

Hormones and sexual differentiation of the brain

G. DÖRNER

Institute of Experimental Endocrinology, Humboldt-University, Berlin, GDR

Abstract Male rats castrated on the first day of life exhibited predominantly heterotypical (homosexual) behaviour after androgen substitution in adulthood. In addition, an increased evocability of a positive feedback effect of oestrogen was observed in such genetic males. In homosexual men, an increased evocability of a positive oestrogen feedback on luteinizing hormone (LH) secretion was also found as compared to heterosexual men. These findings suggest that male homosexuality may be based, at least in part, on androgen deficiency during a critical period of brain differentiation. In addition, we have found significantly increased plasma follicle-stimulating hormone (FSH) and LH levels associated with decreased plasma free testosterone levels in homosexual men, but only in effeminate homosexuals. In view of these data, sexual deviations in the human may be based, at least in part, on discrepancies between the genetic sex and a sex-specific sex-hormone level during brain differentiation in prenatal life. Methods were therefore developed for determining genetic sex and sex-specific sex-hormone levels in amniotic fluid, in order to detect and possibly correct such discrepancies.

Sex hormone-dependent brain differentiation may be mediated, at least in part, by neurotransmitters, which may be regarded as local hormones of the brain. Interestingly enough, we have found permanent abnormalities of mating and other non-mating behaviour associated with permanent structural and chemical alterations in discrete brain regions of rats after neonatal treatment with psychotropic drugs known to affect neurotransmitter metabolism in the brain. Therefore, changes in neurotransmitter concentrations and/or turnover rates induced by psychosocial influences as well as by systemic hormones (particularly by sex hormones), when occurring during differentiation and maturation of the brain, may permanently affect sexual behaviour, sexual orientation and gender role behaviour throughout life.

NEUROENDOCRINE CONTROL OF THE GONADS AND SEXUAL BEHAVIOUR

The gonadotropic function of the pituitary gland was first demonstrated by Aschner (1912), who observed gonadal atrophy in dogs after hypophysect-

omy. Subsequently the gonadotropins were discovered by Aschheim & Zondek (1927) in our laboratories and simultaneously by Smith & Engle (1927) in America.

In 1932 Hohlweg & Junkmann envisaged a so-called sex centre in the central nervous system as controller of hypophyseal gonadotropic functions. Later Barraclough & Gorski (1961) distinguished a so-called cyclic sex centre in rats, located in the preoptic hypothalamic region and regulating cyclic gonadotropin secretion in females, and a so-called tonic sex centre located in the hypothalamic ventromedial arcuate region responsible for tonic gonadotropin secretion in both sexes. Recent data suggest that structures of the limbic system, especially of the amygdala, are also involved in cyclic gonadotropin release (Kawakami & Terasawa 1974; Döcke *et al.* 1975).

Our present knowledge of the hypothalamo-hypophyseal-gonadal system may be summarized as follows. In the medial basal hypothalamus a gonadotropin-releasing hormone (Schally *et al.* 1971) is secreted under the influence of neurotransmitters (Kamberi 1974; Sawyer 1975). It is transported by the hypothalamo-hypophyseal portal vessels to the anterior pituitary, stimulating there the secretion of gonadotropins. The sex hormones exert either only an inhibitory (negative) or also a stimulatory (positive) feedback effect on gonadotropin secretion, depending on sex hormone concentrations during a critical period in the differentiation period of the brain and in the postpubertal functional period as well (Dörner 1976a).

Finally, sex hormones can sensitize hypothalamic mating centres to sensory stimulation which reaches the diencephalon by pathways from the cerebral cortex and/or subcortex mediated by neurotransmitters (Dörner 1972, 1976a). In 1941, Brookhart & Dey demonstrated by means of intrahypothalamic lesions in guinea-pigs a central nervous mating centre responsible for sexual behaviour. In 1968-1969, we distinguished a so-called male mating centre located in the preoptic anterior hypothalamic area and a female centre located in the hypothalamic ventromedial nuclear region (Dörner *et al.* 1968a, 1969). In rats of either sex, predominantly male or female sexual behaviour could be selectively stimulated or abolished either by intrahypothalamic implants of sex hormones or by electrolytic lesions in these hypothalamic regions. Similar findings were meanwhile described by other authors (Nadler 1972; Powers 1972; Carrer *et al.* 1973/74; Barfield & Chen 1977).

We also found that the decrease in female sexual behaviour after bilateral or even unilateral hypothalamic lesions of the ventromedial nuclear region - that is, of the so-called female centre - was associated with a simultaneous increase in male behaviour in rats (Dörner *et al.* 1968b, 1975a). Similar findings were obtained in homosexual men, namely decreased female and increased male

sexual behaviour after unilateral lesion of the ventromedial nucleus (Roeder & Müller 1969; Müller *et al.* 1974; Dieckmann & Hassler 1975). On the other hand, lesions of the medial preoptic area—that is, of the so-called male centre—resulted in decreased male and increased female behaviour in rats (Powers & Valenstein 1972).

The following conclusions may therefore be drawn. Different neuronal reflex circuits are responsible for male and female sexual behaviour. In the medial preoptic anterior hypothalamic area a sex hormone-sensitive control centre is located belonging to a neuronal reflex circuit responsible for male behaviour, whereas in the ventromedial nuclear region a sex hormone-sensitive control centre is located belonging to a neuronal reflex circuit regulating female behaviour. Some antagonistic interrelationships appear to exist between these male and female mating centres (Dörner 1976a).

SEX HORMONE-DEPENDENT DIFFERENTIATION OF SEXUAL BEHAVIOUR

As early as 1936 Pfeiffer observed that in rats, independent of the genetic sex, the lack of testes during a critical neonatal differentiation phase resulted in cyclic release of gonadotropin from the pituitary, whereas the presence of testes during this critical phase gave rise to tonic gonadotropin secretion by the pituitary in later life. In 1938, Vera Dantchakoff reported a remarkable observation on sex hormone-dependent brain differentiation and sexual behaviour which was later confirmed by Phoenix and co-workers (Phoenix *et al.* 1959). Female guinea-pigs, exposed to androgens prenatally, showed increased male and decreased female behaviour in adulthood. On the basis of these results, Phoenix *et al.* distinguished an early organization period and a postpubertal activation period.

Adult females of other species, such as rats (Barraclough & Gorski 1961; Dörner 1972), golden hamsters (Carter *et al.* 1972; Swanson *et al.* 1974) and rhesus monkeys (Eaton *et al.* 1973), were then also found to exhibit predominantly masculine behavioural patterns in adulthood after androgen administration during critical organization periods. On the other hand, Grady & Phoenix (1963) and Harris (1964) reported that male rats orchietomized shortly after birth showed especially strong female sexual behaviour when treated with oestrogen in adulthood. Similar findings were obtained in adult male rats which had been treated with antiandrogen drugs during perinatal life (Neumann *et al.* 1967). All these observations pointed to the significance of the sex hormone level during a critical differentiation phase for the development of sexual behaviour.

OUR OWN INVESTIGATIONS ON SEX HORMONE-DEPENDENT BRAIN DIFFERENTIATION

In the last decade the following findings have been obtained in our laboratories on sex hormone-dependent brain differentiation and sexual behaviour (Dörner 1976a):

1. Male rats castrated on the first day of life showed predominantly heterotypical behaviour after androgen substitution in adulthood (Dörner 1967, 1969, 1970, 1972). In other words, genetic males exposed to a temporary androgen deficiency during the hypothalamic organization period, but to normal or approximately normal androgen levels in adulthood, were sexually excited preferentially by partners of the same sex.
2. These neuroendocrine-conditioned, female-like behavioural patterns could be prevented by androgens administered during the critical hypothalamic differentiation period (Dörner *et al.* 1968b).
3. The higher the androgen level during the hypothalamic differentiation phase, the stronger was the male and the weaker the female sexual behaviour during the postpubertal functional phase, irrespective of the genetic sex. We even observed a complete inversion of sexual behaviour in male and female rats after androgen deficiency in males and androgen excess in females during the hypothalamic differentiation period. According to these findings a neuroendocrine predisposition for primary hypo-, bi- and homosexuality may be based on different degrees of androgen deficiency in males and androgen excess in females during sex-specific brain differentiation (Dörner 1969, 1970).
4. The higher the androgen level during the critical hypothalamic differentiation period, the smaller were the nuclear volumes of the neurons in specific hypothalamic regions regulating sexual behaviour and/or gonadotropin secretion as well as in the medial amygdala, throughout life (Dörner & Staudt 1968, 1969; Staudt & Dörner 1976).
5. In male rats castrated on the first day of life, a strong positive oestrogen feedback effect on luteinizing hormone (LH) secretion (Hohlweg effect) could be induced, similar to that obtainable in normal females, but it could not be induced in males castrated on the 14th day of life or in neonatally androgenized females (Dörner & Döcke 1964; Döcke & Dörner 1966). From these findings it appears that a strong positive oestrogen feedback effect can only be evoked in adulthood if there was a low androgen level during brain differentiation.
6. More recently we have noted the following correlations between sex hormone levels during the hypothalamic differentiation and/or functional periods, on the one hand, and the evocability of a positive oestrogen

feedback effect on LH secretion on the other (see Fig. 1). After a single injection of oestrogen in postpubertally castrated and oestrogen-primed female rats a distinct surge of LH secretion was evoked, while castrated and androgen-primed females displayed a diminished and delayed surge of LH secretion. On the other hand, postpubertally castrated and oestrogen-primed male rats exhibited only a slight, but significant surge of LH secretion, whereas castrated and androgen-primed males did not show any surge of LH secretion after oestrogen injection. These findings suggest that the evocability of a positive oestrogen feedback action on LH secretion

