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Humors and Hormones in Pregnancy: Determinants for Personality Development in the Child

D. Gupta

Department of Diagnostic Endocrinology, University Children's Hospital, University of Tübingen, Tübingen, Germany

Abstract

The concept that humors of the body can influence the humour or the behaviour of a person is age-old. However, the humors and hormones in pregnancy can act as determinants for personality development in the child has emerged only during the last thirty years, and the concept of "endocrine personality" developed. Exposure of the foetus to higher or lower secretion of various hormones in the mother can effect the foetal and neonatal brain development and may cause significant changes at least in certain agreed areas when adult. Perhaps this is what we mean as humor-humours interactions.

Zusammenfassung

Das Konzept, daß humorale Faktoren das Verhalten oder die Stimmung einer Person beeinflussen können, ist schon uralt. Dagegen hat sich die Hypothese, daß Körperflüssigkeiten und Hormone während der Schwangerschaft als Determinanten für die Persönlichkeitsentwicklung bei dem Kind dienen können, erst im Laufe der letzten 30 Jahre entwickelt, was zum Konzept der „endokrinen Persönlichkeit" führte. Eine Exposition des Foeten mit höheren oder niedrigeren Spiegeln verschiedener Hormone im Mutterleib kann die foetale und neonatale Gehirnentwicklung beeinflussen und möglicherweise signifikante Veränderungen zumindestens in bestimmten Hirnregionen beim Erwachsenen verursachen. Vielleicht ist es das, was man

Correspondence to: Prof. Derek Gupta, FRCPath, Department of Diagnostic Endocrinology, University Children's Hospital, Rümelinstraße 23, 7400 Tübingen, Germany

Invited paper

sich unter der Interaktion von humoralen Faktoren mit dem Verhalten (humor-humours interactions) vorstellen muß.

The concept that the humors of the body can influence the humour or the behaviour of a person is age-old, and innumerable attempts have been made to account for it.

Elemental Personality

The ancient medical experts and philosophers in the older civilization almost verged on primitive endocrinology when they presumed that the body was comprised of four basic elements: fire, air, water and earth.

Figure 1 illustrates the concept of the ancient masters where each element has two qualities, with fire being hot and dry, air being hot and moist, water cold and moist and earth being cold and dry. These qualities of hot, cold, moist and dry were then physically attributed to four humors: blood (hot and moist), phlegm (cold and moist), yellow bile (hot and dry) and black bile (cold and dry).

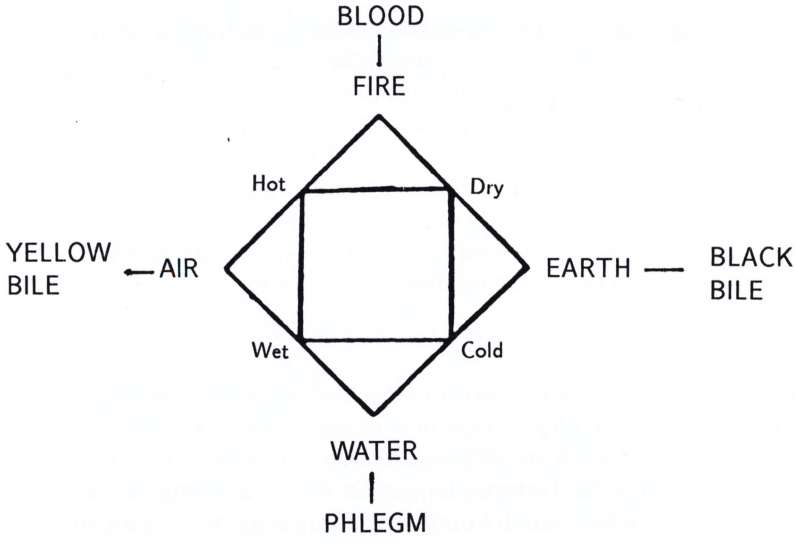

Fig. 1. Scheme of the four qualities and four elements as exhibited in Aristotelian writings and of the four humors as exhibited in the Hippocratic [2] and Aristotelian [1] writings.

