

INVITED NEL REVIEW

Genetic and Epigenetic Effects on Sexual Brain Organization Mediated by Sex Hormones

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Abstract

Alterations of sex hormone levels during pre- or perinatal sexual brain organization – responsible for long-term changes of gonadotropin secretion, sexual orientation, and gender role behavior – can be caused by: 1. Genetic effects, i.e. mutations or polymorphisms of a) 21-hydroxylase genes on chromosome 6, b) 3 β -hydroxysteroid dehydrogenase genes in chromosome 1 or c) X-chromosomal genes, and 2. Epigenetic effects, such as a) stressful situations – especially in combination with mutations – and b) endocrine disrupters, e.g. the pesticide DDT and its metabolites, which display estrogenic, antiandrogenic, and inhibitory effects on the enzyme 3 β -hydroxysteroid dehydrogenase leading to increased levels of dehydroepiandrosterone and its sulfate as precursors of endogenous androgens and estrogens. In connection with the introduction and extensive use of the pesticide DDT, the following findings were obtained in subjects born before as compared to those born during this period:

1. The prevalence of patients with polycystic ovaries (PCO), idiopathic oligospermia (IO), and transsexualism (TS) increased significantly (about 3–4 fold).
2. Partial 21-hydroxylase deficiencies were observed in most patients with PCO and TS and some patients with IO born before this period.
3. In contrast, most patients with PCO and TS and several patients with IO born during the period of massive use of DDT displayed clearly increased plasma levels of dehydroepiandrosterone sulfate (DHEA-S) and DHEA-S/cortisol ratios suggesting partial 3 β -hydroxysteroid dehydrogenase (3 β -HSD) deficiencies. Interestingly enough, geneticists could not find any mutations of 3 β -HSD genes in such subjects. However, o,p'-DDT and/or its metabolite o,p'-DDD are strong inhibitors of 3 β -HSD, indicating their possible co-responsibility for such life-long ontogenetic alterations. Finally, some data suggest that endocrine disrupters may also be able to affect the development of sexual orientation.

Introduction

Sexual brain organization is dependent on sex hormone levels occurring during critical developmental periods. “Sex centers” responsible for gonadotropin secretion are organized by estrogens, “mating centers” controlling sexual orientation are organized by androgens and estrogens, and “gender role centers” responsible for gender role behavior are only organized by androgens (Dörner *et al.*, 1987). Furthermore, the organization periods for sex-specific gonadotropin secretion, sexual orientation, and gender role behavior are overlapping, but not identical. Thus, specific combinations and dissociations in variations of sex-specific gonadotropin secretions, sexual orientation, and gender role behavior are possible.

Hormones and sexual brain differentiation

The following findings on sexual brain differentiation were obtained in extensive animal experiments and clinical studies [1, 2, 3, 4, 5]:

1. Different brain regions were found to be responsible for male- and female-type sexual behavior, i.e. the preoptic-anterior hypothalamic region for male-type and the ventromedial hypothalamic nuclear region for female-type sexual behavior.
2. Alterations of sex hormone and/or neurotransmitter levels during a critical period of brain development lead to permanent structural and biochemical changes of brain regions, which are associated with life-long variations of sexual orientation, sex-typical behavior or gonadal function. Thus, the development of male and female bi- or homosexuality – that means a preference of sexual behavior with partners of the same sex – could be caused by a deficiency of androgens in males and an excess of androgens or even estrogens in females during sexual brain differentiation. Furthermore, unphysiologically high estrogen levels during critical developmental periods of the brain can also lead to polycystic ovaries in females and oligospermia in males [2].
3. A positive estrogen feedback on LH secretion was only evocable in homosexual and transsexual men in contrast to heterosexual men, suggesting that homosexual and transsexual men possess, at least in part, a more female-differentiated brain [6, 7, 8].
4. Meanwhile, female-like structural changes of specific brain regions were also found in homosexual and transsexual men [9, 10, 11].
5. Some experimental and clinical findings suggest that stressful maternal events, if occurring during pregnancy, may represent an etiogenetic co-factor for the development of sexual variations in the offspring by changing sex hormone levels during crit-

ical brain developmental periods of the fetus or newborn [12, 13, 14, 15].

