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NEUROENDOCRINOLOGY AND REPRODUCTION IN THE HUMAN

Report of a WHO Scientific Group

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NEUROENDOCRINOLOGY AND REPRODUCTION IN THE HUMAN

Report of a WHO Scientific Group

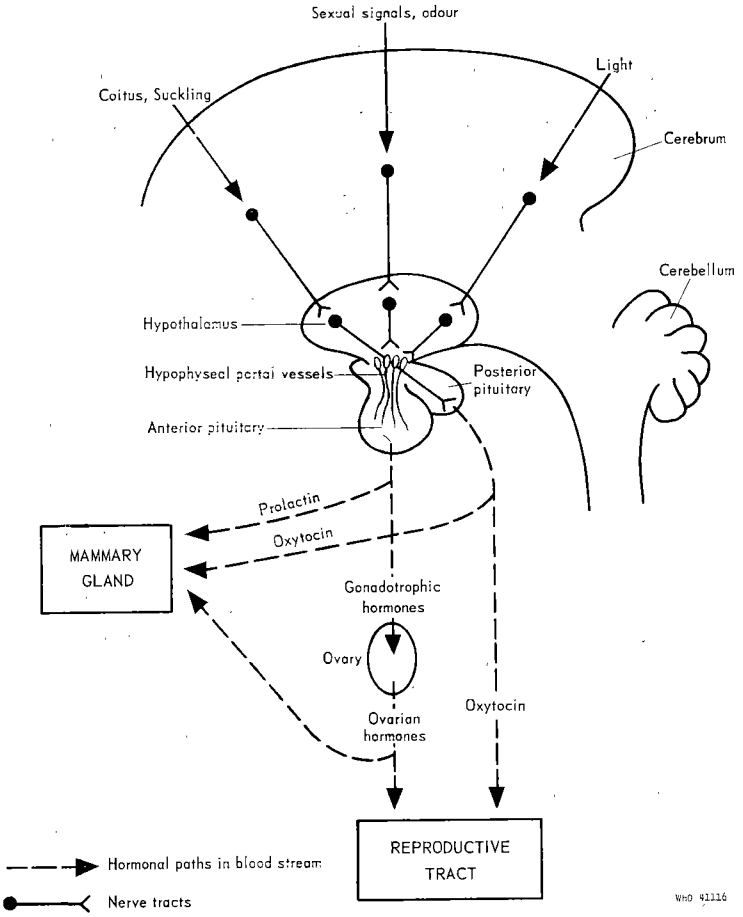
1. INTRODUCTION

1.1 A WHO Scientific Group on Neuroendocrinology and Reproduction in the Human was convened in Geneva from 8 to 14 September 1964 to advise the Director-General on developments and research needs in this field. The meeting was opened by Dr F. Grundy, Assistant Director-General. Professor Laidlaw was elected Chairman, Dr Flerkó Vice-Chairman and Professor Martini and Dr Michael Rapporteurs.

1.2 A hundred years ago the brain and nerves were thought to control all the functions of the body, including reproduction. With the rise of reproductive endocrinology during the second and third decades of this century the nervous element became obscured and the belief grew up that puberty, sexual cycles, pregnancy and lactation were controlled entirely by hormones. The balance has been restored over the last 20 years or so by a growing body of evidence that the nervous and endocrine systems are closely co-ordinated in the control of reproductive function. This knowledge has come to constitute a large part of the new science of neuroendocrinology.

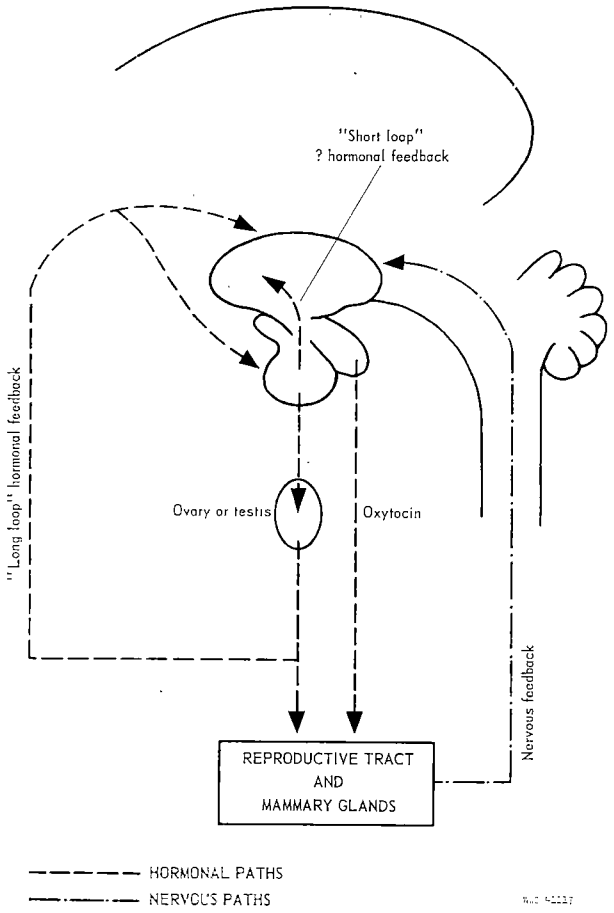
1.3 Human sexual neuroendocrinology can scarcely be said to exist as a separate discipline at the present time, for the new science is based mainly on animal studies. Yet there are many puzzling phenomena that may involve neuroendocrine mechanisms. They include various types of amenorrhoea, phantom pregnancy, disturbed rhythm of menstrual cycles in certain occupations, e.g., airline stewardesses, and various manifestations of homosexuality and transvestism. Ovulation certainly involves a neuroendocrine mechanism, and some, if not all, of the drugs prescribed for use by women to inhibit ovulation act at this level. Potentially the most significant finding of neuroendocrinology for human health and welfare is that pre-natal or post-natal exposure of the developing nervous system to certain hormones or drugs can induce long-lasting effects on sexual activity and behaviour that may become apparent only in the adult and that may not be accompanied by obvious physical signs of abnormality. This fact should be much more widely appreciated.

