THE EFFECT OF RETARDED GROWTH UPON THE LENGTH OF LIFE SPAN AND UPON THE ULTIMATE BODY SIZE [1]

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ONE FIGURE

In a preliminary report, the literature concerning the effect of retarded growth upon the life span was reviewed (McCay and Crowell, '34). In this report was also included a summary in the nature of a progress report dealing with a study employing rats to determine the effect of retarding growth upon the total length of life.

The present summary represents a complete, final report of this experiment employing white rats and covering a period of nearly 4 years. The object of this study was to determine the effect of retarding growth upon the total length of life and to measure the effects of retarded growth upon the ultimate size of the animal's body. In the present study, growth was retarded by limiting the calories.

The growth of an animal can be retarded either by disease or by various nutritional deficiencies. Every laboratory that performs vitamin assays is familiar with the retarded growth and prompt death that result when there is a deficiency of a certain factor such as vitamin A. In such experiments the animal grows little and dies prematurely. However, a borderline level of such an essential as vitamin A may permit a very slow growth and permit the animal to approach or attain

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adult size. Under such conditions the question arises as to the effect of this retarded growth upon the life span and ultimate body size. In the present study we have retarded the growth by restriction of calories, but with a diet designed to provide adequate levels of all other constituents.

In our previous report some of the earlier literature dealing with the interrelationship between the rate of growth and the length of life, was reviewed. The existence of such a relationship has been stressed again very recently by Kermack and associates ('34) in the following words:

It is shown that.these results are consistent with the hypothesis that the important factor from the point of view of the health of the individual during his whole life is his environment up to the age of say 15 years and that improved conditions at later ages have little direct effect.

This is a recognition that factors during the growing period are paramount in their influence upon the subsequent life span.

A few attempts have been made in other laboratories to test the hypothesis that a slow rate of growth results in an increased life span, by feeding a given species, such as mice, the same diet, recording the rate of growth and finally the length of life. At the conclusion of such an experiment the rates of growth and the length of life have been correlated. On the basis of such a study Robertson and Ray ('20) concluded that mice that grew the more rapidly lived the longer. They also concluded that the group that grew the slower was more unstable. Sherman and Campbell ('34) report, however, that rate of growth and length of life of rats on the same diet, vary independently of each other. Earlier, Campbell ('28) found that an improvement in the diet resulted both in increased rate of growth and increased length of life in the same individuals.

It is doubtful if such studies as those of Robertson really test the hypothesis, because the two groups, separated on the basis of growth, are not homogeneous. The slower growing group tends to include the inferior individuals that die prematurely. A genuine test of this hypothesis can be made,

however, if animals are separated into groups at the time of weaning or shortly thereafter. Such groups can be forced to grow at different rates and the length of life can be determined. In this latter case we are dealing with more homogeneous samples. Random selection provides reasonable insurance of similar expectancies of life spans and rates of growth in such groups, if other factors are constant.

EXPERIMENTAL

At the present time it seems that the only method of determining the interrelationship between the rate of attaining maturity and the total length of life is by direct experiments upon homogeneous groups of animals. For this reason 106 white rats were divided into three groups at the time of weaning. One group contained thirty-four individuals and the other two thirty-six. Group I was allowed all the feed desired and grew normally. Group II was restricted in feed intake from the time of weaning. Group III was allowed sufficient feed to permit normal growth for 2 weeks after weaning and then restricted in the same manner as group II.

These animals were confined in false-bottom cages such as those used for vitamin assays except that individuals tended to develop sore feet from time to time as old age approached. In these cases they were placed upon a solid bottom covered with shavings until the feet healed.

A diet was desired that would provide an excess of all recognized essentials for rapid growth except sufficient calories.

The diet designed for these experiments was a synthetic mixture of starch 22, cellulose 2, lard 10, sucrose 10, salt mixture 6, dried yeast 5, cod liver oil 5 and casein 40. The starch was cooked and dried. The cellulose was the regenerated product described elsewhere (McCay, '34). The salt mixture was that of Osborne and Mendel. The casein was not purified.

This diet was made high in all dietary essentials in order that the retarded-growth rats with restricted daily intakes

might have adequate protein, minerals and vitamins. In order to further compensate for the possible shortage of vitamins in the retarded growth groups, an additional 3 drops of cod liver oil and 0.5 gm. of yeast were fed daily to each member of groups II and III. This was estimated to compensate for the vitamins in the larger amounts of diet ingested by the rapidly growing group, no. I.

