

# GENETICS OF THE FEMALE PROSTATE IN RATS<sup>1</sup>

JOHN J. MAHONEY<sup>2</sup> AND E. WITSCHI  
*The State University of Iowa, Iowa City, Iowa*

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## INTRODUCTION

IT IS a well known, but genetically little studied fact, that secondary sex characters have a tendency to become manifest in the contrary sex. Familiar examples are the assumption of nuptial characters, such as cock plumages and changing bill colors by many female birds (WITSCHI 1935, 1936), antlers by the female reindeer, and mammary glands by male mammals. It can hardly be doubted that in all these cases, we deal with a secondary transfer from one to the other sex, rather than persistence of characters of primitive hermaphrodite ancestors.

The situation is more complex when structures pertaining to the genital organs are taken into consideration. In vertebrates, gonochorism is a relatively recent development. Correspondingly, the rudimentary reproductive organs are usually of bisexual character. The embryological separation of males and females occurs relatively late, and involves either the suppression of one of a pair of discrete primordia (e.g., oviducts in males, sperm ducts in females), or the sex-specific secondary differentiation of an originally neutral primordium. This latter course is characteristic for the development of the parts derived from the primitive urogenital sinus. Thus, clitoris and penis both arise from the ventral rim of the cloacal pore. In the evolutionary sense, they are probably of equal age, and only if the clitoris is specifically penis-like in size or shape (as in the extreme case of the spotted hyena, WATSON 1881) can one assume that a partial transfer from the male to the female sex has occurred.

In mammals, *accessory glands of the urogenital sinus region* are usually considered as being characteristic for the male sex. However, bulbo-urethral glands (vestibular glands) attain a considerable size and become secretory in females of several species. Usually, this condition is coincident with the presence of relatively large cavernous bodies and of other parts of the phallic complex. The occurrence of prostatic lobes with active secretory epithelia in adult females, is restricted to fewer species. It is a matter of contention whether some of the urethral glands of the human female actually constitute a prostatic rudiment. RAUTHER (1909) was probably first to observe and describe well-defined female prostates. He found them in the African rat, *Arvicanthis cinereus*, attached to the ventral surface of the vesical urethra. LEHMANN (1938) gave a description of "paravaginal glands" in the primitive insectivore *Hemicentetes* which probably are dorsolateral lobes of prostate glands. In 1940 BRAMBELL and DAVIS reported the regular presence of well developed ventral prostates in

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<sup>2</sup> Now, INDIANA UNIVERSITY MEDICAL CENTER, INDIANAPOLIS.

females of the African rat, *Mastomys erythroleucus*, obviously a close relative of RAUTHER'S species. MATTHEWS (1942) observed well developed female prostates in the East African bat *Coleura afra*. Recently, dorsal prostatic lobes were found in the female cottontail rabbit, *Sylvilagus floridanus* (ELCHLEPP 1946). It is surprising that the sporadic but not infrequent occurrence of ventral prostatic lobes in female rats (*Rattus norvegicus*) was not noticed by any of the early students of rodent anatomy (compare figures 1 and 2). Actually, they were discovered only recently by several investigators engaged in endocrinologic work (MARX 1931; KORENCHEVSKY 1935, 1937; HAMILTON and WOLFE 1937; WITSCHI, MAHONEY, and RILEY 1938; PRICE 1939).

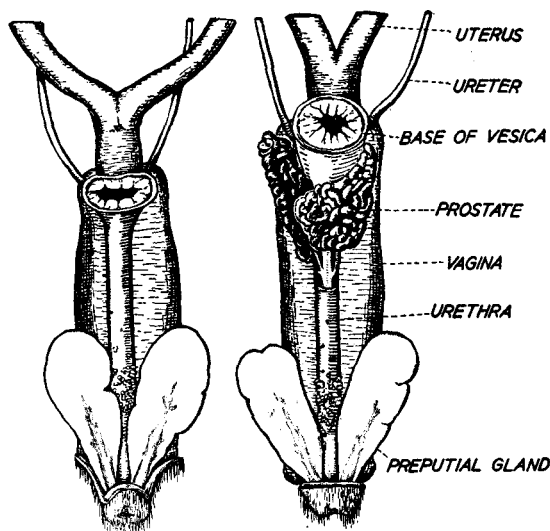


FIGURE 1.—Non-prostate female of the *psp* strain.

FIGURE 2.—Prostate female of the PP strain. Both animals were preserved at the age of 25 days. The lower urethra shows clusters of small urethral glands. A marked swelling of the lower urethra between the preputial glands indicates the location of the clitoris. In figure 2 the ventral wall of the urethra below the prostatic lobes was dissected away to expose the efferent prostatic ducts and their entrance into the urethra.

