Something for everyone

Ubiquitous, all-purpose chemicals are capturing center stage as researchers explore potential uses from abortions to heart disease

by Barbara J. Culliton

A Connecticut Yankee named Samuel Lee once patented a concoction called Bilious Pills and marketed them as a sure cure for yellow fever, jaundice, dysentery, dropsy, worms and female complaints. To the best of anyone's knowledge they never cured a thing, and most circumspect physicians were relieved to see the passing of patent medicines supposedly good for what ails you, whatever it is. Indeed, few clearheaded men of science ever expected to hear anyone tout an all-purpose drug again.

Then came 1970 and prostaglandins. In the pages of the most prestigious scientific journals and in the halls of no less an institution than the New York Academy of Sciences, the most serious of investigators are now proposing that this only recently studied family of hormone-like substances has a spectrum of potential uses that makes the most touted of patent medicines look pale by comparison.

At the moment, there is enough evidence from animal and human studies to say with certainty that prostaglandins are good for inducing abortion early in pregnancy and labor at term. Their use as post-coital contraceptives is being explored (SN: 1/18/69, p. 64) and, ironically, there is speculation that they may be valuable in treating certain cases of male infertility.

Beyond those functions, however, are others. Because prostaglandins open closed airways in the lungs, scientists predict they may be useful in treating asthma and emphysema. Their ability to open clogged nasal passages suggests they may be good for the common cold. Prostaglandins shut off the secretion of gastrin as if they were turning off a faucet, making them candidates for ulcer control. Their talent for lowering blood pressure may place them in the arsenal of drugs for cardivascular disease as well.

To be sure, a host of ifs and maybes surround these agents, whose future as marketable drugs will not be charted until a large body of solid information emerges to answer unknowns of how and why they work. But if the present accelerated pace of research continues —papers on the subject are being written at the rate of two a day worldwide—some answers should not be long in coming.

Last month, prostaglandins, long relegated to scientific obscurity, were the center of attention at a New York Academy of Sciences symposium that drew more than 400 participants. The scientists debated the biochemical roles played by these agents for two days and then devoted the third day to prostaglandins' effects on the reproductive system, the area in which they have been most extensively explored and used to date in medicine.

Prostaglandins are not a single compound but rather a family of chemicals that occur naturally in virtually all body tissues and organs, including the brain, lungs, kidneys, eyes, menstrual fluid and male semen, where they are found in the largest concentrations in human beings. Fourteen distinct prostaglandins have been identified in human tissues and classified in groups called simply A, B, E and F. Chemically, they are derived from fatty acids and have a unique structure that makes them, like steroids, susceptible to molecular tampering in the laboratory.

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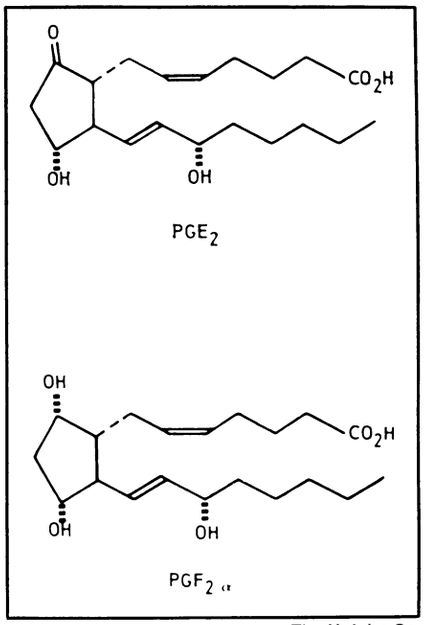

The Upjohn Co.

Two of 14 varieties are most studied.

These ubiquitous substances exert their activity intracellularly, functioning as regulators of cellular behavior. Prostaglandins that leak out of cells, explains Dr. Sune Bergstrom of the Karolinska Institute in Stockholm, are quickly metabolized or broken down, a feature that makes them ideal drugs —at least in theory. If any compound which is not actually used by the cell is quickly and easily discarded by the body, the chances of its causing undue side effects or accumulating dangerously in tissues are diminished.

Constituting a vast network of intracellular regulators, prostaglandins are intimately related to the body's hormonal systems. In this regard, reports Dr. Jane Shaw of the Alza Corp. in Palo Alto, Calif., "They present a paradox, for in some tissues these compounds mimic the action of neurohormones and hormones, while in others they inhibit hormonal response."

