Downloaded from rstb.royalsocietypublishing.org

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Experimental Control of Psychosexuality [and Discussion]

R. W. Goy, D. Price and P. E. Polani

Phil. Trans. R. Soc. Lond. B 1970 **259**, 149-163
doi: 10.1098/rstb.1970.0055

References

Article cited in:
http://rstb.royalsocietypublishing.org/content/259/828/149.citation#related-urls

Email alerting service

Receive free email alerts when new articles cite this article - sign up in the box at the top right-hand corner of the article or click **here**

To subscribe to *Phil. Trans. R. Soc. Lond. B* go to: **http://rstb.royalsocietypublishing.org/subscriptions**

This journal is © 1970 The Royal Society

Downloaded from rstb.royalsocietypublishing.org

Phil. Trans. Roy. Soc. Lond. B. **259**, 149–162 (1970) [149]
Printed in Great Britain

Experimental control of psychosexuality

By R. W. Goy
Department of Reproductive Physiology and Behavior, Oregon Regional Primate Research Center, Beaverton, Oregon 97005, *U.S.A.*

(*MS. received October* 1969)

The effects of hormones upon the development of behavioural characteristics have been reviewed extensively in the past few years (Young, Goy & Phoenix 1964; Levine & Mullins 1966; Goy 1966; Phoenix, Resko & Goy 1968; Whalen 1968). Much of the information contained in these reviews is limited to two species of rodents (rat and guinea-pig). A limitation which perhaps has greater consequences for theoretical considerations is the restriction of information to a set of behavioural traits requiring hormonal activation in adulthood before they can be displayed by the individual. An analogous situation in classical reproductive physiology would be the study of the effects of neonatal or foetal hormone treatments upon the development of prostatic secretory activity. In such a study, the prostate would remain non-secretory unless activated by the appropriate and essential hormones supplied during adulthood either by the gonad or by injection. The behavioural traits most extensively studied have been of a similar nature and include testosterone-dependent responses of the male sexual repertoire like mounting, intromission, and ejaculation or oestrogen–progesterone dependent responses of the female such as oestrous mounting activity and lordosis.

Despite these limitations on the range of data considered by the reviewers, differences in interpretation exist which postulate quite different principles of hormonal action in the developing nervous system. The view has been proposed by Levine (1966) that the embryonic or larval nervous plan is essentially female, and hormones acting at appropriate times in development alter the differentiating process and cause the development of a masculine nervous system. This view for the differentiation of psychological characteristics is not greatly different from that proposed by Harris (1964) regarding the development of cyclic and acyclic neural systems governing pituitary secretion of gonadotrophins. Moreover, it corresponds well to the model provided by embryologists studying the differentiation of sexual morphological characters insofar as the bipotential primordia are concerned. Bipotential primordia like the genital tubercle, genital folds, and urogenital sinus are capable of differentiating into either masculine or feminine forms depending upon the presence or absence of androgens respectively during critical developmental stages. Accordingly a single primordium can differentiate either as a penis or a clitoris, either as a scrotum or as external labia, and separate primordia never exist for these masculine and feminine characters. Correspondingly, for behaviour, neural mechanisms normally destined to mediate feminine behaviour are differentiated under the influence of androgens or other hormones to mediate masculine forms of activity. The differentiating process is viewed as a continuum, and degrees of maleness and femaleness, or degrees of incompleteness of both phenotypes, can be predicted by such a theoretical position. Clearly implied, however, is the corollary that an inverse relationship between the capacities to display masculine and feminine behaviours will normally exist in the adult. That is, feminine

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
The Royal Society is collaborating with JSTOR to digitize, preserve, and extend access to *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences.* www.jstor.org

Downloaded from rstb.royalsocietypublishing.org

characteristics will always be suppressed to an extent which corresponds to the degree of augmentation of masculine characteristics.

In a study of the guinea-pig (Goy, Bridson & Young 1964), some empirical support was obtained for the notion of a continuum of differentiation. When 5 mg of testosterone propionate were injected daily for 6 days at various times in gestation, all female offspring displayed varying degrees of morphological intersexuality at birth. The range of testosterone treatments given provided for considerable variation in clitoral morphology so that some individuals were born with no detectable deviation from normal females and others were born with clitorides which could not be distinguished from the normal male penis. Standardized behavioural tests in

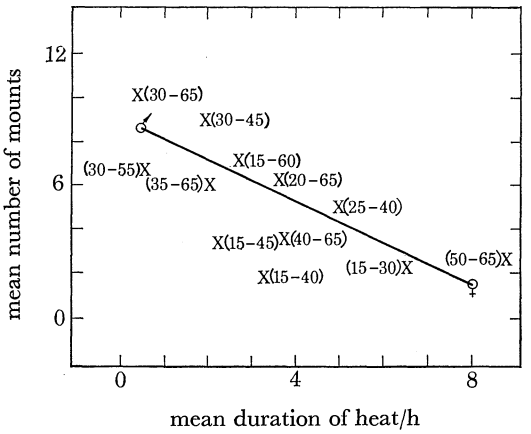


FIGURE 1. Relation between frequency of mounting behaviour and expression of lordosis (duration of heat) for male (♂), female (♀) and female guinea-pigs androgenized during prenatal development (X). The first number within the parentheses associated with each X indicates the gestational age at the time of initial treatment with 5 mg of testosterone propionate. (From Phoenix, Goy & Young 1967).

adulthood given to gonadectomized subjects showed that adult males displayed high rates of mounting activity and little or no lordosis reflex to the normally adequate stimulus. Normal females, in contrast, displayed little or no mounting activity but a vigorous lordosis response as measured by the duration of induced heat. Females from mothers injected with testosterone propionate and given identical tests in adulthood showed correlated changes in these two kinds of behaviour (figure 1). Treatments which were maximally effective in suppressing the lordosis response were associated as well with the greatest augmentation of mounting behaviour. Conversely, treatments which interfered least with the expression of lordosis, so that the response did not differ significantly from that of normal females, were least effective in augmenting the mounting behaviour. Finally, treatments which only partially suppressed the expression of lordosis only augmented mounting behaviour to a moderate degree.

Nevertheless, it is not clear from the psychological data that the analogy of a bipotential primordium is complete and accurate as a model for the development of behaviour, and it is not unreasonable to interpret the experimental facts in terms of separate primordia for masculine and feminine psychosexual traits. In the study of the guinea-pig just described, it was noted that individual reactions to the prenatal treatment with testosterone were quite variable. In a few instances, marked augmentation of mounting without an accompanying suppression of lordosis was obtained. Cases of the converse type were also found. These exceptions imply that

Downloaded from rstb.royalsocietypublishing.org

the augmentation of mounting and the suppression of lordosis induced by prenatal testosteronization are not entirely interdependent, and studies with the rat confirm this impression. In this species, as described below, it has been possible to separate the effects of early androgen on mounting and lordosis by varying the time of early androgen treatment and also by altering the type of androgen injected.

Gerall & Ward (1966) have shown that, for the female rat, variation in the time of testosterone injection can influence the degree to which augmentation of mounting occurs independently of the degree of suppression of lordosis. The effect obtained by them is not unlike the older observation that *variations in the amount of testosterone propionate injected during the sensitive period can dissociate the suppression of lordosis from the suppression of ovulation* (Barraclough & Gorski 1962).