Camera lucida drawings  $\times 3$ .

The bulbo-urethral and prostate glands arise from the epithelial wall of the urogenital sinus. In species in which the vagina completely separates from the urethra (as in the murid rodents, some insectivores, bats and lemuroids) these glands, if present, maintain connections with the latter. Consequently, they may be considered as specialized urethral glands (BRUNER and WITSCHI 1946).

Buds of urethral glands sprout from the walls of the urogenital sinus of the female fetuses of most mammals. The wide distribution of such vestiges suggests a considerable antiquity, possibly even an evolutionary derivation from similar glands in hermaphrodite ancestors. However, in the case of the prostatic lobes of female rats, the high degree of specialization as well as the

irregularity of occurrence indicate that we deal with a male sex character that has been transferred to the female.

A study of the inheritance of the female prostate character was undertaken because in the rat the transfer is recent and evidently still progressing. It is hoped that it may contribute toward the understanding of one of the most intriguing phenomena in evolution: the acquisition of useless characters.

## LATERALITY

Prostatic lobes appear either bilaterally or unilaterally. In cases of the latter type the right side is highly preferred, the ratio averaging about 10:1. For the sake of simplicity, percentages were calculated only for prostate presence, giving same weight to bilateral and unilateral cases.

## ORIGINAL STOCKS

After the discovery of the occurrence of prostates in females of our laboratory stocks, collections of wild gray rats were obtained at the local city dump. Nearly half of a total of 125 females had ventral prostatic lobes (table 1). The origin of this particular population is unknown, and it is impossible to state whether or not this frequency is characteristic for the American rats in general or even for the entire species *Rattus norvegicus*.

TABLE 1

*Occurrence of ventral prostatic lobes in 125 gray females collected at the city dump.*

	RL	R	L	O	TOTAL
Number	39	14	5	67	125
Percent	31.2	11.2	4.0	53.6	100
	46.4%				

The frequencies of prostates in the females of various stocks recently bred in our laboratory are listed in table 2. A colony of black-hooded rats which was started from a single pair obtained from DR. H. STEENBOCK in 1941 is nearly

TABLE 2

*Female prostate occurrence in various unselected laboratory stocks (prior to January 1947).*

STOCK	RL	R	L	O	TOTAL	PROSTATE FREQUENCY
CHILD WELFARE hooded	26	17	3	24	70	65.7%
WISTAR albino	55	193	23	668	939	28.9%
LONG ISLAND albino	6	14	3	239	262	8.8%
Black Hooded ( $p_1p_1$ )	1	3	—	507	511	0.8%
Cinnamon Hooded	—	—	—	29	29	0.0%

free of the female-prostate character. It was used in some cross-breeding experiments as strain  $p_1p_1$ .

The following symbols are used for convenient characterization of selected stocks.  $PP$  designates a nearly regular occurrence of prostates in females (95-100 percent). On the other hand  $p_0p_0$  indicates the complete absence of female prostates. Between these two extremes  $p_xp_x$  stands for any fairly pure breeding stock,  $x$  always assuming the value of percent frequency of prostate occurrence. It is one of the objects of this investigation to decide whether the various values from  $p_0$  to  $P$  represent a single series of allelomorphs or combinations of multiple factors.

#### EFFECTS OF SELECTION

It was thought that the differences in female-prostate frequency of unselected groups may arise, in part, as a result of mixture of genetical types. Therefore, separation through selective breeding was attempted.

#### *Prostate Strain PP*

The WISTAR rat was used to develop the prostate strain. Females with bilateral prostates were chosen from litters with high prostate occurrence, as

TABLE 3

*Effect of selection for high female prostate frequency in the Albino WISTAR colony.*

PERIOD	RL	R	L	O	TOTAL	FREQUENCY
February '37-December '37	55	193	23	668	939	28%
January '38-July '38	73	88	16	52	229	77%
July '38-October '38	74	52	4	26	156	83%
November '38-March '39	—*	—*	—*	—*	303	93%
April '39-June '40	154	33	5	5	197	97%
June '40-March '42	477	108	8	8	601	99%
April '42-December '46	133	55	7	22	217	90%

\* Unknown.

ascertained by laparotomy. They were bred either with their fathers or with their brothers. Later on, the male breeders were chosen on the basis of their progeny records. As may be seen from table 3, the percentage quickly rose above 90, and the ratio of bilateral to unilateral prostates changed from 1:4 to 4:1. Between June 1940 and March 1942, while females without prostates were born only rarely, this strain was used for the first cross-breeding experiment.

