjohn, discovered how to produce prostaglandins by biosynthesis. They started with a common fatty acid such as arachidonic acid; when they incubated it with sheep glands, enzymes in the glands converted the acid to prostaglandins. This biosynthetic method of production permitted the distribution of prostaglandin, at least in small lots of 10 and 20 grams, to researchers all over the world. In 1968, at Upjohn and in the laboratory of Dr. E. J. Corey, professor of chemistry at Harvard, total synthesis began to be achieved for one after another of the prostaglandins.

On the basis of their structures, prostaglandins have been divided into four main categories, E, F, A and B. Three each of the E and F groups—E_1, E_2, E_3, and F_1-alpha, F_2-alpha, F_3-alpha—are considered primary in that none is derived from any of the others. The remaining eight members of the family are produced by modification of the primaries.

As investigators have worked with increased supplies, they have been able to resolve a number of seemingly unrelated mysteries. Almost a quarter of a century ago, Dr. W. Vogt, a German researcher, found a substance produced by the intestines which influenced bowel contractions; he called it *darmstoff*. About 15 years ago, a Welsh physiologist, V. R. Pickles, discovered a substance which caused powerful contractions of the uterus during menstruation; he called it "menstrual stimulant." In 1965, Dr. James B. Lee and a St. Louis University team reported that something in the rabbit kidney lowered blood pressure. Recent research has shown all three substances are prostaglandins.

Among the most dramatic findings were those of Dr. Karim, the pharmacologist in Uganda who knew nothing about prostaglandins but was intrigued by the functioning of the umbilical cord after birth. When he read of prostaglandins in 1966, he obtained samples of the hormones and was quickly able to establish their presence in the amniotic fluid. He determined that an F prostaglandin not only is predominant in the fluid during labor but also appears in the maternal blood at the same time, and that its level in the blood correlates closely with uterine contractions.

His next step was a substantial test of prostaglandins as agents for

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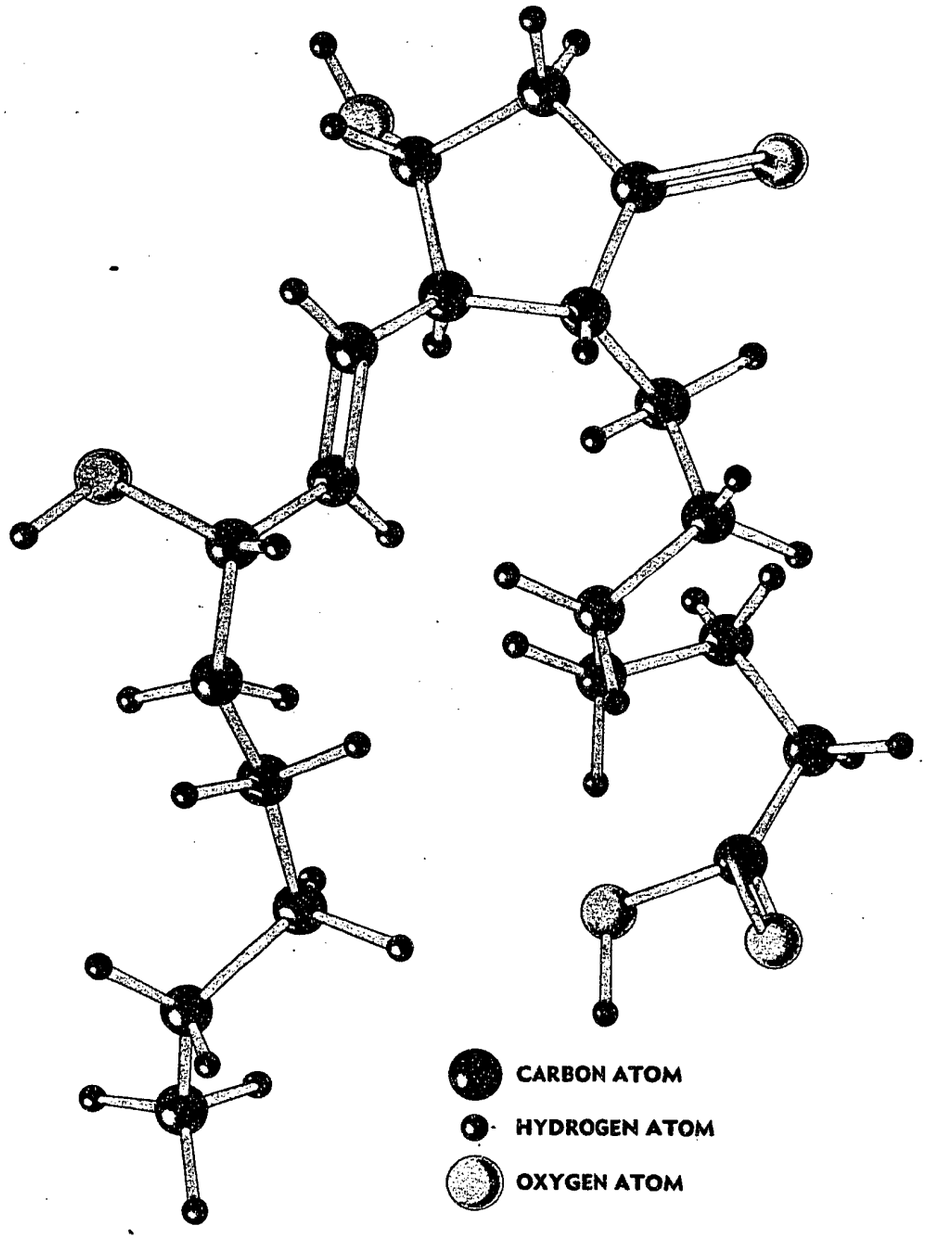
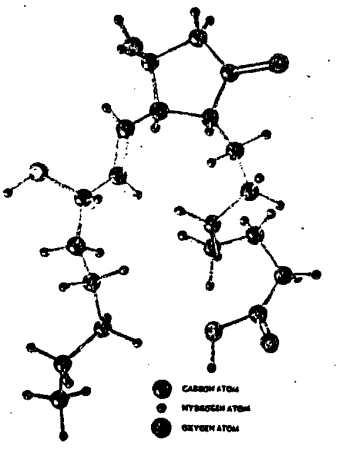
Miracle—Drug