Enzyme deficiencies and sexual brain differentiation

Specific enzyme deficiencies can also affect sexual brain organization. The 21-hydroxylase is involved in the biosynthesis of cortisol (F). In the case of 21-hydroxylase deficiency (21-OHD) the adrenal production rate of 21-deoxycortisol (21-DOF) and the ratio of 21-DOF/F are increased.

On the other hand 3 β -hydroxysteroid dehydrogenase (3 β -HSD) type II is responsible for the biosynthesis of androstendione from dehydroepiandrosterone (DHEA) in the adrenals and gonads. In the case of 3 β -HSD deficiency (3 β -HSDD) the adrenal production rate of DHEA and its sulfate (DHEA-S) and the ratio of DHEA-S/cortisol is increased.

Both enzyme deficiencies (3 β -HSDD, and 21-OHD) can lead to adrenal oversecretion of the weak androgen DHEA in prenatal life, which is aromatized to estrogens in the placenta. In female fetuses, such increased androgen and estrogen levels can result in partial masculinization of the brain. The more so as the increased weak androgen DHEA produced in the adrenals can be converted to the stronger androgens androstendione and testosterone in the skin and brain by the isoenzyme 3 β -HSD type I. In male fetuses, such increased placental estrogens – produced by the increased natural estrogen precursor DHEA in the fetal and maternal adrenals – can lead to inhibition of the fetal testes and hence to decreased secretion of the strong testicular androgens testosterone and dihydrotestosterone, resulting in partial demasculinization of the brain.

Partial 21-OHD was diagnosed by increased 21 deoxycortisol (DOF) /cortisol (F) ratios, which surpassed 1 hour after i.v. injection of 0.25mg ACTH the mean + 2 SD of heterosexual controls. Increased basal plasma values of dehydroepiandrosterone sulfate (DHEA-S) and increased ratios of DHEA-S/F (means + 2 SD of controls) were considered as indications for partial 3 β -HSD deficiency.

In addition, molecular studies of the two 21-hydroxylase genes, located on chromosome 6, were performed. CYP 21 B is the active structural gene for 21-hydroxylase whereas CYP 21 A was considered primarily as “pseudogene”. However, Bristow [16] demonstrated that CYP 21 A may be able to stimulate indirectly the expression of CYP 21 B. In order to detect mutations of CYP 21 A and B genes, 3 different methods were used [for techniques see: 17, 18].

Genetic and epigenetic effects on sexual brain differentiation

Alterations of sex hormone activities during sexual brain organization leading to persistent changes of sexual orientation, gender role behavior, and/or gonadal functions can be caused by the following genetic or epigenetic conditions:

1. Mutations or polymorphisms of genes, e.g.
 - a) mutations or polymorphisms of 21-hydroxylase genes in chromosome 6, e.g. heterozygous deletions of CYP 21 B or homozygous deletions of CYP 21 A or heterozygous point mutations in CYP 21 B [17],
 - b) very rare mutations of the 3β -hydroxysteroid dehydrogenase gene on chromosome 1 and
 - c) mutations or polymorphisms on the X-chromosome, as published by Hamer *et al.* [19],
2. Epigenetic effects, such as
 - a) stressful situations can also affect sex hormone activities during sexual brain organization [17] and
 - b) so-called "endocrine disrupters" were recognized to be possible epigenetic agents on ontogenesis for sexual brain organization; for instance the pesticide DDT and its metabolites display estrogenic, antiandrogenic, antigestagenic and inhibitory effects on the enzyme 3β -hydroxysteroid dehydrogenase, leading to increased levels of dehydroepiandrosterone as precursor of endogenous androgens and estrogens, especially of placental estrogens [20, 21].