The final purification of the prostate strain is unfortunately handicapped by the poor breeder quality of the highly selected males and females. To avoid the risk of losing the entire stock, extreme inbreeding was not attempted.

During the last of the reported periods, selection was no longer exercised and the effect was partly lost (table 3, March 1942 to December 1946). Since the males with the best ancestry records are the poorest breeders, showing almost no sex interest, and the high-bred females care very poorly for their

litters, an unintended negative selection follows the relaxation of rigidly planned breeding.

*Low Prostate Strain ( $p_9p_9$ )*

Attempts at isolation of a genetic strain free of female-prostates from the commercially acquired "LONG ISLAND" stock were not successful. The difficulty of recognizing genetic differences of small magnitude is obvious. When after four years the prostate incidence had resulted in even a slight increase (from 8.8 percent to 9.6 percent) the breeding records were used to segregate "good" and "poor" lines. The best separation permitted the differentiation of genealogic lines with about four and twelve percent frequencies, and their hybrids (compare table 4). A similar breakdown of the records on crossbreeding of

TABLE 4  
*Tentative segregation of the  $p_9p_9$  colony into two lines, and their hybrids.*

PARENTS		FEMALE OFFSPRING					PROSTATE FREQUENCY
MOTHER	FATHER	RL	R	L	O	TOTAL	
( $p_4p_4$ )	( $p_4p_4$ )	2	7	0	207	216	4%
( $p_4p_4$ )	( $p_{12}p_{12}$ ) or ( $p_{12}p_4$ )	6	17	2	323	348	7%
( $p_{12}p_{12}$ ) or ( $p_{12}p_4$ )	( $p_4p_4$ )	1	18	0	152	171	11%
( $p_{12}p_{12}$ )	( $p_{12}p_{12}$ )	23	60	4	635	722	12%
Total $p_9p_9$		32	102	6	1,317	1,457	9.6%

$p_9p_9$  with *PP* give further support to the assumption of such a mixed character of this strain. Of 86  $F_1$  females with a  $p_4p_4$  parent, only 46 percent had prostates while of 229  $F_1$  females with a  $p_{12}p_{12}$  or a  $p_{12}p_6$  parent, 52 percent showed prostates (total frequency 50.6 percent; compare table 5). In consideration of all facts, it was concluded that this colony did not contain the desired genetic non-prostate type. No further attempt to stabilize  $p_4p_4$  and  $p_{12}p_{12}$  strains was made and the entire low prostate strain was discontinued in 1942 when the shortage in technical personnel made a reduction in animal stocks mandatory.

*Non-Prostate Strain ( $p_1p_1$ )*

It was mentioned before, that from a single pair of hooded rats a strain was developed in which female-prostates appear only rarely (4 of a total of 511 cases; table 2). Selection could scarcely be applied here, except that near relatives of the four females with prostates were excluded from the breeding stock. It is doubtful whether this procedure appreciably changes the quality of the strain. The strain is fully fertile in both sexes and is easily propagated.

CROSS BREEDING EXPERIMENTS

*a.  $F_1$  Generations*

Morphological differences between males of the three genetical strains are

not detectable, but hybrid combinations prove that all transmit the female-prostate character of their strain. The first hybrid generations which are summarized in tables 5 and 6 prove that.

1) female-prostate frequency is transmitted by male as well as female gametes,

2) the female-prostate character is incompletely dominant,

3) with the same prostate strain  $PP$  the low-prostate ( $p_9p_9$ ) and non-prostate ( $p_1p_1$ ) strains give different hybrid frequencies—supporting the view that they represent different genetic types,

4) in reciprocal crosses the offspring of  $PP$  mothers have a higher female-prostate frequency than the offspring of  $p_9p_9$  or  $p_1p_1$  mothers.