In a series of experiments, she is attempting to define the relationship between prostaglandins and a substance called cyclic AMP, a chemical widely recognized as a mediator of hormonal effects. Indeed, she says, many of the pharmacologic actions of prostaglandins can be associated with changes in intracellular levels of cyclic AMP, raising them, for example, in the ovaries, corpus luteum and thyroid, and lowering them in fat tissues.

"It is obvious," she observes, "that naturally occurring prostaglandins can be regarded as potential regulators of hormonal action."

Unlike hormones that show high specificity in the tissues in which they

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Dr. Bergstrom—a PG pioneer.

act, prostaglandins appear to show no specificity. What is needed, therefore, as investigators probe the mechanisms of prostaglandin action and as they consider new drug possibilities, is an explanation of the way prostaglandins modify hormone-regulating cyclic AMP activity across the board. From preliminary studies with turkey red blood cells, Dr. Shaw presents data indicating that calcium may be a third actor in this play, influencing prostaglandin activity in relationship to cyclic AMP.

Though prostaglandins only recently entered the scientific limelight, they were first identified and reported in 1935 in the German journal KLINISCHE WOCHENSCHRIFT on the same page that carried the initial account of progesterone, one of the two hormones in oral contraceptives. A hiatus of 11 years followed that work by Dr. U. S. von Euler of the Karolinska Institute. In 1947, he prodded Dr. Bergstrom, then his student, into further work attempting to purify the material. But again, prostaglandin research was shelved for a decade until Dr. Bergstrom returned to it in 1957 and isolated two distinct prostaglandins, identified as PGE_1 and PGF_2 alpha.

Discussing his success with friends at the Upjohn Co. in Kalamazoo, Mich., the Swedish investigator gained the company's support for continuing studies. Since then Upjohn has invested millions of dollars in prostaglandin research, becoming the major supplier of prostaglandins internationally. Though two foreign institutions also developed a capability to produce enough of the substance to meet their own research needs, Upjohn was unquestionably preeminent in the field. Only now is it facing competition from Alza, a newly established research company in California which has attracted many of the leading workers in the field, including Dr. Bruce Pharriss, formerly of Upjohn. Dr. Pharriss first postulated that prostaglandin F_2 alpha exerts its contraceptive or abortive effects by acting on the corpus luteum, a yellow endocrine body necessary to the maintenance of pregnancy in its early stages.

PGF_2 alpha and PGE_2 are now considered the most effective in acting on the reproductive system, with PGE_2 the leading contender for primacy in that drug field.

Extensive clinical research abroad confirms a role of two prostaglandins in causing abortion and in inducing labor at term. At the Makerere University Hospital in Kampala, Uganda, where Dr. Sultan M. M. Karim has pioneered in human trials of prostaglandins, these agents are now being used routinely to induce labor. Using prostaglandins as abortifacients, Dr. Karim reports that of 400 women given PGE_2 early in pregnancy (before the 10th week), only two failed to abort. Prostaglandins also induce abortions in animals. "When a neighbor's prize Siamese became pregnant by the next door ginger tom, much to her owner's distress," he reports, "I gave the pregnant feline PGF_2 alpha, and that solved that."

At the Karolinska Institute, Dr. Marc Bygdeman has used prostaglandins successfully to induce abortion and stimulate labor in more than 200 women. Dr. G. M. Filshie from King's College Hospital in London also reports encouraging results from large-scale human trials, though he cautions that severe diarrhea and vomiting are side effects that will have to be allayed before giving prostaglandins an uncontested seal of approval. Administering the drug directly into the uterus appears to eliminate, or markedly reduce, these complications which occur primarily when prostaglandins are given by intravenous infusion.

Dr. Karim, who favors vaginal administration, declares that this route also cuts side effects while, at the same time, opening the door to widespread use because of the ease and simplicity of the method. Prostaglandins, incorporated in tablets inserted in the vagina, stimulate uterine muscle contractions that result in abortions early in gestation or delivery of a baby at term. This method also offers possibilities as a post-coital contraceptive. Used in a few preliminary studies in women who are three of four days late in menstruating, prostaglandins have been shown to induce bleeding within two or three hours. By offering women the luxury of hindsight in determining whether they wish to be pregnant, prostaglandins could be the ideal contraceptive. □