FIG. 1. NEUROENDOCRINE CONTROL OF REPRODUCTION



1.4 The basic arrangement of the neuroendocrine systems concerned in reproduction is shown for convenience in diagrammatic form in Fig. 1 and 2. Fig. 1 indicates how certain nervous stimuli impinge on the hypothalamus and travel thence via neural and vascular pathways to the pituitary gland, where they elicit the secretion of one or more pituitary hormones. From the anterior lobe (adenohypophysis) come the gonadotrophic hormones—FSH (follicle stimulating hormone) and LH (luteinizing hormone)—and prolactin, which, because of its luteotrophic action in rats and mice, is sometimes called luteotrophin, LTH. From the posterior lobe (neurohypophysis) comes oxytocin, the only hormone from this lobe that is concerned in reproduction. Fig. 2 indicates the hormonal and nervous feedback pathways that modulate the activity of the hypothalamus and pituitary.

FIG. 2. HORMONAL AND NERVOUS FEEDBACK TO HYPOTHALAMUS AND PITUITARY



2. PSYCHOSOMATIC FACTORS IN HUMAN REPRODUCTION

2.1 As one ascends the evolutionary scale the role of psychological factors in reproductive processes becomes increasingly apparent. We have little information about psychological influences in animals, although the neuroendocrine mechanisms in reproduction are generally well established in several species. In the human, not only are data on neuroendocrine mechanisms scanty and indirect but the important psychological aspects have themselves been little studied.

2.2 It is well recognized that there are women with reproductive disorders for which no primary somatic cause can be found. In this category is a group of disorders that has been diagnosed mainly by a process of exclusion

and that includes psychogenic amenorrhoea and dysmenorrhoea, pseudocyesis and certain cases of dysfunctional uterine bleeding. The acquisition of information about these conditions has been greatly hampered by a lack of controlled observation and measurement. Despite the widespread feeling among clinicians that a psychogenic factor is important, there are few data to substantiate this view. There is, moreover, the ever-present difficulty in the psychosomatic field of establishing causal relations between psychological events and bodily changes ; this is particularly evident when reproductive processes are involved.

2.3 Some of the most convincing evidence for the influences of the central nervous system in human reproduction comes from clinical findings in psychogenic amenorrhoea and pseudocyesis. Amenorrhoea can follow an acute psychic trauma, or be a concomitant of stressful conditions, as for instance in wartime. It is also a common disorder in psychotic or psychoneurotic women and in those suffering from anorexia nervosa. Strong emotional attitudes towards pregnancy, either fear of or desire for it, may be associated with absence of menstrual periods together with other symptoms of pregnancy, including abdominal enlargement, breast growth and secretion and such subjective symptoms as " foetal " movement and " labour pains ". The psychological element in these patients is indicated both by the circumstances of origin of the symptoms and by the remission of the symptoms with improvement in the mental state.

2.4 In these amenorrhoeic conditions, measures of hormonal status, such as urinary gonadotrophin assay, vaginal cytology and endometrial biopsy, have shown a variety of patterns. A high proportion of patients with psychogenic amenorrhoea have a subnormal excretion of gonadotrophins (mainly FSH) together with signs of oestrogen deficiency. In other cases gonadotrophin levels are within the normal range but oestrogenic activity is diminished. This could be due to insufficient production of LH, and the development of an adequate LH assay in the human, which would settle this point, is desirable. In some patients gonadotrophin and oestrogen levels are normal but corpus luteum function is minimal. In other cases there is high urinary gonadotrophin excretion but atrophic vaginal smears, suggesting an interference with the ovarian response to gonadotrophin. The mechanism for this apparent lack of response is unknown, but it may possibly involve the autonomic nerve supply to the ovary, though there is at present no good supportive evidence for this. The condition of pseudocyesis in women, in contrast to that of pseudopregnancy in lower mammals, almost invariably has a psychological origin. The hormonal basis in women is not clear, although it is often associated with signs of luteal activity.

