1965

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The interrelation between the hypothalamus and the anterior pituitary gland has been firmly established. It is not the intention of this report to review the literature on this extensive subject. Such reviews are available in "Advances in Neuroendocrinology" (Nalbandov, 2), and since the time of this publication many papers on this subject have appeared in current journals. For the purposes of the present discussion a few fundamental facts will be restated, but the major part of my presentation will deal with my own views of the research areas which should be of special interest to animal scientists concerned with phenomena of reproduction.

A majority of endocrinologists will agree on the following basic points. The adenohypophysis is still considered to be the site of synthesis of all the hormones usually ascribed to it. The neurohypophysial hormones are known to be synthetized in the hypothalamic nuclei; they are present in the median eminence but the neural lobe is considered to be only the storage place for oxytocin, vasopressin in mammals, and oxytocin and vasotocin in birds. The kind of hormones synthesized by the adenohypophysis depend on the proximity of that lobe to the hypothalamus since separation of these two structures by a barrier or by distance causes cessation of the production of the usual hypophysial hormones. In the rat, a profound shift from the secretion of the usual hormonal spectrum to only one hormone - prolactin - occurs if the pituitary gland is removed from the sella and implanted, for instance, in the kidney. This implies that the hypothalamus secretes substances which may direct the synthesis of hormonal precursors into the specific hormones which are usually associated with the adenohypophysis.

The physiological dependence of the adenohypophysis on the hypothalamus is further illustrated by the finding that only those pieces of the anterior lobe autotransplanted into the third ventricle which abut the hypothalamus retain their histological and apparently their physiological integrity. Those portions, too far removed from this so-called hypophysiotrophic area of the hypothalamus, become cytologically abnormal and no longer possess the normal population of hypophysial cells.

It is well established that the hypothalamus also produces so-called "releasing factors" which reach the adenohypophysis via the portal system and which can cause the release of previously synthesized hypophysial hormones into the peripheral circulation.

Specific releasing factors (RFs have been demonstrated either in vivo or in in vitro systems (or in both) for ACTH (CRF), TSH (TRF), LH (LHRF or LRF), somatotrophin (SRF), and FSH (FSHRF). In the rat it has been shown that the hypothalamus produces an inhibiting factor, (not specifically isolated), which prevents release, and perhaps synthesis, of prolactin. Those releasing factors which have been best characterized chemically are small polypeptides which resist heating and can thus be separated from hypophysial trophic hormones. The advent of sephadex column has greatly facilitated research on releasing factors and has made their identification and separation from the hypophysial hormones and non-specific proteins possible.

It remains unclear whether the RFs must signal the release of all hypophysial hormones needed in the routine day-to-day requirements of an animal, or whether they come into play only when superquantities of such hormones are required as in the case of ACTH to meet stress situations, or in the case of LH, to cause ovulation. The fact that releasing factors have been found for FSH and somatotrophin suggest that release of all hormone quantities may require a hypothalamic impetus in the form of releasing factors.

All of these facts are based on work done in rats but in most of the published work the releasing factors were obtained from hypothalamic fragments obtained from cattle, sheep and, in a few cases, from pigs. As far as I know, no work on the effect of releasing factors on domestic animals, other than the chicken, is in progress. This is due to the fact that hypothalamic fragments are small and difficult to accumulate in sufficiently large quantities to be tested on the larger domestic animals which, for the time being, are probably unsuitable even for pilot studies involving systematic injection. Nevertheless such studies should be undertaken using special techniques to make certain that adequate quantities of the releasing factor to be studied reach their target tissue, the pituitary gland. This can probably be accomplished by injecting the substances to be tested via the carotid arteries or by injection directly into the pituitary gland using stereotactic techniques.

The whole concept of releasing factors is so new that their potential uses in the control of animal reproduction are difficult to predict. If speculations are in order, one can anticipate that releasing factors may turn out to be a more natural means of controlling reproductive and

other physiologic functions of animals than the injection of exogenous hypophysial hormones. This is predicted on the grounds that releasing factors act on the pituitary gland directly and govern the release of the animals' own hypophysial hormones. It remains to be seen whether some or all of the releasing factors also enhance the rate of synthesis of hypophysial hormones. Perhaps the use of releasing factors will permit one to get away from phenomena of under- or overstimulation, antibody formation, and other aberrations and obstacles to optimal results. Such difficulties are frequently encountered when exogenous hormones are injected.