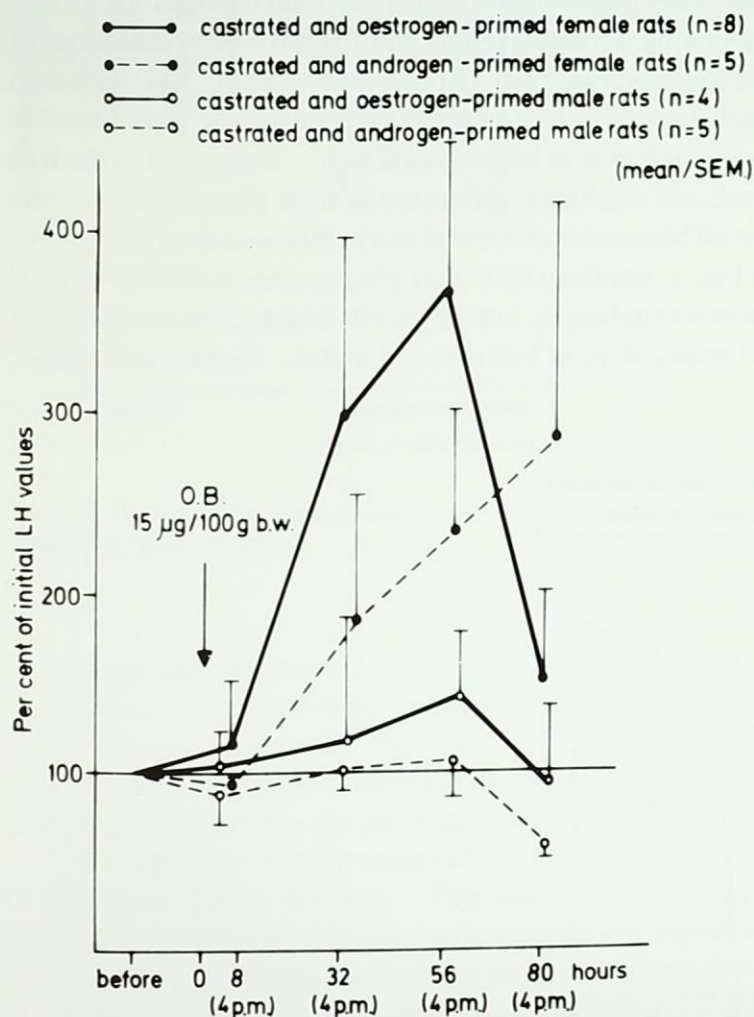


FIG. 1. Serum LH response to a subcutaneous injection of oestradiol benzoate ($15 \mu\text{g}/100 \text{ g}$ body wt.) expressed as a percentage of the mean initial LH values in postpubertally castrated and oestrogen- or androgen-primed female and male rats (means \pm S.E.M.).

depends on the sex hormone level during the critical hypothalamic differentiation phase and the postpubertal priming phase as well.

As shown in Fig. 2, a positive oestrogen feedback effect could also be elicited in intact homosexual men, in contrast to intact heterosexual and bisexual men (Dörner *et al.* 1972, 1975c). This finding suggests that homosexual men may possess—at least in part—a predominantly female-differentiated brain. On the other hand, in postpubertally castrated and oestrogen-primed men, a slight positive oestrogen feedback effect could be elicited (Dörner *et al.* 1975b), as in postpubertally castrated and oestrogen-primed rhesus monkeys (Knobil 1974).

7. More recently, the basal plasma levels of free and total testosterone as well as of follicle-stimulating hormone (FSH) and LH have been measured in homosexual and heterosexual men (Rohde *et al.* 1977). As shown in Fig. 3, significantly lower levels of free plasma testosterone were found in effeminate homosexuals than in heterosexual men. In contrast to the free testosterone levels, no significant difference in total plasma testosterone levels was observed between homosexual and heterosexual males (Fig. 4).

As shown in Fig. 5, significantly higher plasma concentrations of FSH were found in homosexual males, but only in effeminate homosexual males and transsexual males, than in heterosexual males. Significantly higher

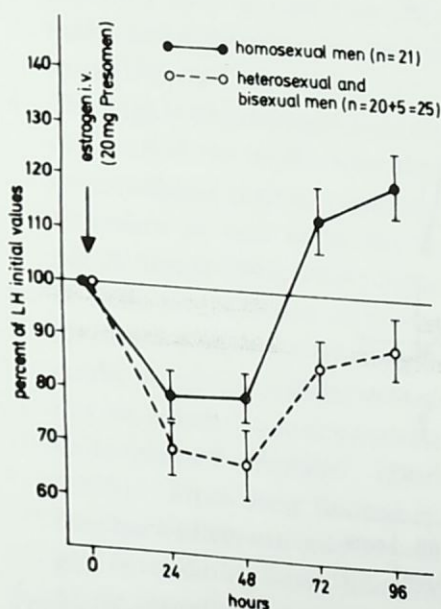


FIG. 2. Serum LH response to an intravenous oestrogen injection expressed as a percentage of the mean initial LH values in homosexual and hetero- or bisexual men.

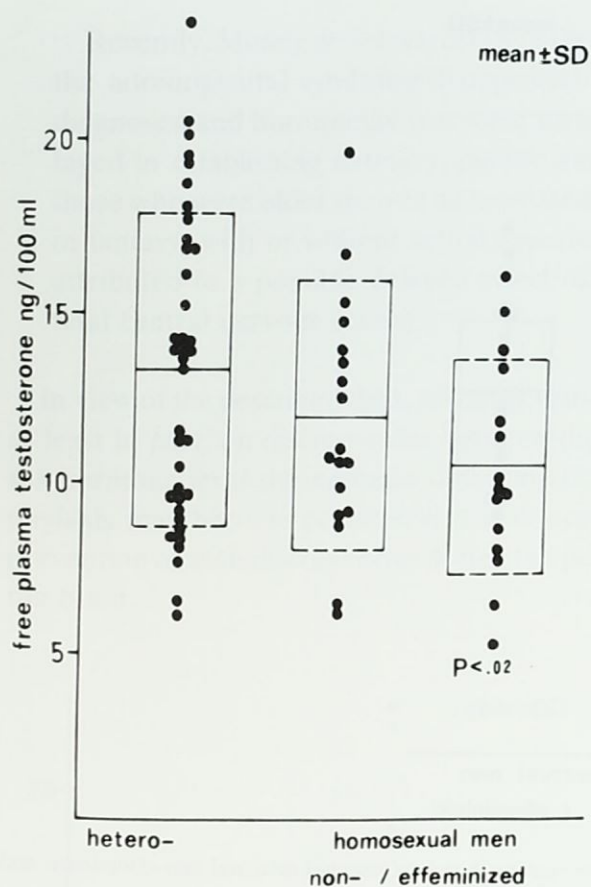


FIG. 3. Free plasma testosterone concentrations in heterosexual men and in non-effeminate and effeminate homosexuals.

plasma concentrations of LH were also observed in homosexual males, particularly in effeminate homosexuals, and in transsexual males, than in heterosexual males (Fig. 6).

In view of our experimental and clinical data, the following hypothesis may be deduced. An androgen deficiency in genetic males during a critical period of brain organization gives rise to predominantly female differentiation of the brain. This androgen deficiency in early life can be largely compensated by increased hypophyseal gonadotropin secretion in later life. Thus, the predominantly female-differentiated brain is postpubertally activated by an approximately normal androgen level, leading to homosexual behaviour.