2.5 Other conditions that have been suggested as being, in some instances, of psychogenic origin are :

(1) disordered adrenocortical function, in which elevated 17-ketosteroids, hirsutism and amenorrhoea have occurred following a psychic trauma;

(2) amenorrhoea and galactorrhoea with diminished gonadotrophin excretion and atrophic vaginal smears, for which no organic basis could be found;

(3) the polycystic ovary syndrome for which a hypothalamic dysfunction has been suggested;

(4) apparent impairment of the response of the endometrium to ovarian hormones, the mechanism for which is completely unknown; and

(5) habitual abortion.

2.6 The tools available for studying the mechanisms of gonadal function and dysfunction are inadequate and need further development. The assay of gonadotrophins in urine is beset with difficulties of extraction, and the usual techniques measure mainly FSH activity. Furthermore not much is known about the relation of urinary excretion to actual production of these hormones in the body. There is need for study of the metabolic fate of human gonadotrophic hormones of pituitary origin. Assay techniques for the determination of blood serum levels of these hormones still await development. Standardized procedures for studying the ovarian response to gonadotrophic hormones are also required.

2.7 There are other stages in the reproductive process at which psychological factors might influence human fertility. Conscious and unconscious rejection of the sex act by either male or female, vaginismus and impotence are commonly reported. These conditions, undoubtedly psychological in origin, may constitute an absolute block to conception. Mechanisms involved in the passage of spermatozoa or ova through the female reproductive tract might also be affected by psychological factors. However, we have no grounds for implicating neuroendocrine mechanisms in such phenomena.

3. THE HYPOTHALAMO-HYPOPHYSEAL SYSTEM

3.1 There is much evidence that the pathway by which the neurohypophysis is regulated by the hypothalamus is distinct from that involved in the control of the adenohypophysis (Fig. 1).

3.2 The neurohypophysis is entirely nervous in origin; its secretory elements are now known to be the neurones of the supra-optic and paraventricular nuclei in the anterior hypothalamus. The axons of these cells, which contain stainable neurosecretion, pass down in the supra-optico-

hypophyseal tract through the median eminence and infundibular stem to release their hormones (oxytocin and vasopressin) into the blood vessels draining the infundibular lobe. The neurosecretion shows characteristic staining affinities, and histochemical evidence indicates that the neurohypophyseal hormones are contained in it. The amount of neurosecretion present varies according to the physiological state of the animal, and it accumulates at the proximal stump if the axons are sectioned. If the axons are interrupted near their origin, the supra-optic and paraventricular cells degenerate and all hormonal activity is lost from the posterior lobe. Animals so treated often have difficulty in labour through loss of oxytocin and may fail to lactate because the milk-ejection reflex is absent. On the other hand, interruption of the supra-optico-hypophyseal tract in the infundibular stem has less severe effects, for, although the infundibular lobe loses all hormonal activity, enough supra-optic and paraventricular cells survive in the hypothalamus to continue production of the hormone, which is then released at the site of severance of the tract. Most investigators agree that neurohypophyseal destruction by itself does not interfere with the function of the adenohypophysis.

3.3 The adenohypophysis develops from buccal ectoderm, and its secretory cells apparently have no direct connexion with hypothalamic cell bodies or axons. The few nerve fibres present in the gland seem to derive mainly from parasympathetic and sympathetic nerves, and they have not so far been shown to play any important part in pituitary function. Although recently it has been shown that there are a few fibres emerging from the median eminence and entering the pars tuberalis, it is doubtful if they constitute a significant innervation to the adenohypophysis.

3.4 The critical link between the hypothalamus and adenohypophysis is the hypophyseal portal system of blood vessels. This structure, present in all mammals and in most lower vertebrates, consists essentially of a plexus of capillaries in the median eminence which drain into straight vessels in the pituitary stalk terminating in a second set of capillaries in the pars distalis of the adenohypophysis. The blood in these vessels constitutes the main supply to the pituitary in most mammals and presumably contains the specific substances (neurohumoral mediators) essential for maintaining normal secretory activity.

3.5 Well-nourished and viable autografts of pituitary tissue in sites other than the sella turcica, e.g., the renal capsule, lose their capacity to secrete FSH and LH but continue to secrete prolactin, which points to the existence of an inhibitory mechanism for prolactin secretion in the hypothalamus. Restoration of FSH and LH secretion can be effected if the intrarenal grafts are perfused with median eminence extracts or if they are regrafted back into the sella turcica, where the portal vascular supply can be re-established,

or alternatively regrafted in a circumscribed midline area of the ventral hypothalamus itself extending from the paraventricular nucleus to the mamillary body (" hypophyseotrophic area ").

