Meetings

Reproductive Failure

Knowledge of reproductive pathology and of anatomic, physiologic, genetic, immunologic, and endocrinologic factors is essential for an understanding of the reproduction processes. In the past several decades, well-planned and well-executed experiments have been conducted on man, domesticated animals, laboratory animals, and captive and free-ranging wild animals. These experiments demonstrated marked differences among species in respect to the pattern of the sexual cycle, time of ovulation in relation to sexual receptivity, fertilizable life of the egg, type of placentation, litter size, and birth weight and puberty weight in relation to adult weight. However, deficiencies in our knowledge of reproductive physiology and pathology still exist. Several aspects of reproduction were discussed at the first conference on Comparative Aspects of Reproductive Failure, held 25–29 July 1966 at Dartmouth Medical College, Hanover, New Hampshire.

The failure of the mammalian blastocyst to implant may be a result of maternal fetal vascular deficiencies or of biochemical changes in the endometrium, endometrial secretions, or the trophoblast. Further investigations in these areas are of utmost importance in clinical approaches for correcting some reproductive failures and for birth control. Prenatal mortality, which is more frequent than previously realized, may occur at all stages of gestation. Mortality at the zygote, morula, or blastocyst stage does not result in a change in the length of the sexual cycle; the regression of the corpus luteum is normal. Mortality at the late blastocyst or postimplantation stage, however, prolongs the length of the sexual cycle as a result of a prolonged life of the corpus luteum.

Abortion in man and animals may be due to frequent chromosomal errors or bacterial, fungal, or viral infections of pathological origin. Spontaneous abortion may also result from early pregnancy following puberty, pregnancy immediately after parturition, nutritional deficiencies, or hereditary factors of mostly unknown origin. Restricted caloric intake or protein deficiency can lead to gonadal hypoplasia, delayed puberty, anestrus, irregular cycles, reduced ovulation rate, increased prenatal mortality, retarded prenatal development, and retarded mammary development.

Prolonged gestation may be due to hereditary factors or to the inability of the fetus to initiate parturition, perhaps through pituitary and adrenal interaction. Studies on prolonged pregnancy and the dynamics of prenatal growth may reveal the role of the fetus in regulating gestation time.

Neonatal mortality may occur from defective maternal behavior, delayed onset of lactation, failure in thermoregulatory functions, reduction in birth weight and vigor, bacterial infections acquired through the umbilical cord or fetal fluids, and hemolytic diseases. Gruenwald reported that infants with birth weights of 2500 g or less should be called "infants of low birth weight" rather than "prematures." The physiological implications of these two groups are very significant. The respiratory distress syndrome of neonate infants is strikingly linked to true prematurity (short gestational age) whereas neonatal growth retardation and hypoglycemia in childhood are related to fetal growth retardation. Neurological characteristics of neonates are governed by their conceptional age rather than their birth weight. For example, in some forms of cerebral palsy there is a predominance of low birth weight following prolonged gestation.

The success of reproductive processes can be used as an indication of the adaptation of the organism to new physical or social environments. For example, in the tropics, at high altitudes, or under social stress, neonatal mortality is higher and birth weight lower than under other environments. Unfavorable environmental conditions influence several metabolic, endocrine, neural, humoral, and cardiovascular factors involved in fetal homeostasis. These mechanisms may alter either the rate of blood flow, the supply of oxygen, placental transfer of nutrients, or permeability of placental membranes. Thus, fetal survival may depend on threshold levels of oxygen and other metabolites, or perhaps a linear relationship exists between the rate of prenatal development and the amount of oxygen and metabolites available to the fetus.

Malformations, which are morphologic changes originating during prenatal life, may affect one or more organs, one or more systems, or the entire body. Congenital abnormalities may result from hereditary factors such as mutation or chromosomal aberration, or microenvironment of disease(s) during pregnancy. They occur more frequently in monozygotic than in dizygotic twins, probably because monozygosity, in itself, is an anomaly. Not all abnormalities, however, are attributed to genes; many occur from accidents during development and therefore are not transmitted to further progeny. The commonly occurring phenotypic expressions of hereditary origin are, for the most part, absence of gonadal tissue, production of abnormal gametes, or the production of fertilizable eggs which result in inherently defective embryos.