Indeed, in adult rats we have found polycystic ovaries, subfertility, and increased male-type sexual behavior in females, but decreased male-type behavior and testicular hypotrophy in males, following perinatal administration of DDT associated with increased blood levels of dehydroepiandrosterone in neonatal life (0.443 ± 0.066 vs. 0.141 ± 0.043 nmol/l in controls; $p < 0.01$; in preparation). In human beings – in connection with the introduction of massive amounts of the pesticide DDT in East-Germany since the 1950s – the following findings were obtained:

1. The prevalence of polycystic ovaries was found to be 3-4 fold increased in women born in East-Germany since 1955 as compared to those born before this period [20].
2. In men born in East-Germany since 1960, a continuous significant decrease of spermiogenesis was observed [21, 22] as described before by other groups for several countries [23].
3. A significant improvement of spermiogenesis and decrease of cryptorchidism was found in men born since 1973 in West-Germany, but not in East-Germany. In this context, it should be emphasized, that the application of DDT was forbidden since

1973 in West-Germany, but only in the late 1980ies in East-Germany. In addition, a slight excess of birth/death rates was observed in West-Germany during the 1990ies following a strong excess of death/birth rates during the 70s and 80s [21].

4. Partial 21-hydroxylase deficiencies, i.e. clearly increased 21-deoxycortisol plasma levels or 21-deoxycortisol/cortisol ratios after ACTH stimulation, were found in most women with PCO born before 1955; i.e. more than 2 standard deviations above the mean of controls (fig. 1) as well as heterozygous mutations in CYP 21 B in those women who were genetically investigated. On the other hand, in most women with PCO born since 1955 (that means since the introduction of DDT) clearly increased levels of dehydroepiandrosterone sulfate and ratios to cortisol were found; i.e. $>$ means + 2SD of controls, suggesting partial deficiencies of 3β -hydroxysteroid dehydrogenase (fig. 2). In this context, it should be emphasized that several other groups could not find any mutations of the 3β -hydroxysteroid dehydrogenase genes in chromosome 1 of such subjects [24]. However, o,p'-DDT and/or its long-time persistent metabolite o,p'-DDD are strong inhibitors of 3β -hydroxysteroid dehydrogenase [25], indicating their possible causal responsibility for such a life-long epigenetic alteration.
5. In men with idiopathic oligospermia born before 1960, a significant predominance of partial 21-OHD with mutations in the CYP 21 B gene was also found (fig. 1), in strong contrast to those born after 1960 with a clear-cut predominance of an apparently epigenetic partial deficiency of 3β -hydroxysteroid dehydrogenase (fig. 2).
6. In most transsexuals born before 1960, hormonal findings also suggested partial 21-hydroxylase deficiency (fig. 1), confirmed by heterozygous CYP 21 B mutations in those who were studied genetically after positive endocrine data. On the other hand, in most transsexuals born afterwards – i.e. after introduction of high DDT amounts – clearly increased dehydroepiandrosterone sulfate levels and ratios to cortisol were found, suggesting again the possible co-responsibility of DDT and its metabolites for the development of transsexualism (fig. 2). It should be emphasized that during the past decades the prevalence of transsexuals was found to be clearly increased [26], as well as of polycystic ovaries and idiopathic oligospermia. Moreover, female-to-male transsexualism is generally combined with PCO, while male-to-female transsexualism is generally associated with oligospermia.
7. Finally, we have also found endocrine indications for partial 3β -hydroxysteroid dehydrogenase deficiency in 6 of 21 homosexuals (= 29%) born since