How did the ancient masters associate the so-called humors with the humour or the character of the person? According to them an optimal mixture of all the humors, where blood is the predominating element, would make a person real sanguine. This sanguine person is optimistic and has a special temperament of courageous, hopeful and amorous disposition. The other personality types are as follows: The choleric is outgoing, extroverted, unstable, and hot-headed, the

melancholic is unstable, withdrawn and introverted; and the phlegmatic being someone who has natural tendency of not being moved easily and warms up very slowly.

Endocrine Personality

This elementary concept of personality associated with four elements, seemingly very irrational, has filtered down even today. The induction of individual's personality by special chemical messengers of hormones, has been made sophisticated by endocrinologists, and the outcome is the concept of endocrine personality.

Take for instance the adrenal personality, whose pattern of life is influenced by high or low secretion of his adrenal glands. A man possessing a pair of high secreting adrenal glands has a vigorous, energetic and persistent character. A woman with this situation is often considered as masculinoid or a hyperactive one who in the society is slightly misfit.

A low secretory adrenal person suffers from various problems and is considered another version of neurasthenic. He is easily tired and irritated. He has cold hands and feet and can not take decision easily.

A thyroid personality, high or low, could be easily recognized. A low secretor during the childhood is often dull and lackadaisical, and if the deficiency is severe may turn up as a cretin. The excessive secretory thyroid personality, on the other hand, is over-active, restless, highly emotional and nervous. These thyroid people with their large poppy eyes and endless energy may not be taken as easy-goer in the surrounding world.

A hyper-secretory gonad personality with excessive sexual zeal is a turbulent and often a tempestuous man. Sometimes violence is an additional attributable character. Gonadal insufficiency, on the other hand, is associated with lightheartedness and timidity, and in severe cases often renders the man behaviourly childish with chubby features. A hypo-gonad personality is often characterized for his tenderness.

Hormones and Humors

The notion with regard to "endocrine personality" just outlined is naturally too simplistic and throughout the last decade the complexities of the hormones and humors are being slowly unravelled. It is true that the chemical messengers produced by various glands travel in the blood and influence the tissues as well as the development of personality. But the complexities have developed especially because many organs which were never thought to be as endocrine glands, are now known to produce humors and hormones which interact on the classical set of hormones.

Figure 2 shows in a schematic form various hormones from a number of endocrine glands which are being controlled by the pituitary gland. The old idea that the brain produced some special factor or factors which could affect many aspects of physiological function, has now proven to be true by the neurohumoral

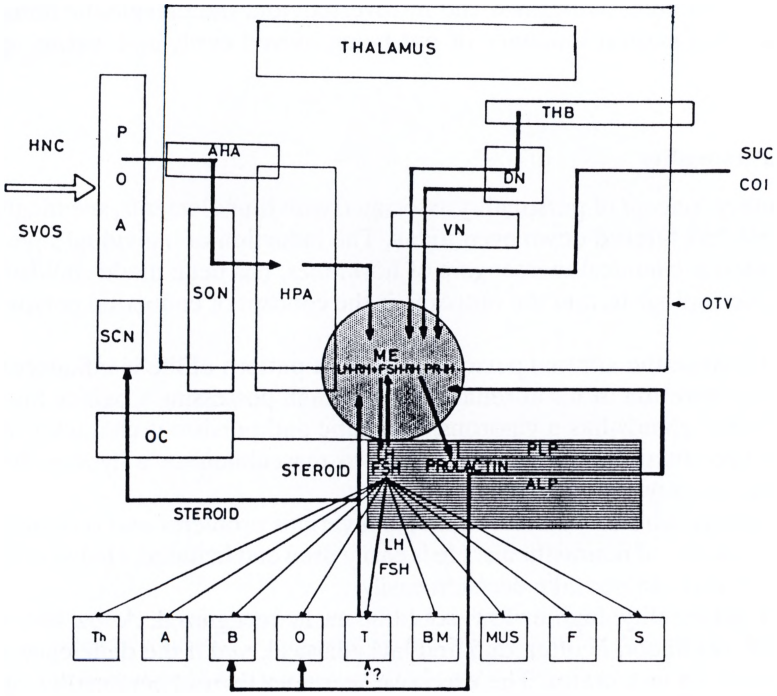

Fig. 2. A schematic view of the interrelationship of the hormones of the CNS, hypothalamus, pituitary and target-organs. Th = thyroid; A = adrenal; B = breast; O = ovary; T = testes; BM = bone maturation; MS = muscular system; F = fat; S = skin; HNC = higher neural control; SVOS = stress, visual and olfactory stimuli; POA = preoptic area; SCN = suprachiasmatic nucleus; AHA = anterior hypothalamic area; SON = supraoptical nucleus; HPA = hypophysiotropic area; COI = coitus; OTV = outer third ventricle; DN = dorsomedialis nucleus; VN = ventromedialis nucleus; OC = optical chiasma; ME = median eminence; ALP = anterior pituitary; PLP = posterior pituitary

