THE EFFECT OF CASTRATION, SPAYING OR SEMI-
SPAYING ON THE WEIGHT OF THE CENTRAL
NERVOUS SYSTEM AND OF THE HYPOPHYSIS OF
THE ALBINO RAT; ALSO THE EFFECT OF SEMI-
SPAYING ON THE REMAINING OVARY

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The object of the present paper is to report on the condition of several of the internal organs of the albino rat after castration, spaying or semi-spaying. These series of spayed and semi-spayed animals were prepared by Dr. Stotsenburg and have been used by him for studying the growth of the body in weight as affected by the respective operations (Stotsenburg '13). The castration of the animals here used was also performed by Dr. Stotsenburg but in this series the growth of the body was not followed, the effect of this operation having been previously determined (Stotsenburg '09).

I wish to acknowledge the courtesy of Dr. Stotsenburg in allowing me to make the postmortem examinations in all of these interesting cases.

All the necessary details concerning the operations and the care of the animals have been already given by Stotsenburg ('09, '13) but two points should be mentioned here as these are important for the interpretation of the results: (1) in all instances the operation was performed on young rats about a month old and (2) in the cases of castration the testes with epididymis were removed.

Regarding the method of examination of the various organs, as well as the significance of the various formulas used in determining the calculated values from the observed values, the reader is referred to a paper published recently by myself (Hatai, '13).

The total number of litters used by Stotsenburg for the spayed series was 17. These comprised 38 spayed and 35 control rats. In the case of semi-spayed there were 12 litters comprising 25 semi-spayed and 23 control rats.

A few of these litters however lost either some of the operated animals or of the controls before my examination, also some of the organs were used for histological preparations, so that the number of litters, as well as number of individuals represented in the present tables is less than that given by Stotsenburg in his paper.

On the other hand it is important to state in this connection that all of the animals from which complete data were obtained were also used in making the present tables. For determining the modification in the operated groups, the following method was adopted:

First the percentage deviation of the controls from the calculated values for any character as given by the formulas, was determined and then the corresponding percentage deviation of the operated animals. The algebraic difference of the two values thus obtained gives the difference between the operated and controls. In the tables here given the body length was always taken as the basis for comparison.

The values obtained are given in the accompanying tables and designated as "Percentage by which the operated animals differ from the controls." This method is necessary since the observed body length which is taken as the basis for the weight of the organs is only rarely identical in both operated and controls, and thus a direct comparison of the observed values is rarely justified.

CASTRATION

This experiment is based on 11 litters comprising 25 castrated and 12 control rats. The series was divided into four groups each containing 3 litters—except one group, containing 2 litters. In every case the operated and control rats which are compared belong to the same litter. This precaution minimizes the variability of the characters under consideration, since the

variability is greater when individuals of different litters are compared (Jackson '13). This method was followed also in the other two series, that is, the spayed and the semi-spayed. The results of the observations are given in table 1.

BODY WEIGHT

Stotsenburg ('09) has shown that in the albino rat castration does not modify the growth of the body in weight. This conclusion is fully supported by the present series. We notice in table 1 that the observed body weight of the castrates is nearly identical with that of the controls, the average body weight of castrates being 122.1 grams contrasted with 123.5 grams for the controls at the same age.

We notice further from the table that not only the growth of the body in weight remains unmodified, but the relation between body length and body weight characteristic for this series is unaffected by castration.

The difference in body weight between the castrated and control rats when body length is taken as the basis for the computation is 3.63 per cent in favor of the controls. This difference can certainly not be regarded as significant when we also consider the normal fluctuations in this character.

In those species which respond to castration by an overgrowth several investigators have noted a definite effect on the development of the skeleton. Poncet ('97) noted that the bones, particularly the femur, the tibia and fibula, of the castrated rabbits were longer. Fichera ('05) and Lannois, and Roy ('02) noted an elongation of the leg bones in castrated guinea pigs, in oxen, in capons and in some other animals. Numerous other confirmatory observations can be found in the literature (see Vincent '12 and Marshall '10).

Since however in the rats not only the growth of the body as a whole remains unaltered, but a perfect normality is shown in the relation between length and weight of the body, it seems improbable that alterations in the length of the leg bones should occur. Observations on this point however are now being made.