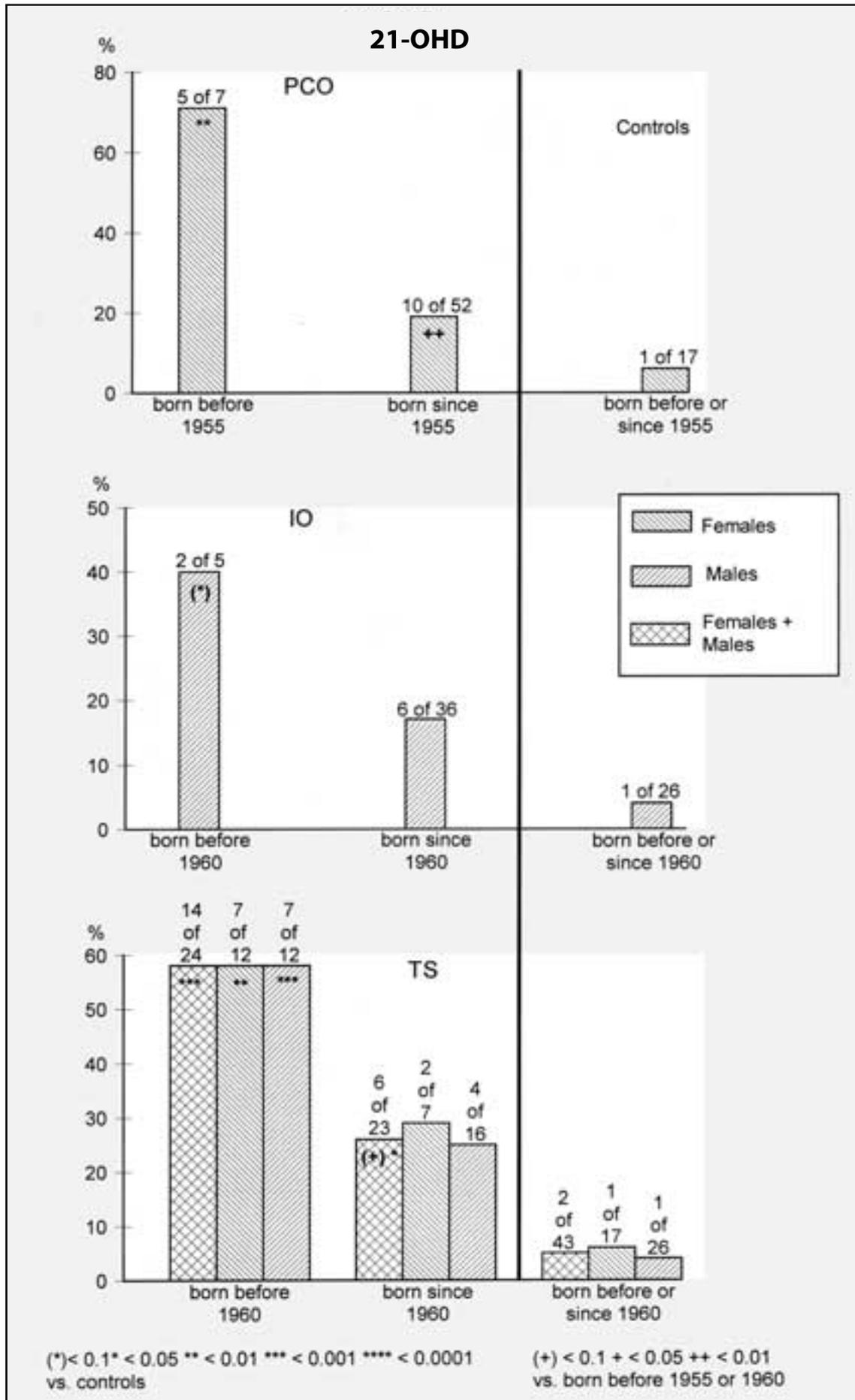


Fig. 1. Partial 21-hydroxylase deficiencies (21-OHD) in women with polycystic ovaries (PCO), in men with idiopathic oligospermia (IO), and in transsexuals (TS: female-to-males, and male-to-females).