8. In genetic females, the results of animal experiments in various species, supported by some clinical findings, suggest that androgen excess during a

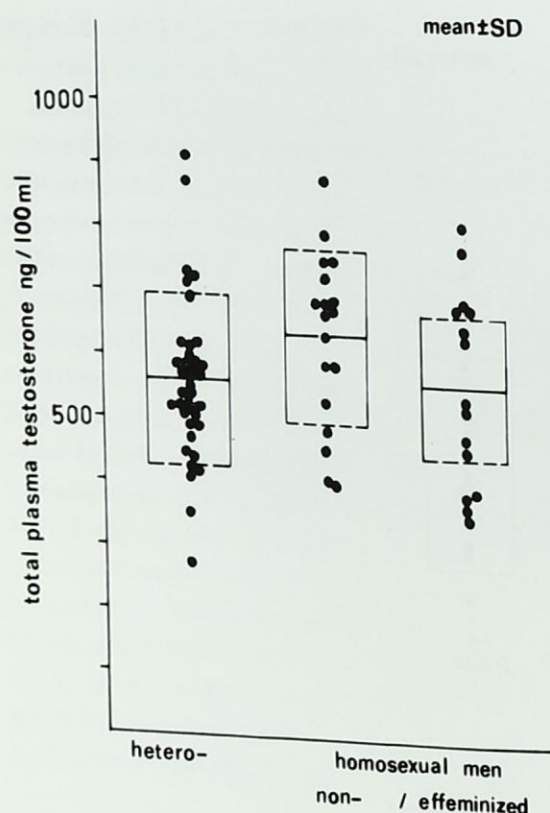


FIG. 4. Total plasma testosterone concentrations in heterosexual men and non-effeminate and effeminate homosexuals.

critical period of brain differentiation can lead to a predisposition to hypo-, bi- or even homosexual behaviour in postpuberal life. In female rats, unphysiologically high androgen and/or oestrogen levels during the hypothalamic differentiation period caused anovulatory sterility and/or a neuroendocrine predisposition to female hypo-, bi- or homosexuality (Dörner 1971a; Dörner & Hinz 1972). In this context it should be mentioned that androgens are converted to oestrogens, at least in part, by the neural tissue of fetal and neonatal rats (Reddy *et al.* 1974). A complete masculinization of sexual behaviour in female animals was observed after combined pre- and postnatal androgen treatment (Dörner 1968; Ward 1969; Sachs & Pollak 1973).

9. As demonstrated in Fig. 7, we have observed a slight increase in the plasma testosterone level in lesbian women. However, a significant increase was only found in those (nine out of 21) lesbian females showing some virilism (Dörner *et al.*, unpublished data). Similar findings were obtained by Griffith *et al.* (1974).

Recently, Money & Schwartz (1977) reported on 17 young women with the adrenogenital syndrome (congenital adrenal hyperplasia) who were diagnosed and hormonally corrected from early infancy. They were delayed in establishing dating, romantic and erotic interests. Most of all, those who were older showed an increased rate of awareness of bisexuality in fantasy, with or without actual experience. These findings were also attributed to a possible delayed effect of excess androgenization on the fetal central nervous system.

In view of the described data, sexual deviations in the human may be based, at least in part, on discrepancies between the genetic sex and a sex-specific sex-hormone level during brain differentiation. Therefore, a genuine prophylaxis may become possible, if it is desirable at all, in the future by the prevention of such discrepancies during the period of sexual differentiation of the brain.

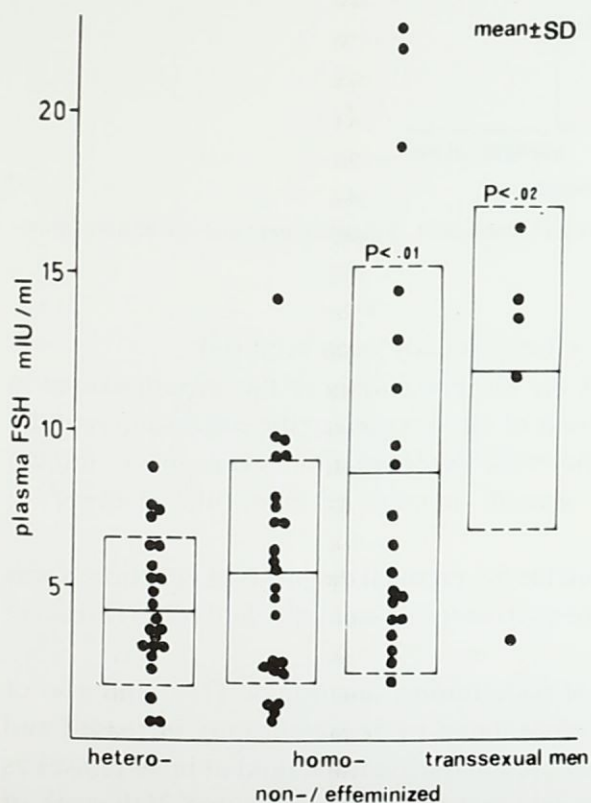


FIG. 5. Plasma FSH concentrations in heterosexual men, non-effeminate or effeminate homosexuals, and transsexual men.

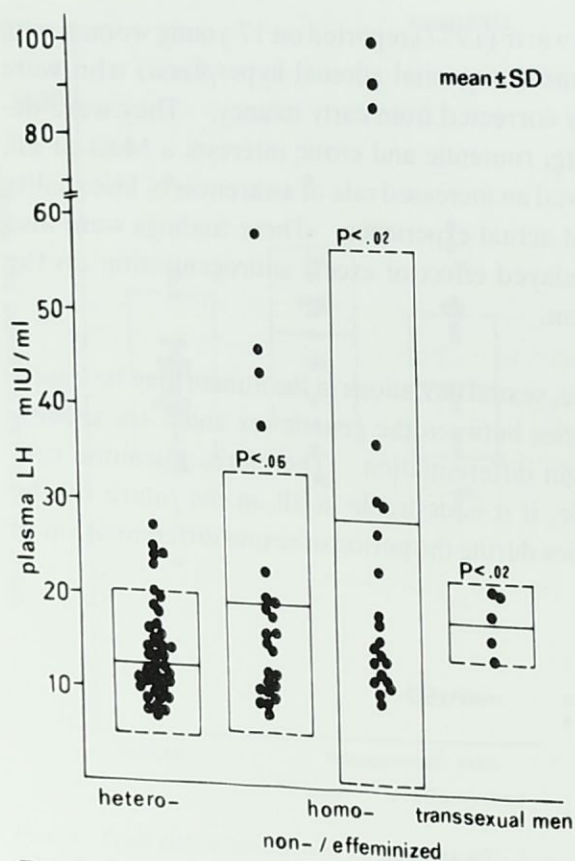


FIG. 6. Plasma LH concentrations in heterosexual men, non-effeminate and effeminate homosexuals, and transsexual men.

Three preconditions for this aim have already been achieved:

1. Our comparative studies of the morphogenesis of the hypothalamus in 84 human fetuses and hundreds of rats have led to the conclusion that the critical period of sex-specific brain differentiation occurs in the human between the fourth and seventh months of fetal life (Dörner & Staudt 1972).
2. A simple and reliable method for the prenatal diagnosis of genetic sex was developed using fluorescence microscopy of amniotic fluid cells (Dörner *et al.* 1971b).
3. As shown in Fig. 8, levels of testosterone glucuronide (TG) and also of unconjugated testosterone were found to be significantly increased and FSH levels significantly decreased in the amniotic fluid of male fetuses as compared to that of female fetuses between the 16th and 26th week of pregnancy (Dörner 1972, 1976a; Clements *et al.* 1976; Dörner *et al.* 1977b).

Therefore, the examination of amniotic fluids for genetic defects should be supplemented in the future by the determination of hormone levels in order to detect abnormalities that might lead to maldifferentiation, especially of the brain; this is all the more important as hormone-induced teratogenic effects may be accessible to preventive therapy.

In conclusion, unphysiological concentrations of hormones (e.g. of sex hormones) occurring during brain differentiation can act as 'teratogens'.

They can lead to permanent disorders of mating and non-mating behaviour associated with permanent structural alterations in discrete regions of the brain (Dörner & Staudt 1968, 1969; Raisman & Field 1971).

