Meetings

Prostaglandins in Fertility Control

There is a rapidly increasing interest in the use of prostaglandins for fertility control. Only 15 months have passed since the publication of the first reports from Sweden and Uganda describing the abortifacient effect of certain prostaglandins. During this period, exploratory clinical trials were initiated in a number of centers in Canada, Great Britain, Sweden, Uganda, United States, and Yugoslavia. All these centers were represented at a workshop conference on prostaglandins in fertility control, which was sponsored by the World Health Organization Research and Training Centre on Human Reproduction at Karolinska Institutet, Stockholm, and held 8 to 10 March 1971.

Until recently, shortage of supplies of prostaglandins was a major factor limiting research on prostaglandins. The availability of synthetic prostaglandins can be expected to change this situation significantly, and it may be anticipated that in the near future a large number of investigators in many countries will begin clinical studies of prostaglandins in fertility control.

In view of these several considerations, the organizing committee convened the clinical investigators who were engaged in this field, in order to provide an opportunity for the exchange of information, for delineating areas of agreement and disagreement, and for discussing ways and means of accelerating development.

In an introductory paper, Dr. S. Bergström (Sweden) gave a brief review of the chemistry, physiology, and pharmacology of this group of ubiquitously occurring hormonal compounds.

Introductory reviews were also given of the basic principles of planning multicenter trials of fertility-regulating agents by C. Tietze (United States) and of monitoring side effects by M. Vessey (Great Britain).

N. Wiqvist (Sweden) reviewed the smooth muscle–stimulating properties of the prostaglandins that are of fundamental importance for their use as abortifacients. Frequent and intense uterine contractions can be induced by the intravenous infusion of PGE_1, PGE_2, and $PGF_{2\alpha}$ during the menstrual cycle as well as during the first two trimesters of gestation. Coordinated and effective uterine contractions do not appear until 3 to 6 hours after the start of the infusion. The intrauterine pressure developed in the early pregnant uterus during prostaglandin infusion is very high compared to that in the midpregnant uterus.

It was reported by E. Coutinho (Brazil) that the intravenous injection of $PGF_{2\alpha}$ stimulates the motility of the human tube in vivo, whereas PGE_2 has an inhibitory effect. Whether the effect of prostaglandins on tubal motility is involved in their antifertility effect remains to be established.

At the time of the conference, clinical experience with the induction of abortion by intravenous administration of $PGF_{2\alpha}$ and PGE_2 was limited to approximately 600 cases, that is, approximately 300 cases with each of the two compounds. Reports on the effect of $PGF_{2\alpha}$ were given by S. Karim (Uganda); M. Bygdeman and N. Wiqvist (Sweden); C. H. Hendricks, G. G. Anderson, F. Naftolin, R. J. Pion, E. J. Quilligan, and R. L. Vande Wiele (United States); J. M. Beazley, G. M. Filshie, and K. Hillier (Great Britain); R. Nyberg (Sweden); L. Andolsek (Yugoslavia).

It is difficult to compare the results of the various investigators because of the great differences in the protocols followed. Thus there was a considerable variation in the doses administered and the infusion periods employed. In most cases the number of subjects studied by a single investigator did not exceed ten. Considerably larger series were reported from Great Britain, Sweden, and Uganda. In some of these studies, a fixed dose regimen was followed, in others, the doses were increased until adequate uterine contractions were obtained. In some series, the infusion time was limited to 8 hours, in others, it was continued up to 48 hours. A total of 158 complete or incomplete abortions were reported in 300 trials. The dose range necessary for abortion with $PGF_{2\alpha}$ was 50 to 100 μg/min.

Only six investigators reported on the intravenous infusion of PGE_2 for the induction of abortion. In these series, 204 of 298 subjects were reported not to have required subsequent surgical intervention. Approximately ten times less PGE_2 (5 to 10 μg/min) than $PGF_{2\alpha}$ (50 to 100 μg/min) was needed to induce abortion. The time reported for a successful termination varied from 7 to 36 hours. Although PGE_2 appeared to have a somewhat higher "success rate" than $PGF_{2\alpha}$ it was apparent that the data presented did not permit assessment of the advantages and disadvantages of $PGF_{2\alpha}$ as compared to PGE_2 nor of one protocol as compared to another. On the other hand, the limited experience indicates that both $PGF_{2\alpha}$ and PGE_2 are superior in their effect to PGE_1.