TABLE 1. EFFECTS OF ANDROSTENEDIONE ON THE DEVELOPMENT OF LORDOSIS AND INTROMISSION IN MALE RATS CASTRATED ON THE DAY OF BIRTH

		tests following exogenous oestradiol and progesterone			tests following exogenous testosterone propionate:‡
treatment	*N*	mean lordosis quotient†	% tests positive for lordosis after fingering	% tests positive for ear quiver	mean frequency of intromissions
day 1	6	90	94	72	0.75
day 20	5	12	6	0	6.00
day 1 + Δ^4	7	78	85	28	8.15

† The quotient is obtained by the ratio of the number of lordoses to the number of times mounted multiplied by 100.

‡ During these tests two *S* from the day 1 group and one from the Δ^4 group were eliminated from the study because of illness. (From Goldfoot *et al.* 1969.)

In considering the general problem of the degree of independence which might exist in the neural anlagen for masculine and feminine characteristics, we viewed as critical the experimental determination of a set of conditions which would permit the relatively complete development of both kinds of behaviour in the same individual. Previous work had demonstrated that genetic male rats castrated within a few hours of birth would develop in such a manner that, as adults, a vigorous lordosis could be brought to expression by appropriate hormone treatment, but that the complete display of masculine behaviours could not be activated despite injection of large amounts of testosterone (Grady, Phoenix & Young 1965). In short, genetic males deprived of endogenous androgens by castration developed essentially as behavioural females rather than males. Other studies indicated that the predominant endogenous androgen during the first 10 days of postnatal life in the male rat was testosterone, and androstenedione was not found in the peripheral plasma in concentrations detectable by gas-liquid chromatography (Resko, Feder & Goy 1968). Consideration of both these results suggested that the suppression of lordosis in the genetic male was normally accomplished by the presence of endogenous testosterone and that the suppressive effect might be specific to that androgen. We hypothesized that castration of the genetic male at birth might result in the development of relatively complete masculine and feminine responses if an androgen less specific than testosterone for the suppression of lordosis was supplied by injection. This hypothesis was confirmed when male rats were castrated on the day of birth and injected with androstenedione every other day through day 19 of life (Goldfoot, Feder & Goy 1969). Males treated in this manner readily display

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

lordosis in adulthood when injected with oestrogen and progesterone, and also display mounting, intromission and ejaculation when injected with testosterone propionate (table 1). This result is in sharp contrast to the result obtained with males castrated at birth and given no androgenic replacement therapy (day 1, table 1) and to the result obtained when males are castrated at later ages (day 20, table 1). In the former subjects, generally only lordosis and mounting can be activated in adulthood, not intromission and ejaculation. In the latter subjects, only mounting and intromission could be activated, not the lordosis response.

TABLE 2. EFFECTS OF VARYING AMOUNTS OF ANDROSTENEDIONE ON DEVELOPMENT OF LORDOSIS IN CASTRATED MALE AND FEMALE RATS

group	sex	neonatal treatment (μg)	N	mean lordosis quotient of males and females: test 2	test 3
1	♂	vehicle	9	83.3	86.6
2	♂	25	10	77.0	82.0
3	♂	50	9	34.4	24.4
4	♂	100	9	14.4	11.1
5	♂	150	10	0.2	0.1
6	♀	vehicle	8	87.5	83.7
7	♀	25	10	82.0	83.0
8	♀	50	9	45.5	45.5
9	♀	100	10	18.0	13.0
10	♀	150	9	0.2	0.1

From an experiment by Dr Jeffrey Stern.

TABLE 3. EFFECTS OF VARYING AMOUNTS OF ANDROSTENEDIONE ON DEVELOPMENT OF MOUNTING, INTROMISSION, AND EJACULATION IN CASTRATED MALE RATS†

group	neonatal treatment (μg)	ejaculations / tests × 100	mean intromissions to ejaculate	mean mounts per minute	mean intromissions per minute	mean time to ejaculate (min)
1	vehicle	0	—	0.89	0.001	—
2	25	83.3	16.80	0.64	0.88	16.5
3	50	88.8	17.95	0.75	0.88	16.5
4	100	74.9	14.45	0.63	0.72	13.5
5	150	96.6	16.48	0.74	1.01	15.9

† Subjects were castrated on the day of birth and injected daily for 20 days with vehicle or various doses of androstenedione. (From an experiment by Dr Jeffrey Stern.)

This extraordinary effect of androstenedione on development of the genetic male rat has been confirmed in a more extensive parametric study by Dr Jeffrey Stern (1969) at the University of California in Berkeley. His results show that high doses of androstenedione suppress development of the lordosis in both the genetic male castrated at birth and the genetic female (table 2). Nevertheless, smaller dosages such as the administration of 25 μg of androstenedione daily to males castrated on the day of birth fails to suppress lordosis, and permits the development of complete masculine behaviour (table 3).

The development of behaviour in the male rat following neonatal castration and replacement therapy with androstenedione is remarkably similar to the behavioural development of the normal male hamster. In the latter species, genetic males, even though the testes remain

Downloaded from rstb.royalsocietypublishing.org

intact throughout development, retain or develop the ability to display lordosis in adulthood as well as mounting, intromission and ejaculation (Eaton 1969). Moreover, suppression of lordosis in genetic females can only be achieved by the injection of very large amounts of testosterone during the neonatal period of differentiation (Crossley & Swanson 1968). Neither endogenous testicular secretions nor exogenous testosterone propionate in amounts far in excess of those normally effective in the rat are capable of suppressing the development of lordosis in the hamster. Apparently some protective mechanism, the nature of which remains unknown although it is presumably genetic, operates to render the suppressive actions of androgen less effective in this species. The hypothetical protective mechanism appears to be tissue-specific, for it does not prevent or interfere with the contributions of early testicular secretions to the development of masculine behaviours.

TABLE 4. AVERAGE FREQUENCY OF MOUNTING AND PRESENTING PER BLOCK OF 10 TRIALS

	mounts		presents	
	1st year	2nd year	1st year	2nd year
♂ 1242	11.5	9.6	0.0	3.0
♂ 1243	16.7	8.7	0.2	3.6
♂ 1617	4.4	1.8	0.8	1.8
♂ 1620	1.1	0.0	1.4	2.2
♂ 1625	0.4	0.4	1.2	0.2
♂ 1636	0.0	0.8	0.0	3.2
♂ 1657	0.5	0.2	0.3	0.4
♂ 1658	1.2	5.6	2.8	4.4
♂ 1662	0.1	0.2	0.0	15.2
♂ 1954	1.8	0.8	1.6	0.0
♂ 1958	2.8	3.2	0.2	0.4
♂ 1960	4.0	2.2	0.7	0.6
mean	3.70	2.79	0.76	2.91
♀ 1239	0.9	0.2	0.8	8.0
♀ 1616	0.9	0.0	0.1	0.0
♀ 1619	2.1	2.0	0.0	0.2
♀ 1640	3.3	9.0	0.1	0.0
♀ 1656	0.0	0.0	0.4	3.6
mean	1.44	2.2	0.28	2.36
♀ 1252	0.1	0.0	5.0	3.0
♀ 1551	0.0	0.0	0.0	3.4
♀ 1642	0.0	0.0	2.3	5.2
♀ 1649	0.0	0.2	1.0	1.4
♀ 1654	0.0	0.0	0.1	0.2
♀ 1769	0.0	0.0	1.8	10.8
♀ 1838	0.0	0.0	0.5	0.0
mean	0.01	0.02	1.52	3.42

(From Goy 1968.)