observations. As neurohumoral agents a number of releasing or inhibiting factors are now discovered from the hypothalamus which are seen to control the synthesis and release of the pituitary hormones. Besides this, the central nervous system and the pineal gland also produce a large number of hormones and neurotransmitters which have all-round effect on the body as well as on the personality. Moreover, these new set of substances, such as opioids and the pineal hormones, have been seen to influence the body's host-defence mechanism. Any alteration in their synthesis and secretion might alter the person's ability to fight against infection. Thus, a person with low secretion of these compounds might be susceptible to many infections which could change the course of his life and behaviour pattern.

In animals it has been observed that higher level of monoamine turnover could be equated with greater degree of restlessness or motor activity. Zuckerman[3] elaborated a sensation-seeking hypothesis based on monoamine turnover

in humans. In this sensation-seeking scale human behaviour is divided as follows:

a. thrill- and adventure-seeking (participation in risky sports and fast driving);
b. experience seeking (seeking sensation through the mind, senses and non-conforming life-style);
c. disinhibition (seeking sensation through social stimulation and the release of inhibitions through social drinking); and
d. boredom susceptibility (aversion to monotonous, invariant situations and restlessness in those situations).

Zuckerman[3] tried to explain the various groups of sensation-seekers and equated higher levels of sensation-seekers with higher level of gonadal hormones and their effects as increasing neurotransmitter metabolism in the brain.

Foetal Brain Development and Hormones

It is already known that in the evolutionary process intelligence increases in parallel with enlargement of cerebral cortex, and the information processing capacity of the brain is closely related with the cerebral cortex area. Such considerations as these led to a general belief that there is a strong correlation between the size of human brain and intelligence. In fact many men of outstanding ability had really large brains. Kant's brain is reputed to have weighed 1600 g and Schiller's brain was 1785 g. The largest human brain, so far known, that was reliably measured was that of Turgenev weighing 2010 g, while the average weight of male brain is 1440 g[5]. However, there are also eminent people whose brain had average weight such as Gauss (1492 g) and Liebig (1352 g). The famous writer Anatole France had a brain weighing only 1017 g, which is a weight usually associated with idiocy[4].

During the foetal and neonatal period of brain development if the brain is exposed to the imbalance of hormones and humors then severe consequences can occur. We have already outlined briefly in the section of "endocrine personality!" how the personality is influenced by higher or low secretion of these chemical messengers. In this section the focus will be on how this imbalance can affect the development of foetal and neonatal brain.

Thyroid Hormones

Deprivation of the thyroid hormones to the foetal and neonatal brain can induce severe consequences. These hormones are absolutely essential for the brain development, and without them the offspring could be a cretin. It is known that the brain weight of cretins could be about 40% below normal, and with somatic changes the mental development becomes defective and slow. His growth process is slow, speech development delayed, and he develops a kind of inertia and disinterest to environment. His muscles are weak and he has no interest in physical sports. His intelligence is far below normal.

Adrenal Hormones

Evidence from the animal experiments indicates that excess corticosteroids could reduce the total number of cells in the brain during foetal and neonatal life. Corticosteroids have some controlling effects on the brain growth and Meyer[6] demonstrated that adrenalectomy in early life caused brain enlargement.

Although in humans effects of excess corticosteroids in Cushing syndrome are well-known, the exact consequence of these steorids in brain development during foetal life are not known. Hypoadrenalism, as seen in Addison's disease, causes muscular weakness. It seems that deficiency of corticosteroids casts influence on brain development as the Addisonian subject is highly irritable and devoid of taking any concrete decisions.

Adrenal androgens, on the other hand, have great influence on the brain development during foetal and neonatal life. In congenital adrenal hyperplasia (CAH) because of the defect of the enzyme 21-hydroxylase, corticosteroids are produced less, while the adrenal androgens are secreted in large quantity. If the foetus is male, he develops precocious pubertal development, while in female foetus, the genitalia becomes masculized. Figure 3 demonstrates such a picture of external genitalia of 3 girls with CAH having different degrees of virilization. In many such instances surgical correction may be necessary to restore normal appearance.