Intravenous administration of prostaglandins in the higher doses used often produced distressing side effects. Nausea, vomiting, and diarrhea were frequent side effects with doses of $PGF_{2\alpha}$ greater than 50 μg/min. Erythema or phlebitis (or both) at the infusion site was common with PGE_2. Headache, pyrexia, tachycardia, arhythmia, and blurring of vision was reported in a number of cases (mainly from the U.S. group). In addition, three cases of hypotension and collapse were reported. Great differences in individual tolerance were noted.

The studies conducted in the United States followed protocols designed more as a tolerance study to evaluate side effects of stepwise increasing doses, and larger amounts were administered than those found sufficient, in the experience of other investigators, to induce abortion.

A total of 60 cases were reported by M. Bygdeman and N. Wiqvist (Sweden) and M. P. Embrey (Great Britain) in which $PGF_{2\alpha}$ and PGE_2 had been administered at intervals of 1 to 2 hours extraamniotically into the uterine cavity through a thin, indwelling catheter. The prostaglandin was given over periods ranging from 7 to 24 hours. $PGF_{2\alpha}$ was used in doses ranging from 250 to 750 μg and PGE_2 in doses between 50 and 200 μg. Of the 60 trials, 46 were reported to have resulted in complete abortion. The total dose required for induc-

ing abortion by this route was generally less than 5 and 3 mg, respectively; that is, approximately 5 percent of that required by intravenous administration. The incidence of generalized side effects was low compared to that seen after intravenous administration. Apart from some nausea and pain associated with the contractions, no vomiting or diarrhea was reported. Although the disadvantage of an indwelling catheter was recognized, it was agreed that the apparent advantage of administering prostaglandins locally at the site of action encourages further exploration of this route of administration, especially in the second trimester as an alternative to treatment with hypertonic salt solution.

It had been established that prostaglandins are absorbed from the vagina both in monkeys and humans. S. Karim (Uganda) reported on the vaginal administration of prostaglandins. After being given intravaginally 20 and 50 mg of PGE_2 and $PGF_{2\alpha}$, respectively, every 4 hours, in a small volume for one or two consecutive days, 56 of 60 cases (6 to 23 weeks pregnant) were reported as "successes." Side effects similar to those occurring during systemic administration were reported in approximately 25 percent of the trials. There was a consensus of opinion that the prostaglandins administered vaginally exert their action after absorption into the systemic circulation. It is likely therefore that the efficacy and side effects of vaginally administered prostaglandins will be similar to those produced by similar concentrations in the plasma of intravenously infused prostaglandins.

In a limited number of cases prostaglandins were administered *intravaginally* or *intravenously* 3 to 7 days after the first missed period (S. Karim, N. Wiqvist, and M. Bygdeman). The efficiency of the method could not be assessed on the basis of these preliminary trials. In several cases pregnancy continued, and repeated administrations were required. The possibility of effects on fetal development makes it essential to follow each case closely.

The effect of prostaglandins in infrahuman primates was reviewed by G. Duncan (United States). Of special interest are the results of studies in which pregnancies in rhesus monkeys were successfully terminated with prostaglandins (PGE_2, $PGF_{2\alpha}$, and 15-methyl-$PGF_{2\alpha}$) given by the vaginal route. In contrast to the situation in humans, the conceptus is not expelled in the rhesus monkey after the administra-

tion of prostaglandins. Termination of pregnancy induced by prostaglandins in such animals is associated with heavy vaginal bleeding. Observable side effects are virtually nonexistent. There is a rapid decrease in circulating "progestin" in the plasma after administration of prostaglandin in early pregnancy. This seems to suggest a direct effect of prostaglandin on steroidogenic function of the corpus luteum in this species.

Recent progress in the metabolism and analysis of prostaglandins was described by B. Samuelsson (Sweden). This work provided information on the initial step in the biological inactivation of prostaglandins and on the time course of the appearance of metabolites in plasma. The results are of importance for more detailed pharmacokinetic studies, the design of analogs of prostaglandins and the development of methods for quantitation of plasma prostaglandins. A new method by which individual prostaglandins can be identified and determined quantitatively in extracts of body fluids in subnanogram quantities by means of a combination of gas chromatography and mass spectrometry with an isotope carrier technique was described.