The example provided by the hamster is not entirely exceptional, and a strong parallel exists in the development of sexual behaviour in the rhesus monkey. As reported previously (Goy 1968) young male rhesus display the sexual presentation as frequently as young females. Testosterone propionate injected into pregnant females, while strongly virilizing genital morphology of female offspring, fails to suppress development of the sexual presentation behaviour (table 4). In the rhesus, as in the hamster, neither endogenous testicular secretions nor exogenous testosterone propionate suppress development of sexual presentation, but both

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

are associated with an augmentation of mounting compared with the expression of mounting in normal females.

These studies on the development of sexual behaviour suggest that in all likelihood separate neural bases exist for the tissues that are destined to mediate these masculine and feminine modes of conduct. The differentiation of the Wolffian and Müllerian ducts and associated structures provide a corresponding morphological model for such a point of view. As applied to behaviour, the model is most completely accepted by Whalen (1968) in his suggestion that neural mechanisms mediating all aspects of male and female behaviour exist in every individual, presumably even in the adult state. Accordingly, the role played by hormones early in development is not organizational in the sense of controlling the differentiation and ultimate fate of a single neural primordium. Instead, the primary action of embryonic hormones is regarded as one of altering the hormonal thresholds for activation of male and female neural mechanisms by hormonal stimulation in adulthood. That is to say, both masculine and feminine neural mechanisms exist in every adult, but the amounts of androgen and oestrogen required to activate these mechanisms and bring behaviour to expression have been conditioned or determined by the prior action of embryonic hormones. Thus, if androgens have been present in sufficient amounts during the appropriate early stage, then the male neural mechanisms will have been permanently sensitized to later stimulation with androgens and the sensitivity of the female behaviour mechanisms to the later activational properties of the ovarian hormones will have been permanently reduced.

The suggestion was made long ago (Goodale 1918) that every individual contains the neural mechanisms necessary for the mediation of behaviour normally characteristic of the opposite sex. The numerous reports in the literature demonstrating that feminine behaviour can be elicited from adult males following treatment with large amounts of oestrogen and progesterone, or under unusual conditions of sexual stimulation, or both, are consistent with this view of the inherent bisexuality of the nervous system (Kun 1934; Ball 1939; Engel 1942). Corresponding data exist for the activation of masculine behaviours in adult females (Hu & Frazier 1939; Ball 1940; Beach 1942; Klein 1952; Goy & Young 1958).

The general truth of this point of view that the mammalian nervous system is inherently bisexual is not disputed, but the proposition that early hormones modify thresholds for hormonal activation of behaviour in adulthood and do not organize neural structures involved in the mediation of patterns of behaviour seems to be only narrowly valid. If the actions of embryonic, foetal, or larval hormones are strictly limited to the role of conditioning thresholds for hormonal activation, then this theoretical position cannot account for psychologically dimorphic behaviours which do not require hormonal activation. Alternatively stated, the hormones present during critical early developmental stages can make little or no contribution to the development of sex-related behaviours that are expressed by the individual independently of hormonal activating systems. Instead, factors of early experience, social conditioning, genetical and somatotypic influences would have to regulate the adoption of masculine and feminine modes of conduct.

Studies of the development of social behaviours in young rhesus monkeys provide examples of a variety of psychological dimorphisms which do not require activation by gonadal hormones for their overt expression. The period of life from birth through approximately $2\frac{1}{2}$ years of age is characterized by gonadal quiescence in the male (Resko 1967) and probably in the female as well. During this same period of development, the social behaviour of young males and

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

females differs markedly. In standard observations males perform specific patterns of threat, aggressive play, and chasing play significantly more often than females of the same age and comparable rearing experience (Goy 1968).

If the gonads are removed at birth, the differences between the sexes are not eliminated. Parenthetically, it is important to remind the reader that castration at birth in the rhesus monkey, as in the guinea-pig, is not comparable to castration on the day of birth in short gestation species like the hamster and rat. In the rhesus and guinea-pig the periods of morphological and psychological sexual differentiation, i.e. the periods when hormones exert their organizing actions, are probably completed before birth. In recent unpublished studies by W. D. Joslyn, males and females gonadectomized on the day of birth were compared with intact subjects for the frequency of performance of specific threat and play patterns during the first year of life (table 5). For the four kinds of behaviour illustrated, castrated males and intact males did not differ significantly from one another, but both differed significantly from normal females. Frequencies of performance remained low in ovariectomized females and did not differ significantly from average frequencies characterizing intact females.

TABLE 5. PERFORMANCE OF FOUR KINDS OF SOCIAL BEHAVIOUR BY NORMAL MALE AND FEMALE RHESUS AND BY MALES AND FEMALES GONADECTOMIZED AT BIRTH

		average frequency per animal per block of 10 trials			
	N	threat	play initiation	rough and tumble play	pursuit play
⊗♀	3	7.0	4.0	3.6	0.2
♀	23	5.6	9.2	9.0	1.1
⊗♂	2	35.0	49.2	39.3	5.3
♂	27	23.5	38.6	29.1	7.8

The factors of early experience and the prenatal endocrine environment operate conjointly to permit development of these behavioural characteristics of the rhesus monkey which, although sex-related, require no hormonal activation at the time they are displayed. If rhesus monkeys are reared in conditions of social deprivation, the performance of these patterns of play by deprived males never attains the levels characteristic of socially reared males. Similarly, the development of sexual behaviour is in some way partially or completely thwarted in males deprived of early social experience (Harlow 1965).

In our own experiments on the development of these behaviours in rhesus monkeys we have been unable to perform the experiments essential to proving that genetic males deprived of testicular androgens prenatally would develop along feminine lines. As an alternative to this direct approach, we have injected testosterone propionate into pregnant rhesus and studied the behavioural development of their virilized female offspring. The parameters of these prenatal treatments are described in table 6. In all four types of behaviour (threat, play initiation, rough and tumble play, and pursuit play), the virilized females were more active than normal females. The performance of rough and tumble play, which is representative of all behaviours, is illustrated in figure 2 for normal males, normal females and the virilized or pseudohermaphroditic females. The behaviour of genetic males receiving comparable prenatal testosterone treatments is not altered.