There are still great controversies whether this excessive androgen exposure prenatally causes permanent changes in the brain development and influences gender identity. In Baltimore, Money and his colleagues carried out a series of observational studies on the CAH girls, exposed prenatally with excess adrenal androgens. These studies as well as our own observations show that these girls already before puberty go for rough and tumble play and are identified as tomboyish. They prefer outdoor play to doll play and more concerned with career in later life than feminine household activities. In recent period, however, there are reports contradicting these observations[8]. According to this child psychiatrist, it is not the CAH-girls, but their parents think their daughters are more for fighting, romping, wild play and outdoor activities. According to this report the CAH-girls really do not differ from the normals in their "tom-boyish" attitude. The only difference was found that these girls more frequently wished to be a boy and drew men or boys more often than the normal girls did. Earlier, Money and Schwarz[7] reported that romantic image and dating patterns are different in the CAH-girls from the patterns observed in normals. Recently, Money at al.[9] observed that a high percentage (11 out of 30) of young CAH-girls consider themselves either homosexual or bisexual. These investigators from this observation have concluded that this high percentage of deviant sexual image is due to androgenization of the brain during foetal and neonatal life.

A particularly interesting finding among the CAH-girls, prenatally exposed to excessive androgens, is that in many instances the patients have high IQ. However, the puzzling thing is that the patients actually are not different from their parents and unaffected siblings in this respect. After analyzing the data from various angles, Erhardt and Baker[10] tried to give an alternative hypothesis to explain the elevation of IQ in families who have children with CAH. Their ap-

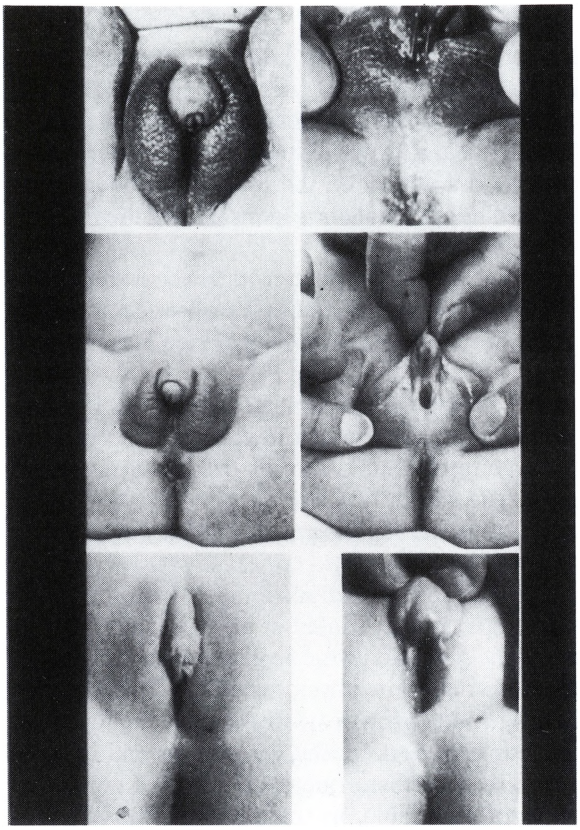

Fig. 3. External genitalia of 3 CAH girls with different degrees of virilization

proach is from genetic angle. As the transmission is autosomal recessive, both parents have to be carriers to produce a child with CAH. The majority of the unaffected siblings should also be carriers. It is conceivable that the recessive genetic trait may be linked somehow to another trait favouring postnatal intellectual development. The critical test for this hypothesis will be whether the carriers and non-carriers differ in intelligence.

Another interesting observation has emerged with regard to prenatal exposure of the foetus with progesterone, given as a drug against toxaemia of pregnancy [11]. According to this report the children, prenatally so exposed, have higher IQs and perform much better in the schools. Although other reports on such exposure could not substantiate these findings it is possible that prenatal exposure to progesterone might improve spatial and mathematical abilities. Some reports also mentioned that these children are more introverted and socially less interactive.

Gonadal Hormones

Gonadal hormones have widespread influence on the brain differentiation and development during foetal life. It is now known that these hormones influence the pattern of dendritic organization and synaptic connections between cells.