TAIL LENGTH

The tail of the castrated rats is slightly longer than that of the controls; the difference is somewhat over 5 per cent and occurs in three out of the four groups (see table 1).

Other experiments now in progress in our laboratory also indicate the same relation. Consequently the difference found in the present case should not be disregarded on account of its small magnitude. The following conclusion is therefore made tentatively: that the castrated rats, when compared with their controls tend to have slightly longer tails.

BRAIN WEIGHT

The difference in brain between castrated and controls is 0.33 per cent in favor of the latter (table 1). Although this difference is so slight, nevertheless by reason of its persistent occurrence it cannot be neglected. It has been found previously (Donaldson and Hatai '11) that castration in the albino rat reduces the weight of the brain and the weight of the cord also somewhat below those weights in the normal control rats. The deficiency in the castrates amounted (as an average of all groups) to 3 per cent in the brain and 5.3 per cent in the spinal cord. The deficiency in the present experiment is far less, nevertheless its constancy in direction, as well as the similar tendency among both the spayed and the semi-spayed rats (see tables 2 and 3) force us to conclude, though with considerable reserve, that castration tends to reduce the relative weight of the central nervous system. The difference in this deficiency among different strains suggests that the reduction may vary considerably according to the general condition of the rats under experiment.

WEIGHT OF SPINAL CORD

Contrary to the case of the brain, the weight of the spinal cord of the castrates is heavier than that of the control rats. The difference amounts to 3.01 per cent. Thus the present series gives in the cord results contrary not only to the brain but also contrary to our previous findings in which we noted a deficiency

in the cord of the castrates which amounted to 5.3 per cent (an average of all groups—Donaldson and Hatai '11). For the lack of agreement in this character between the two series no adequate explanation can yet be given.

PERCENTAGE OF WATER IN THE BRAIN AND IN THE SPINAL CORD

Previous work (Donaldson and Hatai '11) has shown that castration does not modify the percentage of water either in the brain or in the spinal cord. The present series supports this conclusion as will be seen from table 1.

The difference between the castrated and control rats gives 0.07 per cent in the case of the brain and 0.17 per cent in the cord, both in favor of the control. The difference is however too small to be significant and thus justifies our previous statement.

WEIGHT OF HYPOPHYSIS

The hypophysis shows a most striking difference in weight between the castrated and control rats. The difference amounts to nearly 74 per cent in favor of the castrated rats. The difference is shown not only in the final average but also in all four groups and in each litter. This enlargement of the hypophysis following castration is certainly the clearest alteration so far found.

So far as I know there is only one investigator who used the albino rat for studying the effect of castration on the weight of the hypophysis. This is Barnabo ('08) who gives three series of experiments which were conducted in the following manner:

Series 1. Bilateral section of vas deferens. This series comprises three rats.

Series 2. Section of vas deferens on one side and castration on the other. This series comprises two rats.

Series 3. Bilateral castration. This series comprises three rats.

The operation was performed on sexually mature rats (112 grams in average body weight) and the period between operation and death was on the average seventy-six days. The average weight of the hypophysis was 0.015 grams corresponding to the

final body weight of 151 grams. (The hypophysis was not examined in two rats.) Barnabo concludes that the weight of the hypophysis is not altered as the result of operation. No data given regarding the control rats, and it is merely stated "*Per altro controllo mi sono poi servito di animali normali.*"

It is true that Barnabo's experiment (except series 3) is different from that of my own, not only in the method of operation, but by reason of the fact that Barnabo operated on the sexually mature animals, while the rats examined by me were operated on while still very young (about twenty-five to thirty days of age). Thus the two experiments may not be strictly comparable, nevertheless according to our formula (Hatai '13) which is based on large numbers of normal rats, the weight of the hypophysis given by Barnabo is almost 150 per cent heavier than it ought to be for the body weight given. It seems highly probable that Barnabo did not realize the existence of the striking sex difference in the weight of the hypophysis, and thus the operated rats may have been compared with the normal female albino rats, in which case but slight differences might appear as the weight of the hypophysis in the female is more than twice that in the male (Hatai '13).

There are several investigators who also have noted in other animals an enlargement of the hypophysis as the result of castration. For instance Fichera ('05) noted it in guinea pigs, rabbits and several other animals, and Kon ('08) in man. The clinical observations on the subject are very numerous, but these will not be discussed at the present moment.