The recent elucidation of the principal urinary metabolites of the primary prostaglandins has made it possible to obtain the first estimates of the amounts of prostaglandins formed in the human species. The figures reported for PGE_1 plus PGE_2 were 20 to 50 μg per 24 hours in women and 100 to 200 μg per 24 hours in men. Radioimmunoassays for prostaglandins have also been described; however, the specificity of these assay methods remains to be established. Cross reaction with various circulating metabolites appears to be a major problem. Such metabolites are formed very rapidly and occur in the plasma in larger amounts than the parent compounds.

The interactions between prostaglandins and steroid hormones are being studied by several investigators [Anderson and Vande Wiele (United States), Bygdeman and Wiqvist (Sweden)]. Under the experimental conditions used, the intravenous administration of prostaglandins did not affect the concentrations of estrogens, progesterone, or 17α-hydroxyprogesterone in the peripheral plasma.

However, it was reported by Vande Wiele that the infusion of prostaglandin resulted in a marked decrease in chorionic gonadotrophin in the plasma. This decrease occurred within a few

hours after the start of the infusion and was not accompanied by changes in concentrations of steroids. The mechanism of action by which prostaglandins diminish circulating HCG levels is incompletely understood at present.

While the potential of prostaglandins in fertility control is considerable it was obvious to all participants that present information on the properties and effects of the prostaglandins as fertility-regulating agents is still too limited to warrant indiscriminate clinical trials outside of carefully controlled studies in hospital facilities. The importance of fundamental research as a necessary prerequisite for later applied studies also emerged from the review of the current state of knowledge on prostaglandins for fertility control. It was agreed that exploration of the potential of the prostaglandins in the regulation of human fertility would be accelerated if a number of common clinical protocols including the administration of various prostaglandins in different ways, and the design of comparative trials with other fertility-regulating methods could be agreed upon internationally. Even such a fundamental question as the definition of a successful abortion (complete or incomplete) has not been uniform in all studies reported. Under a common protocol the results from different centers could be compared and a consensus based on a sufficient number of cases could be reached more quickly.

The participants of the conference indicated their willingness to participate in such collaborative studies.

It was also felt that international collaboration in the form of coordinated metabolic studies on various types of patients treated according to these protocols would be of great value. It was concluded that another, more specialized meeting was needed during the autumn of 1971 to discuss the various methodological problems and metabolic studies. The participants also agreed that the creation of an international task force would complement efforts now under way and would help to establish guidelines for clinical trials that may be expected to expand rapidly once prostaglandins become readily available.

The suggestion was made and approved that the World Health Organization Research and Training Centre on Human Reproduction at Karolinska Institutet should take the initiative in convening a task force for initiating such studies.

A second meeting of a smaller group

was convened at the same place on 25 and 26 August 1971. After a review of the new experience gained in the meantime, two protocols for intrauterine administration (extra- and intraamniotic) were agreed upon for preliminary evaluation during a 4-month period. These and other clinical results as well as various analytical methods will be discussed at a third meeting organized by the Centre in January 1972.

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Forthcoming Events

April

17–19. Society of **Economic Paleontologists and Mineralogists**, Denver, Colo. (Mrs. R. Tener, P.O. Box 979, Tulsa, Okla. 74101)

17–19. American Assoc. of **Petroleum Geologists**, Denver, Colo. (N. C. Smith, Box 979, Tulsa, Okla. 74101)

17–20. **Atomic and Molecular Physics** Conf., 4th, Sussex, England. (Meetings Officer, Inst. of Physics, 47 Belgrave Sq., London SW1X 8QX)

17–20. **Medical Advisers in the Pharmaceutical Industry**, intern. conf., London, England. (W. L. Burland, Conf. Management, 29 Old Bond St., London, W.1)

17–20. **Seed Ecology**, Loughborough, England. (W. Heydecker, School of Agriculture, University of Nottingham, Sutton Bonington, Loughborough, LE12 5RD)

17–21. **Dosimetry** Techniques Applied to Agriculture, Industry, Biology, and Medicine, Intern. Atomic Energy Agency, Prague, Czechoslovakia. (J. H. Kane, Div. of Technical Information, U.S. Atomic Energy Commission, Washington, D.C. 20545)