It is quite possible that androgens act locally on the hypothalamus during development. Animal experiments have demonstrated that oestrus cycle and ovulation in female rats could be stopped by applying androgens during the first few days of life usually called the "critical period".

It is known for a very long time that androgens produced by the foetal testes impose a masculine pattern of brain development, and in the absence of androgens the brain develops a female pattern. There is ample evidence accumulated from animal studies to this respect.

However, in humans the evidence for a role of gonadal hormones in influencing psychosexual differentiation emerge mainly from clinical observations. Erhardt and Meyer-Bahlburg[12] elaborated four premises of behaviour where the effects of gonadal hormones can be clinically visible: a. gender indentity; b. gender role; c. sexual orientation and d. intelligence and cognitive differences which are usually sexually linked.

The extraordinary example of gender role deviations emerge from three villages in the Dominican Republic. Imperato-McGinley et al.[13] presented these remarkable cases where they lacked the special enzyme 5α-reductase, which converts the dominant androgen, testosterone to its physiologically active metabolite, 5α-dihydrotestosterone. During foetal growth in these subjects, although some parts of genital system, for example vas deferans, epididymis and seminal vesicles develop normally due to a little testosterone available, the penis and scrotum appears as clitoris and associated labia, as there was no 5α-dihydrotestosterone available. Consequently, the male babies born had female-type genitalia and a feminine body contour and were reared as girls (Fig. 4). However, the problem started at puberty. During this time some of these male pseudohermaphrodites are already married to male partners.

With puberty in these so-called "girls" phallus started growing, and the labia-like scrotum became pigmented, and testes descended in the scrotum. Their voice deepened and the "girls" developed a male-type muscular shape. According to Imperato-McGinley et al.[13] in these rural villages of the Dominican Republic nineteen of the thirty-three subjects raised as "girls" and postpubertal psycho-sexual data were obtained from most of them. In the male gender identity gradually evolved over several years. They had to stay married to males and feared ridicule by the society if they behaved differently. There are instances where childless "aunts" had been seen to visiting the brothels, and these individuals were rendered as the object of derision in the society.

Green[14] reported more cases of 5α-reductase deficiency during foetal life where the boys after birth though reared as "girls" because of the shape of their external genitalia, later felt that something was wrong. With growth and development, they discarded the female type toys and craved for male type of games and play. With the onset of puberty they felt attracted towards women and underwent physical virilization. Later, being aware of the medical facilities outside

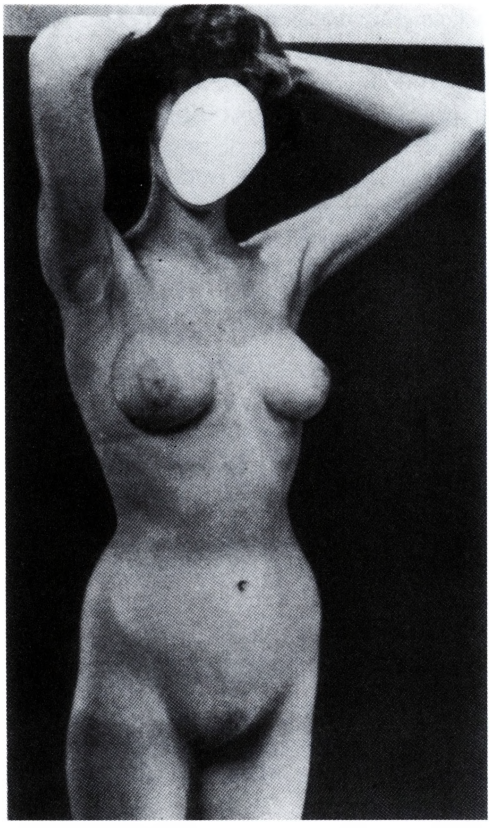

Fig. 4. A male subject with testicular feminization.

their own country, they fled from their own home, sought clinical advice and care and led life as men.

Deprivation of Sex Hormones During Foetal Development: Animal Experiments

The clinical observations indicate that testicular androgens secreted during foetal and neonatal period may be the inducer of "masculinization" of the central nervous system. The cases of testicular feminization, especially where the enzyme 5α-reductase is defective, demonstrate that although the subjects become phenotypically female, but their behaviour patterns change and become more masculine with the onset of puberty. It is possible that the enzyme defect may be partial and with maturation when more testosterone is produced some 5α-dihydrotestosterone is produced which finally casts influence in the behaviour pattern. And it is also possible that prenatal absence of testosterone does not cause complete feminization of the CNS in humans.