On the other hand, Marrassini and Luciani ('11) also using guinea pigs, rabbits and some other animals, recently obtained contrary results, that is they found that castration does not produce any noticeable enlargement of the hypophysis in the forms studied by them. Marrassini and Luciani's experiments were carried on in a very satisfactory manner, since their operated animals were contrasted with well chosen controls, and in addition the number of animals used was much greater than in most of the other researches. The probable cause of the conflict in these results will be discussed later.

SPAYING EXPERIMENTS

The present series contains 15 litters comprising 27 spayed and 27 control rats. The series is divided into five groups each containing three litters, according to the method described. The results of the observations are shown in table 2.

Body weight. At the time of maximum body weight, that is, at 271 days in age, Stotsenburg ('13) records an average body weight of 226 grams for spayed rats in this series and 176 grams for the corresponding controls. This gives a difference of 28.4 per cent in favor of the spayed animals.

At the time of killing however, some of the rats had lost weight through lung infection or had died, and consequently the body weights given by Stotsenburg and those given by the present writer are not the same.

Nevertheless we see clearly that the spayed rats made a better growth not only in length, but in entire body weight as can be shown by the following differences.

At the same age, the body length of the spayed is 2.8 per cent longer, and when body length is equated, the body weight of the spayed is 3.07 per cent heavier than that of the controls.

We further notice that at the time of examination, the body weight of the spayed was on the average 158.9 grams against 141 grams of the control. This gives a difference of 12.7 per cent in favor of the spayed against 28.3 per cent, at the time of the maximum weight. This means that during the interval the spayed rats lost more than the controls. This loss was mainly in fat.

Tail length. Unlike castration, spaying does not modify the length of the tail. The difference of 0.61 per cent or one millimeter in absolute measurement in favor of the spayed, seems to be too slight to insist on.

Brain weight. Similarly, as in the case of the castrates, the spayed rats show a slight reduction in brain weight (-0.39 per cent) when compared with that of the controls. To determine how far we can rely on this difference, additional data are necessary.

Spinal cord weight. Like the brain, the spinal cord of the spayed shows the figure below (-1.57 per cent) that of the controls.

TABLE 2
Showing the weight data for the sprayed compared with those for the control rats. Sprayed Series (15 litters).

ALBINO RATS	BODY LENGTH	BODY WEIGHT	TAIL LENGTH	WEIGHT OF		PER CENT WATER		HYPOPHYSIS	AGE days	NO.
				Brain	Spinal Cord	Brain	Spinal Cord			
Group I. { Control.....	159	99.5	149	1.664	0.460	78.29	71.51	0.0062	273	5
{ Operated.....	166	130.9	145	1.698	0.479	77.89	71.67	0.0088	273	4
Group II. { Control.....	164	115.4	145	1.766	0.472	78.59	71.51	0.0077	250	5
{ Operated.....	165	109.6	152	1.728	0.470	77.99	71.00	0.0089	250	6
Group III. { Control.....	176	138.5	154	1.807	0.500	78.19	71.47	0.0081	229	6
{ Operated.....	179	151.7	160	1.860	0.516	78.39	71.55	0.0098	229	7
Group IV. { Control.....	185	165.1	156	1.862	0.556	78.28	71.51	0.0104	287	6
{ Operated.....	191	183.6	163	1.862	0.557	78.20	71.44	0.0118	287	6
Group V. { Control.....	196	186.7	167	1.877	0.625	77.44	69.39	0.0135	305	5
{ Operated.....	203	218.9	180	1.915	0.659	77.66	69.84	0.0131	305	4
<i>Controls</i>										
Observed (average).....	176	141.0	154	1.795	0.523	78.16	71.08	0.0092	269	27
Calculated from formulas.....	176	136.8	153	1.740	0.496			0.0090		
Percentage deviation from calculation = A.....	0	3.07	0.65	3.16	5.44			2.22		
<i>Operated</i>										
Observed (average).....	181	158.9	160	1.813	0.536	78.03	71.10	0.0105	269	27
Calculated from formulas.....	181	149.7	158	1.764	0.516			0.0099		
Percentage deviation from calculation = B.....	0	6.14	1.26	2.77	3.87			6.06		
Percentage by which the operated animals differ from the controls. i. e., B - A.....	0	3.07	0.61	-0.39	-1.57	-0.13	0.02	3.84		

Weight in gms.; length in mm.

