PROLONGING THE LIFE SPAN

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The preservation of life, the defending of the human body from decay, and of rendering it a fit tenement for the soul to inhabit, in that season in which she is most capable of exerting her noblest faculties, are grave and serious subjects with which no trivial matters ought to mingle.
—*Hermippus Redivivus.*

In this day when both children and animals are being fed to attain a maximum growth rate, it seems little short of heresy to present data in favor of the ancient theory that slow growth favors longevity. A hundred years ago when men first became conscious of the need for the accessory factors which we now term vitamins, the field of nutrition was broad. Students attempted to study the requirements of both adult and growing animals. To-day research has tended to narrow into a channel of primary interest in the young, growing animal. Interest is centered on the growth and apparent health of this animal. After it becomes an adult it is no longer an "apple of the eye" of the nutritionist, but primarily a carcass that provides dissecting material for the pathologist. The nutrition student is too busy pouring vitamins, minerals and proteins into the young and growing to be much concerned with the grown.

The philosophy which dominates the field of nutrition assumes that a young animal which grows rapidly is the ideal for maximum health both during the growing period and during adult life. This philosophy has developed under the influence of several stimulants. In the first place, a young animal such as the white rat, which is the central interest in most nutrition laboratories, grows to maturity in about three months. Studies of the growth of this animal provide opportunities for numerous discoveries in the course of a short-time period. Technical journals are cluttered to-day with thousands of reports concerning the growth of the white rat. But if one tries to discover the length of life of this widely used animal, he will not find five good reports in the entire literature.

A second stimulus to this interest in the growing animal and disregard of the adult is due to the public interest in the young and growing. The healthy adult is a matter of little interest, even to himself, and the sick one usually rates as a pest. This philosophy belongs properly to the butcher. Every producer of meat animals wants to rear them rapidly because it is economical. These animals are killed as soon as they mature. What agricultural expert can tell the effect of the feeding during the growth period upon the milk-producing capacity of a cow during her entire life? What chicken specialist can tell the effect of the rate of growth of the chicken upon the egg production of the laying hen? Who can tell you the effect of the rate of growth of a child upon its susceptibility to disease during adult life? Who can give assurance that the child that matures rapidly will not die after a short life span?

A third stimulus whose importance may be overlooked is that of commercial advertising. While preparing this note I selected at random one of the copies of the *Journal of the American Medical Association*, which is published weekly. More than a fifth of the advertising in this journal was devoted to fortified foods for children, chiefly for defenseless babies that are more or less easily coerced into engulfing various vitamin

concentrates. It must be possible to market such products. Who can estimate the effectiveness of such constant advertising in the *Journal* of the American physician in creating and moulding his philosophy and his recommendations in feeding children? Is it any wonder that the pediatrician has become an advocate of rapid growth? Even the manufacturer of scales does his part by buying space in this same professional journal in order that no one shall neglect to keep his child up to date in weight. Thus has been created an enthusiasm for growth and growth stimulants. And what profit in dollars can be made from any other philosophy?

Before becoming involved in experiments and data it may be well to refer briefly to three philosophers. In his treatise upon the generation of animals Aristotle states:

> The period of gestation is as a matter of fact determined generally in each animal in proportion to the length of its life. This we should expect, for it is reasonable that the development of the long lived animals should take a longer time.

If we turn to the Opus Majus of Roger Bacon (1214–1294) we read:

> Another example can be given in the field of medicine in regard to the prolongation of human life, for which the medical art has nothing to offer except the regimen of health. But a far longer extension of life is possible. At the beginning of the world there was a great prolongation of life, but now it has been shortened unduly.

Further in this same work we read:

> Therefore in regard to this we must strive, that the wonderful and ineffable utility and splendor of experimental science may appear and the pathway may be opened to the greatest secret of secrets, which Aristotle has hidden in his book on the Regimen of Life. For although the regimen of health should be observed in food and drink, in sleep and in wakefulness, in motion and in rest, in evacuation and retention, in the nature of the air and in the passions of the mind, so that these matters should be properly cared for from infancy, no one wishes to take thought in regard to them, not even physicians, since we see that scarcely one physician in a thousand will give this matter even slight attention. Very rarely does it happen that any one pays sufficient heed to the rules of health. No one does so in his youth, but sometimes one in three thousand thinks of these matters when he is old and approaching death, for at that time he fears for himself and thinks of his health. But he cannot then apply a remedy because of his weakened powers and senses and his lack of experience.