Prostaglandin. *The molecular structure of the one called E_1, one of the 14 varieties known. All are basically similar, but their potentialities range from treatment of emphysema to "after-the-fact" birth control.*

Drawing by WALTER HORTENS



The new mystery drug

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the inducement of labor and childbirth in women at or near term. His subjects were 300 women, mostly Bantus, who needed inducement because of postmaturity, premature rupture of the membranes, or other complications of pregnancy. Using intravenous injections, he administered oxytocin, a standard labor-inducing drug, to 100; it failed to induce labor in 44. Another group of 100 received F_2-alpha, which failed in 33. The remaining 100 were given E_2, which brought on labor in 96.

It seemed to Karim that if prostaglandins could induce labor late in pregnancy, they might induce abortion early. "When a neighbor's prize Siamese became pregnant by the next door ginger tom, much to her owner's distress," he recalls, "I gave the Siamese F_2-alpha and that solved that."

By 1969, both Karim in Uganda and Dr. G. M. Filshie of King's College, London, were reporting successful therapeutic abortions, using intravenous injections, with only minor side effects of vomiting and diarrhea in some patients. There were reports that one prostaglandin administered orally at or near the time for delivery successfully induced labor.

But then came reports that prostaglandins did not always trigger complete abortion, including expulsion of the conceptus, the fertilized ovum. In some cases, the injections induced dilation of the cervix, but curettage had to be used to complete the abortion. Medical authorities took a hard look at some of the early studies and found the definition of success had not been standardized; when dilation

alone occurred the case may have been listed as a successful abortion.

Cautions Dr. Leon Speroff of Yale: "Clearly, dilation of the cervix is not a successful abortion. If one is trying to evaluate the efficacy of an abortifacient agent, use of the term 'success' must be reserved for a complete abortion." How often and under what circumstances prostaglandins produce complete abortion, and how that success rate might be increased by changes in dosages and methods of administration, are questions to be answered by future research. But even when they are only partially successful, the compounds still could have considerable value in therapeutic abortion. Says Dr. Speroff: "The fact that prostaglandins may dilate the cervix but not result in expulsion of the conceptus raises the possibility of their use prior to curettage, thereby eliminating the use of dilators with their attendant danger of perforation. Perhaps, too, anesthesia requirements would be lowered or eliminated."