3.6 The precise site of origin in the hypothalamus of the neurohumoral mediators is not known with certainty, but cells of the arcuate nuclei and the other areas which contribute axons ending in close apposition to the primary capillary plexus of the hypophyseal portal system are probably concerned. The active substances are concentrated in the median eminence, but large amounts of this tissue are required to extract sufficient amounts of the mediator substances for chemical characterization. Much painstaking work has established that the mediators are polypeptides, closely akin to, but not identical to, the neurohypophyseal hormones.

3.7 There is now some evidence for the existence of a subsidiary vascular pathway in association with the classical hypophyseal portal system, which conveys blood from the pituitary stalk in an upward direction to the hypothalamus. Its significance has yet to be determined, but it could provide an anatomical route for a hormone feedback direct from the pituitary to the hypothalamus (Fig. 2). With regard to the main portal vessels to the pars distalis of the pituitary, it has been demonstrated that these have a strictly regional distribution within the gland. This raises the possibility that separate neurohumoral mediators may be formed at different hypothalamic sites and conveyed to particular cell populations in the pituitary. Other studies have suggested that vasomotor charges in the hypophyseal portal system may influence adenohypophyseal secretion, and this interesting idea deserves further examination.

4. THE MECHANISM OF SEXUAL RHYTHM

4.1 The recurrent oestrous or menstrual cycles of many mature female mammals depend upon the rhythmic secretion of hormones by the adenohypophysis and ovary. However, the rhythm is not intrinsic to these glands but is imposed by the central nervous system. If in the adult female the neurohumoral link between the pituitary and hypothalamus is severed, the cycles are abolished. The dominating position of the hypothalamus is further demonstrated by the fact that the infantile pituitary, if grafted in contact with the hypophyseal portal system of an adult female, is induced to secrete gonadotrophic hormone long before it would normally do so. A process of maturation occurs in the hypothalamus during the growth of the individual, which is responsible for the onset of gonadotrophic activity associated with puberty. This process can be interfered with experimentally, e.g., by lesions placed in the hypothalamus just behind the optic chiasma, which result in precocious puberty. In this connexion,

however, it is of interest that, in the human, tumours in the posterior hypothalamus are more usually associated with sexual precocity, while tumours in the anterior area tend to produce hypogonadism.

4.2 In those mammals that have been studied, there is a difference between the two sexes in the gonadotrophin-regulating properties of the hypothalamus, the masculine pattern being characterized by a continuous non-cyclic and the female pattern by a cyclic activity. A major factor determining whether the immature hypothalamus will develop into the adult male or female type is the hormonal environment of the brain during embryonic or neonatal life. Administration of testosterone during this critical period permanently inhibits cyclic activity, while oestrogen treatment of males interferes with normal male sexual development and behaviour. Recent work has shown that if male rats are castrated at birth the hypothalamus, when mature, functions in the female fashion. Evidently therefore the androgen produced by the neonatal testis is normally adequate to " imprint " the male pattern on the developing brain. Such influences may well operate also in the human, and the treatment of pregnant women or young children with certain steroids, e.g., some of the synthetic progestogens, may entail a hitherto unrecognized hazard.

4.3 The nature of the hypothalamic mechanism controlling the cyclical changes in the adult female is still incompletely understood. It is evident, however, that in those mammals (including man) that ovulate spontaneously, the trigger that releases an ovulating dose of gonadotrophin from the adenohypophysis derives from a periodic hypothalamic function or " clock ". Central nervous depressant drugs applied at a critical time of day may arrest the " clock " and postpone the cycle by 24 hours, and this process may be repeated indefinitely. In the rat it now seems fairly certain that the clock mechanism involves the pre-optic and septal regions, electrical stimulation of which can advance ovulation by premature release of gonadotrophic hormone.

5. NERVOUS INFLUENCES ON THE HYPOTHALAMUS

5.1 The inherent oestrous rhythms of mammals discussed in the last section are subject to at least three kinds of external or environmental modulating influences (Fig. 1).

5.2 First there are the external stimuli that determine the time of onset of reproductive cycles in many seasonal breeding animals. Light is a dominant factor here. The female ferret, for example, normally comes into oestrus during March and may have two litters before going into anoestrus at the end of July. If, however, extra light is provided artificially to extend the

length of " day ", from October onwards the ferret can be induced to breed in the winter. In sheep, on the other hand, the opposite relation of cycles to day-length holds, i.e., normally ewes commence oestrous cycles in the autumn, when days are shortening. It is possible to make ewes come into oestrus in spring, under laboratory conditions, by exposing them to a sequence of naturally lengthening days followed by one of artificially shortened days. The reversal of annual breeding season that follows translocation of animals, e.g., sheep and deer, from the northern to the southern hemisphere is almost certainly a related phenomenon.

