Meetings

Long-Term Effects of Perinatal Hormone Administration

A U.S.–Japan seminar on long-term effects of perinatal hormone administration, sponsored by the U.S. National Science Foundation and the Japan Society for the Promotion of Science, was held in Tokyo, 18 to 22 September 1972, with 25 participants from Japan, 12 from the United States, and 1 from Sweden. The Japanese coorganizer was Professor K. Takewaki, the founder of an increasingly active school of research in this area. The discussions, of the effects on the brain-pituitary neuroendocrine axis, on behavior, and on peripheral target organs (especially reproductive), are certainly of significance to the fields of environmental biology (where hormones represent but one class of stimuli whose effect upon the developing fetus or newborn can have repercussions in adult life) and tumor biology (where it is already evident that exposure of the developing human fetus to abnormal amounts of estrogen can result in the development of vaginal cancer in the young adult). Indeed, almost a decade before the disturbing clinical reports of Herbst, Greenwald, Henderson, Tsukada, and their co-workers, experimental biologists such as Dora Jacobsohn, Thelma Dunn, and Noburu Takasugi and Howard Bern had warned of the possible human implications of their studies on laboratory mice. The papers presented at this seminar emphasized that brief exposure to hormones can result in permanent changes at the levels of the nervous system, the endocrine system, and the target organs responding to hormones, or at any combination of these levels.

The fact that the perinatal hormonal environment is a critical factor in determining the functional development of the brain, with respect to the neural control both of hypophysial gonadotropin (GTH) function and of sexual behavior, has been documented by many investigators. Barraclough (Maryland) presented data which indicate that there is a one-to-one relation between unilateral electrical excitation of the medial preoptic area (POA) and the release of luteinizing hormone (LH) in the normal female rat; moreover, the anatomical pathway which subserves the release of LH is uncrossed. Kawakami (Yokohama) reported his studies on the electrophysiological characteristics of this pathway in the normal and androgenized female rat and in the male. Although cyclic changes were observed in the female in the amount of current needed to stimulate the POA in order to alter single-unit activity within the arcuate nucleus, no cyclic changes were observed in either the male or androgenized female. Moreover, the latency between POA stimulation and arcuate response was longer in the androgenized animals. This suggests that, in the normal female and in the animal exposed to androgen perinatally, there is a difference in the anatomical pathway connecting these two critical regions for the secretion of ovulation hormone. On the basis of the secretion of gonadotropin following electrical stimulation of several neural sites, Terasawa (Yokohama) reported that the androgenized female differs functionally from the normal female at the level of extrahypothalamic structures such as the hippocampus and amygdala. The precise site of androgen action is unknown.

In attempts to induce luteinization in the polyfollicular ovaries of neonatally estogenized female rats, Takewaki (Kawasaki Medical College) reported that pregnant mare's serum gonadotropin (PMSG) induced luteinzation in persistent-estrous rats when neonatal estrogen treatment had been brief; with longer estrogen treatment, the response to the PMSG was less, and even the combination of PMSG with progesterone was without effect. Machida (Gerontology Institute, Tokyo) suggested that the preoptic suprachiasmatic region of the hypothalamus is involved in luteinization in neonatally estrogenized rats after exposure to stressful stimuli.