NEUROTRANSMITTERS AS ENVIRONMENT-DEPENDENT ACTIVATORS (OR INHIBITORS) AND ORGANIZERS OF THE BRAIN

In my opinion, hormones may be defined as chemical messengers that are produced in specific cells and exert biological effects on other cells of the same

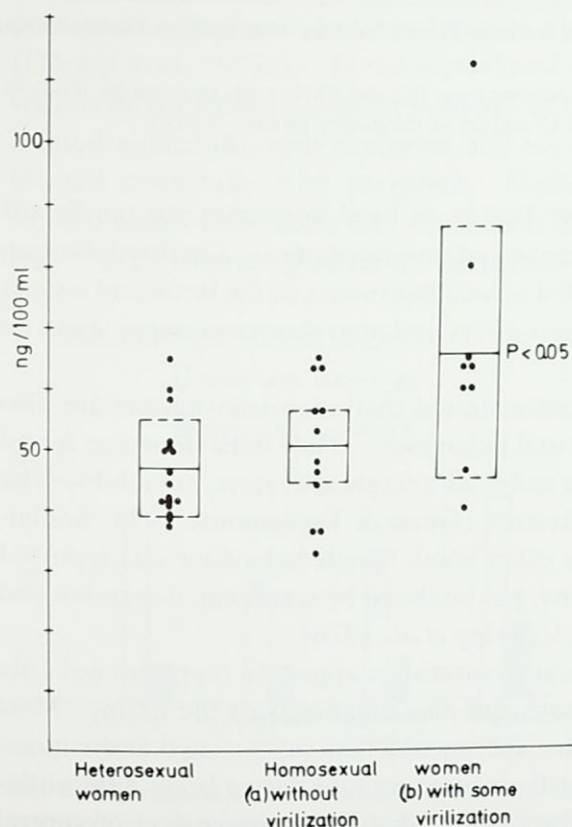


FIG. 7. Total plasma testosterone concentrations in heterosexual women and homosexual women with or without some virilization.

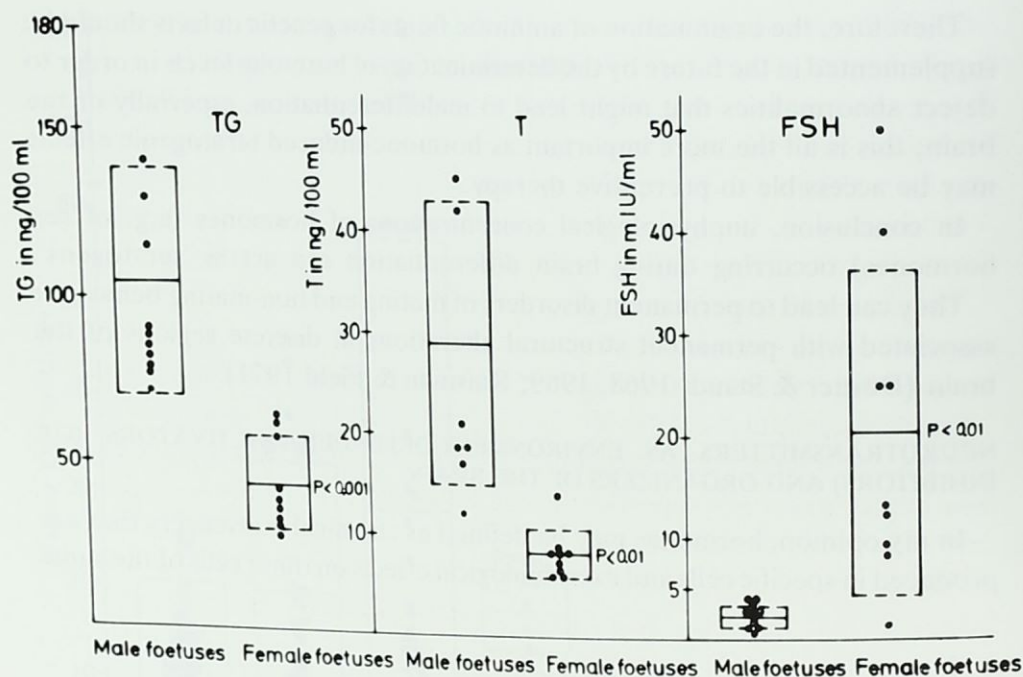


FIG. 8. Testosterone glucuronide (TG), testosterone (T) and FSH levels in amniotic fluids of male and female fetuses between weeks 15 and 26 of pregnancy (means \pm S.D.).

organism by acting either locally—that is, as local hormones—or on distant target cells—that is, as blood-borne or systemic hormones. On this definition neurotransmitters may be regarded as local hormones of the brain and a strict differentiation between neurotransmitters and neurohormones appears to be no longer justified.

In recent years it has been demonstrated that neurotransmitters are also responsible for the control of sexual behaviour. Male behaviour was found to be stimulated by acetylcholine and β -adrenergic activators, but inhibited by serotonin and α -adrenergic activators (Gessa & Tagliamonte 1975; Soulairac & Soulairac 1975). On the other hand, female behaviour was reported to be stimulated by noradrenaline, but inhibited by serotonin, dopamine and adrenaline (Everitt *et al.* 1975; Crowley *et al.* 1976).

Fascinatingly enough, such neurotransmitters appear to represent not only temporary activators or inhibitors, but also organizers of the brain. Most recently, we have obtained some experimental data suggesting that the quantity of neurotransmitters and/or their turnover rate during brain differentiation is able to predetermine the quality—that is, the reactivity—of central nervous controllers throughout life (Dörner 1976a; Dörner *et al.* 1976, 1977a, c).

Rats were treated with the monoamine oxidase inhibitor pargyline, the monoamine depletor reserpine or the acetylcholine esterase inhibitor pyridostigmine during the first two weeks of life. These animals showed significant permanent changes, not only in their sexual behaviour but also in conditioned avoidance behaviour, emotional reactivity and exploratory activity, throughout life.

As demonstrated in Fig. 9, male sexual activity was permanently decreased in males treated neonatally with pargyline or reserpine, but permanently increased in those treated with pyridostigmine. Male sexual activity was also increased in adult male rats treated neonatally with *p*-chlorophenylalanine (unpublished data).

Females treated neonatally with pargyline also showed a permanent decrease, and those given pyridostigmine a permanent significant increase, in male mounting behaviour (Fig. 10).

The permanent behavioural changes produced by psychotropic drugs administered during the period of brain differentiation were associated with permanent structural and biochemical changes in specific brain regions (Dörner *et al.* 1977c). In the medial and central amygdalar regions, highly significantly increased nuclear volumes of the nerve cells were found in rats treated neonatally with reserpine and even more markedly in adult males treated neonatally with pargyline. Nuclear structures in the pargyline-treated males were more like those of control females than of control males. Furthermore, significantly decreased concentrations of noradrenaline

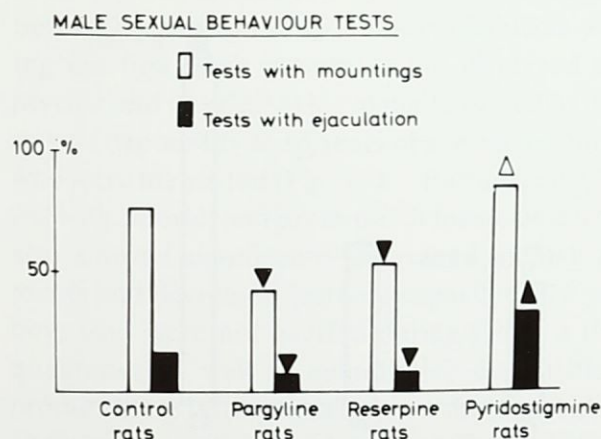


FIG. 9. Male sexual behaviour in juvenile and adult male rats after treatment with pargyline, reserpine or pyridostigmine during the first two weeks of life. Male sexuality was expressed as a percentage of positive tests with mountings and ejaculation on exposure to castrated and oestrogen-treated female rats. ▼, significantly decreased and ▲, significantly increased as compared to the controls (▼ and ▲, $P < 0.001$; △, $P < 0.05$).

and dopamine were found in the hypothalamus of adult rats treated neonatally with pargyline.

According to these data, the unphysiological concentrations and/or turnover rates of neurotransmitters apparently produced by psychotropic drugs during brain differentiation can act as teratogens. Similar teratogenic effects may be induced by the unphysiological neurotransmitter concentrations and/or turnover rates produced by abnormal levels of systemic hormones (e.g. sex hormones) as well as by abnormal psychosocial conditions during brain differentiation. Hence, the effects of systemic hormones and psychosocial influences on the differentiation and functioning of the brain appear to represent supplements rather than alternatives, since they are both mediated by neurotransmitters.

As outlined in Fig. 11, neurotransmitters appear to represent common mediators of systemic hormones, of the external environment and of nutritionally dependent metabolic variables equally for the differentiation, maturation and functioning of the brain. Thus psychosomatic interrelationships may become more conceivable and psychosomatic disturbances more accessible to preventive therapy.