During the past three decades, the study of hereditary traits has provided information on the embryonic stages at which pathogenesis may cause many malformations. Degeneration of the embryo is the most commonly occurring result of pathogenic invasion. More precise timing of these processes are now being studied by experimental teratology. With recent advances in chemical embryology, biochemical genetics, molecular biology, and biophysics, the last barriers between teratology and pathology are diminishing.

It is emphasized that the science of reproductive biology should progress from discrete, seemingly unrelated disciplines toward broad, universally applicable concepts based on comparative aspects. A variety of species could be employed for comparative research in reproductive failure to study the effects of ageing, general nutritional deficiencies, specific nutritional deficiencies, toxins, poisons, drugs, and vaccines. Studies could be initiated on

the physio-pathology of intersex dealing with cytodifferentiation of fetal gonads, polyploidy and sex phenotype, sex-chromosome mosaicism, and placental enzymes using modern techniques of electron microscopy, tissue culture, and karyotype analysis.

Sophisticated instrumentation and new experimental approaches are now available such as experimental hybridization, inter-species egg transfer, injection with virus or bacteria, interference with the function of the gonads or the placenta, microsurgery, cell fusion, fetal surgery, placenta surgery, tissue and organ culture, teratogenic drugs, overcrowding in utero by superovulation or by egg transfer, and immunological and cytogenetic techniques. Therefore, it is hoped that subsequent conferences on reproductive failure will deal with instrumentation and methodology of reproductive biology. Standardized terminology to be used for reproductive physiology, biochemistry, and immunology would also be highly desirable in order to facilitate interdisciplinary communication.

The second symposium, to be held 31 July to 4 August 1967 at Washington State University, will be limited to a specific topic, "The mammalian oviduct." There have been numerous conferences on the ovary, the uterus, the placenta, and so forth, but there has yet been little emphasis on the biology and method of studying the mammalian oviduct. Sufficient work has now been done and there is enough interest that an excellent symposium could be developed. The program chairmen are E. S. E. Hafez of Pullman and R. J. Blandau of Seattle.

The proceedings of the conference, edited by Kurt Benirschke, are being published by Springer, New York. The proceedings include: *Overall Problem in Man* (A. T. Hertig); *Overall Problem in Domestic Animals* (E. S. E. Hafez); *Cytogenetics of Abortions* (D. H. Carr); *Enzyme Defects* (D. Y. Y. Hsia); *Chemomechanics of Implantation* (B. G. Böving); *Steroid Hormones* (K. J. Ryan); *Protein Hormones* (J. B. Josimovich); *Prolonged Gestation* (P. B. Kennedy); *Ovulation and Egg Transport* (R. J. Blandau); *Experimental Hybridization* (M. C. Chang and J. L. Hancock); *Hybrid Sterility and Fertility* (K. Benirschke); *Zebroids* (J. M. King); *Human Malformations* (J. Warkany); *Experimental Teratology* (V. H. Ferm); *Malformations Due to Genetic Mechanisms* (F. B. Hutt); *Bacterial Infections* (A. B. Hoerlein); *Fetal Infections in Man* (S. G. Driscoll); *Toxoplasmosis* (J. K. Frenkel); *Fungus Infections* (C. G. Bridges); *Virus Infections* (D. N. Medearis); *Ontogeny of Immune Response* (A. M. Silverstein); *Immunologic Interactions between Mother and Fetus* (M. Galton); *Reproduction and Failure at High Altitude* (J. Metcalfe); *Sterility and Social Interactions in Mammals* (R. L. Snyder); *Immobiliation of Large Animals* (T. H. King); and a Placental Pathology symposium of many contributors.

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