The changes in social behaviour which occur following treatment of genetic females with testosterone propionate prior to birth are paralleled by changes in mounting activity which at

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

these early ages is also independent of gonadal hormone activation. The augmentation of the frequency of mounting has already been illustrated in table 4, where the extent of the sexual dimorphism is readily apparent. But a more subtle aspect of the masculinizing effects of prenatal testosterone deserves attention. Briefly it is that the development of mounting behaviour in young rhesus males shows a gradual shift in the ratio of mature to immature mounts during

TABLE 6. AMOUNT AND TEMPORAL DISTRIBUTION OF PRENATAL INJECTIONS OF TESTOSTERONE PROPIONATE (TP) IN RHESUS MONKEYS†

number of offspring	genetic sex	gestational age *R* started	gestational age *R* ended	amount and number of injections of TP into mother: mg × days	mg × days	mg × days	total mg
828	♀	40	69	20 × 30	—	—	600
829	♀	40	69	20 × 30	—	—	600
1239	♀	38	66	25 × 25‡	—	—	625
1656	♀	40	111	10 × 50 →	5 × 22	—	610
836	♀	40	89	25 × 10 →	15 × 20 - - - →	10 × 20	750
1616	♀	39	88	25 × 10 →	15 × 20 - - - →	10 × 20	750
1619	♀	39	88	25 × 10 →	15 × 20 - - - →	10 × 20	750
1640	♀	39	88	25 × 10 →	15 × 20 - - - →	10 × 20	750
1558	♂	42	92	25 × 10 →	15 × 20 →	10 × 20	750
1561	♂	39	45	25 × 7	—	—	175
1618	♂	43	92	25 × 10 →	15 × 20 →	10 × 20	750
1644	♂	44	113	10 × 50 →	5 × 20	—	600
1645	♂	39	129	25 × 10 →	10 × 19§ →	5 × 22§	550
1648	♂	39	119	25 × 3 →	5 × 78	—	465
1653	♂	43	134	25 × 10 →	10 × 17 →	5 × 24	540
1966	♂	40	109	15 × 10 →	10 × 40 →	5 × 20	650

† From Phoenix, Resko & Goy 1968, with permission of the authors.
‡ Injected 6 days per week.
§ Injected on alternate days.

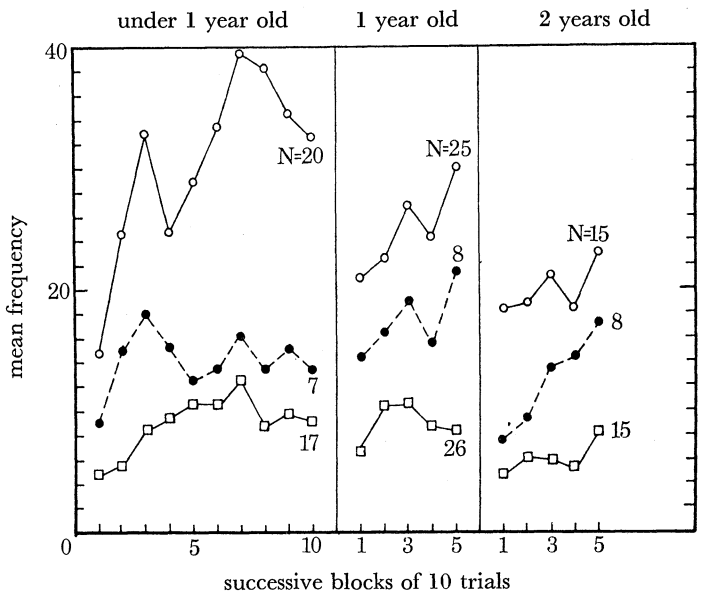
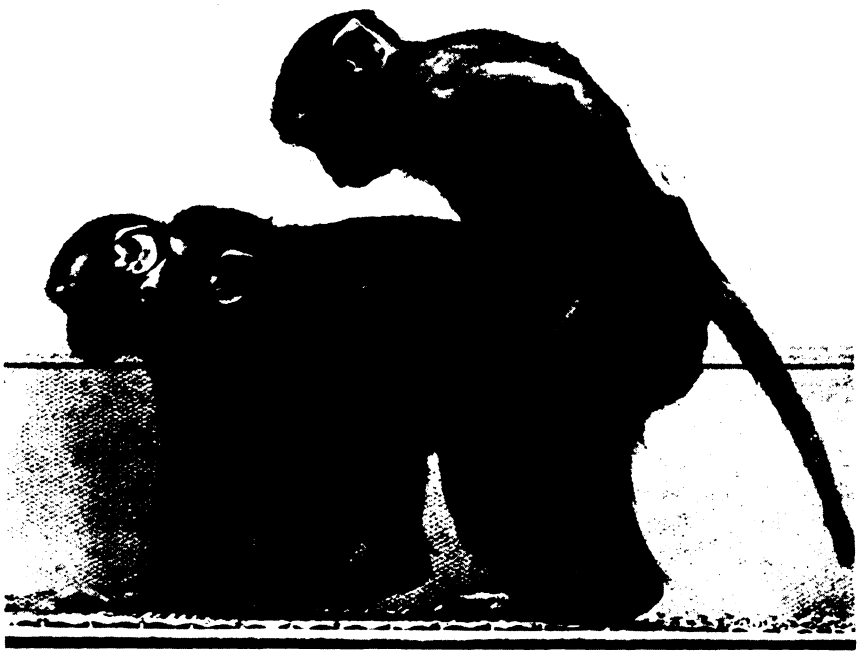


FIGURE 2. The frequency of performance of rough and tumble play by normal male (○—○), female (□—□) and pseudohermaphroditic female (● - - - ●) rhesus at various ages before adolescence. (From Phoenix, Resko & Goy 1968, with permission of the authors.)

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

3



4

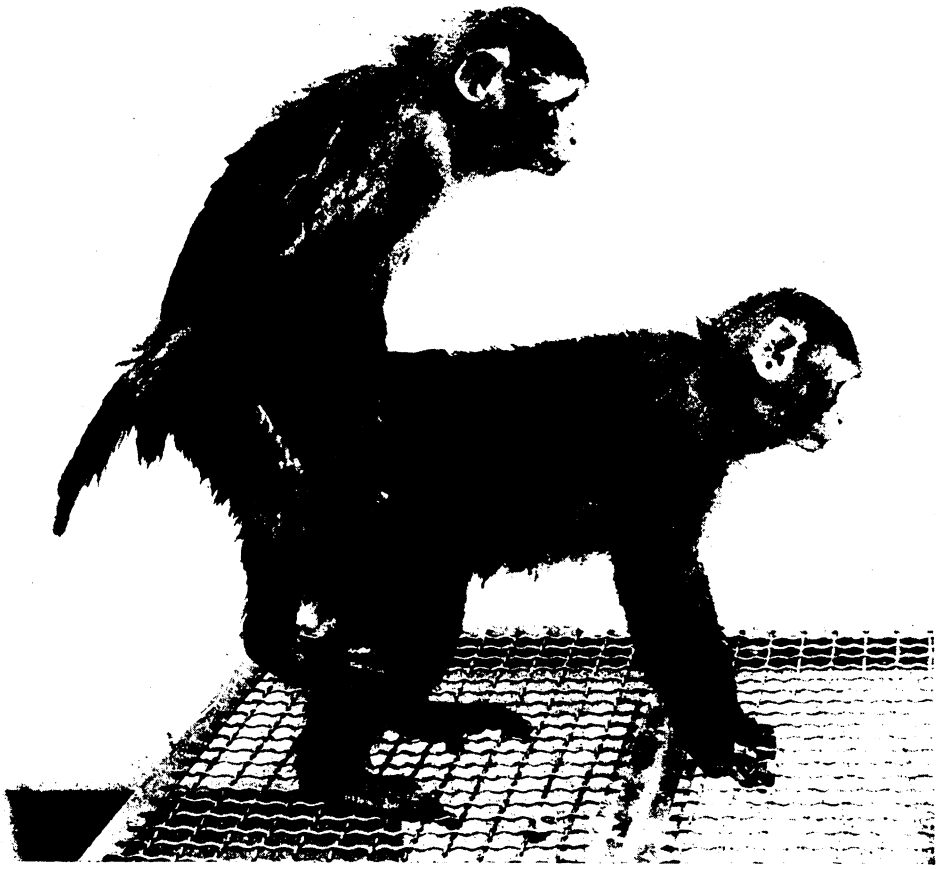


FIGURE 3. Illustration of the immature mounting pattern characteristic of rhesus males before 1 year of age. Note position of the feet and compare with figure 4.