Most recently, we have investigated the possible influence of qualitative and

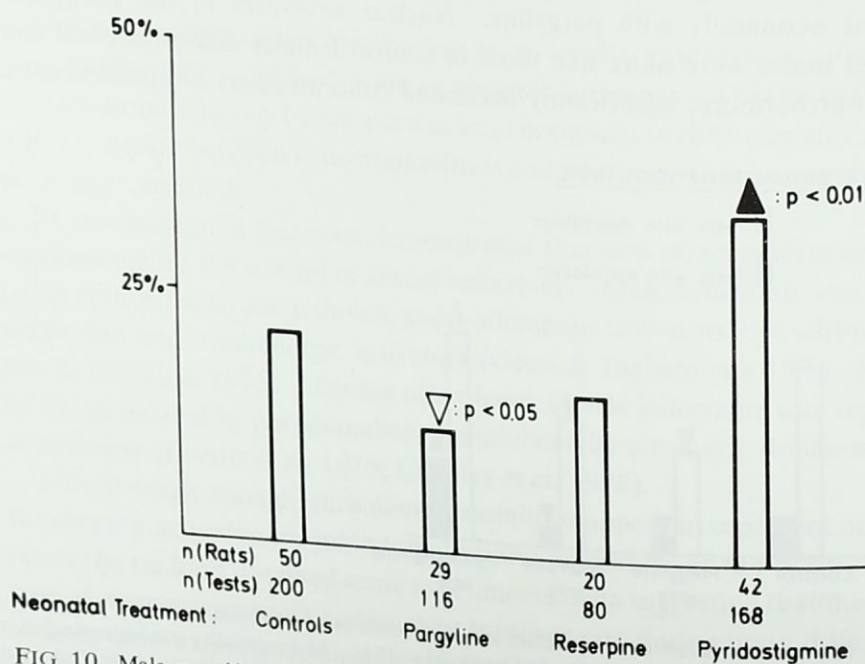


FIG. 10. Male sexual behaviour in adult female rats after treatment with pargyline, reserpine or pyridostigmine during the first two weeks of life. Male sexuality was expressed as a percentage of positive tests with mountings on exposure to castrated and oestrogen-treated female rats.

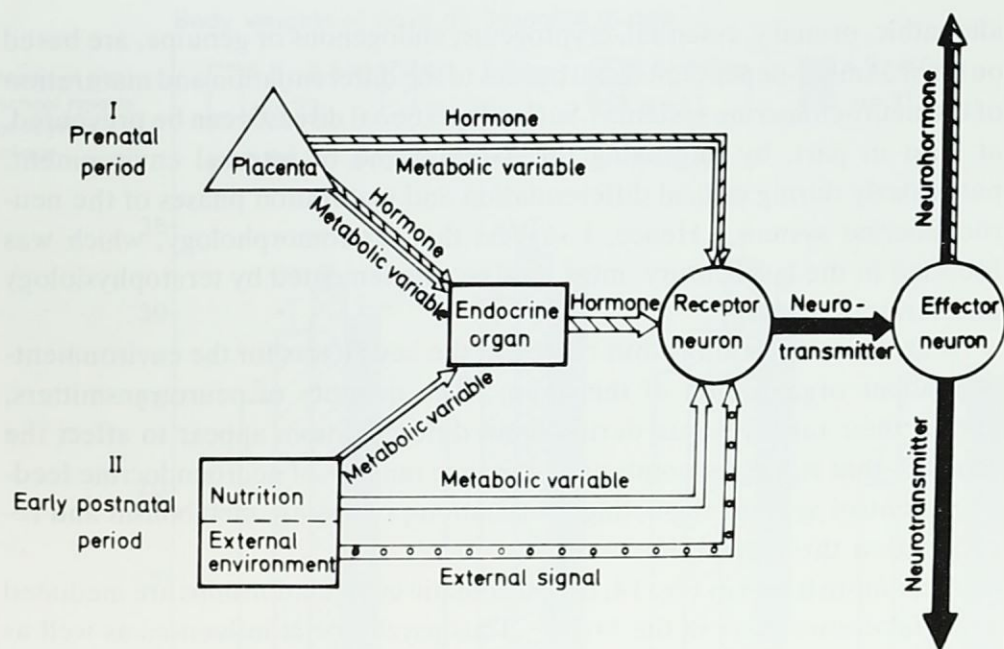


FIG. 11. Schematic representation of possible effects of systemic hormones, metabolic variables and external environmental signals on brain differentiation mediated by neurotransmitters and permanently affecting fundamental processes such as reproduction, metabolism and/or information-processing.

quantitative dysnutrition in early postnatal life on mental, psychic and physical achievements in later life. Some exciting findings have been obtained (Dörner & Grychtolik 1978). Human subjects who were purely bottle-fed during the first three months of life displayed significantly decreased mental, psychic and physical achievements as well as decreased learning capacity and social adaptability at 16 years of age when compared to subjects of similar age who were breast-fed (Fig. 12). Furthermore, boys who were artificially overfed with calorie- and protein-rich formulas during the first three months of life also showed significantly decreased mental, psychic and physical achievements and decreased learning capacity at 16 years of age when compared to boys who were not overfed during the first three months (Fig. 13). Thus, qualitative as well as quantitative dysnutrition in early postnatal life can produce long-lasting ill-effects on the mental, psychic and physical capacities and performance in the human. Similar harmful effects of over-feeding in the perinatal period have been obtained independently in animal experiments (Ryan 1977; Coupain *et al.* 1977).

In my opinion, many diseases affecting fundamental processes such as reproduction, metabolism and information-processing, previously called

idiopathic, primary, essential, cryptogenic, endogenous or genuine, are based on environment-dependent disturbances of the differentiation and maturation of the neuroendocrine system. Such adaptational diseases can be prevented, at least in part, by improving the external and or internal environment, particularly during critical differentiation and maturation phases of the neuroendocrine system. Hence, I suggest that teratomorphology, which was founded in the last century, must now be supplemented by teratophysiology and teratopsychology.

Neurotransmitters may thus represent the key factors for the environment-dependent organization of the brain. The quantity of neurotransmitters, and/or their turnover rate during brain differentiation, appear to affect the quality—that is, the set points and tolerance ranges—of neuroendocrine feedback control systems regulating information-processing, metabolism and reproduction throughout life.

As demonstrated in Fig. 14, psychosomatic interrelationships are mediated by neurotransmitters in the brain. Thus psychosocial influences as well as

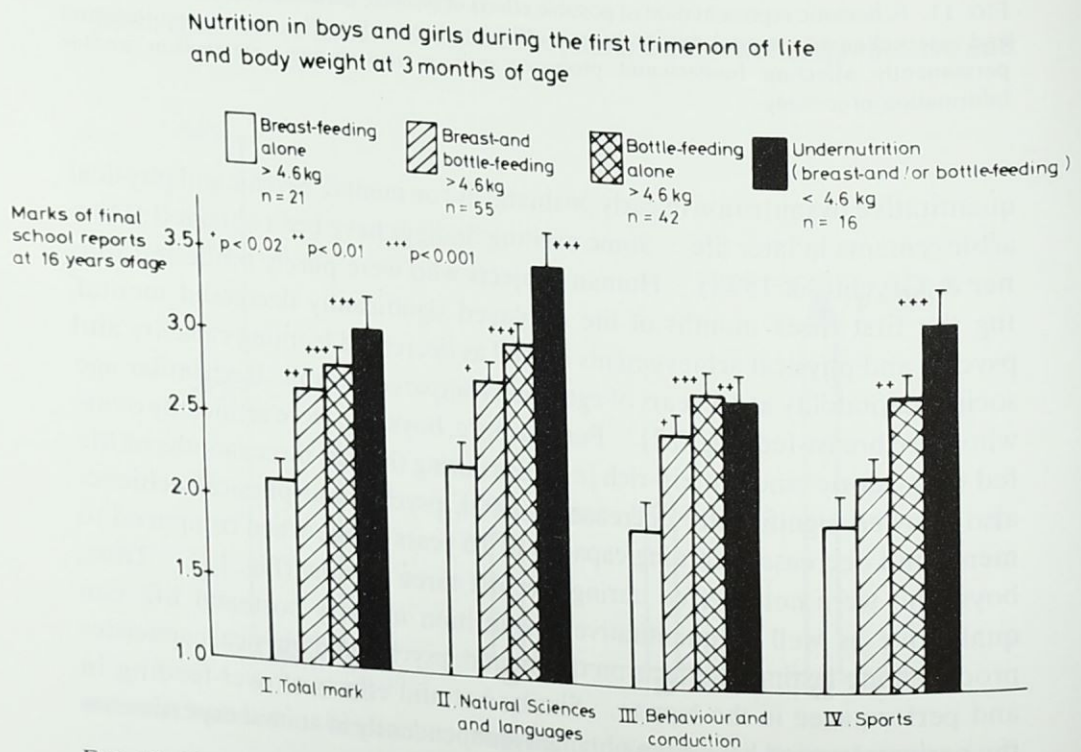


FIG. 12. The influence of breast- and bottle-feeding during the first three months of life on mental, psychic and physical achievements at 16 years of age (means \pm S.E.M. of school marks: 1, very good; 2, good; 3, satisfactory; 4, pass; 5, unsatisfactory).