In the use of this diet which is rich in essentials such as protein, it is recognized that the group ingesting food ad libitum, may be subject to injury by the excess above the requirements of the body. It is not likely that such injury was produced in the present case, however, since the animals that matured rapidly had life spans similar to those found previously in our colony upon stock diets.

In a study of retarded growth the animal can be retarded for a long period and then allowed to grow. Osborne and Mendel ('15) employed this method. An optional procedure consists in holding the animal at a constant weight for a period of weeks, then allowing it to make a slight gain at a normal growth rate and following this in turn by another period of constant body weight. This procedure was used in an earlier study with brook trout (McCay, Dilley and Crowell, '29). This 'stairstep' method was employed in the present study with rats.

The feed for each animal of the retarded growth groups was weighed separately each day. The individuals were weighed three times weekly. The allowance of feed was thus adjusted to hold the body weight of each member of the retarded groups as nearly constant as possible. Usually a growth of 10 gm. was permitted to each individual of the retarded groups at intervals of 2 to 3 months. The period of holding them at a constant weight was determined by the appearance of the animals. As soon as any members of the retarded groups seemed to be failing from the deficiency of calories the entire group was allowed to grow to the extent of the 10 gm.

Two different methods were employed during the period of 10 gm. growth. Part of the time an allowance of sucrose was given in addition to the usual maintenance allowance of feed. Growth became normal in every case showing that the diet was adequate except for calories. In most cases, however, fresh beef liver was fed during this growth period. An equal allowance of this liver was given the animals of group I.

At the time the surviving rats were 766 days old, the retarded-growth groups were each subdivided. Half of each group was given all the feed it desired. The other half in each case was continued on the restricted intake until the 911th day. From that period all animals were allowed all the diet desired. The purpose of this subdivision was to determine if any difference in the power to resume growth existed between the 766th and the 911th days. Osborne and Mendel ('15), in the case of one rat, found growth was resumed after retardation for 552 days. After this retardation the rat attained a weight of 204 gm. and they stated that this was 'full size' for the female of this species.

In figure 1 are plotted the growth curves for the three groups. The curves at the top for group I show the rates for males and females separately. In the case of the retarded-growth animals the growth rates of the two sexes were maintained the same until the time for the resumption of growth. The ends of these curves show clearly that the male rat grows more rapidly and attains a larger size than the female even after growth has been retarded for more than 900 days. The power to grow still exists in the rat body after this period of 900 days.

At the top of figure 1 are shown the number of each sex alive in each group at various times. It will be observed that about forty rats were alive at the time of the first division on the 727th day.

These growth curves indicate that the retarded-growth rats attained about the same final weight as those of Osborne and Mendel, namely, 200 gm., but by comparison with the growth

curves for group I it is evident that the 'normal' size was not reached by the animals of the retarded-growth groups.

In table 1 are summarized the data regarding the weights attained which indicate the final size of the animal in terms of body weights.

In group I only animals that reached an age of 177 days or more are included. In groups II and III only those that
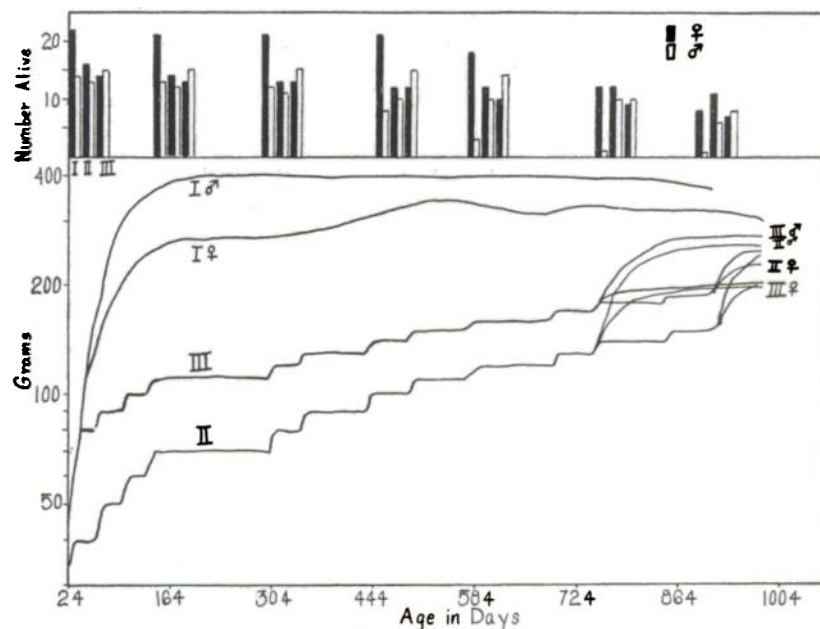