FIGURE 4. Illustration of the double foot-clasp mount characteristic of the mature male rhesus.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

the first 3 years of life. Initially, most of the mounting displayed by the young male is characterized by standing at the rear of the partner with the feet flat on the floor, clasping the partner's hips or back with the hands, and exhibiting rhythmical pelvic thrusts. At later ages, most of the mounting consists of clasping the partner's legs or ankles with the feet, placing the hands gently on the partner's rump and thrusting. The two types of mounting behaviour are illustrated in figures 3 and 4. In the situation in which we study the animals, normal females do not show this systematic progression in the development of the mature male mounting pattern. Pseudohermaphroditic females, however, closely parallel the developmental pattern of the genetic male (table 7).

TABLE 7. CHANGES WITH AGE IN THE RATIO OF MATURE TO IMMATURE MOUNTS DISPLAYED BY NORMAL MALE AND PSEUDOHERMAPHRODITIC FEMALE RHESUS MONKEYS

	N	3½–9 months old	*N*	12–15 months old	*N*	24–27 months old	*N*	36–39 months old
♂	27	0.1	30	0.7	21	2.5	14	3.0
♀	7	0.1	8	1.8	8	2.8	7	3.0

TABLE 8. AGE AT MENARCHE IN NORMAL AND PSEUDOHERMAPHRODITIC FEMALE RHESUS

	date of birth	age at menarche in days	age at menarche in months	number of menstrual episodes during each year of life				
				2nd	3rd	4th	5th	6th
822	11. v. 61	1057	34.7	0	1	7	5	—
823	11. v. 61	730†	24.0	2	7	11	10	—
830	29. vi. 62	885	29.1	0	9	10	—	15
831	17. vii. 62	647	21.3	4	8	6	—	13
833	9. viii. 62	956	31.4	0	3	5	9	11
1252	11. vi. 64	1030	33.9	0	2	9	9‡	—
1551	30. xii. 64	1014	33.3	0	2	10	4‡	—
1642	14. iv. 65	911	29.9	0	5	7	—	—
1649	23. iv. 65	861	28.3	0	5	12	—	—
1654	27. iv. 65	923	30.3	0	1	10†	—	—
1769	26. v. 65	867	28.5	0	6	11†	—	—
1838	17. vii. 65	910	29.9	0	1	5†	—	—
2320	8. iv. 66	953	31.3	0	4	—	—	—
2350	29. iv. 66	903	29.7	0	6‡	—	—	—
2362	10. v. 66	897	29.5	0	4‡	—	—	—
2551	4. vii. 66	855	28.1	0	5‡	—	—	—
2575	4. viii. 66	834	27.4	0	5‡	—	—	—
2577	6. viii. 66	738	24.3	0	5‡	—	—	—
mean	—	887.3	29.2	—	—	—	—	—
828	27. vi. 62	926	30.4	0	5	7	—	7
829	8. vii. 62	1221	40.1	0	0	7	—	8
836	18. iii. 63	1030	33.9	0	3	3	9	13
1239	28. v. 64	1058	34.8	0	1	6	10	—
1616	15. iii. 65	1175	38.6	0	0	6	—	—
1619	17. iii. 65	1187	39.0	0	0	7	2‡	—
1640	10. iv. 65	1135	37.3	0	0	7	1‡	—
1656	28. iv. 65	1150	37.8	0	0	7	—	—
1664	10. v. 65	1193	39.2	0	0	7‡	—	—
mean	—	1119.4	36.8	—	—	—	—	—

† Estimated.
‡ Incomplete year.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

The syndrome of anovulatory sterility has not been induced by the testosterone treatments given prenatally to these pseudohermaphroditic rhesus females. Other abnormalities of pituitary-ovarian function have been observed, however. The most conspicuous of these is a marked delay in menarche. Among normal laboratory-reared rhesus females, the onset of menstruation occurs at 29.2 months on the average, but the first appearance of menstruation is delayed until 36.8 months of age on the average among pseudohermaphroditic females (table 8). As the table shows, the number of menstrual episodes does not differ markedly in pseudohermaphrodites compared with normal females once the menarche has occurred. In collaborative work with Dr J. A. Resko, we have collected blood on either day 7, 8, or 9, and again on day 16, 17, or 18 of the cycle and assayed for progesterone by means of gas-liquid chromatography in order to determine whether or not ovulation and corpus luteum function could occur in these testosteronized females. During the earlier days of the cycle (presumptive follicular phase), progesterone, as expected, was always low or undetectable in both normals and pseudohermaphrodites. In addition, neither group of females showed elevated levels of progesterone on days 16 to 18 prior to the eighth cycle following the menarche. In the eighth and later cycles, however, both groups showed elevated levels of progesterone characteristic of the luteal phase (table 9).

TABLE 9. COMPARISON OF PROGESTERONE LEVELS FROM NORMAL AND PSEUDOHERMAPHRODITIC FEMALE RHESUS DURING EARLY AND LATER CYCLES*

	no. of females	no. of cycles sampled	length of cycles (median and range)	sampled no. of days before mens. (median and range)	amount of progesterone (μg/100 ml)
early cycles (2nd to 7th)					
normal ♀	7	9	28 (23–33)	10.9 (6–16)	ND
pseudohermaphroditic ♀	3	4	32.2 (31–34)	13.8 (13–15)	ND
later cycles (8th to *N*th)					
normal ♀	11	13	26.3 (23–31)	9.5 (6–14)	0.694† (ND–1.470)
pseudohermaphroditic ♀	5	8	27.0 (25–29)	9.8 (8–12)	0.768 (0.520–1.400)

* Only cycles lasting 23 to 34 days were used in this analysis. Shorter and longer cycles were excluded.
† The anovulatory cycle with ND progesterone was not included in the estimation of the mean.

The evidence for production of luteal levels of progesterone has been obtained for only 5 of the 9 pseudohermaphrodites. The possibility exists that ovulation has been impaired or totally blocked in the remaining experimental subjects, but we are unable to establish this securely at the present time because the cycles during which blood was collected were abnormal in length (shorter than 23 or longer than 34 days). When blood is collected from cycles which are abnormal in length, there is little point in assaying for the amount of progesterone. For example, in a cycle lasting 60 days, the absence of progesterone on day 18 cannot be interpreted as a failure in ovulation since that event might not have occurred until day 44 of the lengthened cycle.