5.3 Second, there are the external factors that can influence the phasing of oestrous cycles within the period of reproductive activity. In the laboratory rat, the cycle can be shifted 12 hours out of phase by keeping the animals in the dark during daytime and supplying artificial light during the hours of darkness. A more subtle effect involving social aspects is seen when female mice are crowded together. Under these conditions the introduction of a male to the group synchronizes previously irregular cycles, so that about half the females come into oestrus and mate on the third day. A related phenomenon is the pregnancy-block effect in mice. In this, the introduction of an alien male distinct from the successful mate has the capacity to restart oestrous cycles and thus prevent continuation of pregnancy. Olfactory stimuli have been shown to play a critical role in both these situations.

5.4 The third type of external stimuli are those that interrupt the sequence of oestrous cycles during the reproductive period. Coitus and suckling are perhaps the most obvious examples in mammals. In some rodents, copulation induces pseudopregnancy by stimulating the secretion of prolactin (LTH) by the adenohypophysis and prolonging the secretory activity of the ovarian corpora lutea. Suckling may interrupt the sexual cycles of many mammals including man. In the human, as already noted (para. 2), there are also other factors, social and psychological, that have a comparable effect. That environmental factors such as light may also participate in human reproduction is suggested by the occurrence of earlier menarche in blind girls and menstrual irregularities in certain occupational groups, e.g., airline stewardesses.

5.5 The elucidation of the nervous pathways and mechanisms by which the various external, emotional and sexual stimuli bring about changes in reproductive function is still very incomplete. Anatomical and electrophysiological data show that there is a remarkable convergence of afferent projections to the hypothalamus, involving both a wide array of sensory modalities and a wide distribution of originating nervous structures. In implicating particular central nervous pathways in particular neuroendocrine phenomena, much reliance has been placed on the results obtained by lesioning techniques, which are by their nature difficult to interpret. In no

single case is there comprehensive information on the receptors excited, the peripheral sensory and spinal tracts transmitting the stimuli to the brain, and the central nervous pathways serving as the route to the hypothalamus.

5.6 Because release of oxytocin from the neurohypophysis is quickly revealed by its effect on the uterus or lactating mammary gland, data on the nervous pathways involved in its secretion exceed those available for any of the adenohypophyseal hormones. Electrical stimulation of a number of nervous structures in the brainstem and forebrain has been reported to excite the release of oxytocin. On the other hand the lesion evidence implicates very few of these structures in the natural milk-ejection reflex. This seems to involve a predominantly ipsilateral path in the lateral funiculus of the spinal cord, rather diffuse ascending systems in the brainstem, and the periventricular fibres entering the hypothalamus. The functional significance of the forebrain limbic structures whose stimulation elicits oxytocin release is unknown, but they may participate in higher nervous mechanisms concerned in emotional or conditioning processes.

6. HORMONAL INFLUENCES ON THE HYPOTHALAMUS

6.1 Gonadal hormones act on the hypothalamus in the adult animal in at least two ways, namely, to regulate the secretion of gonadotrophins and to activate the mechanisms responsible for the expression of sexual behaviour.

6.2 It is generally agreed that, in the cyclical control of FSH and LH secretion, the rising level of blood oestrogen during ovarian follicular growth inhibits further FSH secretion and facilitates the release of LH by the hypothalamic trigger mechanism (para. 4.3), so bringing about ovulation and the formation of corpora lutea. Gonadotrophin secretion is depressed by exogenous oestrogen and enhanced by ovariectomy. Lesions of the anterior hypothalamic area interfere with this feedback mechanism so that persistent follicular activity results, with prolonged oestrogen secretion by the ovary. Grafts of ovarian tissue placed in this anterior area, but not in the posterodorsal part of the hypothalamus or in the pituitary itself, cause a reduction of ovarian activity as indicated by uterine atrophy. Direct implantation of oestrogen in the anterior area has a similar effect. The absence of compensatory ovarian hypertrophy following unilateral ovariectomy in rats with anterior hypothalamic lesions also indicates that this part of the hypothalamus is involved in the oestrogen-responsive system. However, it does not appear to be the only area affected by oestrogenic hormone, because oestrogen implantation in the median

eminence-arcuate zone halts gonadotrophic secretion and causes ovarian atrophy; evidence in species other than the rat implicates the posterior tuberal region as a site of inhibitory oestrogenic feedback.