Fig. 1 Growth curves for rats allowed to grow rapidly, no. I, and for those retarded in growth by limiting the calories, nos. II and III. The columns at the top show the numbers alive by sex and group at various periods of the experiment. The top of these columns provides a mortality curve.

survived to make the final growth with ad libitum feeding are considered. These data are striking in the uniformity of the final weights of the retarded animals. The males of these retarded animals are significantly heavier than the females. Thus the undeveloped male of the species retains its potential growth power at a higher level than the female even after the male has lived for a period equal to nearly twice the average life span for this sex.

In terms of weight the difference between the final size of the animals that grew normally is significantly higher than those of the retarded groups. It is evident that animals retarded in growth for the long period that we have used are unable to attain the same final weight as those that grew rapidly to maturity. The tendency of white rats to attain a greater body weight than they did 20 years ago has been

TABLE 1

Maximum weights in grams attained by groups and sub-groups. 'G' signifies the half of the group allowed to finish growth after 766 days and 'R' after 911 days

GROUP	MEAN MAXIMUM WEIGHT ATTAINED	MEAN AGE OF ATTAINING MAXIMUM WEIGHT	MAXIMUM WEIGHT ATTAINED BY ANY INDIVIDUAL	NUMBER OF ANIMALS CONSIDERED
	gm.	*Days*	*gm.*	
I ♂	439±10	359±25	542	12
I ♀	355± 8	588±17	474	21
II ♂	262±13	1005±25	352	7
II ♀	210± 5	951±12	244	13
III ♂	267±12	903±17	358	9
III ♀	227± 5	918±26	260	10
IIG ♂	264±22	998±40	352	4
IIR ♂	259±17	1013±31	288	3
IIG ♀	223± 4	936±21	244	7
IIR ♀	195± 7	968± 8	233	6
IIIG ♂	266±20	851±18	358	5
IIIR ♂	268±13	968± 6	316	4
IIIG ♀	212± 5	840±18	238	6
IIIR ♀	256± 3	1036±27	260	4

observed in such laboratories as those at Yale. This suggests that there may be a close relation between the early growth rate and the final size since it is well recognized that the better knowledge of nutrition and selection have made it possible to stimulate growth and final size beyond the rates attainable 20 years ago. Our data suggest that a body of a certain size can be attained after very long periods of retarded growth, but that the attainment of the maximum size possible for a given species is impossible if growth is not permitted during early life. This is shown in table 1

by the attainment of the same maximum weights by groups II and III but both sexes of III g, the half of the group allowed to grow at 766 days, attained the maximum weights more quickly since they were larger when growth was permitted. They did not grow heavier, however, than those of group II.

The length of life for each individual of each group is given in table 2. The greatest length attained by any individual was 1421 days. There were members of each of the retarded-growth groups, nos. II and III, alive after all the members of group I had died. These data indicate clearly that some factor tended to promote longevity in the case of groups II and III. This effect is much more marked in the male sex than in the female. In two preceding reports (McCay and Crowell, '34; McCay, '34) it has been noted that the male rats of our colony tend to live an average of about 500 days.

The average life span of the male rats in the retarded-growth groups was 820 days in one case and 894 in the other. Upon the best diet among five, Slonaker's ('31) male rats averaged 767 days at the time of death while those of Campbell ('29) averaged 635 days upon her best diet. No male rat in Slonaker's recent experiments attained an age of 1200 days while one male among each six members of this sex of our retarded-growth groups exceeded this age. The males of our retarded groups tended to exceed the females in length of life.