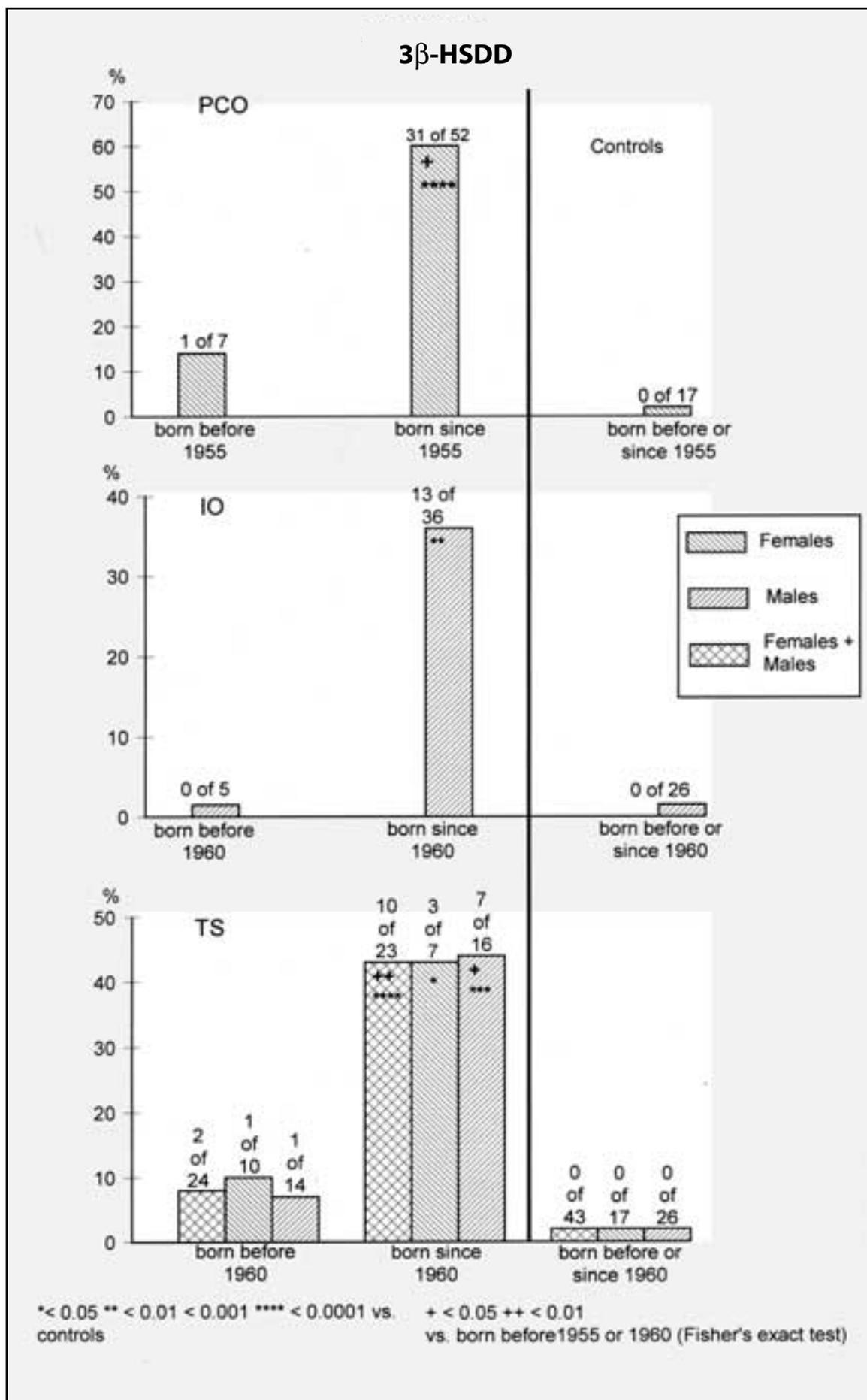


Fig. 2. Partial 3 β -hydroxyteroid dehydrogenase deficiencies (3 β -HSDD) in women with polycystic ovaries (PCO), in men with idiopathic oligospermia (IO), and in transsexuals (TS: female-to-males, and male-to-females).