6.3 Another approach is to study the site of uptake of labelled oestrogen given by systemic injection. Oestrogen appears to be taken up selectively by the hypothalamus, pre-optic and septal regions and is virtually absent from other brain structures, though it is taken up by non-nervous target organs such as the uterus and vagina. Maximal uptake by the hypothalamus occurs at two to five hours after injection and thereafter the activity wanes; some of it apparently leaving the hypothalamus via the portal vessels to the adenohypophysis. Nothing is yet known about the uptake of progesterone by the hypothalamus, although experiments involving EEG or single-neurone recording indicate that progesterone has important effects on the excitability of neural mechanisms in the pre-optic and lateral hypothalamic areas concerned with gonadotrophic function.

6.4 All these data now indicate the presence of neural elements in the brain that are specifically sensitive to gonadal steroids. However, present knowledge has been gathered from very few laboratory species and is certainly incomplete both as regards the site and mode of action of the gonadal hormones. In recent years much progress has been made with the study of the mode of action of androgens on seminal vesicles and the prostate in the rat and of oestrogens on the hen oviduct and the rabbit uterus. The sequence of biochemical effects occuring after the administration of these steroids to castrated animals, e.g., the synthesis of phospholipids and nucleoproteins, has been studied in great detail. It seems appropriate to apply similar refined biochemical techniques, as well as histochemical and electrophysiological techniques, to the study of nervous tissues sensitive to hormonal action.

7. NEUROENDOCRINE ASPECTS OF SEXUAL BEHAVIOUR

7.1 In those mammals with cycles of oestrus or heat behaviour, the tissue changes essential for successful fertilization must be synchronized with the behavioural changes essential for successful mating. Unless the behaviour of the female towards the male changes from the non-receptive to the receptive pattern at the right time, fertilization cannot occur. It is, perhaps, self-evident that the brain must mediate these behavioural changes.

7.2 There is no doubt that gonadal hormones play a very prominent part in the promotion of sexual behaviour in laboratory mammals. Prepuberal gonadectomy abolishes adult sexual performance in many species. Reference has been made (para. 4.2) to the influence of gonadal steroids administered during the embryonic or neonatal periods in determining the subse-

quent direction of sexual development and behaviour in the adult. It seems likely that the essential neural mechanisms responsible for the patterns of sexual behaviour already exist in the brain of the mature animal and are accessible to the priming action of gonadal hormones and external stimuli. The " organizational " effects of hormones in early life may be contrasted with their " activational " effects later on. The prevalent influence of hormones is perhaps seen more clearly in the female than in the male, and there are many detailed species differences. For instance, in the mouse, rat and guinea-pig, oestrogen and progesterone act synergistically to induce mating, in the ferret progesterone antagonizes the behavioural effect of oestrogen, while in the cat and pig progesterone is relatively unimportant.

7.3 It is also evident from comparative studies that phylogenetic advancement is associated with a progressive emancipation from the strict behavioural dependence on sex hormones, and, although the sexual behaviour of infra-human primates can be markedly influenced by the administration of sex hormones, mating is not confined to a restricted part of the menstrual cycle. This emancipation reaches its extreme expression in the human in which no very clear relationship between hormone levels and sexual activity has been established, although the data are sparse.

7.4 Developmental, environmental, nervous and endocrine factors, and many others, influence sexual behaviour. The sight of a female in the oestrous posture will stimulate the male cat to mount. The odour of the male cat induces oestrous rolling behaviour in the female cat, and the odour of the boar elicits the immobilization response in the sow. However, although information from the distance receptors and sensations from the pelvic erogenous zones contribute importantly to sexual arousal, they are not essential for its expression. Anosmic, blinded and deaf animals or those with anaesthesia of the perineum following combined sacral cord section and abdominal sympathectomy will continue to show oestrous behaviour and mate successfully. The essential neurological mechanisms involved do not appear to reside in the neocortex in the female animal, since chronic decortication fails to abolish signs of heat or to prevent mating.

7.5 Recent work involving implantation of small quantities of solid oestrogen in the brain of cats has helped to clarify the location and response characteristics of the neural system mediating sexual behaviour in female cats. Implants of oestrogen are maximally effective in producing sustained oestrous behaviour in ovariectomized cats only if placed in certain parts of the hypothalamus, when the cats remain continuously receptive to the male despite the persistence of atrophic genital tracts. It is noteworthy that this distribution coincides in part with the area of maximal uptake of tritium-labelled oestrogen by the brain following its subcutaneous administration (para. 6.3) and with the so-called hypophyseotrophic area (para. 3.5).

7.6 Experiments with rhesus monkeys have shown that the patterns of sexual behaviour and of grooming behaviour between members of a pair of animals are intimately related and influenced by the hormonal state of the female. In addition to cycles of mounting activity there are clear-cut cycles of grooming behaviour, both of which are related to the menstrual cycle. Since grooming activity is a means by which an individual defines its position and status in the highly organized primate society, it is of interest that it is susceptible to hormonal influences. Little is known of the neuroendocrine aspects of the control of sexual and social behaviour in the primate.