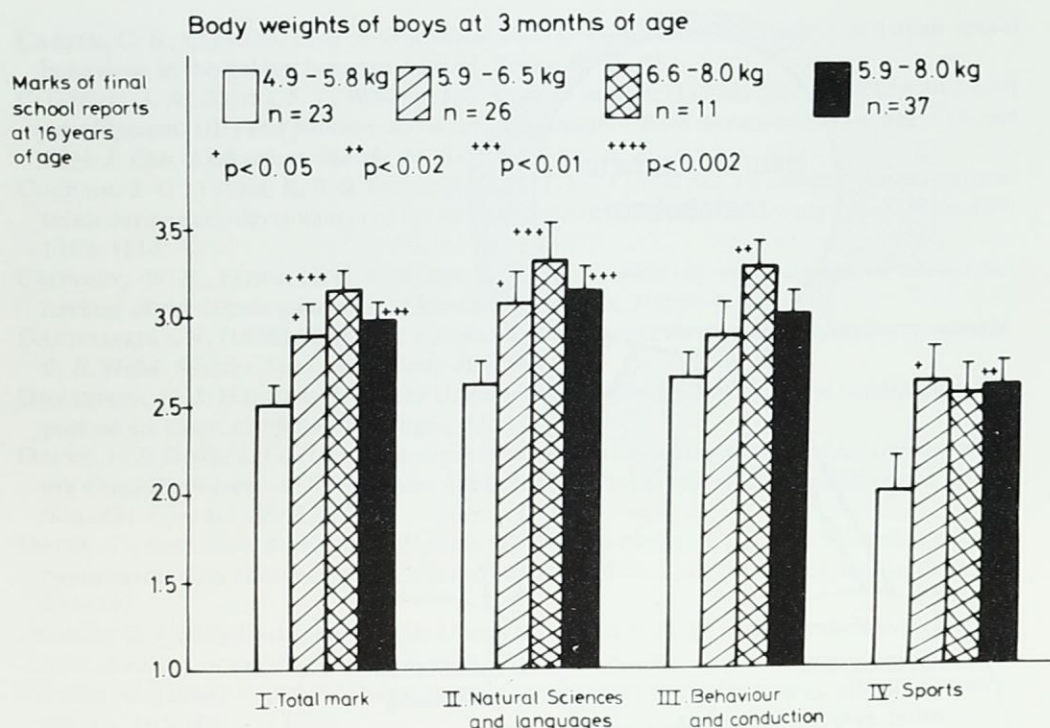


FIG. 13. The influence of perinatal over-nutrition in boys on mental, psychic and physical achievements at 16 years of age (means \pm S.E.M. of school marks: 1, very good; 2, good; 3, satisfactory; 4, pass; 5, unsatisfactory).

nutritionally dependent metabolic variables or hormones can affect neurotransmitter metabolism, resulting in alterations in information-processing, metabolism and/or reproduction. These fundamental processes of life influence, in turn, psychosocial conditions and the concentrations of metabolic variables and hormones. Hence, psychosomatic interrelationships are controlled by closed-loop neuroendocrine systems that are combined with each other by neurotransmitter metabolism in the brain. Thus it is also conceivable that changes in the external environment, particularly in psychosocial conditions, as well as changes in the internal environment—that is, in metabolic variables and hormones—can produce alterations in information-processing, metabolism and reproduction as well. That is to say, 'crossing-over' reactions between these systems are possible. Such environmentally dependent effects on fundamental processes are mostly reversible when they take place during adulthood by temporarily affecting gene expression in neurons, but are more or less irreversible when they occur during critical differentiation and maturation periods of the brain by affecting gene expressibility in neurons for the entire life of the individual.

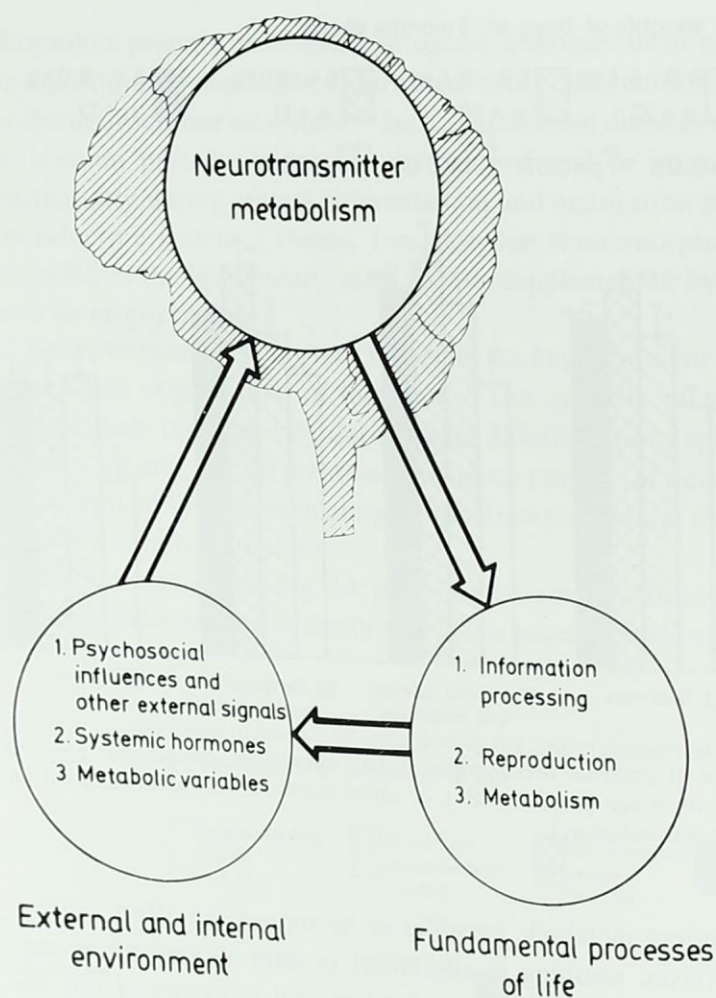


FIG. 14. Psychosomatic interrelationships mediated by neurotransmitters in the brain.

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Discussion

Sachar: The issue of testosterone function in homosexuals has been much studied in the US. The original report by Kolodny *et al.* (1971) suggested that testosterone secretion was reduced in Kinsey 5 or 6 homosexuals, but this could not be replicated by other laboratories (Rose 1978) and it seems that the first experiment had failed to control the drug history of the subjects. Alcohol intake, narcotic intake and marihuana smoking all depress testosterone levels (Rose 1978; Mirin *et al.* 1976). The control groups were all-American boys who didn't touch any of those drugs, whereas the homosexuals came from a more free-living population. Did you take account of these variables in your studies? Did you have rigorous control of alcohol and narcotic intake and marihuana smoking among your homosexuals?

Dörner: Marihuana smoking is not possible in our country, and the intake of large amounts of alcohol and narcotics can also largely be excluded in our cases. Huttunen *et al.* (1976) have found normal testosterone concentrations in 17 hospitalized alcoholics after a large dose of alcohol. In effeminate homosexuals, we only found some decrease in the free testosterone level because of increased sex-hormone-binding capacity. Several authors have measured total testosterone concentrations and have also not found any difference between homosexual and heterosexual males (Birk *et al.* 1973; Barlow *et al.* 1974; Pillard *et al.* 1974; Tourney *et al.* 1975).

Sachar: You also found differences in LH and FSH concentrations which were not found in the American investigations.

Dörner: Our findings of increased LH values in homosexual males are in agreement with those of Kolodny *et al.* (1972) and Doerr *et al.* (1976), and do not agree with the data of Parks *et al.* (1974) and Tourney *et al.* (1975). Higher FSH values in homosexual males were also found by Kolodny's and Tourney's groups, but the values did not differ significantly from those of heterosexual males. However, none of these authors have differentiated between effeminate and non-effeminate homosexual males. We only found significantly increased FSH levels in the effeminate ones. In five out of six transsexual men we also found significantly higher FSH levels than in 25 heterosexual men.

Sachar: My point was that the same high LH concentrations are found in men with high alcohol levels (Rose 1978).

Pirke: We have studied a group of about 40 homosexual men and have compared them with age-matched control groups (Doerr *et al.* 1973, 1976). We observed small but significant elevations in the concentrations of LH, free i.e. not protein-bound testosterone, oestradiol and oestrone in

peripheral plasma. The total plasma testosterone concentration was normal. We do not know how to interpret these data. The small increase in plasma testosterone certainly does not cause homosexuality and is seen in other pathological and physiological conditions, such as liver disease and old age (Pirke & Doerr 1973). It would be helpful if other groups would study plasma oestrogens in male homosexuals; we could thus learn whether the increase in oestrogen concentrations was just an accidental finding in the homosexuals we studied or a characteristic finding in homosexuality.