1955 but in none of 39 heterosexuals ($p < 0.01$). Furthermore, Schmidt *et al.* [27] reported about a significantly increased frequency of bi- and homosexual students born in West-Germany between 1950 and 1960 as compared to those born between 1935 and 1940. DDT was used as pesticide in West-Germany from the late 1940s up to 1972. A significant increase of the prevalence in patients with transsexualism (TS) or idiopathic oligospermia (IO) began some years later than in those with PCO. This observation may be based on the fact that the development of IO and male-to-female TS could be essentially affected by the antiandrogenic effect of the DDT-metabolite DDE. Its concentration is clearly elevated some years after administration of DDT due to the transformations to and storage of DDE in fat tissues and its long half-life time of several years.

Most recently – in connection with the reduction and prohibition of DDT in western countries since the late 1960s and early 1970s – we have observed in West-Germany (Hesse) a clear-cut improvement of spermiogenesis in men since 1995 [21], while Kesteren *et al.* [28] reported after a strong increase also about some beginning reduction of transsexualism in the Netherlands and Schmidt *et al.* [27] of bi- plus homosexuality in West-Germany during recent years.

In each case, bi- and homosexuality should be considered as natural variants of sexual orientation with complete tolerance and acceptance, as well as equal rights and duties [14, 20]. On the other hand, transsexualism, oligospermia, and polycystic ovaries should be prevented as far as possible by a neuroendocrine prophylaxis, e.g. by prohibition of endocrine disrupters or early glucocorticoid treatment in subjects with specific gene mutations accompanied by altered sex hormone levels.

In 83 % of patients with PCO, IO or TS who displayed clearly increased DOF/F ratios after ACTH injection suggesting partial 21-OH deficiency, we have found severe heterozygous mutations of CYP 21 B on one allele [18]. A similar percentage of homozygous or compound heterozygous mutations of CYP 21 B (87 %) could be demonstrated with our molecular genetic methods in patients with congenital adrenal hyperplasia [29].

On the other hand, in homosexuals with clearly increased DOF/F ratios after ACTH stimulation no heterozygous mutations of CYP 21 B, but only homozygous or compound heterozygous polymorphisms of the so-called 21-OH pseudogene CYP 21 A were observed [20]. In this context, it should be mentioned that all of us display genetic polymorphisms. The more so homosexuality should be considered as a natural variation of sexual orientation.

All heterozygous mutations of CYP 21 B we have found in patients with PCO, IO or TS displayed severe forms; e.g. 8-bp deletions with 0 % 21-OH activity, splice site mutations of A → G in intron 2 with minimal enzyme activity and I172 N mutations with about 5% 21-OH activity [30]. In this context, it should be emphasized that heterozygous mutations on one allele with 0% or minimal 21-OH activity should have a similar effect on sexual brain organization – i.e. differentiation in prenatal life plus maturation in prepubertal and pubertal life – as slight homozygous or compound heterozygous mutations on both alleles with about 50% 21-OH activity. Such mutations can be found in subjects with late-onset congenital adrenal hyperplasia.

Moreover, the adverse organizational effects in generally untreated subjects with severe heterozygous mutations of CYP 21 B on the human ontogenesis could be expected to be even stronger than in glucocorticoid treated subjects with slight homozygous or compound heterozygous mutations of CYP 21 B. This expectation could be of special significance in subjects with severe heterozygous CYP 21 B mutations associated with stressful situations, especially in prenatal life.

Most of all, our findings support the theory inaugurated in the 1970s [2, 31] that sex hormone activities in pre- and early postnatal life, which can be altered by genetic as well as by epigenetic effects, are able to program sexual brain organization and hence sexual orientation, gender role behavior and gender identity as well as gonadal functions throughout life.