7.7 Bisexual or homosexual activity is common among lower mammals. Most obvious, perhaps, is the mounting and pelvic thrusting behaviour shown by female animals e.g., cows, guinea-pigs, rats and rhesus monkeys. It would seem that both sexes possess something of the repertoire of sexual behaviour of the opposite sex. Brain lesions or the administration of heterologous hormones can enhance these effects. The anomalies of sexual activity encountered in the human do not appear to differ in essentials from those in other mammals.

7.8 Clinical experience shows that it is difficult to relate changes in libido in the human female to the menstrual cycle. Premenstrual, postmenstrual and pre-ovulatory peaks have been reported. Neither ovariectomy or menopause on the one hand nor oestrogen therapy on the other appear markedly to influence female libido, but androgenic treatment often enhances it. In men, castration is followed by a gradual loss of libido over a number of years. There is also evidence that oestrogen therapy diminishes male sexual drive. In panhypopituitarism, there is loss of both potency and libido. Reliable data are lacking mainly because no accepted measures of libido in the human are available. There would nevertheless appear to be a notable lack of correlation between hormonal status and several types of sexual anomaly, such as homosexuality or gross hypersexuality in both men and women.

8. EFFECTS OF DRUGS ON REPRODUCTION

8.1 Apart from the gonadotrophins and the sex steroid hormones, a wide range of drugs has been found to influence reproductive function. Two tests that have been much used to identify a specific neuroendocrine effect in mammals are (*a*) blockade of copulation-induced ovulation in the rabbit and (*b*) blockade of spontaneous ovulation in the rat (4.3). Drugs shown to inhibit the release of gonadotrophin in such tests include: the anticholinergic agents atropine and methantheline; the antiadrenergic drugs

dibenamine and dibenzyline; hypnotic doses of the barbiturates pentobarbital and phenobarbital; the tranquillizers reserpine and chlorpromazine; and morphine, ether and other general anaesthetics.

8.2 These groups of drugs very likely act in different ways on the central mechanism that activates the release of an ovulating amount of gonadotrophin. Many studies have been made on the neuropharmacological action of some of these blocking agents, e.g., on brain thresholds to electrical stimulation or on EEG reactions, but their biochemical mode of action is still largely unknown, at least in so far as their neuroendocrine effects are concerned. Also, the nature and extent of all their other effects have not been clarified. The tranquillizing drugs, for example, have many actions on the central and peripheral nervous system and are known to affect secretion of adrenocorticotrophic hormone (ACTH) and other pituitary hormones. Even their effects on reproduction are not confined to a single process. Reserpine and chlorpromazine, besides blocking LH release, stimulate prolactin secretion and may induce lactation. It has also been shown that these drugs may interfere with the response of the ovary to exogenous gonadotrophins. In species (such as the rat) in which oestrogen and progesterone act synergistically to induce oestrus, the administration of reserpine in place of progesterone will substitute for its action.

8.3 Recently it has been found that a single dose of reserpine given to four-day-old female rats may delay puberty, reduce the LH content of the pituitary, and disrupt postpuberal sexual rhythmicity. These findings indicate a long-term interference with the neural mechanisms controlling gonadotrophin secretions. The finding that certain tranquillizers and gonadal hormones (para. 4.2), when given during a critical period in the early life of animals, may have a delayed effect on sexual rhythmicity has important implications for the human. When natural or synthetic gonadal or adrenocortical hormones and drugs with a central nervous action are given during pregnancy or early childhood it is imperative that careful thought be given not only to early effects on the child, but also to late influences on its sexual development. These considerations should be borne in mind particularly in the testing procedures for new drugs.

8.4 In addition to the neuropharmacological agents discussed above, synthetic derivatives of dithiocarbamoylhydrazine have been shown to produce atrophy of the gonads and thence of the accessory organs of both sexes in several species. In women these compounds abolish the mid-cycle peaks in urinary gonadotrophins and oestrogens, and therefore presumably suppress ovulation. After the menopause they depress, but do not abolish, gonadotrophic excretion. The known effects are rapidly reversible after the end of treatment, but the precise mechanism of their action remains obscure.

8.5 A derivative of diphenylchloreothylene known as clomiphene, chemically related to synthetic oestrogens, has been shown to have antigonadotrophic and anti-oestrogenic activity in several laboratory species. The animal results have proved a poor guide to its action in the human, for in marked contrast this same substance induces ovulation in a high proportion of anovulatory women. Pregnancy can occur in such patients after infertility lasting many years. However, a number of untoward effects have been reported, the most important of which are the increased incidence of multiple pregnancy and excessive ovarian enlargement. In this case there is little available evidence to indicate whether the major effects are at the neural, pituitary or ovarian level.