It is as an after-the-fact contraceptive that prostaglandins will doubtless receive the most public attention. Though much remains to be done, a good deal has already been established. A group of Upjohn investigators has shown that prostaglandin is the mysterious uterine factor which each month causes the corpus luteum to regress. The corpus luteum—literally, yellow body—regularly develops after ovulation in the cavity left by the discharged ovum in the ovary. It produces a hormone, progesterone, that readies the uterus to receive and nest the egg if conception occurs. It had been known that when fertilization does not take place, something caused the corpus luteum to regress and stop producing progesterone. When that happens, menstruation follows. When the researchers tried administering F_2-alpha to rats for any consecutive three-day period from day 4 through day 13 after mating, the corpus was affected and pregnancy was terminated.

Trials in humans followed and are still going on. By September, 1970, at a conference on prostaglandins sponsored by the New York Academy of Sciences and attended by more than 500 physicians and scientists from around the world, Karim could report that he and his colleagues had effected normal menstruation in 11 of 12 women who had conceived and missed their periods for two to seven days. Vaginal suppositories containing either E_2 or F_2-alpha were used. Each woman received two, the second inserted four hours after the first. There were side effects—nausea and abdominal pain similar to menstrual pain—but these, it seemed to both Karim and the women, were a small price to pay. At the same meeting, Dr. Marc Bygdeman of the Karolinska Institute reported similar results, without side effects, when F_2-alpha was injected directly into the uterine cavity a few days after the first missed period. In current tests, 200 women in Sweden, Britain and Uganda are using prostaglandins instead of conventional contra-

HE TESTED THEM: *Dr. Sultan H. M. Karim, who found that prostaglandins could induce labor in women—and abortion for a cat.*

ceptives to induce abortion as soon as they miss a period. The use of prostaglandins as a contraceptive has no connection with recently publicized research in which a synthetic form of the female hormone estrogen has been used, in effect, as a morning-after pill.

Aside from their potential value in contraception and therapeutic abortion, prostaglandins may, paradoxically, help at least some infertile males to have children. According to studies by Dr. Bygdeman at Karolinska and Dr. Bengt Samuelsson at Stockholm's Royal Veterinary College, male fertility may be related at least partially to prostaglandin levels in the semen. In 40 per cent of the semen samples taken from men with otherwise unexplained infertility, the researchers have found low levels, about half of those for normally fertile men. They are now trying to determine whether the deficiency can be overcome and fertility increased. "We pick out men with a low content," says Dr. Samuelsson. "We then carry out tests to make sure neither the man nor the woman has other abnormalities. E_1 is then mixed with the infertile male's semen, and artificial insemination is undertaken." The hope is that the added prostaglandin will stimulate uterine contractions, thus moving the sperm more quickly to the Fallopian tubes to meet the ovum. But both investigators emphasize that there is not yet enough information to support this theory.

THE catalogue of current prostaglandin research, apart from the investigations in the area of reproduction, is a lengthy one, holding the promise of alleviation of a variety of human ills:

- At the Upjohn laboratories, Dr. André Robert, a French-Canadian, has shown that when dogs are given either E_1 or E_2 intravenously, their gastric secretions are reduced. In experiments with rats, he has demonstrated that ulcers ordinarily produced in a variety of experimental ways, including administration of cortisonelike drugs, are prevented by E_1. It seems likely that there is a relationship between the reduced gastric secretions and the prevention of ulcers. And since it is now known that the stomach produces E prostaglandins which may play a role in the normal regulation of secretions, the theory has been developed that people with ulcers may have a deficiency of the compounds.

Working on that assumption, investigators in New York, Chicago and San Francisco gave prostaglandin intravenously to human volunteers, including some with ulcers. Their gastric secretions were greatly reduced. The next step will be to determine if ulcers can be cured this way; if they can, an attempt will be made to find a more convenient, oral method of administration.

- Such is their versatility that the same prostaglandins, E_1 and E_2, which inhibit stomach secretions, nicely open up air passages to the lungs and also constrict blood vessels in the nasal passages to produce a decongestant effect. Dr. M. F. Cuthbert of London Hospital Medical College has used an E_1 aerosol in asthmatic patients with promising results. And at Emory University in Atlanta, Dr. Richard T. Jackson, whose subjects included some persons with colds, has found that the same compound has a nasal decongestant effect that lasts up to 14 hours.