Dörner: Dr Pirke finds elevated oestradiol and oestrone levels but normal testosterone and, in contrast to us, increased free testosterone levels due to decreased sex-hormone-binding capacity (Doerr *et al.* 1976). However, a decreased sex-hormone-binding capacity appears to be incompatible with a significantly increased oestrogen plasma level (Stahl *et al.* 1975).

Nieschlag: We should be aware of the limited value of a single hormone determination. Most hormones show considerable fluctuations in blood, some predictable, some not. The point that particularly interested me, Dr Dörner, was on FSH, because this is a hormone shown to fluctuate very little. Your homosexual subjects had an increased FSH concentration. Since we know that increased FSH usually reflects a defect in spermatogenesis, have you investigated their ejaculates?

Dörner: No, we haven't studied that. It has been shown, however, that oligospermia or azospermia is not more typical of homosexuals than of heterosexuals (Parr & Swyer 1960; Doerr *et al.* 1973). As you know, it is particularly difficult to get sperm samples from transsexual men.

Pirke: We have studied the ejaculates of homosexual men (Doerr *et al.* 1973) and have found them to be normal.

Dörner: I would like to repeat that we observed a rise in FSH levels only in effeminate homosexual and transsexual males. But I would never consider homosexual behaviour to be a direct consequence of increased FSH levels or decreased free testosterone levels in adulthood. However, these findings may indicate that there might have been hormonal abnormalities, particularly androgen deficiency, in prenatal life, giving rise to female differentiation of the brain and to homosexual behaviour in adulthood. In this context, Gupta *et al.* (1976) have given testosterone antiserum to male rats during brain differentiation and have found increased female-like and decreased male-like sexual behaviour, combined with decreased testosterone and increased FSH levels, in adult animals.

Nieschlag: Clinically the fertility of patients with high FSH levels is decreased. If we extrapolate this to your subjects we should find a higher incidence of infertility in homosexuals. However, Dr Pirke found no abnormal

ejaculates, indicating undisturbed fertility in his homosexual subjects. These findings are at variance with your elevated FSH levels.

Dörner: I agree that patients with clear-cut disorders of spermatogenesis have high FSH levels. But I don't agree that all males with increased FSH levels must also display disorders of spermatogenesis. In other words, spermatogenetic defects generally result in increased FSH levels, but increased FSH levels need not result in spermatogenetic defects.

Green: How do you define 'effeminate' and 'non-effeminate' homosexuals and 'virile' lesbians as against 'non-virile' lesbians? What were your behavioural or other criteria?

Dörner: Effeminate and non-effeminate homosexual males were characterized on the basis of their general behavioural patterns, including sex-specific gestures, the use of perfume and ornaments, and a sex-specific manner of walking. On the other hand, virile and non-virile lesbians were differentiated by the presence or absence of virilism, particularly hirsutism.

Bancroft: As a general point, many of the comments being made seem to be based on the assumption that homosexuals are a homogeneous group, whereas from the point of view of many characteristics which may be relevant to hormones, they are extremely heterogeneous. If one really wants to use hormone levels or positive feedback or anything else to show the determination of homosexual preference *per se*, one must control these other factors. An example of this in Dr Dörner's study is the pattern of sexual activity in the effeminate men. It may be that many of them are relatively inactive in their pattern of sexual arousal or frequency of orgasm. Their principal homosexual role may be as relatively passive partners with active homosexual males. If you compared them with a group of heterosexual males who were equally inactive, you might find a very similar endocrine picture. It is surely crucial, if one wants to say anything about homosexual preferences as such, to control for these other behavioural variables which can also be relevant to the endocrine factors.

Sachar: Are you suggesting that the amount of successful sexual activity can also have an influence on testosterone levels?

Bancroft: I think it can, but I think it also works the other way round, that if people have relatively low testosterone levels they may have low sexual activity. It is a two-way process.

Keverne: In other words, plasma testosterone may be a reflection of the behaviour rather than a determinant of it?

Bancroft: I think both are true.

Dörner: The plasma free testosterone level in 35 male homosexuals was significantly lower ($P < 0.01$) than in 38 male heterosexuals of similar

age. However, nine out of the 35 male homosexuals showed particularly high sexual activity, and the mean free plasma testosterone level of those nine subjects was not significantly different from that of the male heterosexuals (Stahl *et al.* 1976).

Besser: There is another possible explanation of Dr Dörner's results in the homosexuals besides the ones that Dr Sachar suggested. It is becoming clear that homosexuals are carriers of Australia antigen-positive subclinical hepatitis (Catterall & Dane 1977) transmitted among them by direct person-to-person transfer. Such hepatic disease could produce precisely the biochemical changes that you have shown, Dr Dörner, namely increased levels of sex-hormone-binding globulin, a reduction in free testosterone, raised LH concentrations and oligospermia, and hence the high FSH concentration. I agree with Dr Nieschlag that one cannot explain the changes in FSH level purely on testosterone. One has to evoke some other effect on spermatogenesis. All of it could occur with hepatitis.

Dörner: Dr Besser, thank you for the suggestion. I cannot believe, however, that only the effeminate homosexual males as well as the transsexual males are carriers of Australia antigen hepatitis. Promiscuous anal intercourse was clearly denied by the transsexuals.

Crown: I am unhappy about Dr Bancroft's implied equation of 'masculine' and 'feminine' homosexuality with active and passive types. The evidence, both from Kinsey and clinical evidence, is that individuals cannot be classified in this way. They practise both modes.

Bancroft: That is true for the majority of homosexuals, but there are some men who play only a passive role in sexual intercourse with a male partner and who often are not orgasmic themselves. That may be the group studied by Dr Dörner; we don't know because we lack that information. This must be controlled in such studies.

Dörner: I agree with Dr Crown. We were unable to differentiate clearly between homosexual males playing a passive role and those playing an active role. On the other hand, we were able to differentiate between effeminate and non-effeminate homosexual males.

Green: Dr Dörner, do you know whether any of the transsexuals you studied had been taking sex steroids, as transsexuals frequently do? They typically lie about it, too. Do you have good drug histories for your transsexual patients?

Dörner: The transsexual males were under careful psychiatric observation, which confirmed that they were not taking sex hormones.

Herbert: We have been focusing on the interchange between laboratory and clinical work, and to me the most interesting feature of Dr Dörner's paper was

the fact that we have here an example of a direct extrapolation from laboratory experiments to clinical practice. I want to take up two aspects of his work: firstly, the hypothalamic lesions made in male homosexuals, and secondly the idea of diagnosing homosexuality before birth by looking at androgen levels in the amniotic fluid. It seems to me that your model demonstrates both the strengths and weaknesses of such extrapolations, Dr Dörner. I don't understand, for example, why you equate female sexual behaviour in rats, which is a *behaviour pattern*, with paedophilic homosexuality in man, which is an *erotic preference*; and I am not convinced that paedophilic homosexuality is the same thing as female sexual behaviour. I wonder how you made the jump between these behaviours in rats and humans?

Dörner: I have never equated female sexual behaviour in male rats with homosexuality in man. We have only cautiously compared male rats, castrated at birth and given androgen replacement in adult life, with homosexual men. Both show a permanent and significant sexual preference for partners of the same sex. We have tested male rats, castrated on the first day of life and given androgens or reimplanted with testes in adulthood, for their preference for male or female partners. These males, androgen-deficient during the period of brain differentiation in neonatal life but with normal or approximately normal androgen levels in adulthood, showed a clear-cut preference for partners of the same sex. In contrast, normal intact male rats or males castrated on the 14th day of life, with androgen replaced in adulthood, displayed a clear-cut sexual preference for partners of the opposite sex.

According to these findings the androgen level during brain differentiation appears to determine the preference for partners of the same or the opposite sex – that is, 'homophilic or heterophilic eroticism'. In other words, irrespective of genetic sex, the higher the androgen level during brain differentiation, the higher the sexual responsiveness to partners of the female sex and the lower the responsiveness to partners of the male sex in adulthood.

Regarding the effects of hypothalamic lesions, neuroendocrine-conditioned homosexual behaviour in male rats – that is, the preference for partners of the same sex in neonatally castrated males given androgens in adulthood – could be suppressed by stereotaxic lesions of the so-called female mating centre in the hypothalamic ventromedial nuclear region (Dörner *et al.* 1968). Hence the conclusion was drawn in this paper: 'If our data can be confirmed in other species, a destruction of the so-called hypothalamic female mating centre could be considered as a means for suppressing homosexuality in human males'. Soon after this, Roeder & Müller (1969) reported that they had succeeded in suppressing homosexual behaviour in men by stereotaxic lesion of the hypothalamic ventromedial nucleus. This treatment was resorted to in

paedophilic homosexual men, because they had been repeatedly detained for this act.