8.6 Finally it may be mentioned that the separation of a potent antigonadotrophic principle (malatonin) from extracts of the pineal gland, offers the possibility of a non-steroid biological material for controlling fertility. Incidentally, this development once more focuses attention on the problem of the role of the pineal gland in reproduction.

9. RESEARCH NEEDS

The following proposals are not placed in any particular order of priority. The references in parentheses indicate the relevant passages in the body of the report.

The Scientific Group considers that the further development of techniques in the following areas is desirable for the advance of reproductive neuroendocrinology.

(1) Assays of the individual human endogenous gonadotrophins, suitable for clinical application (2.6).

(2) Autoradiography, fluorescent-antibody, spectrophometric interference and histochemical and biochemical techniques in combination with electron microscopy especially for (*a*) a study of the cells that supply axons to the region of the primary capillary plexus of the hypophyseal portal system, and the detection in them of neurohumoral mediators (3.6), and (*b*) a study of the effect of different hormonal states on hypothalamic cell structure and function (6.4).

(3) Computer techniques for evaluating electrophysiological data obtained in neuroendocrine studies (5.5, 5.6, 6.3).

(4) Improved lesioning techniques including methods of creating reversible and/or trackless inactivations of restricted loci in the brain (5.5).

The Scientific Group considers that the following research areas deserve attention.

(1) Comparative studies (interspecific and intraspecific) in mammals and primates with particular reference to :

(*a*) patterns of reproductive activity (5.2, 5.3, 5.4) ;

(*b*) exteroceptive factors (visual, olfactory, acoustic, etc.) (5.2, 5.3, 5.4, 7.4) ;

(*c*) neuroendocrine factors in sexual, parental and related social behaviour (7, *et seq.*) ;

(*d*) " critical " periods in development and the " sexualizing " effects of steroid hormones on the brain (4.2) ;

(*e*) long-term or delayed effects on sexual development and behaviour caused by central-nervous-system drugs administered during gestation or in the prepuberal period (8.3).

(2) Studies of the synaptic connexions of hypothalamic neurones, with special reference to the afferent and efferent pathways concerned in the regulation of pituitary activity (3.6, 5.5).

(3) Studies of the endogenous production of gonadal and gonadotrophic hormones in prepuberal animals including man (4.2).

(4) The functional significance of the regional distribution of hypophyseal portal vessels to the pars distalis of the pituitary (3.7).

(5) Investigation of the possibility of vasomotor control of the hypophyseal portal system as a means of modulating anterior pituitary secretion (3.7).

(6) The mechanisms involved in the selective uptake of labelled hormones by the brain, and the study of biochemical changes elicited by their presence (6.3, 6.4).

(7) Hypothalamic lesion studies in species with spontaneous ovulation and an active luteal phase (6.2).

(8) Direct effect of gonadal hormones on single hypothalamic neurones studied with combination of micro-injection and unit recording techniques (6.3, 6.4).

(9) Studies of the possibility of a direct local feedback of gonadotrophic hormones on the hypothalamus (3.7).

(10) Studies of the receptor mechanisms involved in neuroendocrine reflexes initiated by, for example, olfactory, mating and suckling stimuli (5.5).

(11) A wider exploration of brain structures with regard to the feedback action of gonadal hormones (5.5, 5.6).

(12) Studies of pineal function in relation to reproduction (8.6).

(13) Further investigation of a possible role of the peripheral autonomic pathways in reproductive processes (2.4, 3.3, 3.7).

(14) Research on the application of tissue-culture techniques, using pituitary, gonad or brain tissue, for studying problems of the origin and metabolic effects of neurohumoral mediators and the biochemical and morphological changes induced by sex hormones (3.6, 6.4).

10. RECOMMENDATIONS

The Scientific Group recommends that WHO should encourage the establishment of one or more information centres relating to human reproduction. Among the information that might be assembled and made available could be the following:

(1) social, cultural, ethnic and climatic variations in age at puberty and at menopause and in the length of the menstrual cycles (5.4);

(2) data on the relationship of psychological factors to reproductive disorders (2, *et seq.*);

(3) clinical data relating to the development of disorders of sexual structure and function as early or late consequences of drug treatment during gestation or childhood (4.2, 8.3);

(4) reproductive and hormonal disorders associated with central-nervous-system lesions in men and women (4.1, 5.5); and

(5) social, psychological and endocrine studies in cases of gonadal dysgenesis, testicular feminizing syndrome and in a variety of forms of pseudohermaphroditism (7.8).

Such data is even more scarce for the human male than for the female. Particular attention should be paid therefore to the collection of information in the above categories applicable to men.

The Scientific Group further recommends that WHO should encourage the organization by appropriate national medical bodies of neuroendocrine clinical research units to improve the services available by interdisciplinary teams including endocrinologists, biochemists, neurologists and psychiatrists. An important function of such groups would be to develop more reliable diagnostic and assay procedures.

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