On the basis of results obtained in rats and rabbits, it appears that it may become possible to control the time of ovulation by the use of LHRF. It remains unknown whether FSH- and LHRF's may provide a tool by which the number of maturing follicles may be increased and the rate of their maturation hastened. If these interventions turn out to be feasible, they may eventually provide a far more natural means of synchronizing estrus cycles than the ones presently used. Similarly, it appears possible that growth and perhaps fattening processes may be influenced by the use of TSHRF and somatotrophin RF. These hopes are predicated on the possibility of obtaining releasing factors in sufficient quantities for such applications. In view of the success of complete synthesis of such complex molecules as ACTH, synthesis of the relatively simple small RF molecules appears within reach. Perhaps the general interest of the scientific community and of commercial companies may hasten the day when synthetic RFs may become available in sufficient quantities for experimentation in domestic animals. In the meantime some groundwork can and should be laid by those of us interested in reproduction and in animal growth. Much valuable experience can be gained by experimenting on smaller animals such as guinea pigs and chickens on problems pertaining to reproduction and growth. The techniques of obtaining hypothalami and of extracting them for releasing factors are relatively simple and easy to master.

I would like to devote the remainder of my time to the discussion of phenomena which clearly involve participation of the hypothalamus in hypophysial control of reproductive function but which, in my opinion, have not been given the attention they deserve by American reproductive physiologists. I shall omit the details of the fascinating studies on rats and mice performed by Whitten and by Bruce which showed that odor of males is capable of profoundly modifying the reproductive behavior of females. The Whitten effect demonstrates that presence of males can in fact synchronize time of ovulation in a group of females by hastening or delaying heat and ovulation in a significant number of members of a mouse population. The Bruce effect is equally fascinating in that it shows that male odor can interrupt a previously initiated pregnancy at the early blastocyst stage by causing the cessation of release of hypophysial prolactin, the LTH of mice. (For details of the Whitten and Bruce effects, the interested reader should consult the papers by Bruce and by Parkes in "Advances in Neuroendocrinology.")

Reminiscent of the Whitten effect is the observation originally made in New Zealand and later confirmed in Tennessee that in sheep the onset of the breeding season may be advanced by weeks if ewes are exposed to rams several months prior to the expected onset of the breeding season as compared to ewes which had not been exposed (Smith et al., 5).

Some years ago we were greatly puzzled by the fact that pigs which did not settle to repeated services on their home farms and which were sold as being sterile to research workers at the University of Illinois, conceived at the first service after being shipped by truck to the new location. Our data showed that about 50 percent of the hogs sold as "sterile" had no anatomical or endocrine abnormalities (Wilson et al., 6). Infections, male sterility, or nutritional deficiences having been largely ruled out as the possible causes of "sterility," the truck ride was the only event that intervened between "sterility" and sudden fertility. The reason for this marked change in fertility level remains unknown. Similarly puzzling is the observation made by several independent workers but not adequately documented in the literature, that a significant amount of synchronization of sexual activity occurs in normal gilts if they are shipped from one place to another. About 5 to 7 days after arrival at the new place of habitation, a significantly greater number of shipped females show heat than would be expected to do so on a random basis. In one experiment (du Mesnil du Buisson et al., 1), 45 percent or 465 prepubertal females showed heat 1 to 9 days after being shipped, while only 180 females should have been in heat during this period had the random nature of this phenomenon not been disrupted by shipping. In addition to the effect of synchronization, the same experiment also indicates that the onset of sexual maturity was hastened either by the stress of transportation, or by the new environment, or by the daily checking of the females for heat by males.

The French group of workers has other studies which implicate the hypothalamo-hypophysial axis as a mediator in the modification of reproductive responses.

