Regulation of Mammalian Reproduction

The status of knowledge on the regulation of mammalian reproduction was reviewed at a conference (27 September to 1 October 1970) at the National Institutes of Health in Bethesda under the joint auspices of the Center for Population Research and the Fogarty International Center. The keynote address was delivered by M. G. Candau (Wolrd Health Organization), who emphasized the need for worldwide efforts in research and training in reproductive physiology in view of increasing international recognition of the problems resulting from uncontrolled population growth. Candau was introduced by E. Egeberg (Department of Health, Education, and Welfare), representing U.S. commitment to this important field.

Under the chairmanship of S. J. Segal of the Population Council, sessions were held on: (i) the regulation of pituitary function, (ii) the regulation of sperm production, (iii) sperm maturation and fertilization, (iv) the biology of the ovum, (v) transport of gametes in the fallopian tube, and (vi) corpus luteum function. Each session included formal papers and extended discussion and the concluding session was devoted entirely to informal presentations and additional discussion.

There have been significant advances in delineating the complex feedback mechanisms involved in hypothalamic-pituitary-gonadal interactions. Uptake and physiological effects of steroid sex hormones in brain tissue, and the source of the hypothalamic releasing factor, were reviewed. Both LH (luteinizing hormone) and FSH (follicle stimulating hormone) releasing activities and prolactin inhibiting activity can be identified in tissue of the ventromedial hypothalamus, but the possibility remains that these factors may arise in higher brain centers and reach the median eminence by way of the cerebrospinal fluid. Evidence from several laboratories suggests involvement of an adrenergic link in the stimulatory and inhibitory actions of gonadal steroids on gonadotropin secretion and a role of alpha adrenergic receptors in the release mechanism for gonadotropins. Studies of circulating levels of gonadal and gonadotropic hormones before, during, and after sexual maturation and during the estrous cycle were described. Much remains to be learned about negative and positive feedback effects exerted by gonadal steroids, but methods

with sufficient sensitivity, specificity, and precision for studies in humans are becoming available.

Data on humans indicate that the cycle of follicular maturation leading to ovulation is initiated by gradual increases in pituitary secretion of FSH and LH beginning late in the luteal phase of the preceding cycle and continuing through menses into the subsequent cycle. A series of reports indicated that, in a variety of species including rat, monkey, and human, rising levels of estrogen during the follicular phase of the cycle appear to be the trigger for the LH peak and the induction of ovulation. These data suggest possible new developments in contraceptive technology, including the use of exogenous estrogens to induce ovulation early in the follicular phase when endometrial preparation for implantation is not yet adequate.

Reports on spermatogenesis and the development of fertilizing capacity of spermatozoa included morphological, physiological, and endocrine studies. A possible mechanism for the regulation of events within the seminiferous epithelium is suggested by electron microscopic studies of the blood-testis barrier, which divides the epithelium into two compartments. Gonadotropic hormones apparently have access only to the basal compartment, and there is circumstantial evidence that the later stages of germ cell differentiation, which occur in the adluminal compartment, may be controlled by interchange of chemical substances from adjacent regions of specialization within the Sertoli cell cytoplasm.

The maturation of spermatozoa in the epididymis apparently requires an appropriate hormonal milieu, suggesting new ways to control male fertility without the potential genetic hazards of suppression of spermatogenesis. Alteration of the amounts of androgen in the epididymis may be the explanation for the reported antifertility effect in the rat when low doses of the antiandrogen, cyproterone acetate, are given continuously. These results seem promising since the antifertility effect is reversible and is apparently accomplished without altering the spermatogenic or androgenic functions of the testis.

In vitro studies of sperm capacitation and fertilization suggest that capacitation may not require any specific factor in the female reproductive tract, but only a set of conditions highly favorable to sperm motility and survival. On the other hand, a factor associated with oocytes and their cumulus cells is implicated as the stimulus for the vesiculation reaction and release of the acrosomal enzymes that permit sperm penetration through the egg investments. Progesterone in high local concentrations may be the active agent in initiating the acrosome reaction, but a specific protein is also a possibility. This work has not yet progressed sufficiently for assessment of its potential applicability to fertility regulation, but a number of possible approaches to controlled intervention can be envisioned.

The physiology of the fallopian tube was considered in relation to the transport of eggs and sperm and the environment in which fertilization occurs. Particularly interesting were reports on the muscular contractility of the oviduct, which is independent of that of the uterus in pattern and in response to physiologic and pharmacologic stimuli. Uterine contractions appear to be under systemic control mediated by secretions

of the posterior pituitary; in contrast, oviductal motility may be primarily under local control. Outbursts of activity in the circular muscle layer are apparently caused by the local release of small quantities of norepinephrine at regular intervals from the adrenergic nerve endings. The frequency, duration, and intensity of these outbursts is influenced by ovarian steroids.

Studies of egg transport in living animals suggest that the pattern of oviductal contractions at the time of ovulation is produced by the sequential action of estrogen and progesterone. Sex steroids also influence the development and beat of the oviductal cilia and the volume and constituents of oviductal fluid. The fallopian tube in the female, like the epididymis in the male, seems to be an endocrine target organ and normalcy of the hormonal environment is apparently required for normal reproductive function. Fertility may thus be regulated by altering the local hormonal milieu.

The roles of pituitary and placental trophic hormones in the formation and maintenance of the corpus luteum in a variety of species were discussed, but no clear pattern of hormonal control has emerged. Antiserums to individual hormones are a particularly promising new tool for further studies of the requirements for luteal function in the estrous cycle and pregnancy. It is not yet clear whether luteal regression in the nonfertile cycle results from passive withdrawal of luteotrophic support or the active intervention of a luteolytic mechanism which, in pregnancy, may be counteracted by a luteotrophic stimulus from the conceptus. The postulated uterine luteolytic factor has not yet been isolated or identified, but there is significant evidence for its existence in some species. Recent data indicate that, in the pig, uterine flushings from the late luteal phase contain a protein factor that causes morphologic changes and rapid cell death in granulosa cell cultures. Studies of corpus luteum function in monkeys and women after hysterectomy cast doubt on the existence of a naturally occurring uterine luteolytic factor in primates, but a factor from lower mammalian forms may prove to be active in the human and thus may represent a promising prospect for human fertility control.

The conference reviewed a wide range of current research on the physiological regulation of mammalian reproduction. These investigations contribute to the pool of basic scientific knowledge required for new developments in contraceptive technology, and a number of potentially vulnerable links in the complex mechanisms controlling the reproductive process can now be identified. Nevertheless, much more fundamental research will be required before these and other leads can be exploited and new approaches to the control of human fertility can be made available.

More than 130 scientists from the United States and 23 foreign countries participated in the conference. The proceedings of the conference will be published in book form (*1*).

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Reference

1. S. J. Segal, R. Crozier, P. A. Corfman, P. Condliffe, Eds., *The Regulation of Mammalian Reproduction* (Thomas, Springfield, in press).