So far most studies on the differentiation of the brain in the male have been descriptive. With the exception of neonatal castration, most experiments have merely contrasted the regulation of gonadotropin secretion in the adult male with that of the female. Gorski (University of California, Los Angeles) reported that the secretion of androgen responsible for masculine differentiation in the male rat appears to be at least partially dependent on postnatal pituitary activity, since treatment with antiserum against gonadotropins prevents the normal suppression of lordosis behavior seen in the male. Arai (Juntendo, Tokyo) reported that the injection of exogenous gonadotropins could activate the testis and induce hypothalamic masculinization of gonadotropin-regulating mechanisms before day 3 of age in a strain of rats in which orchidectomy as late as day 3 is still compatible with the development of the female (cyclic) pattern of gonadotropin release. Arai also removed the testes at varying intervals after gonadotropin injection and found that the testes had to be present for only approximately 12 hours after hormonal stimulation to secrete sufficient androgen to masculinize the brain. Although this rapid masculinization of the brain is consistent with previous studies in which barbiturates were used to antagonize the effect of exogenous androgen in the female, Hayashi (University of California, Los Angeles, and Tokyo) showed that the POA of the female rat must be exposed to an implant of crystalline androgen for approximately 72 hours before masculinization is observed. The discrepancy in the length of exposure to androgen required for masculinization invites further study; its resolution may elucidate the precise site of androgenization, as well as the possible mechanism of androgen action on the brain.

The molecular aspects of androgenization have received attention recently. McEwen (Rockefeller) reported the existence of a 4*S* estrogen-binding protein in both the plasma and brain of the neonatal rat, a binding protein which may protect the fetal brain from maternal hormones. Further study of the ontogeny of specific hormone-binding substances within the brain may elucidate the mechanism of hormone-induced differentation. Whalen University of California, Irvine) reported that estrogen uptake and metabolism in the brain of the male rat are similar to

those in the female; yet the adult male does not respond behaviorally to estrogen administration. His preliminary data, however, suggest that, in contrast to the female, estrogen apparently does not pass into neuronal nuclei in the male.

Perinatal hormone administration also permanently alters behavior. In the monkey, although postnatal administration of androgen is without effect, prenatal androgen injection produces a female which displays characteristic male sexual behavior. In contrast to the androgenized female rat, the primates have normal ovulatory cycles although puberty is delayed. However, Goy (Wisconsin) indicated that in addition to the prenatal hormone environment, postnatal social factors also determine adult behavior in the primate. Gerall (Tulane) pointed out that age is another critical factor. He tested neonatally castrated male rats for lordosis behavior and reported that the younger the animals when first tested, the higher the initial lordosis scores. Lisk (Princeton) reported that maternal nest-building behavior in the mouse is dependent on perinatal androgen exposure. Estrogen-progesterone treatment can induce nest building in the female or neonatally castrated male, but not in the normal male or in the androgenized female mouse. Kimura (Komaba, Tokyo) reported that the neonatally estrogenized mouse is less responsive to male pheromones. Finally, Kawashima and Shinoda (Tokyo) presented data which indicate that the perinatal hormonal environment may alter maze learning and Skinner-box performance. Newborn male rats treated with high doses of estrogen performed less well in these experimental situations. Although in each of these experiments one must be careful to separate potential perinatal effects of gonadal hormones directly on the brain, and indirect effects produced by a modification of adult gonadal function, these studies do suggest that the modification in brain function produced by the perinatal hormonal environment may be very extensive.

The responses of target organs (vagina, mammary gland, and prostate) to neonatal treatment received some detailed consideration. Here, as at other levels of hormone intervention, the existence of a critical period for severe hormonal effects to be visualized was evident, especially in the precise analysis by Takasugi (Okayama) of the histogenesis of estrogen-independent vaginal cornification after neonatal estrogen treatment of mice. A specific cell type, present only for the first few days after birth, gives rise to the cells that eventually show irreversible cornification under the influence of neonatal estrogen treatment. If adequate estrogen is not provided during the first days after birth, these special cells disappear, and the irreversible cornification cannot later be induced. The induction of irreversible cornification (estrogen independent) in the mouse vagina is accompanied by a great reduction in nuclear receptor sites for estradiol (Shyamala, Mori, and Bern, Berkeley). Comparable analyses are needed to elucidate the histogenesis of the metaplastic prostatic lesions (Arai) after neonatal estrogen treatment of rats and mice, and also in studies of mammary responses (Mori and Bern). The thesis that neonatal exposure to steroid hormones affects the nature of the response of adult organs to the same hormones was exemplified by Kincl's (Brookdale Hospital, Brooklyn) studies on steroidogenesis in the male rat and by Lisk's evaluations of uterine sensitivity in the female rat.