Domestic mammals show a variant of the long-known lordosis reflex of small laboratory mammals which has been analyzed in pigs by Signoret (4). He has confirmed the observations of many practical pig breeders that a sow in heat will become rigidly immobile when, in the absence of a boar, a man sits on her or even simply exerts manual pressure on the back. The degree to which this response can be obtained appears to be genetically controlled.

In cross-bred swine used for experimental work at the University of Illinois, 90 percent to 100 percent of all females respond to the test by rigid immobility. In the breed (Large White) used by Signoret, only about 50 percent of the females spontaneously responded to the signal, while the other 50 percent of the females in heat (and of course all females which are not in heat) escape attempts to be sat upon or attempts to exert manual pressure. Signoret noted that the proportion of females responding could be greatly increased if a male was present and he proceeded to fractionate the role of the male in eliciting the reflex. He found that 90 percent of the females showed the reflex if they could smell the males, (produced by infiltration of the area with male urine), and if they could listen to a recording of his typical rutting call. If, in addition to the odor and the call, they could also see the male, a further 7 percent showed the reflex, and if they could also have physical contact with him, the remaining 3 percent showed the reaction. The recorded call alone raised the response from 46 percent to 71 percent but, if the rhythm of the call was altered, only 9 additional percent of the females responded. Odor alone (impregnation of the area with the contents of the male preputial gland) raised the percentage of positive responses from 50 to 81 percent.

How the phenomena of sound and odor can intensify psychological heat, which is normally attributed to the action of estrogen on the central nervous system, remains completely unknown and invites further study. Of great interest is the fact that there is a very significant relationship between the readiness with which the rigidity reflex can be induced and the fertility of swine (table 1).

Olfaction in pigs, in addition to being related in some way to the intensification of the psychological heat response, is perhaps implicated in LH releases. Signoret and Mauleon (4) removed the olfactory bulbs from pigs and found that their cycles became irregular or ceased completely. The corpora lutea in the ovaries of these females disappeared, and there was an increase in the number of vesicular follicles which were about half as large as those of ovulatory size. These observations suggest the possibility that absence of olfactory bulbs does not interfere with FSH secretion but seems to prevent LH release either in toto or at least in sufficient quantities to cause the ovulatory spurt and ovulation. The morphology of these ovaries is reminiscent of the ovaries of rats in constant estrus which can be produced either by continuous lighting or hypothalamic lesions or by the single treatment of prepubertal rats with steroid hormones. In all of these cases the continuous follicular condition of th ovaries is known to be caused by a derange ment of the LH storage and/or release mecha nisms.

It was the intent of this brief review to ca attention to some aspects of neuroendocrinolo which remain, in my opinion, inadequately explored by those of us working with reproductive physiology of domestic animals. The involvement of the hypothalamus in the control of pituitary function can no longer be doubted. Some of the data reviewed strongly support the possibility that many environmental factors (odor, crowding, excitement, etc.), play an important role in significantly modifying the endocrine relationships between the hypothalamus-hypophysial axis and the endorgans. It seems important to start intensive investigation of the degree to which the exteroceptive factors do modify the endocrine stability of domestic animals, especially insofar as reproductive phenomena are concerned. It appears equally important to initiate research on the possible use of hypothalamic releasing factors in the control of physiological function of animals other than the laboratory rat.

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Table 1.--Relation of conception rate in swine to their spontaneous ability to show the "immobility reflex"

| | Nullipara | | Multipara | | All Females | |
|---|---|---|---|---|---|---|
| Behavior | Total number | Percent conceived | Total number | Percent conceived | Total number | Percent conceived |
| Very calm | 351 | 56.7 | 520 | 68.6 | 871 | 63.8 |
| Calm | 1120 | 49.4 | 1507 | 54.5 | 2627 | 52.3 |
| Agitated | 345 | 31.3 | 461 | 36.2 | 806 | 34.1 |
| No information | 16 | 68.7 | 18 | 55.5 | 34 | 61.7 |
| All | 1832 | 47.5 | 2506 | 54.1 | 4338 | 51.3 |

Data adapted from: du Mesnil Du Buisson. 1961. Ann. Zootech. 10:57-67.