TABLE 5

*First generation female offspring from reciprocal crossings of the  $PP$  and  $p_9p_9$  strains.*

$P:$	$\text{♀ } PP \times \text{♂ } p_9p_9$					$\text{♀ } p_9p_9 \times \text{♂ } PP$					TOTAL $F_1$ FEMALES
$F_1:$	RL	R	L	O	TOTAL	RL	R	L	O	TOTAL	
	32	53	2	56	143	33	37	3	100	173	316
	Prostate frequency				61%					42%	50.6%

TABLE 6

*First generation female offspring from reciprocal crossings of the  $PP$  and  $p_1p_1$  strains.*

$P:$	$\text{♀ } PP \times \text{♂ } p_1p_1$					$\text{♀ } p_1p_1 \times \text{♂ } PP$					TOTAL $F_1$ FEMALES
$F_1:$	RL	R	L	O	TOTAL	RL	R	L	O	TOTAL	
	4	16	1	14	35	2	8	1	27	38	73
	Prostate frequency				60.0%					28.9%	43.9%

The fourth point calls for further comment. The difference between the reciprocal groups is statistically significant, in both combinations (table 5 and table 6). In the first one it can be shown that the high frequency among the  $Pp_9$  females is partly the result of the mixed nature of the  $p_9p_9$  parent stock. But this cannot explain the entire difference. Sex-linked inheritance is ruled out since all females carry a paternal as well as a maternal X chromosome. There remain two possible explanations for consideration. During fetal development some physiological factor might shift manifestations of the character toward the maternal type, or the males of the  $PP$  strain might not have been as uniformly and not as highly selected as the females. No direct support for the former alternative was found. On the other hand it is at least conceivable that the genetic purification of the males becomes delayed, because they do not directly exhibit the genic character and selection is made only on the basis of breeding records. In other words, it is possible that the males were not all of a  $PP$  constitution but partly hybrids, for example, of  $Pp_{80}$  or similar type. For reasons explained above, such hybrids may unintentionally have

been given preference in setting up mating combinations. The question will be discussed again in connection with the results of backcrosses.

*b. Back-Cross Generations*

If, as implicitly assumed so far, the prostate factor is monogenic, backcrossing  $F_1$  with the recessive parental stock must yield equal numbers of hybrid and of homozygous recessive females.

*Low-prostate hybrids  $\times$  low-prostate stock (table 7)*

The prostate incidence in the hybrid group was 50.6 percent (table 5), in the  $p_9p_9$  stock 9.6 percent (table 4). In the backcross the expected frequency is therefore 30.1 percent; with this the observed 28.4 percent (table 7) compares favorably.

TABLE 7

*Backcrosses of  $F_1$  females and males with the low-prostate strain.*

PARENTS		FEMALE OFFSPRING	
FEMALE	MALE	NUMBER	PROSTATE FREQUENCY
1) $Pp_9$	$p_9p_9$	320	30%
2) $p_9P$	$p_9p_9$	428	24%
3) $p_9p_9$	$Pp_9$	52	29%
4) $p_9p_9$	$p_9P$	305	32%
Total		1,105	28.4%

*Non-prostate hybrids  $\times$  non-prostate stock (table 8)*

The prostate frequency was 43.9 percent in hybrids (table 6) and 0.8 percent in the  $p_1p_1$  stock (table 2). Therefore, the calculated expectancy for the backcross generation is 22.4 percent. Since the average of this experiment is based on relatively small numbers, the observed 15 percent incidence (table 8) is a satisfactory approximation.

If the original strains are homozygous and the  $F_1$  generation is genetically uniform, the  $F_1$  females *without* prostates should transmit the same frequency as  $F_1$  females *with* prostates. This expectation is tested by a breakdown of combination 1 of table 7. It shows that 20 females *with* prostates littered 176 B.C. females of which 29 percent had prostates, while 13 females *without* prostates produced 144 B.C. females, 31 percent with prostates. Evidently the manifestation of the prostate character is independent of actual presence or absence of prostates in the mother. Therefore, it appears that manifestation (in  $F_1$ ) does not depend on a supporting action of modifying genes.

The analogous analysis of combination 2 (table 7) gives a somewhat different picture. From 17 females *with* prostates, 134 B.C. females were obtained with a prostate occurrence of 33 percent; but 29 females *without* prostates produced 294 daughters of which only 19 percent had prostates. This low frequency indicates that some of the 29  $F_1$  females without prostates carried a paternal prostate factor which was not  $P$  but one of lower value, possibly  $p_{80}$

or less. Therefore, the analysis of the backcross data corroborates the assumption that some males of the prostate strain were not of the highest class obtainable by selection. What appeared as a shift in the maternal direction in the  $F_1$  generation is now shown to have a genetic basis. It is the consequence of a residual impurity of the selected male stock.

*c.  $F_2$  Generations*

The four possible second offspring combinations of the  $PP \times p_1p_1$  crossings were obtained. The total number of  $F_2$  females is too low to give this experiment much weight, though it is gratifying that the outcome is in good agreement with the calculated expectation of prostate frequency (table 9).