The average life span of the females of the three groups is probably the same. No marked extension results from retarding the growth of this sex as far as our data indicate. Our data are somewhat distorted, however, due to the loss of two members of group II very early in the experiment. These were lost during a period of extremely hot weather. The best females in Slonaker's experiments lived an average of 848 days while the better of our retarded female groups averaged only 826 days. On the other hand, no female animal exceeded an age of 1250 days in Slonaker's study while four

of our retarded females, or about 10 per cent, exceeded this age.   The average age of Miss Campbell's female rats on her better diet was 664 days.   It is difficult to provide an explanation for this span of Campbell's animals which is so much shorter than either those of our own colony or those of Slonaker.   Before studying the data of Slonaker it seemed

TABLE 2

Life span of individuals in days

			GROUP		
I ♂	I ♀	II ♂	II ♀	III ♂	III ♀
71	74	41	48	548	134
162	485	249	62	580	341
338	520	313	259	602	479
354	559	758	260	650	565
397	699	758	260	723	577
401	713	780	296	832	641
499	719	797	342	845	663
544	722	964	410	919	810
561	724	1006	755	978	822
563	733	1137	887	998	894
588	817	1244	901	1022	901
627	824	1294	904	1028	920
733	855	1321	925	1168	999
927	857		938	1218	1080
	870		980	1306	1111
	984		999		1123
	997		1041		1132
	1023		1107		1210
	1039		1225		1297
	1074		1232		
	1143		1261		
	1189		1304		
			1421		
483	801	820	775	894	826

that reproduction might have shortened the span of Miss Campbell's females, but this is hardly tenable when we consider that Slonaker's females also reproduced.

Since half of each retarded group of rats was allowed to complete its growth after 766 days and the remaining half retarded until after 911 days, it was thought that some difference in life span might result.   The number of animals

alive at the time final growth was permitted was too small. The great variability in life spans of this limited number of cases made it impossible to find significant differences when these data were subjected to statistical treatment.

Hair growth

Hair samples were clipped from the backs of rats on the 440th and 746th days of the experiment. The diameters of ten hairs from each rat were measured under the microscope with three readings at different places near the center of the hair. The diameters of these hairs are included in table 3. The hair of the female is always finer than that of the male even if the animals are maintained at the same body weight. At 460 days of age when group III animals weighed 140 gm. and those of group II weighed 100 gm., the hair of all retarded-growth animals was finer than that of the members of group I that were mature in size. At 746 days when group III had attained a mean weight of 170 gm. the hair had become as coarse as that of group I. The hair of group I had changed little if any. The hair of group II, the average weight of each member being 130 gm., had grown coarser but was still finer than that of the other groups.

When correlated with the body weight and age, these data indicate that hair grows coarser with both the increase in size and the increase in age of the individual. The hair changes may indicate that the rat is losing the qualities that characterize youth including the power to grow to a maximum size. It will be recalled from table 1 that our rats retarded for more than 700 days could not attain full adult size, while Osborne and Mendel claimed their rats could attain normal size after more than 500 days of retardation.

Organ weights

At the time of death the rats were dissected and the weights of the heart, liver, spleen and kidneys were recorded. The blood was pressed from the heart before weighing. Only these data for animals that lived to grow without restriction

are included in table 3. These are the same animals whose maximum weights are recorded in table 1. No animals are included if they died before the opportunity to grow was provided. The number of animals upon which these organ

TABLE 3

The effect of retarded growth upon the size of organs, hair and bones

	GROUP					
	I ♂	I ♀	II ♂	II ♀	III ♂	III ♀
Body weight in grams less organs, less gastro-intestinal tract[1]	214.5	148.6	133.1	103.6	120.5	110.6
Mean hair size in milli-meters at 460 days	0.073	0.066	0.060	0.053	0.054	0.051
Mean hair size in milli-meters at 746 days	0.071	0.063	0.064	0.059	0.070	0.062
Mean volume of femur in cubic centimeters	0.605	0.445	0.422	0.353	0.445	0.379
Mean weight of femur in grams	0.741	0.540	0.486	0.398	0.484	0.432
Density of femur	1.22	1.21	1.15	1.13	1.09	1.14
Mean length of femur in centimeters	3.85	3.48	3.43	3.26	3.54	3.36
Mean smallest diameter of femur in centimeters	0.35	0.32	0.33	0.31	0.34	0.32
Mean weight of liver in grams[2]	11.49 (11)	10.06 (18)	9.33 (7)	6.82 (13)	8.55 (9)	8.72 (10)
Mean weight of kidneys in grams	3.29	2.58	2.06	1.78	2.17	1.96
Mean weight of spleen in grams	0.82	0.81	0.47	0.47	0.75	0.75
Mean weight of heart in grams	2.04	1.81	1.57	1.16	1.55	1.21
Mean body length (nose to anus) in centimeters	21.9	19.8	18.4	18.0	18.1	17.5

[1] The organs include those listed as well as the lungs and genital organs.

[2] The numbers in parentheses give the number of animals used for organ weights.

weight data are based is shown by the figures in parentheses after the mean liver weight data. These numbers also refer to the oldest animals in each of the groups of table 2.