Percentage of water in the brain and spinal cord. The difference between the spayed and controls with respect to water content is negligible, and thus it is concluded that spaying does not modify the water content of these structures.

Weight of hypophysis. The weight of the hypophysis in the spayed is slightly greater than that of the controls; the difference amounts to 3.84 per cent. This amount of difference however will easily fall within the experimental error on account of the minuteness of the gland as a whole.

Furthermore, when this difference, 3.84 per cent or 0.0004 grams in absolute weights compared with the difference shown by the castrated rats (73.62 per cent) we feel still safer in concluding that the difference is most likely due to slight experimental errors or incidental variation and that consequently spaying does not modify the weight of the hypophysis.

The present results on the spayed rats are contrary so far as the hypophysis is concerned, to the results obtained, for instance, by Fichera ('05) in guinea pigs and rabbits, and Kon ('08) in women. These investigators noticed a striking enlargement of the hypophysis as the result of spaying. On the other hand Marrassini and Luciani ('11) find no hypertrophy following spaying in guinea pigs and rabbits. Thus we see that discordant results are again presented by these authors. The observations of Marrassini and Luciani appear to have been the more carefully made.

In this connection the following general comment on the subject of the removal of sex glands may be made.

The question of the enlargement of the hypophysis following the removal of either of the sex glands is difficult to solve, not because the operation is complicated, but because the hypophysis is such a minute organ and its normal variability is great.

This difficulty is further increased by the fact that its variation in weight tends to be greater when different litters, or still more, when different strains of the same race, are compared. These difficulties however may be reduced to a minimum by taking both the control and the operated animals from the same

litter and thus making comparisons within the litter. This is certainly the safer method in determining any alterations following an operation. When this method is not available, a considerable number of animals both for control and for operation must be examined in order to determine the extent of variation shown by the two groups.

A search through the literature reveals the fact that such a method as that mentioned above has not been used by most investigators, and thus the conclusions have been drawn mainly from a few operated animals contrasted with even a less number of controls, which in turn did not certainly belong to either the litter or the strain of the operated animals themselves. These facts throw doubt on the correctness of the results thus obtained and indeed the recent work of Marrassini and Luciani ('11) who worked with great care and who, contrary to the previous investigators, find no enlargement of the hypophysis in either guinea pigs or rabbits, accentuate these doubts more strongly.

SEMI-SPAYED RATS

The present series contains 12 litters comprising 21 semi-spayed and 20 controls. The series is divided into four groups, each containing three litters. The result of the observations is given in table 3.

Body weight. In this series the weight of the body at 280 days in age is given by Stotsenburg ('13) as 140 grams for semi-spayed and 145 grams for controls. At the time of killing (326 days) however, some of the rats had gained in weight, particularly the semi-spayed. As is shown in the table above, a substantial increase in body length and weight of body was made by the semi-spayed over that of the controls after 280 days of age. The difference in body weight, when body length is taken as the basis for the comparison, between the semi-spayed and the control, is insignificant amounting to only -2.65 per cent.

From this it is concluded that semi-spaying does not modify the normal relation existing between body weight and body length, and consequently a slight overgrowth in body weight shown at the time of examination was not due to an accumulation of fat.

TABLE 3
Showing the weight data for the semi-spayed compared with those for the controls. Semi-spayed Series (12 litters)