The changes induced in rhesus females by treatment of their mothers with testosterone propionate during a restricted period of pregnancy are diverse in character. It is not possible at the present time to hypothesize actions of the early androgen upon a single set of neural

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

structures which would account for masculinization of threat-like and play behaviours, sexual conduct and the mechanisms responsible for regulating the onset of puberty. The distinct possibility exists that not all of these effects represent 'masculinizing' changes in neural tissues alone, but the functional characteristics of other organ systems may also have been altered by the prenatal actions of the administered testosterone. Inasmuch as the patterning of behaviour has been influenced over a broad period of juvenile and pre-adolescent development, however, and since these behavioural patterns seem not to be influenced by actions of the gonadal hormones during this same period of development, the hypothesis of a neural organizing influence of the prenatal androgen seems likely.

The nature of this influence of early androgen is subtler for the social traits studied in the monkey than it is for the kinds of behaviours previously investigated in rodents. Whereas the sexual behaviours of rodents require hormonal activation for their display and the contribution of early experience is of less importance than in higher mammals, the social behaviours of young rhesus monkeys depend heavily upon proper experience and are virtually independent of hormonal activation. The organizing effects of early androgen upon the sexual behaviours of rodents can be at least partially accounted for by alterations in the sensitivity of specific neural structures to the activational properties of oestrogens, progesterone, and androgens in adulthood. In contrast, the organizing effects of early androgen upon the development of experientially dependent social behaviours in the rhesus have to be conceptualized in terms of a predisposition to acquire specific patterns of conduct that are normally characteristic of the genetic male.

This interpretation of the effects of prenatal androgen upon the development of behaviour in pseudohermaphroditic monkeys is not thought to be incompatible with interpretations of psychosexual development in certain instances of human female pseudohermaphroditism. For those who have worked extensively with the latter type of subject (Money 1955, 1965; Hampson & Hampson 1961), an emphasis, which in the light of present evidence may be unwarranted, has been placed on early experience. In clinical investigations, by the nature of the circumstances, little or nothing is known of the type of androgenization which has caused the morphological virilization. Neither the onset of the abnormally high level of androgen, the duration of the period of androgenization, nor the chemical nature of the androgen can be known. All of these variables, as indicated in this report and many others, are critical in the determination of the extent to which psychological and morphological virilization will develop in animals other than man. As the early reports of human hermaphroditism suggested, the determination of psychosexuality may be primarily a matter of social experience. On the other hand, a growing body of evidence suggests that for the human, as for other mammals, the effectiveness of social experience is influenced in turn by the type of hormone present during an early period of embryonic, foetal or neonatal differentiation (Money & Ehrhardt 1968; Diamond 1968). It would be premature at this time to attempt to reconcile data and interpretations for man and animals, or to do more than suggest that the divergence between these various studies of psychosexual determination has been more than slightly lessened. With the limitations of present information it is not even possible to reconcile diverse interpretations of studies restricted to experimental animals. There is reason for optimism, however, that as more information is gained about the broad relationships existing between hormones and the determination of various psychological characteristics that the gaps between different theoretical interpretations will be bridged.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

We wish to acknowledge the support of Grants from the U.S. Public Health Service (FR 00163 and MH 08634) which have made possible much of the work described.

References (Goy)

Ball, J. 1939 Male and female mating behavior in prepubertally castrated male rats receiving estrogens. *J. comp. Psychol.* **28**, 273–283.

Ball, J. 1940 The effect of testosterone on the sex behavior of female rats. *J. comp. Psychol.* **23**, 151–165.

Barraclough, C. A. & Gorski, R. A. 1962 Studies on mating behaviour in the androgen-sterilized female rat in relation to the hypothalamic regulation of sexual behaviour. *J. Endocr.* **25**, 175–182.

Beach, F. A. 1942 Male and female mating behavior in prepuberally castrated female rats treated with androgens. *Endocrinology* **31**, 673–678.

Crossley, D. A. & Swanson, H. H. 1968 Modification of sexual behaviour of hamsters by neonatal administration of testosterone propionate. *Proc. Soc. Endocr., J. Endocr.* **41**, 13–14 (abstract).

Diamond, M. 1968 Genetic-endocrine interactions and human psychosexuality. In *Perspectives in reproduction and sexual behaviour*, pp. 417–443 (ed. M. Diamond). Bloomington: Indiana University Press.

Eaton, G. G. 1969 Perinatal androgen's role in the ontogenesis of coital behavior in the male hamster (*Mesocricetus auratus*). Ph.D. Dissertation, University of California, Berkeley.

Engel, P. 1942 Female mating behavior shown by male mice after treatment with different substances. *Endocrinology* **30**, 623.

Gerall, A. A. & Ward, I. L. 1966 Effects of prenatal exogenous androgen on the sexual behavior of the female albino rat. *J. comp. physiol. Psychol.* **62**, 370–375.

Goldfoot, D. A., Feder, H. H. & Goy, R. W. 1969 Development of bisexuality in the male rat treated neonatally with androstenedione. *J. comp. physiol. Psychol.* **67**, 41–45.

Goodale, H. D. 1918 Feminized male birds. *Genetics* **3**, 276–299.

Goy, R. W. 1966 Role of androgens in the establishment and regulation of behavioral sex differences in mammals. *J. Anim. Sci.* (Suppl.) **25**, 21–35.

Goy, R. W. 1968 Organizing effects of androgen on the behaviour of rhesus monkeys. In *Endocrinology and human behaviour*, pp. 12–31 (ed. Richard Michael). Oxford University Press.

Goy, R. W., Bridson, W. E. & Young, W. C. 1964 Period of maximal susceptibility of the prenatal female guinea pig to masculinizing actions of testosterone propionate. *J. comp. physiol. Psychol.* **57**, 166–174.

Goy, R. W. & Young, W. C. 1958 Responses of androgen-treated spayed female guinea pigs to estrogen and progesterone. *Proc. Am. soc. Zool., Anat. Rec.* **131**, 560 (abstract).

Grady, K. L., Phoenix, C. H. & Young, W. C. 1965 Role of the developing rat testis in differentiation of the neural tissues mediating mating behavior. *J. comp. physiol. Psychol.* **59**, 176–182.

Hampson, J. L. & Hampson, J. G. 1961 The ontogenesis of sexual behavior in man. In *Sex and internal secretions*, pp. 1401–1432 (3rd ed., ed. W. C. Young). Baltimore: Williams and Wilkins.

Harlow, H. F. 1965 Sexual behavior in the rhesus monkey. In *Sex and behavior*, pp. 234–265 (ed. F. A. Beach). New York: John Wiley and Sons.

Harris, G. W. 1964 Sex hormones, brain development and brain function. *Endocrinology* **75**, 627–648.

Hu, C. K. & Frazier, C. N. 1939 Masculinization of adult female rabbit following injection of testosterone propionate. *Proc. Soc. exp. Biol. Med.* **42**, 820–823.

Klein, M. 1952 Administration of sex hormones and sexual behavior. *Ciba Fdn. Colloq. Endocr.* **3**, 323–337.

Kun, H. 1934 Psychische Feminierung und Hermaphrodisierung von Männchen durch weibliches Sexualhormon. *Endokrinologie* **13**, 311–323.