However, the data from animal experimental models show that the absence of male sex hormones during foetal development can severely influence the CNS and alter the behaviour pattern in male rats.

In our own studies [15] we administered testosterone and gonadotropin antisera to pregnant rats, and in some instances to nenonatal pups during the "critical period". We had 4 groups of pregnant rats. Groups II and IV were given daily injection of testosterone antiserum (TA) on days 15 and 16 of gestation, while groups I and III received saline. On days 3 and 5 after birth, the male pups of groups III and IV received testosterone antiserum. Thus, the pups of group I were the controls, of group II were given testosterone antiserum only prenatally; of group III only neonatally and of group IV received both prenatal and neonatal injections. The experimental design for gonadotropin antisera (GA) was similar.

Sexual behaviour study was carried out when the animal reached the age day 90–95. An automatic movie camera (Minolta Super 8-D-10) was used and set to record one frame every 4 seconds or 150 in the total test period of sexual behaviour study. After behaviour study, the animals were sacrificed and blood was collected for hormonal evaluation. The following sexual behavioural patterns were taken and expressed as the average frequency of occurrence of the parameter per test period for the male animal.

a. Sniffing and following; sniffing of the anogenital region of the female.
b. Biting: male biting.
c. Mounting: includes all attempts whether or not signs of intromission are visible.
d. Total sex: the sum of all the preceding scores.

Figure 5 shows the average body weight of the control group and the testosterone antiserum-treated groups. All the antiserum-treated groups weighed significantly less than the controls. In fact their body weight was comparable with female animals at that corresponding age.

All the male rats of groups II–IV treated with TA did not achieve successful impregnation with experienced females. The control animals injected only with saline, on the other hand, displayed normal fertility.

There is no significant difference between the TA-treated males and the controls in frequency of total sex behaviour scores during male/female interactions (Fig. 6). Differences, however, do exist between the TA-treated groups from the saline treated group when other indices of sexual behaviour are examined. The TA-treated animals demonstrated a markedly reduced frequency of mounting with signs of pelvic thrusting and rarely ejaculated. These deficiencies in sex behaviour were compared to the control group account for the unsuccessful impregnation with an experienced female. As demonstrated in this slide when the absolute mounting scores are expressed as percentage mounting index (no. of mountings/total sex events $\times$ 100) the difficiency of TA-treated groups in displaying full male sexual behaviour was clearly apparent.

When the test animals were placed with experimental stud males in the observational cage and the female sexual behaviour as shown by the test animals towards the stud male was scored. This female sexual behaviour is expressed as the lordosis quotient (no. of lordoses/number of mounts $\times$ 100). The TA-treated animals showed significantly ($p < 0.01$) high number of lordosis when compared

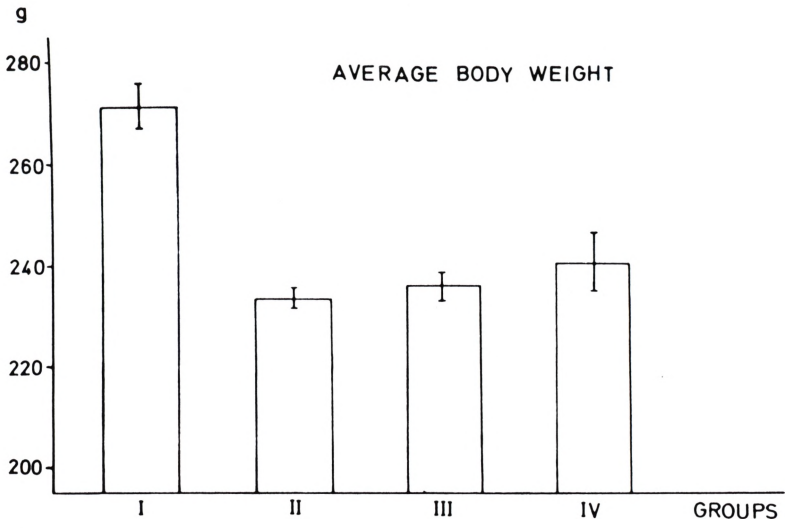

Fig. 5. Effect of testosterone antisera given during foetal development and neonatal period on adult body weight. For details see text.