ALBINO RATS	BODY LENGTH	BODY WEIGHT	TAIL LENGTH	WEIGHT OF		PER CENT WATER		HYPOPHYSIS	OVARIES	AGE days	NO.
				Brain	Spinal Cord	Brain	Spinal Cord				
Group I. { Control..... { Operated.....	157	105.0	148	1.703	0.479	77.92	70.67	0.0078		286	3
	169	121.6	152	1.736	0.498	77.94	70.59	0.0082		286	4
Group II. { Control..... { Operated.....	175	144.6	151	1.762	0.516	78.06	71.13	0.0109		347	4
	172	134.9	147	1.766	0.505	78.03	71.17	0.0099		347	5
Group III. { Control..... { Operated.....	190	159.3	166	1.785	0.562	78.25	70.87	0.0117	0.0520 (double)	343	7
	192	161.9	171	1.770	0.580	77.86	70.28	0.0110	0.0421 (single)	343	6
Group IV. { Control..... { Operated.....	195	180.0	170	1.776	0.598	77.90	70.18	0.0154	0.0394 (double)	326	6
	198	199.2	177	1.819	0.623	77.77	69.93	0.0140	0.0386 (single)	326	6
<i>Control</i>											
Observed (average).....	179	147.5	159	1.757	0.539	78.03	70.71	0.0115	0.0457 (double)	326	20
Calculated from formulas.....	179	144.4	156	1.754	0.508			0.0096	0.0464 (double)		
Percentage deviation from calculation = A.....	0	2.14	1.92	0.17	6.10			19.79	-1.50		
<i>Operated</i>											
Observed (average).....	183	154.4	162	1.773	0.550	77.90	70.49	0.0108	0.0404 (single)	326	21
Calculated from formulas.....	183	155.2	160	1.773	0.524			0.0104	0.0471 (double)		
Percentage deviation from calculation = B.....	0	-0.51	1.25	0	4.98			3.84	-14.13		
Percentage by which the op- erated animals differ from the controls. i.e. B - A....	0	-2.65	-0.67	-0.17	-1.12	-0.13	-0.22	-15.95	-12.73		

Weight in gms.; length in mm.

Tail length. Tail length with respect to body length is not modified by semi-spaying. The difference is negligible, amounting to 0.67 per cent in favor of the controls.

Brain weight. Here again the brain weight tends to be small in the semi-spayed to about the same degree as has been noted in the case of the spayed rats; the difference is 0.17 per cent in favor of the controls.

Spinal cord weight. The weight of the spinal cord of the semi-spayed is a little over 1 per cent below that of the controls. Here also the difference is very small, nevertheless there appears a constant tendency to slight reduction in the operated rats when compared with the unoperated.

Percentage of water in the brain and in the cord. It is clear from the table that the water content in the semi-spayed is practically identical with that of the controls; the difference between the two being 0.13 per cent in the case of the brain and 0.22 per cent in the case of the spinal cord in favor of the controls.

Consequently we conclude that the water content in the central nervous system is not modified by semi-spaying.

Weight of hypophysis. The weight of the hypophysis in the operated rats is practically normal to body length, while that of the control rats is considerably heavier than the body length calls for. Furthermore, the normality of all other characters in the semi-spayed rats indicates that the difference of nearly 16 per cent shown by the hypophysis in favor of the control rats is not due to the diminution of this organ in the semispayed, but is rather due to the abnormal size of it in the control rats. Without being able to explain this high value in the controls, I conclude nevertheless that the weight of the hypophysis in the operated rats is not modified.

Weight of ovaries. We note here a beautiful instance of compensatory growth. The weight of the ovary of one side in the semi-spayed is almost twice the weight of the normal single ovary; the average departure from the double weight being only 7 mgms. or -14 per cent. Exactly what structures are responsible for such a compensatory growth of the ovary still requires to be investigated.

This observation is not new but the facts noted in this case furnish one more instance in a particularly clear form.

Touching the enlargement of the ovary we note, for instance, that Bond ('06) has shown in rabbits that a removal of one ovary is followed by compensatory growth of the remaining ovary. Bond however asserts that this compensatory growth takes place only when the animals are allowed to become pregnant or at least to have sexual intercourse.

Carmichael and Marshall ('08) tested the question of compensatory growth by using rabbits also. The main conclusion reached by them is that the compensatory growth of the ovary occurs independently of both sexual intercourse and pregnancy; a conclusion contrary to that reached by Bond. This agrees however with the results obtained by the present writer on the albino rat.

By removing portions of the remaining ovary, Carmichael and Marshall showed further that the power of compensatory growth possessed by the remaining ovary is relatively greater the larger the amount of ovarian tissue which has been removed.

It is interesting to note that their method of determining the amount of hypertrophy was to compare the weight of the remaining ovary with that of the other which has been removed two to five months earlier. The rabbits were fully grown at the time of operation. Our study of the albino rats (Hatai '13) shows that the ovary grows in weight even after the rats have become mature, and consequently the amount of compensatory growth can only be determined closely by knowing the amount of normal growth during the period under consideration.