Levine, S. 1966 Sex differences in the brain. *Scient. Am.* **214**, 84–90.

Levine, S. & Mullins, R. F., jun. 1966 Hormonal influences on brain organization in infant rats. *Science, N.Y.* **152**, 1585–1592.

Money, J. 1955 Hermaphroditism, gender and precocity in hyperadrenocorticism: psychologic findings. *Bull. Johns Hopkins Hosp.* **96**, 253–264.

Money, J. 1965 Influence of hormones on sexual behavior. *A. Rev. Med.* **16**, 67–82.

Money, J. & Ehrhardt, A. A. 1968 Prenatal hormonal exposure: possible effects on behaviour in man. In *Endocrinology and human behaviour*, pp. 32–48 (ed. Richard Michael). Oxford University Press.

Phoenix, C. H., Goy, R. W. & Young, W. C. 1967 Sexual behavior: General aspects. In *Neuroendocrinology*, Vol. II, ed. by L. Martini & W. F. Ganong, pp. 163–196. New York: Academic Press.

Phoenix, C. H., Resko, J. A. & Goy, R. W. 1968 Psychosexual differentiation as a function of androgenic stimulation. In *Perspectives in reproduction and sexual behavior*, pp. 33–49 (ed. M. Diamond). Bloomington: Indiana University Press.

Resko, J. A. 1967 Plasma androgen levels of the rhesus monkey: effects of age and season. *Endocrinology* **81**, 1203–1212.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

Resko, J. A., Feder, H. H. & Goy, R. W. 1968 Androgen concentrations in plasma and testis of developing rats. *J. Endocr.* **40**, 485–491.

Stern, J. 1969 Neonatal castration, androstenedione, and the mating behavior of the male rat. *J. comp. physiol. Psychol.* **69**, 608–612.

Whalen, R. E. 1968 Differentiation of the neural mechanisms which control gonadotropin secretion and sexual behavior. In *Perspectives in reproduction and sexual behavior*, pp. 305–340 (ed. M. Diamond). Bloomington: Indiana University Press.

Young, W. C., Goy, R. W. & Phoenix, C. H. 1964 Hormones and sexual behavior. Broad relationships exist between the gonadal hormones and behavior. *Science, N.Y.* **143**, 212–218.

Discussion on paper by R. W. Goy, p. 149

D. Price: The early experiments of Zaaijer, Ortiz and myself on secretory ability of foetal guinea-pig testes in ontogeny brought out a point that may be relevant to psychosexual differentiation in this species. We demonstrated that in the period of 30 to 35 days, which is a critical one for sex differentiation of the reproductive ducts, the testes are secreting androgens. Also, there is localization of 3β-hydroxysteroid dehydrogenase activity in the interstitial cells of the testes, indicating the capacity for steroidogenesis (Price, Ortiz and Deane, reviewed in Price & Ortiz 1965). This is precisely the stage in which Goy and his co-workers reported that female foetuses are most susceptible to exogenous testosterone as an agent causing masculinization of behaviour. It seems possible that the male type of psychosexual differentiation may be promoted in the male in this period by testicular androgens which also are responsible for sex differentiation of the ducts. Our studies have demonstrated that androgens are secreted normally and that they may be steroidal. Bloch (1967*a*, *b*) found that homogenates of guinea-pig testes at mid-gestation (presumably 35 days) can convert labelled pregnenolone and progesterone to testosterone and androstenedione. We believe that foetal guinea-pig testes are not only capable of secreting a number of different hormones but are normally doing so and that some, at least, may be steroids which may be similar or identical to testicular androgens secreted postnatally.

R. W. Goy: We also believe that there are various androgens important in psychosexual differentiation. Testosterone gives the best duplication of masculinity. Androstenedione is not so effective nor are oestrogens, but there are limits to what testosterone can accomplish in the conversion of the genetic mammalian female. For psychosexual differentiation, as for masculinization of the genital tract, there may be more than one morphogenetic substance. My colleagues, John Resko, H. Feder and I (1968) have measured androgens during the last half of the period of sexual differentiation in rats, i.e. during the postnatal period but not before birth, which is a difficult experiment involving large numbers of animals. At this stage there is little or no androstenedione, but substantial amounts of testosterone, although this result may not apply to all animals. In monkeys, during a comparable period of late foetal development both androgens appeared to be present in the plasma of males, whereas in female foetuses only androstenedione is found. This is more evidence implicating testosterone as the active substance, although dihydrotestosterone and other androgens were not measured. Thus it seems clear that at least for the later stages of sexual differentiation in both rat and monkey the androgens normally associated with testicular function in the adult are present during the period of development when they could play a role in masculinization of the brain.

P. E. Polani: Have any measurements been made of brain growth at the time when the animals become sensitive to the androgens?

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Downloaded from rstb.royalsocietypublishing.org

R. W. Goy: We have not carried out any studies on changes in the brain during these early developmental periods. One study by Pfaff (1966) on sex differences in brain morphology showed that when animals become adult there are four subcortical nuclear groups in which significant differences between the sexes exist with respect to nuclear and nucleolar size. When male rats are castrated seven days postnatally their brain measurements are intermediate between male and female, or differ significantly from males but not from females.

References

Bloch, E. 1967*a* *In vitro* steroid synthesis by gonads and adrenals during mammalian fetal development. *Proc. 2nd Int. Congr. on Hormonal Steroids; Exc. Med. Congr.* Ser. 132, pp. 675–679 (eds. L. Martini, F. Fraschini & M. Motta). Amsterdam: Excerpta Medica Foundation.

Bloch, E. 1967*b* The conversion of 7-^{3}H-pregnenolone and 4-^{14}C-progesterone to testosterone and androstenedione by mammalian fetal testes *in vitro*. *Steroids* **9**, 415–430.