Most of the published studies dealing with the phenomena discussed at this seminar have been concerned with the steroids, both with their effects and with influences upon their secretion. However, new emphasis on the importance of the thyroid, of the thymus, and of prolactin was forthcoming. Kikuyama (Waseda) reported that hypothyroidal states during the perinatal period retarded the attainment of sexual maturity in female rats, probably because of an underdeveloped pituitary gland. In view of the stimulatory effect of thyroxin on neuronal and glial maturation [Timiras (Berkeley) especially emphasized the influence on membranogenesis], hypothyroid rats may produce less hypophysiotropins in the hypothalamus. According to Ishikawa (Showa, Tokyo), functional differentiation of adenohypophysial cell types is dependent on these factors. These observations are relevant to understanding the physiopathology of cretinism in man. Nishizuka and Sakakura (Aichi Cancer Institute, Nagoya) emphasized that the neonatal presence of the thymus was necessary for the normal development of the ovaries. They suggested that neonatal thymectomy permanently affected the hypothalamo-adenohypophysial axis. Kincl discussed the protective effect of the thymus in altering the degree of responsiveness to neonatally administered steroids. Perinatal prolactin appears to synergize with estrogen with regard to both vaginal responses and mammary development (Mori, Kohmoto, and Bern). It seems important that combinations of hormone excesses and deficiencies simulating possible pathological conditions in pregnancy be used in future experiments. In his concluding statement, Kohrman (Michigan State) emphasized the special interdependence of experimental and clinical investigations in this field.

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Forthcoming Events

August

12–15. American Soc. for **Horticultural Science,** Raleigh, N.C. (C. Blackwell, ASHS, P.O. Box 109, 914 Main St., St. Joseph, Mich. 49085)

12–17. Conference on **Making Service Industries More Productive through Computers and Automation,** Engineering Foundation, Henniker, N.H. (A. McAdams, Cornell Univ., Ithaca, N.Y. 14850)

12–17. **Mixing Research** Conf., Engineering Foundation, South Berwick, Maine. (EF, 345 E. 47 St., New York 10017)

12–17. **Organometallic Chemistry,** 6th intern conf., Amherst, Mass. (M. D. Rausch, Univ. of Massachusetts, Amherst 01002)

12–17. International **Ornithological** Congr., 16th, Canberra, Australia. (Secretary-General, IOC, P.O. Box 84, Lyneham, A.C.T., Australia 2602)

12–18. **Mechanical, Electrical, and Allied Engineering Branches,** 5th Pan American Congr., Bogotá, Colombia. (E. T. B. Gross, Rensselaer Polytechnic Inst., Troy, N.Y. 12181)

13–14. Symposium on the **Economic Condition of the Texas Seafood Industry,** Center for Marine Resources, Texas A & M Univ., Corpus Christi (S. M. Gillespie, Dept. of Marketing, Texas A & M Univ., College Station 77843)

13–14. **Metric** Assoc., Chicago, Ill. (R. W. Mattoon, Dept. 482, Abbott Labs., North Chicago 60064)

13–16. **Potato** Assoc. of America, Guelph, Ont., Canada. (H. J. Murphy, 114 Deering Hall, Univ. of Maine, Orono 04473)

13–16. Society for the **Study of Amphibians and Reptiles** and the **Herpetologists'** League, joint annual mtg., Tacoma, Wash. (W. R. Heyer, Biology Dept., Pacific Lutheran Univ., Tacoma 98447)

13–16. Society for the **Study of Reproduction,** 6th annual, Athens, Ga. (C. Cruse, 113 N. Neil St., Champaign, Ill. 61820)

13–17. Australian and New Zealand Assoc. for the **Advancement of Science,**