Brawer: With respect to your particular model in which male rats were castrated neonatally and later given androgen, and they showed lordosis when put with males, it seems to me that basically you have made a female hypothalamus by gonadectomizing the true male, and then at a later date you have given the animal androgen which is aromatized in the rat hypothalamus. This is equivalent to giving an injection of oestrogen and makes the model inapplicable to the human.

You have essentially made a female hypothalamus and then stimulated it with a hormone that ordinarily stimulates the female hypothalamus.

Sachar: You mean you would get the same results with oestrogen?

Brawer: Yes, you would.

Dörner: That's true in rats, and the effect would be even stronger, because in rats oestrogen is the most effective hormone for activating the sexual response to the masculine stimuli of male partners in the female-differentiated brain of homosexual males as well as of heterosexual females. In the human, on the other hand, androgen is the most effective hormone for activating the sexual response to the masculine stimuli of male partners in the female-differentiated brain of homosexual men and heterosexual women. Therefore, the experimental model of homosexual behaviour in male rats produced by androgen deficiency during brain differentiation followed by high androgen levels during brain activation appears to be particularly applicable to the human.

Ehrhardt: My feeling about your study, Dr Dörner, is that if you want to extrapolate to human beings from your data on rats you must define human behaviour more precisely. If you were to collaborate with psychiatrists and psychologists who define effeminacy, who take drug histories, and who record health states, then you and your colleagues should be able to define the human behavioural side very clearly. Without this, it is difficult to discuss your findings, because we lack the crucial information in the human homosexuality work; especially in view of the fact that intervening variables such as health state and degree and type of homosexuality may have a profound influence on the hormonal differences you find.

Dörner: But you can't expect to obtain more information about the behavioural side in homosexuals from endocrinologists than is generally given by psychologists and sexologists. In this context, I should add that all the homosexual men we studied showed clearly predominantly or even exclusively homosexual behaviour which rated 5 or 6 on the Kinsey rating scale.

Hertoft: The social conditions of the homosexuals should also be specified. From animal studies we know that sex-hormone levels are influenced

by stress factors—noise, warmth, crowding and so on. In most societies homosexuals live under very stressing conditions and are forced to hide their homosexuality to a greater or lesser extent and to accept a life on heterosexual premises. We do not know how this stressing life influences their hormonal pattern—what is cause and what is effect.

Short: I would like to take up Dr Dörner's point about the use of positive feedback as a diagnostic tool for brain sex. This is actually deceptive. If one looks for positive feedback in normal men and women, men are not capable of discharging LH in response to ethinyl oestradiol, whereas normal women show the characteristic positive feedback response of LH secretion in response to ethinyl oestradiol. Dr David Baird has studied two intact testicular feminization patients, and although they have a female habitus and normal female sexual behaviour they appear to have a male hypothalamus, as shown by the absence of positive feedback. So I don't think that one can use the presence or absence of positive feedback as a predictive index of sexual behaviour (Van Look *et al.* 1977; Aono *et al.* 1978).

Dörner: Leyendecker *et al.* (1971) showed a positive oestrogen feedback effect in a genetic male with gonadal dysgenesis. On the other hand, Aono *et al.* (1978) did not demonstrate a positive feedback action of oestrogen on LH release in patients with the testicular feminization syndrome, as you say. I agree with these authors when they write: 'It could be assumed that the androgen insensitivity of the hypothalamus during foetal life in TSF patients might cause cyclic gonadotrophin secretory conditions. But the present patients with TFS displayed no LH release after oestrogen administration. The discrepancy between this hypothesis and the present findings could be explained by the following mechanism: testosterone secreted from the testes of TFS patients can be readily converted to oestradiol in the hypothalamus and this oestrogen may induce a male type gonadotrophin secretion.' In view of these findings, during brain differentiation androgen itself may be responsible for the masculinizing organizational effect on sexual behaviour, whereas oestrogen converted from androgen in the brain may be responsible for the masculinizing organizational effect on gonadotropin secretion.

Short: There are also problems of interpretation of apparent positive feedback effects, since one can get a rebound of LH levels in men because ethinyl oestradiol depresses the testosterone level, so when you stop giving the ethinyl oestradiol the LH levels rise slightly. But this is not to be confused with the pronounced LH elevation seen in positive feedback in women.

Green: I am intrigued by the feedback (Hohlweg) effect that Dr Dörner reported (Dörner *et al.* 1975). We published this study in the *Archives of Sexual Behavior* because we thought it was provocative, and I am disappointed

that no one has either replicated or failed to replicate it. It is one of the few studies that attempts to address central nervous system mechanisms. Dr L. E. Seyler has since reported a differential effect on LH release between men and women after priming with oestrogens and giving LH-RH (Seyler *et al.* 1978). He has tested female-to-male transsexuals — women who want to become men — who have normal menstrual histories. More recently he has tested female homosexuals. He states that both groups show a typical male response rather than a typical female response. So this is a second study which purports to find a differential central nervous system mechanism, a hypothalamic-pituitary axis mechanism. These are attempts to get at basic mechanisms. They probably have a better chance of success than single determinations of hormones in plasma, which are vulnerable to so many confounding factors. I hope someone will try to replicate your original study, Dr Dörner, and also Dr Seyler's work.

Bancroft: Do the endocrinologists accept Dr Seyler's procedure as a test of positive feedback — measuring a response to LH-RH after priming with diethylstilboestrol, in quite high dose? He claims a reduced response in the normal male and an enhanced response to LH-RH in the normal female, with the female transsexual showing a pattern more similar to the male than the female pattern.

Goy: Does it matter at what stage of the cycle the woman is tested?

Bancroft: The priming is supposed to take care of that.

Besser: Superficially one would have to accept the data, and in fact the positive feedback effect in the normal female occurs both at pituitary level and at hypothalamic level. In a gonadotropin-deficient woman you can get normal cycling and show positive feedback pituitary effects, by just giving LH-RH, so it may be a purely pituitary effect; but there is in addition an augmenting effect via the hypothalamus because LH-RH secretion is increased at the time of the oestradiol surge at mid-cycle (Mortimer *et al.* 1975; Nillius & Wide 1975; Mortimer 1977).

So there is no doubt that both pituitary and hypothalamic effects exist. Presumably the increased secretion of gonadotropin from the pituitary is partly a making available of releasable stores of gonadotropin, and in addition a result of the increased priming from the hypothalamus. I couldn't comment on the particular experiments without knowing the precise protocol, but certainly one can demonstrate both positive and negative feedback in women by giving oestrogen, whereas in men one can only demonstrate negative feedback, in terms of LH-RH response.

Goy: You are not dealing with castrated individuals? What is the nature of the sex difference in castrated men?

Besser: We have tested castrated men and they do have an altered response – they have a high basal level of LH and an excessive response to LH-RH. I don't think one can demonstrate positive feedback effects in castrated men.

Goy: This has been done in the rhesus monkey. Positive feedback was found in castrated males (Knobil 1974).

Herbert: One has to be careful about defining positive feedback. Positive feedback to oestrogen is one thing, but a response to LH-RH is a different story.

In one case you are assessing pituitary response to increased LH-RH, which can be altered by oestradiol, certainly; in the second case the LH-RH levels may be changed by oestrogen but you are essentially dealing with the effect of oestrogen directly on a neural system.

Besser: But where is the site of action of gonadal steroids on positive feedback?

Herbert: This is what is disputed. Some people say it is largely hypothalamic. Knobil says that the effects are all in the pituitary (Krey *et al.* 1975).

Besser: This phenomenon was demonstrated in the human first, and Knobil has confirmed this in non-human primates (as yet unpublished, I believe).

The findings are that you can administer to gonadotropin-deficient female patients long-term LH-RH, and produce normal cyclicality of gonadotropins, positive feedback effects at mid-cycle, normal oestradiol responses, normal progesterone secretion, and a normal menstrual cycle. You can give LH-RH for two years to a woman who has never gone through puberty and produce normal puberty with normal cycles, and that is purely at the pituitary level, with positive and negative feedback working there (Mortimer *et al.* 1975; Nillius & Wide 1975; Mortimer 1977).

Herbert: This is surely an assumption? It may be that giving LH-RH, which we know has neural interactions, enables the brain to respond to oestrogen; moreover, the term 'positive feedback' refers to an effect of oestrogen, not to LH-RH. The LH-RH may simply make it possible.

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