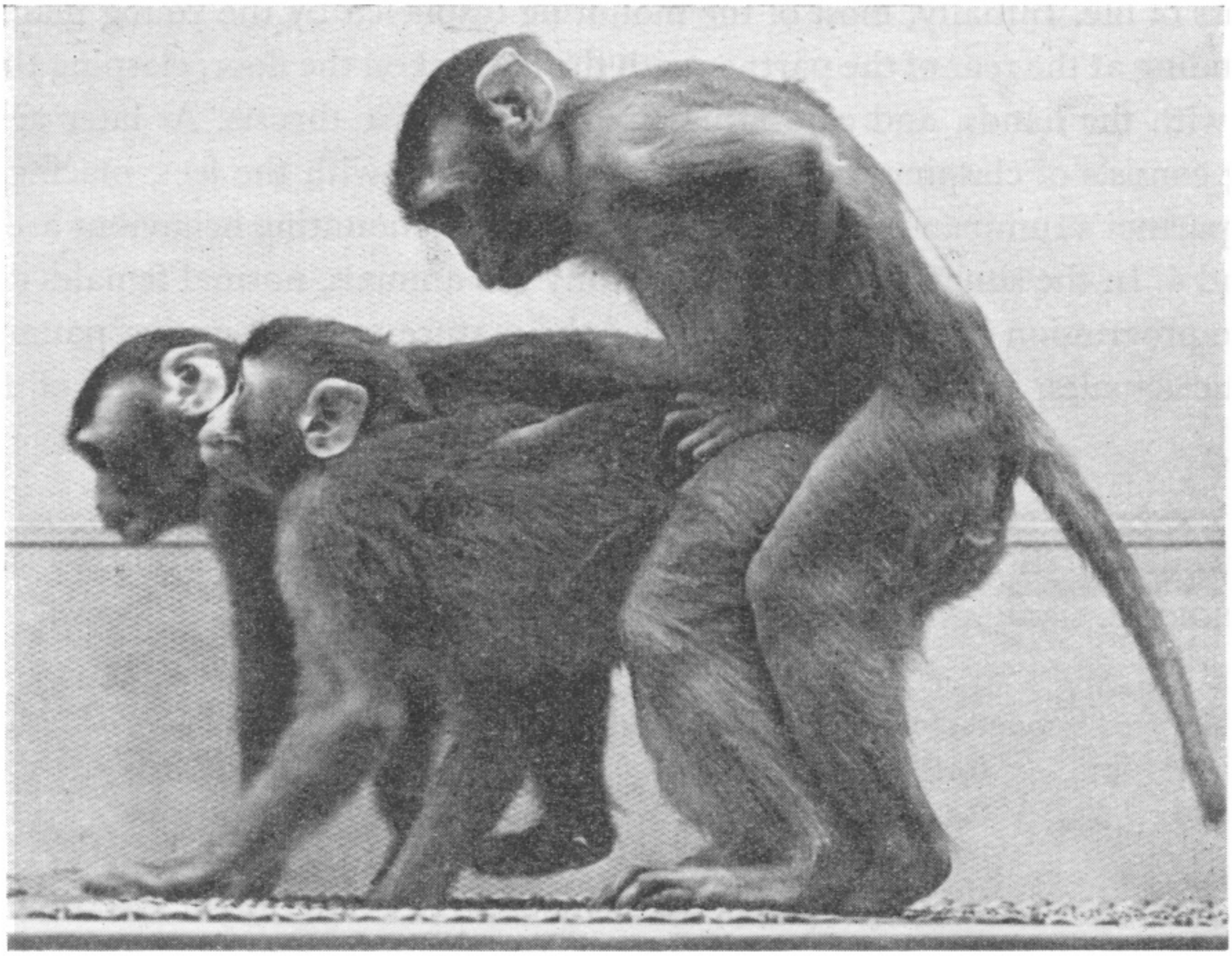
Pfaff, D. W. 1966 Morphological changes in the brains of adult male rats after neonatal castration. *J. Endocr.* **36**, 415–416.

Price, D. & Ortiz, E. 1965 The role of fetal androgen in sex differentiation in mammals. *Organogenesis*, pp. 629–652 (eds. R. L. DeHaan & H. Ursprung). New York: Holt, Rinehart and Winston.

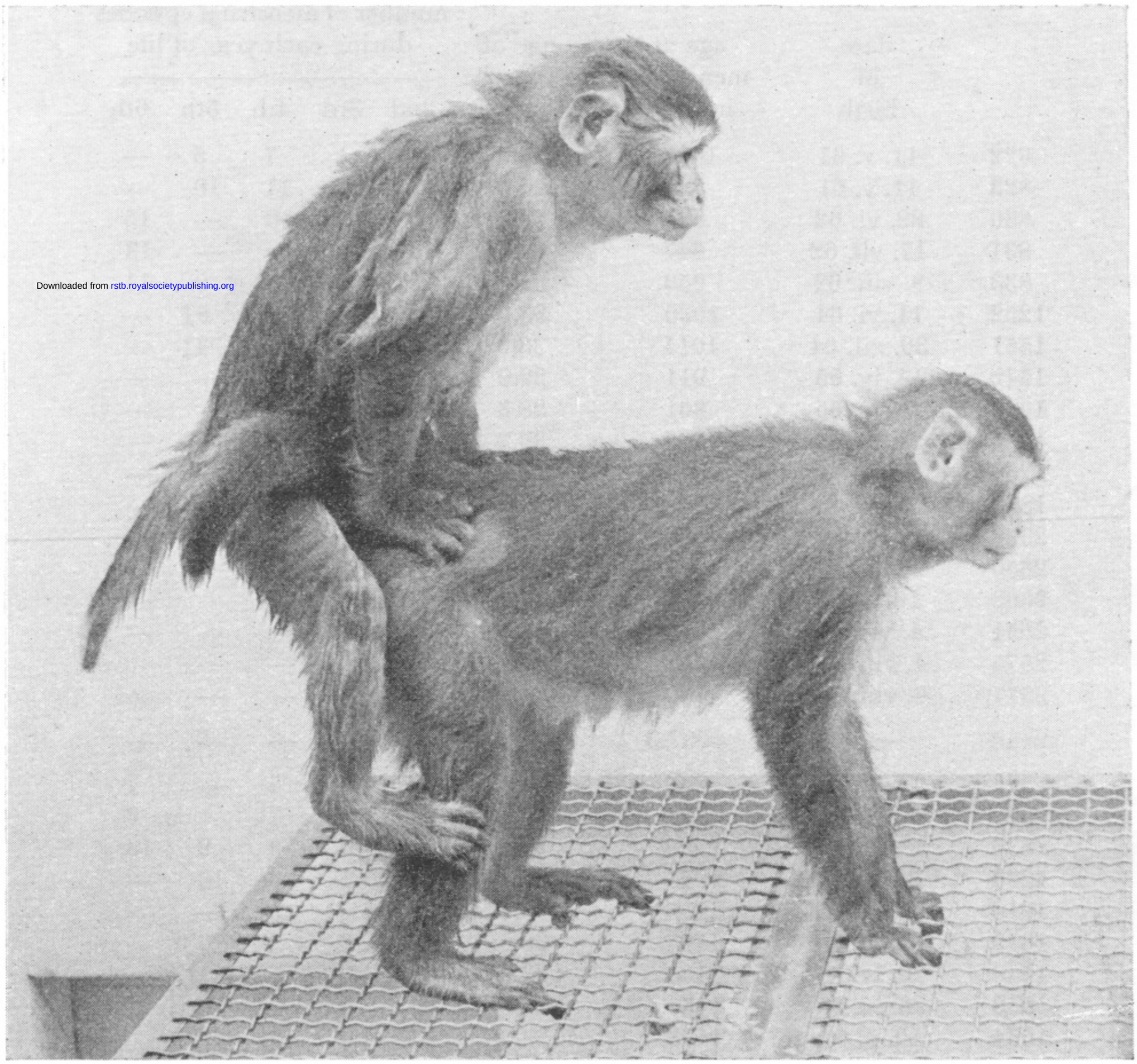
Resko, J. A., Feder, H. H. & Goy, R. W. 1968 Androgen concentrations in plasma and testis of developing rats. *J. Endocr.* **40**, 485–491.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES



3



4

Downloaded from rstb.royalsocietypublishing.org

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

FIGURE 3. Illustration of the immature mounting pattern characteristic of rhesus males before 1 year of age. Note position of the feet and compare with figure 4.

FIGURE 4. Illustration of the double foot-clasp mount characteristic of the mature male rhesus.