In another paragraph Roger Bacon continues:

> Since I have shown that the cause of a shortening of life of this kind is accidental, and therefore that a remedy is possible, I now return to this example which I have decided to give in the field of medicine, in which the power of medical art fails. But the experimental art supplies the defect of medicine in this particular. For the art of medicine can give only the proper rules of health for all ages. For although noted authors have spoken inadequately concerning the proper regimen of the aged, it has been possible, however, for medicine to give such a regimen. This regimen consists in the proper use of food and drink, of motion and rest, of sleep and wakefulness, of elimination and retention, of the air, and in the control of the passions of the mind. But if from birth a man followed a proper regimen to the end of his life he would reach the limit of life set by God and nature, in accordance with the possibility of a proper regimen. But since it is impossible for this regimen to be followed by any one, and since few, nay, scarcely any one at all, from youth pay any heed to this regimen, and very few old people observe it as it is possible, therefore the accidents of old age of necessity come before old age and senility, namely, in the period of the prime of life, which is the age of human beauty and strength. In these times this period of life does not continue beyond forty-five or fifty years.

This scientist and monk of the middle ages continues:

> Not only are remedies possible against the conditions of old age coming at the time of one's prime and before the time of old age, but also if the regimen of old age should be completed, the conditions of old age and senility can still be retarded, so that they do not arrive at their ordinary time, and when they do come

THESE TYPICAL RATS ARE BOTH 900 DAYS OLD

THE ONE ON THE LEFT GREW RAPIDLY AND "NORMALLY" TO MATURITY WHILE THE PHYSIOLOGICALLY YOUNG ANIMAL ON THE RIGHT WAS RETARDED IN GROWTH AND FORCED TO MATURE SLOWLY.

they can be mitigated and moderated, so that both by retarding and mitigating them life may be prolonged beyond the limit, which according to the full regimen of health depends on the six articles mentioned. And there is another farther limit, which has been set by God and nature, in accordance with the property of the remedies retarding the accidents of old age and senility and mitigating their evil. *The first limit can be passed but the second cannot be.*

As every one is well aware, this usefulness of the experimental method in attacking the problems of longevity remained unheeded, as it has to this hour. A few hundred years after these words of Roger Bacon we read the statements of Lord Francis Bacon (1561–1626):

We make the third part of medicine regard the prolongation of life; this is a new part, and deficient, though the most noble of all; for if it may be supplied, medicine will not then be wholly versed in sordid cures, nor physicians be honored only for necessity, but as dispensers of the greatest earthly happiness that could well be conferred on mortals for though the world be but as a wilderness to a Christian travelling through it to the promised land, yet it would be an instance of the divine favor, that our clothing, that is, our bodies, should be little worn while we sojourn here. And as this is a capital part of physic, and as we note it for deficient, we shall lay down some directions about it.

In the light of our experimental data which follow, six of these rules of Lord Bacon may prove interesting:

(1) The cure of diseases requires temporary medicines but longevity is to be procured by diets.

(2) It seems to be approved by experience that a spare and almost Pythagorean diet, such as is prescribed by the stricter orders of monastic life or the institutions of hermits, which regarded want and penury as their rule, produces longevity.

(3) Animals which come later to perfection (I am not speaking of growth in stature only but of the other steps to maturity as man puts out first his teeth, then his signs of puberty, then his beard, etc.) are longer lived for it indicates that the periods return in wider circles.

(4) To grow long and slowly is a sign of longevity and the taller the stature the better the sign. But on the other hand, rapid growth to a great stature is a bad sign but to a shorter stature less bad.

(5) I would have men duly to observe and distinguish that the same things which conduce to health do not always conduce to longevity.

(6) Again there are other things very beneficial in prolonging life yet that are not without danger to the health unless guarded against by proper means.

Finally before considering data it is worth noting some statements from a

more modern work, "La Philosophie et la Longevité," of Jean Finot. In 1906, just as the extensive modern interest in vitamins was taking form, Finot wrote:

> Here is a fact in another type of idea, which has cost the lives of millions of men. From many observations we have learned that the vitality of the world's animals is in direct relation to the duration of adolescence. The more the period of adolescence is extended, the more that of maturity is increased. All the education and instruction given to children is in violent contradiction to this law. All our efforts tend to the most rapid advancement toward physical and intellectual maturity.

As we enter the contemporary field of experimental science we need not be surprised that real data bearing upon the problems of longevity are almost as scarce as they were in the time of Aristotle or Roger Bacon.

In 1917 Osborne and Mendel[1] reported an experiment in which they attempted to prolong the lives of rats by retarding the growth. They found the reproductive activities of these rats extended to a greater age in the females, but unfortunately their rats died of disease before they determined the effect of retarded growth upon the life span. In 1917 Northrup[2] presented data with fruit-flies showing the entire life cycle was extended if you increased the larval period by inadequate feeding. The entomologist has long been aware that the total life cycle is prolonged by slowing down one of the stages of development.

In 1928 Raymond Pearl[3] in his book on "The Rate of Living" showed the significant negative correlation between the rate of growth and duration of life of cantaloup seedlings.