HE NAMED THEM: *Nobel winner Prof. Ulf S. von Euler, who recognized the importance of prostaglandins back in the 1930's, and called them that because he then thought they were produced only by the prostate.*

- One of the major uses for prostaglandins may be in the treatment of hypertension, a problem that affects 20 million Americans and is considered a prime factor in heart disease. In a small proportion of cases, no more than 15 per cent, there is a definite physical abnormality, such as a marked narrowing of a blood vessel or an adrenal gland tumor, where the cause of hypertension is clear and can usually be corrected surgically. But in the vast majority of cases, the origin is obscure. As a result, the search for antihypertensive drugs has had to be empirical; those that have been found, while useful and often even lifesaving, are far from ideal.

One researcher, Dr. James B. Lee of St. Louis University School of Medicine, believes that a deficiency of certain prostaglandins naturally present in the kidneys may explain many if not most cases of hypertension. Nine years ago, while at Harvard, Lee found that kidney extracts injected into animals caused a striking drop in their blood pressure. He has since established that three active compounds in kidney tissue are the prostaglandins F_2, F_2-alpha, and A_2. The only apparent function of A_2 is to lower blood pressure. Animal

HE SNARED THEM: *Prof. Sune Bergstrom, who gave prostaglandin research its breakthrough in 1957 by isolating the first two of the 14 now known. It took five years more to establish their chemical structures.*

experiments have demonstrated that it does its job by relaxing small arteries, thus easing blood flow. Studies in a human patient with hypertension have shown the same artery-relaxing effect and a striking fall in pressure. "This," says Lee, "supported the theory that high blood pressure is a deficiency disease."

Recently Lee has given A_1 to hypertensive patients, bringing pressures down from a mean elevation of 200/100 to a normal 140/80. And, within five minutes after infusion of A_1, he has noted two other desirable reactions: increases in the flow of blood to the kidneys and in excretion of salt and water, two processes often abnormally impeded in hypertensive patients. Lee believes that "introduction of long-lasting compounds, particularly if effective by mouth, may well augur a new era in the concept, diagnosis and treatment of hypertension."

● Prostaglandins may also play a role someday in medication to combat thrombogenesis, the formation of dangerous blood clots. Involved in such clotting are

platelets, disklike objects in the blood. Under some circumstances, platelets aggregate, or come together, and adhere to the internal wall of a blood vessel. There they form a thrombus, or clot, that may lead to fatal blocking of the vessel. Some investigators now are convinced that prostaglandins normally regulate platelet aggregation. In test tube experiments, they have been able to show that E_1 inhibits both aggregation and adhesiveness, and they have also used it to suppress thrombus formation in damaged animal arteries. Some recent preliminary work even suggests that prostaglandins may be able to break up and dissolve existing thrombi.

Other researchers in the cardiovascular field report that prostaglandins appear to have a digitalislike effect on the heart muscle, increasing its efficiency without the toxic effects that digitalis sometimes produces.

● Recent experiments with animals raise the possibility that prostaglandins may have some value in treating arthritis. At New York University Medical Center, Drs. Robert B. Zurier and Franco Quagliata induced arthritis in rats, then treated some of them with E_1. The untreated animals developed severe, persistent arthritis; those injected with E_1 had little or none.

Some prostaglandin research has not yet advanced beyond the stage of fascinating speculation. Prostaglandins in excess seem to be involved in preventing the normal breakdown of fat cells. Are prostaglandins related to the problem of obesity? It has also been determined that brain tissue is rich in prostaglandins, which are released upon stimulation. Are prostaglandins involved in that most mystifying field of all, human behavior?

They are not the only unanswered questions. Though it has been 40 years since the original clues to prostaglandins were uncovered, scientists recognize that they really know very little about them. It has been far more difficult to chart their functions than it was to study the hormones produced by the thyroid, pituitary and other special glands. To check on the functions of gland-produced hormones, investigators could remove the glands from experimental animals and note the results of deprivation; as a double-check on their findings, they could inject the hormones and watch the effects. But with prostaglandins produced by virtually all tissues in the body, such approaches have not been possible.

With ultimate medicinal uses in mind, pharmaceutical laboratories have been producing dozens of antiprostaglandin compounds. One type interferes with the body's production of prostaglandins; a second, enough like prostaglandins to occupy the sites where they normally act, blocks their effects by usurpation. Encouraging evidence that such research is on the right track came recently in a report described as "of enormous significance" by the British journal The New Scientist.