TABLE 8

*Backcrosses of  $F_1$  females and males with the nonprostate strain.*

PARENTS		FEMALE OFFSPRING	
FEMALE	MALE	NUMBER	PROSTATE FREQUENCY
1) $Pp_1$	$p_1p_1$	49	16%
2) $p_1P$	$p_1p_1$	47	13%
3) $p_1p_1$	$Pp_1$	3	13%
4) $p_1p_1$	$p_1P$	5	
Total B.C.		104	15%

TABLE 9

*Second generation female offspring of  $PP \times p_1p_1$  crossings.*

$F_1$ COMBINATIONS	$F_2$ FEMALE OFFSPRING				TOTAL
	RL	R	L	O	
$Pp_1 \times Pp_1$	2	2	—	7	11
$Pp_1 \times p_1P$	6	1	1	4	12
$p_1P \times Pp_1$	2	3	—	4	9
$p_1P \times p_1P$	5	8	—	13	26
Total	15	14	1	28	58
Frequency observed					52%
Frequency expected					47%

## DISCUSSION

In amphibians, the development of secondary sexual differences is entirely hormone controlled. Transplantation of gonads from one sex to the other, or experimental reversal of the sex of the gonads is followed by a complete change of all somatic sex characters. Technically, we may speak of *hormone-controlled manifestation*. In the amniote vertebrates a new type of control has developed



which permits sexual differentiation of auxiliary sex characters to develop at early prepuberal stages, before sex hormones are produced in appreciable quantities. It is clearly linked with the sex determining chromosome mechanism, but does not follow the so-called sex-linked mode of inheritance. Like primary sex differentiation, it depends on the balance between the X and Z chromosome complexes, and it is therefore proposed to call this an *X/Z controlled manifestation*.\* Both types of control usually result in a sex-limited development of secondary characters, though notable exceptions to this rule are known to occur. Thus in the starling, the female produces considerable amounts of an androgenic hormone, and causes some male secondary characters to develop during every breeding season (WITSCHI and MILLER 1938). Since chromosome control, like the better known hormone control, must be essentially a chemical process, the spontaneous formation of prostate glands in female rats of the *PP* strain may originate in an analogous way, that is, from a changed X/Z ratio. In other words, prostatism may indicate a shift of the genetic balance of the female toward a hermaphrodite constitution. The previously mentioned observations on the changed reproductive behavior and competence of the *PP* strain would find an immediate explanation on the principle of such an interpretation. Since the rat has sex chromosomes of the XY type and the factor responsible for female prostate development is not sex-linked, it follows that the mutated gene should be located in the Z chromosome and increase its male determining potency.

On the other hand, there remains the possibility that the balance of sex determining genes is unaltered, and the change has occurred in a more specific gene—one which affects the responsiveness of the prostatic region of the fetal urogenital sinus. The concurrent physiological modifications would have to find a separate explanation.

No decision on these alternative interpretations can be reached on the basis of the presented material here. A more exhaustive discussion would have to include a vast body of comparative data, and carry beyond the scope of the present contribution. A complete discussion would also have to expand on the fact that early hormone treatments considerably increase the area of prostate production in female rodents. The bearing of these experiments on the theory of gene action and morphogenic induction has been pointed out in earlier publications (MAHONEY 1942; BRUNER and WITSCHI 1946).

#### SUMMARY AND CONCLUSIONS

Hereditary prostate formation in female rats may reach a penetrance of 99 and possibly 100 percent.

\* One has often spoken of a balance between sex chromosomes and autosomes; but among the "autosomes" there must be at least one pair of chromosomes that are mainly or entirely responsible for the "autosomal" component. While the XX (or XY) chromosomes carry mostly or exclusively female determining factors, the male determining genes are located in a second pair, the ZZ (or ZW) chromosomes. Either one of the two pairs of sex chromosomes may serve as a basis for the evolution of a heterochromosome mechanism of sex inheritance. In the rat this role fell to the XX pair.

The determining factor is monogenic and occurs in a series of quantitative alleles.

It is transmitted identically by both sexes (not sex-linked).

In hybrids of high and low prostate strains, manifestation of the character is intermediate.

Groups with low manifestations, whether of pure bred or of hybrid stock, show a prevalence of unilateral, mostly dextral prostate cases.

Hybrid females from carefully selected stocks breed the same whether they have prostates or not. Manifestation apparently is not influenced by modifying genes.

Like primary sex differentiation, the sex-limited occurrence of prostates in males depends on the ratio between the X and Z chromosome complexes (X/Z controlled manifestation). The appearance of prostates in females possibly is caused by a shift in the genic balance of the female toward the hermaphrodite type, though alternative interpretations are not excluded.

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