With the exception of group III, the livers of the males are larger than those of the females. In group III they are

about the same. The livers are smaller in the retarded groups than in those that matured rapidly, no. I. In spite of the fact that these are the livers of very old animals, they bear a close relation to the body weight at the time of death. These body weights, less the gastro-intestinal tracts and less the organs given in this table plus the lungs, are shown in the first line of table 3. Many of these animals were thin and emaciated at the time of death.

The kidneys of the males are consistently larger than those of the other sex. The kidneys do not correspond to the body weights at the time of death according to the tables of Donaldson ('24). On the other hand, these kidneys correspond very closely to the maximum weights attained by these various animals. If the maximum body weights of these rats of groups I♂ to III♀, respectively, are calculated from the kidney weights by the use of Donaldson's tables, one gets values of 420, 325, 240, 215, 268 and 235 gm., while from table 1 one can secure the mean maximum weight values for the same groups. These prove to be 439, 355, 262, 210, 267 and 227 gm., respectively. The similarity of these values is striking. Two explanations are apparent. One is that the kidneys of all groups were enlarged at the time of maximum weight and have decreased proportionately as the animal body wasted away before death. In the light of the findings of McLennan and Jackson ('33), however, it is more likely that the kidneys remained very close to their maximum weight even when the animals died in extreme old age. The shrinkage of the liver also corresponds to the findings of these authors. Due to the high protein content of our diets some enlargement of these kidneys might have been expected.

The spleens of the opposite sexes in the three groups are the same in weight. The spleens of group II are small, but no explanation for this size is available.

The hearts of all animals are much larger than even the maximum weights of the animals would indicate. These values exceed the highest given by Donaldson. This indicates that these hearts were considerably enlarged at the time of

death. This may be part of the pathology of old age or it
may be due to some constituent of our diets. In our labora-
tory it has been observed that the hearts of guinea pigs can
be enlarged in the course of a few months by feeding cod
liver oil at levels lower than that employed in these diets.
It cannot be stated at this time if this is the responsible agent
in this case.

The hearts of the females are consistently lighter than
those of the males. The hearts of the retarded groups are
also lighter than those of group I. These organ data
strengthen the thesis that the retarded animals failed to
attain the body size of those that matured rapidly. Inasmuch
as the male organs in the retarded groups are larger than
the corresponding ones of the opposite sex, in most cases,
this affords some indication that these organs may have
shared in the retention of the superior growth potential that
characterized the males of the retarded animals.

Bone growth

In order to study the growth of the bones in the three
groups, all animals were preserved in formaldehyde. After
the last animal had died, the femurs were removed. After
these had dried in air the last traces of tissue were removed.
The maximum length and the minimum diameter of each
femur was measured.

Some of the femurs of the retarded groups proved to be
very fragile. Some crumbled in the course of dissection.
Part of these femurs from the retarded groups proved to be
only thin cylinders of bone.

After the length and diameter were measured, each femur
was weighed in air and then weighed suspended in water.
The volume of each was then calculated. These measure-
ments upon the femurs are included in table 4.

The bone measurements fit the general picture of the final
size attained by the various groups. The bones of the males
are consistently larger than those of the females in all groups.
The bones of the retarded animals of the same sex are con-

siderably smaller than those of group I which grew to maturity rapidly. Inasmuch as the femurs of the males of the retarded groups are larger than those of the females there is some indication that the bones as well as the organs and the entire body shared in the final growth at the end of the long retardation. All measurements indicate that the femurs of group III were slightly larger than those of the same sex of group II. This suggests that some advantage in bone growth resulted from the initial gain in body weight which was allowed group III at the very beginning of the experiment.

As soon as the bones of groups II and III were weighed in water it was evident that they were less dense than those of group I. Some of the femurs of II and III floated. Some contained a small hole and immediately filled with water. These latter were discarded. In considering these data it will be observed that the bones from groups II and III were from extremely old animals while those from no. I were much younger.

The values for the density are the same for the opposite sexes, but the animals that grew to maturity early had bones of greater density. The capacity for bone growth may be lost earlier than that for other parts of the body.

Maintenance requirements of retarded-growth animals

The calories needed for maintaining the individuals of groups II and III at fixed levels of body weights were ascertained with accuracy for each. This was essential to maintain the body weights at fixed levels. The requirements at these various weight levels are summarized in table 4.

The females consistently require more calories for maintenance at the various weight levels.