17–21. **Inner Shell Ionization Phenomena**, intern. conf., Atlanta, Ga. (R. W. Fink, School of Chemistry, Georgia Inst. of Technology, Atlanta 30332)

18–21. **Acoustical** Scc. of America, Buffalo, N.Y. (Miss B. H. Goodfriend, ASA, 335 E. 45 St., New York 10017)

19–21. **RNA in the Immune Response**, New York Acad. of Sciences, New York, N.Y. (W. Likely, NYAS, 2 East 63 St., New York 10021)

19–22. **International Communication** Assoc., Atlanta, Ga. (M. S. MacLean, Jr., Univ. of Iowa, Iowa City 52240)

20–22. Louisiana **Acad. of Sciences**, Baton Rouge. (B. F. Dowden, Dept. of Biological Sciences, Louisiana State Univ., Shreveport 71105)

20–22. Ohio **Acad. of Science**, Marietta. (J. H. Melvin, OAS, 445 King Ave., Columbus)

20–22. American Assoc. of Colleges of **Pharmacy**, Houston, Tex. (C. W. Bliven, AACP, 850 Sligo Ave., Silver Spring, Md. 20910)

20–23. Cooper **Ornithological** Soc., Las Cruces, N.M. (W. H. Behle, Dept. of Biology, Univ. of Utah, Salt Lake City, 84112)

21–22. Iowa **Acad. of Science**, Iowa City. (R. W. Hanson, Dept. of Chemistry, Univ. of Northern Iowa, Cedar Falls 50613)

21–22. North Carolina **Acad. of Science**, Greenville. (J. G. Boyette, Dept. of Biology, East Carolina Univ., Greenville, 27834)

21–22. **Modern Optics**, American Physical Soc., New York State Section, Poughkeepsie, N.Y. (D. T. Teaney, IBM Research Center, P.O. Box 218, Yorktown Heights, N.Y. 10598)

22. American Soc. of **Hospital Pharmacists**, Houston, Tex. (J. A. Oddis, 4630 Montgomery Ave., Bethesda, Md. 20014)

22–28. American **Pharmaceutical** Assoc., Houston, Tex. (W. S. Apple, APA, 2215 Constitution Ave., NW, Washington, D.C.)

23–24. Congress on **Environmental Health**, American Medical Assoc., Los Angeles, Calif. (F. W. Barton, Council on Environmental and Public Health, 535 N. Dearborn St., Chicago, Ill. 60610)

23–26. Association of American **Geographers**, Kansas City, Kan. (J. W. Nystrom, AAG, 1146 16th St., NW, Washington D.C. 20036)

23–26. American **Oil Chemists'** Soc., Los Angeles, Calif. (J. C. Lyon, 508 S. 6 St., Champaign, Ill. 61820)

23–28. American Soc. for **Microbiology**, Philadelphia, Pa. (R. W. Sarber, ASM, 1913 Eye St., NW, Washington, D.C. 20006)

24–26. **Communications Satellite Systems**, 4th conf., American Inst. of Aeronautics and Astronautics, Washington, D.C. (W. L. Prichard, COMSAT Labs., Box 115, Clarksburg, Md. 20734)

24–26. **Speech Communications and Processing**, Inst. of Electrical and Electronics Engineers, Inc., Boston, Mass. (W. D. Chapman, IBM Corp., P.O. Box 12275, Dept. E82, Bldg. 060, Research Triangle Park, N.C. 27709)

24–26. **Frontiers in Education**, Inst. of Electrical and Electronics Engineers, Inc., Tucson, Ariz. (IEEE, 345 E. 47 St., New York 10017)

24–26. **Reactor Materials Performance**, American Nuclear Soc., Richland, Wash. (T. T. Claudson, Pacific Northwest Lab., Battelle Memorial Inst., P.O. Box 999, Richland 99352)

24–27. **Chemical Vapor Deposition**, American Nuclear Soc., Salt Lake City, Utah. (F. A. Glaski, Fansteel Inc., 10258 Norris Ave., Pacoima, Calif. 91331

24–27. American **Physical** Soc., Washington, D.C. (W. W. Havens, Jr., APS, 335 E. 45 St., New York 10017)

24–28. Society of **Manufacturing Engineers**, Chicago, Ill. (R. W. Taylor, 20501 Ford Rd., Dearborn, Mich. 48128)