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ADDENDUM: PROFESSOR GÜNTER DÖRNER

1. **Pioneer of Developmental Neuro endocrinology:**

It was demonstrated that hormones, neurotransmitters and cytokines are pre- and early postnatal organizers of the brain and the neuro-endocrine-immune system (NEIS), which is responsible for the control of fundamental processes of life, such as reproduction, metabolism and growth, information processing and immune responsiveness.

2. **Founder of Functional Teratology, i.e. Teratophysiology and Teratopsychology:**

Unphysiological concentrations of hormones, neurotransmitter and cytokines were recognized to be possible endogenous teratogenes during the critical organization period of the "NEIS, leading to malfunctions and important diseases in later life. Functional Teratology is considered as a most important part of Epigenomics and Functional Genomics for Preventive Medicine.

3. **Introduction of a Neuro-Endocrine-Immune Prophylaxis;**

A primary preventive therapy was recommended by optimizing the physicochemical, biological and social environment or correcting gene-conditioned unphysiological concentrations of hormones, neuro transmitters and cytokines during the organization of me NEIS.

4. **Former Editor-in-Chief:** Experimental and Clinical Endocrinology.

Member of Int. Soc. Neuroendocrinology; *Member* Int. Soc. Psychoneuroendocrinology; *Member* Worlds Association of Sexology; *Honorary Member* of German Society of Endocrinology; *Honorary Member* of Hungarian Society of Endocrinology; *Honorary Member* of Czech Society of Sexology; *Honorary Member* of Slovak Endocrinological Society; **Honorary Editor** of the Neuroendocrinology Letters; **Honorary Editor** of the Int. J. of Prenatal and Perinatal Psychology and Medicine.

Proposal for Changing the Status of Homosexuality Under the W.H.O.'s Classification of Diseases

1. Bisexuality and homosexuality should be recognized as natural sexual variations. The individual manifestations of sexual orientation lay on a continuum.
2. Bisexuality and homosexuality are based on gene and/or environment dependent neuroendocrine alterations of sexual brain organization.
3. A heterozygous form of steroid 21-hydroxylase deficiency was found to exist in homosexual females. Such genetic enzyme alteration gives rise to increased adrenal androgen production (particularly in the case of stressful events in both pre- and postnatal life) leading to a more male-type sexual brain organization (i.e. female homosexuality).
4. Findings obtained in identical and non-identical twins, as well as in families with an increased prevalence of homosexuality, suggest that heterozygous gene alterations and/or early environmental influences (e.g. prenatal stress) leading to androgen deficiency can predispose males to a more female-type sexual brain organization (i.e. male homosexuality).
5. In agreement with this theory, a more female type positive estrogen feedback effect on luteinizing hormone secretion could be evoked in most homosexual men, in contrast to heterosexual men.
6. In this context, it should be emphasized that heterozygous alterations of recessively active genes are a general attribute for healthy human beings. Consequently, homosexuality caused by such heterozygous gene alterations and/or early environmental influences can no longer be considered as an illness. This definition should be cancelled as soon as possible in the WHO classification of diseases, as there is not necessarily a need for therapy in homosexuals without specific complication, or their desire for such.
7. Millions of human beings could be liberated from needless pressure and suffering by such a measure. This liberates homosexuals from pathological labelling and other forms of discrimination.
8. For the tenth revision of the WHO classification of diseases the following statement is intended to be taken up under F66.1:
"Homosexuality *per se* is not regarded as a mental disorder"
This statement should be extended to:
"Homosexuality *per se* is neither regarded as a disease nor as a mental disorder".

This resolution, based on the proposal of Prof. Günter Dörner M.D. from the Humboldt University in Berlin, was approved by the participants of the 9th International Congress of the International Society of Prenatal and Perinatal Psychology and Medicine in Jerusalem, March 26–30 1989.