Our results on the albino rats however indicate that the conclusion reached by Carmichael and Marshall was essentially correct, as the amount of normal growth of ovarian tissue during the several intervening months is probably not large in the adult rabbits.

Remarks on the weight of the hypophysis. It is to be noted that in the albino rats the hypophysis presents a sexual difference which is very marked (Hatai '13) as the hypophysis of the female is more than twice as heavy as that of the male. In the Norway rats the sex difference is very slight and probably still less, if present

at all, in the case of guinea pigs and rabbits, so far as we are able to determine from existing data furnished by the several investigators.

What this sex difference in the albino rats actually means, I cannot say.

One point is clear from the preceding, namely, that the hypophysis reacts differently according to the sex after the removal of the sex glands. Thus we noticed that spaying in the female does not produce the enlargement of the hypophysis, but on the other hand, overgrowth and obesity invariably follow this operation.

Castration produces in the male a striking enlargement of the hypophysis while overgrowth and obesity are entirely absent. This peculiar relation between the response of the hypophysis on the one hand and overgrowth and obesity on the other, is worthy of further consideration.

Clinical as well as experimental evidence (Cushing '09, and for a general account on the subject, see Vincent '12) shows with a high degree of probability that 'hypo-secretion' of the pituitary gland produces abnormal accumulation of fat possibly due to lowered oxidation. Thus if a compensatory growth of the hypophysis does not follow, as is the case after spaying, the product of the unaltered gland must be employed for two purposes; one, to replace the ovarian hormone and two, for the normal uses, whatever these may be. Spaying thus appears to overtax the normal secretion coming from the unmodified gland and consequently to produce phenomena similar to those following hypo-secretion. On the other hand, the compensatory hypertrophy of the hypophysis in the male albino rat after castration appears to prevent the phenomena of hypo-secretion, and consequently the body changes, overgrowth and obesity, are prevented. The value of this view must be tested. Nevertheless it seems to offer a reasonable explanation for the true growth and the accumulation of fat following spaying on the one hand, and the absence of these reactions after castration, on the other.

The result of semi-spaying in the albino rats gives still further evidence in support of the view just presented.

Semi-spaying produces neither an enlargement of the hypophysis, nor an abnormal fat deposition in the body. This is explained by the fact that the remaining ovary enlarges to twice its normal size, thus we may conclude that the normal secretory function is performed adequately by the tissues of the enlarged ovary, and consequently the changes which would follow hyposecretion of the hypophysis are prevented.

SUMMARY

The conclusions here given apply to the domesticated albino rat (*Mus norvegicus albinus*) and in the absence of direct evidence should not yet be extended even to the wild Norway.

1. *Body weight.* The growth of the body in weight is not modified by castration or by semi-spaying. Spaying however increases body growth, some of the increase in weight being due to fat.

2. 'The normal relation between body weight and body length is not modified in the castrated or the semi-spayed. In the case of the spayed, it is modified by the presence of fat; that is, the animal is heavy for its body length.

3. *Tail length.* The tail tends to be slightly longer in castrates, but no alteration occurs in the other two series.

4. *Brain weight.* In all series the difference between the operated and non-operated is almost negligible, nevertheless in all the operated groups it constantly falls below that in the non-operated.

5. *Spinal cord weight.* In the castrated series the weight is higher than in the controls, but follows the brain in the other two series; the spayed and the semi-spayed.

6. *Percentage of water.* The water content of the nervous system is not altered by any of the operations.

7. *Hypophysis.* A striking and constant increase in the weight of the hypophysis is shown after castration, but practically no change after either spaying or semi-spaying.

8. *Ovaries.* In the semi-spayed series the compensatory growth of the remaining ovary is almost perfect and the single ovary has therefore nearly twice its normal weight.

9. *Relations of sex glands to hypophysis.* After removal of the sex glands, it appears that when compensatory growth of the hypophysis occurs, then there is no overgrowth or obesity. On the other hand, both these effects follow when the enlargement does not occur, as in the spayed rats.

In the semi-spayed, neither enlargement of the hypophysis nor overgrowth and obesity occur because the enlargement of the remaining ovary enables it to furnish the normal amount of ovarian secretion.

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