For years, scientists have watched the lowly aspirin relieve some of the most frequent discomforts of man, including their own, without knowing why or how it worked. The New Scientist reported that researchers at the Institute of Basic Medical Sciences at the Royal College of Surgeons in London had demonstrated that aspirin is really countering the effects of a prostaglandin which, under some circumstances, induces fever, headaches and inflammation. The finding was proof that a simple, safe and effective antiprostaglandin medication is already in use, and that others may be possible.

FREQUENTLY, however, the research findings concerning prostaglandin include as many questions as answers. While prostaglandin E_1 from human seminal fluid contracts the seminal organs of the guinea pig, it has the opposite effect on the corresponding organs of the rabbit. F_1-alpha and F_2-alpha contract all segments of the human uterine tubes; E_2 relaxes all segments; E_1 and E_2 contract one end and relax the other end. While E_1 stimulates the uterus of rat, guinea pig and cat as well as human, it inhibits the uterus of the rabbit. What does all this mean?

Even the reason for the high concentration of prostaglandins in human semen—as much as 100 times greater than anywhere else in the body—remains a mystery. Dr. von Euler and some other investigators believe that prostaglandins may not only facilitate ejaculation but cause uterine contractions helpful in transporting the ejaculate. "Should both these possible effects be proved," says von Euler, "we have in prostaglandins unique hormones; di-

viding their activity between two different organisms to facilitate reproduction." That theory, too, trails questions behind it. Apart from man, only sheep and monkeys have significant amounts of prostaglandins in their semen. And, as Dr. E. W. Horton, a leading British prostaglandin investigator, has noted wryly, other animals seem to have no trouble reproducing successfully.

Even in their relation to the body's hormone systems the prostaglandins present a confusing picture. In some tissues they further the action of thyroid and other hormones but in others they inhibit such action. A hormone need not affect a cell directly by entering and stimulating the inner machinery. Instead, it acts on the cell wall, where it causes an enzyme to be released from the wall to the cell interior. The enzyme is needed for the production of a remarkable substance called cyclic AMP, often regarded as a "second messenger"—hormones being the first messengers. It is cyclic AMP which carries out hormonal dictates within the cell.

Some researchers have developed a theory to resolve the seeming contradictions in the way prostaglandins behave in various tissues. They believe prostaglandins are part of a vast bodily monitoring system in which they encourage or inhibit hormonal activities indirectly by controlling the enzyme in the cell wall required for production of cyclic AMP. Some support for this belief was reported recently at the Vanderbilt University School of Medicine, where a research team led by Dr. G. A. Robinson found that prostaglandins are the only known agents which can raise the level of cyclic AMP in some cells and decrease it in others.

ALTHOUGH the therapeutic dividends of prostaglandin research promise to be extraordinary, there seems little disposition to rush imperfectly understood drugs into the marketplace. As Yale's Dr. Speroff says: "The future of prostaglandin research may well have a critical relevance to human welfare. . . . Enthusiasm is justified but enthusiasm has to be tempered by caution to avoid poor studies, inefficient effort and premature use."

Everywhere, the drugs are

Prostaglandins: We're only at the threshold

currently available only to qualified researchers and not for general medical use. Clinical trials in this country, under license by the Food and Drug Administration, began only last year. There is some possibility that prostaglandins may become available to doctors in a few countries within a year for injections to induce labor and abortion. But it probably will be several years before the drugs can meet stringent Government requirements for evidence of efficacy and safety and become available for general use in this country.

Both here and abroad, investigators are checking on known side effects and how they may be minimized or avoided. They are also trying to determine whether any undesirable heart, blood, gastrointestinal and endocrinological changes may be brought about by prostaglandins—and how to nullify them if they do occur.

Eventually, many of the prostaglandins may become available in oral as well as injectable form. And modifications of the drugs, so-called analogues, which are already being developed and tested in the laboratory, may prove more desirable than the originals. That would hardly be surprising. The naturally occurring steroid hormones cortisone and hydrocortisone have been succeeded by man-made modifications, such as prednisone and prednisolone, which for specific therapeutic jobs are more effective and produce fewer undesirable side effects.

Nor would it be surprising if many still-unsuspected uses for prostaglandins remain to be found. Four years ago, surveying the state of prostaglandin research, Dr. John W. Hinman of Upjohn observed: "This is an account of beginnings and is of necessity an unfinished story. But the gateway to a new frontier has been opened."

An army of researchers has since crossed the frontier. But even now, the great challenge of the prostaglandins is that nobody has any idea how vast the territory may be. ■