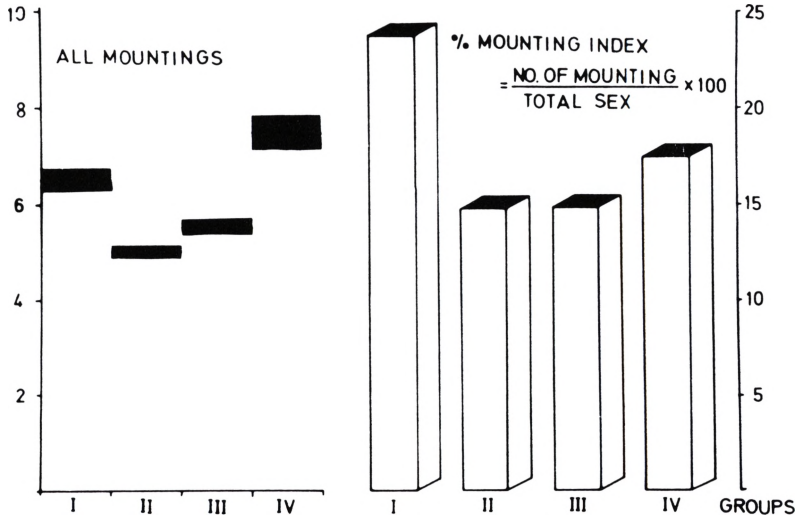

Fig. 6. The average frequency of mounting (left) as shown per 10 min by the male rats (right). For the calculation of percent mounting index see text.

to the control males. The control animals demonstrated lordosis only very seldom.

Hormonal Evaluation

Figure 7 demonstrates the mean levels of circulating plasma testosterone, LH and FSH in the control as well as in the TA-treated animals, when they were

between 90–95 days old. The value of the control group shows good agreement with the normal values for adult male rates of the same strain observed in the Department. All the TA-treated animals whether injected during foetal life or neonatally, show similar levels of testosterone between themselves which were significantly ($p < 0.02$) lower than the levels seen in the control group. Both LH and FSH levels were found to be significantly increased in all TA-treated groups in comparison to the untreated ones. Again the time of TA administration did not have any differentiating effect.

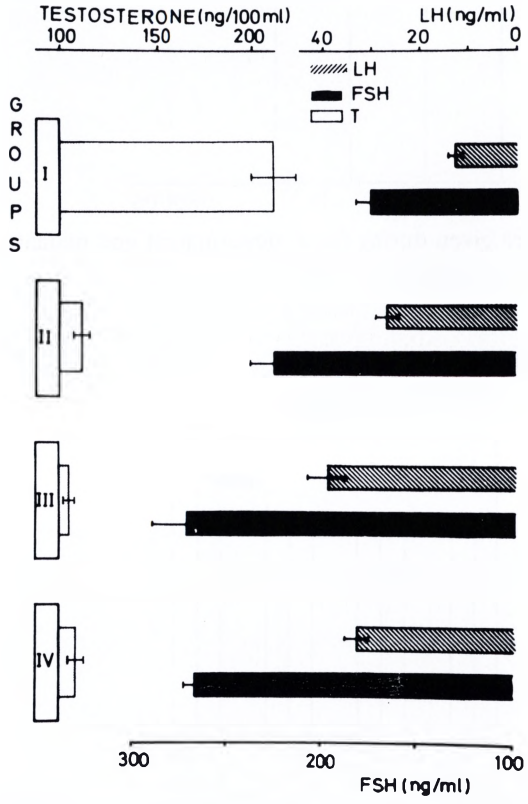

Fig. 7. Circulating level of testosterone, LH and FSH in male rats during adulthood, given TA during foetal and neonatal development. The bars indicate + S.D.

The results reported here conform and extend observations of the earlier investigators with regard to infertility induced in the male rats by administering TA and GA during foetal development or during the critical first 5 days of life. It seems that TA had been successful to reduce the circulation level of testosterone below that required for the masculine differentiation of the brain. It is also evident from group II that this testosterone antiserum, which is in the γ-globulin fraction, was successfully able to pass the placental barrier which was evident from the reduced level of circulating testosterone and hypospadias of testes in

this group of male animals. The hormonal effects produced by the administration of TA either during foetal development or within the first 5 days of life were in many respects comparable to the results of neonatal castration. The experimental animals showed significantly lower levels of testosterone and higher levels of gonadotropins as is shown by animals with reduced androgen production.