The 't' values for these data were computed by the method of Livermore ('34). In group II the odds are 255:1 and in group III 9999:1 that the differences in calory requirements by the opposite sexes are significant.

Morris, Palmer and Kennedy ('33) found the female rat to be less efficient than the male in the utilization of food.

Part of this inefficiency of the female sex can be attributed to the slower growth rate. Part may be due to this higher maintenance requirement which exists when both sexes are forced to maintain the same body weight.

TABLE 4

Calory requirements for maintenance of the body weight at various levels

	GROUP II			GROUP III	
Body weight level	Average calories per day per 100 gm. rat		Body weight level	Average calories per day per 100 gm. rat	
	♂	♀		♂	♀
gm.			*gm.*		
40	33.4±0.69	34.7±0.19	80	26.8±0.80	27.7±0.75
50	28.6±1.16	30.4±0.97	90	22.6±0.63	23.5±0.67
60	25.0±0.72	27.3±0.52	100	21.1±0.58	22.2±0.58
70	21.0±0.34	22.5±0.27	110	18.3±0.26	19.6±0.28
80	21.9±0.33	23.5±0.25	120	18.7±0.26	20.2±0.23
90	20.5±0.52	21.4±0.48	130	19.4±0.30	20.3±0.43
100	20.6±1.06	21.9±0.55	140	18.4±0.23	19.2±0.24
110	18.4±1.00	18.8±0.26	150	16.9±0.35	16.6±0.24
120	20.9±0.18	20.8±0.52	160	19.0±0.33	20.7±0.54
130	20.9±0.46	20.1±0.45	170	18.3±0.57	19.5±0.64

TABLE 5

Gross pathology at the time of death, in per cent of entire group [1]

GROUP NO.	LUNGS	KIDNEYS	GENITAL TRACT	TUMORS
	Per cent	*Per cent*	*Per cent*	*Per cent*
I ♂	78.0	14.0	...	14.0
I ♀	54.0	36.0	45.0	18.0
II ♂	58.0	16.0	8.0	8.0
II ♀	35.0	9.0	22.0	22.0
III ♂	85.0	50.0	...	7.0
III ♀	35.0	8.0	15.0	10.0

[1] This table is based on the number of animals in any one group showing definite types of infections on post mortem examination.

Pathology at the time of death

In the course of nearly 4 years in which this experiment was in progress many different pathological conditions were observed that are rarely seen in rat colonies. This was due to the maintenance of old animals in contrast to the usual

breeding colony for rats where individuals are usually discarded shortly after middle life.

The roughness of the fur coats of the old animals became apparent much earlier in those that matured rapidly. This is well illustrated in the photograph included in our preliminary report. As the experiment progressed many animals became blind. This happened so gradually that no quantitative data were secured, but a rough estimate would include at least half of the animals that lived beyond 2 years.

Old rats were frequently afflicted with diseases of the urinary tract. At times bloody urines were observed. In some cases individuals were treated with hexamethylenetetramine, but such treatment was usually futile. The old rat undoubtedly is a fertile experimental animal for the urologist.

In table 5 an attempt has been made to summarize some of the observations of the gross pathology at the time of death. The failure of the lungs is obvious in many cases, but this must have been secondary to many of the other failures that occurred in the old bodies.

SUMMARY

Rats were retarded in growth and not allowed to attain maturity until after periods of 766 and 911 days. The rat body still retains the power to grow at these extreme ages. After such periods of retardation the rat cannot attain a body size equal to that of an animal that grows to maturity younger. This conclusion is based upon the smaller size of the entire body, the weight of such organs as the heart, and the size of the bones represented by the femur. Even after these long periods of suppressed growth the male rat retains a growth potential greater than the female although the males of the retarded groups grow no larger than the normal females of this species. The hearts of all these animals dying in old age were larger than normal while the livers were smaller. The kidneys corresponded in weight at the time of death to the maximum weight attained by the body. The femurs of members of the retarded groups were less dense than those that matured normally.

In both retarded groups individuals of both sexes attained extreme ages beyond those of either sex that grew normally. The mean age of the males of both retarded groups was greatly increased in comparison with 'rapid growth' males while the mean age for the females was about the same in all three groups. The males of the retarded groups exceeded the females in age in contrast to the 'rapid-growth' group.

At a constant weight level in the course of retarded growth the female requires more calories for maintenance than the male. In the course of retarded growth, the diameter of the hair as well as the growth of the body reflects the retardation.

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