Treatment with TA during these critical periods of life seemed to have permanent effect on the masculine sexual apparatus as reflected by underdeveloped phallic size and infertility associated with the experimental animals. Further the TA-treated animals during adulthood demonstrated reduced capacity of displaying masculine sexual behaviour which was reflected in lower frequency of percent mounting and higher lordosis quotient when compared to the control group.

The results demonstrate that although the percent mounting index in TA-treated animals was reduced, the other behaviourial component such as sniffing, following or biting did not have significant difference in the treated and untreated groups. It is thus of interest to note that one essentially masculine behaviourial component, sniffing and following, was not affected by the lower level of circulating testosterone due to testosterone antisera.

This considerable divergence in behaviour which emerged between the TA-treated and untreated animals may reflect a change either in the amount or pattern of steroid binding in the CNS. On the other hand it could be the change in effects which steroids exert on the CNS. It is now known that levels of brain serotonin are indirectly related to level of non-social aggression, and one of the main effects of androgens during early developmental period seems to be to reduce serotonin levels.

Neurotransmitters

Like serotonin, a number of amino acids, such as gamma-aminobutyric acid (GABA) and dopamine, are extremely important in relation to the personality development. From recent evidence, it has been postulated that GABA might serve to restrain behavioural responses, from feeding to aggression. Clinical studies indicate that in the situation of over-arousal, such as epilepsy or anxiety, GABA levels are lowered in the patients. According to Borsook et al.[16] GABA is probably involved in the generation of circadian rhythms and pace-keeping activities of the suprachiasmatic nucleus.

The use of dopamine, which is believed to be involved in neuron-to-neuron signalling, is well known to the clinicians, especially for the Parkinsonian patients. In recent period it has emerged that majority of the drugs which are used for the treatment of schizophrenia, are antagonistic to dopamine. This evidence actually indicates that schizophrenia may be the result of the overactivity of the dopaminergic process.

All these observations have led to establish the influence of the neurotransmitters on mood and behaviour and finally on personality. It is obvious that during embryological shaping of the nervous system, the imbalance in neurotransmitter production can seriously influence the personality development in later life.

Animal experiments have led to the understanding that serotonin-depleted and norepinephrine-depleted animals behave oppositely in many tests. In a novel situation the serotonin-depleted animals appear to be frightened and hyperaroused. The norepinephrine animals behave oppositely [17]. The results imply that serotonin-depleted animals mimic aspects of human anxiety stages, whereas norepinephrine-depleted mimic aspects of human depression and retardation. This conclusion could be supported by the observation that those drugs which are serotonin-agonists help in treating anxiety in humans, whereas those agents used to treat fundamental depression are generally norepinephrine-potentiators.

Conclusion

However, the basic problem is how one can define personality. Although temperament, intelligence and emotional status are taken as some of the factors which constitute personality, there are other definitions and hypothesis (Powell, 1984) [18]. Thus, in this complex area when one seeks to establish the biological basis of personality is faced with more questions than answers. According to Gray (1987) [19] there are three contributing factors: an approach system which responds to rewarding stimuli and facilitates behaviour that encourages exposure; a fight-flight system that responds to aversive stimuli; and behavioural inhibition system that responds to stimuli which give rise to unpleasant consequences. Examining the behaviour patterns poteniated by various hormones and humors, it is thinkable that dopamine participates in the approach system: GABA, serotonin and endorphins serving to oppose the fight-flight system.

Because of the emergence of all these new informations with regard to behaviour and biochemical data, one can realize that the imbalance of hormones and humors during foetal life can influence the personality, at least in certain agreed areas, and the consequences are far-reaching. Although large amount of data emerge from animal models and there are species-specific behaviour, many of the most basic drives and biological rhythms are consistently present in very diverse species. Thus, it will not be far from the truth to say that the effect of any hypo- or hyperpresence of the humors and hormones in the foetus is most likely to alter the "tuning" of the subject when it is grown up. Perhaps this is what we mean as humor-humour interaction.

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