In our laboratory in 1927 an experiment was designed to study the relationship between the protein level in the diet of brook trout and the deficiency of an accessory factor we term "H" (to differentiate it from the vitamins required by higher animals). The diets for the series of groups of brook trout were all deficient in this essential vitamin, factor H. Therefore in the course of six months or less every trout was doomed to die. In addition to this vitamin deficiency, which was common in all diets, the amount of protein in the various diets was varied. One group received 10 per cent. protein, another 25 per cent., another 50 per cent. and a fourth 75 per cent. To secure growth, a diet for brook trout must contain about 14 per cent. protein. In this experiment all groups grew at about the same rate, except those upon the low level of protein. They failed to grow, but kept alive. However, the trout that grew died in about twelve weeks. Those that failed to grow upon this low protein level lived twice as long as those that grew. Thus it was postulated by us in 1928 that *something was consumed in growth that is essential for the maintenance of life.* At a later date this experiment was repeated and again it was found that trout that grew lived about half as long as those that were retarded in growth if both were kept upon a deficient diet.

While considering these studies with fish it may be well to review briefly the difference between the growth rates of fish and those of higher, warm-blooded animals.[4] If a young elephant in a zoo gained a pound in a day no one would be excited, but if the mouse that steals the elephant's food were to gain a pound a day it would be news. Therefore in considering the growth rate of any animal it must always be considered in terms of the body weight of the individual. Thus it can be stated better that the mouse and the elephant gain a given per cent. of their respective body weights

[1] T. B. Osborne, L. B. Mendel and E. L. Ferry, *Science*, 45: 294, 1917.

[2] J. Northrup, *Jour. Biol. Chem.*, 32: 123, 1917.

[3] R. Pearl, "The Rate of Living," Chap. 7, 1928.

[4] C. M. McCay, *Science*, 77: 411, 1933.

FEMALE RATS AT THE AGE OF TWO YEARS AND EIGHT MONTHS

THOSE ABOVE BELONGED TO GROUP 1 WHICH GREW TO MATURITY RAPIDLY. THE PHYSIOLOGICALLY YOUNG ONES BELOW ARE THE SAME AGE BUT THEY WERE RETARDED IN GROWTH AND MATURED LATE.

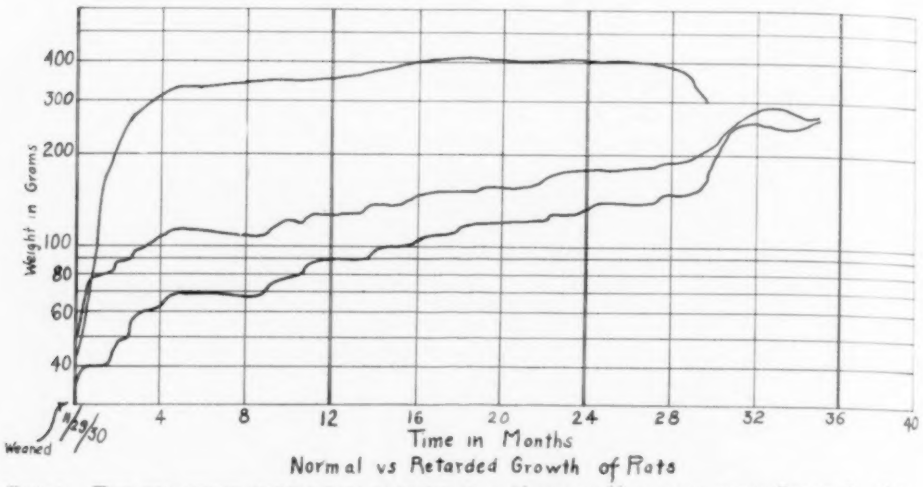

CHART. THE TOP CURVE SHOWS THE GROWTH OF A "NORMAL" ANIMAL FROM GROUP 1. THE TWO LOWER CURVES ARE TYPICAL FOR ANIMALS RETARDED IN GROWTH.

in a unit of time such as a day or month. In practise we determine such relationships automatically by plotting growth curves upon semi-logarithmic graph paper. Most higher animals from their early life in the uterus grow at a constantly decreasing rate. The baby tends to grow more rapidly than the boy of sixteen. This is not so with fish such as brook trout. In a given year during the growing season they maintain a constant growth rate. In other words, in each month the brook trout increases its weight by a constant per cent. of the body weight at the beginning of the month. If the entire life span of a brook trout is considered, however, it is found that the growth curve remains logarithmic during successive years. This curve is much steeper during the "fry" stage and during that of embryonic growth than it is during the second and third years of life. Thus the trout really decreases its growth rate as it ages and does not afford an exception to the findings of Minot that warm-blooded animals decrease their growth rates as they become older. Not only is this growth rate logarithmic but it is much slower than that for a pig or a chicken. No one has published growth curves of warm-water fish for comparison, however. Not much is known about the life span of fish, but it is well recognized that they are long lived. There is a record of a carp that lived 367 years, of a pike that lived 267 years. The authenticity of these records may be questioned, but it can be accepted that fish have long life spans.

As the discovery that trout live longer when they fail to grow is reviewed, the old law which Buffon (1707–1788) seems to have taken from Aristotle is worth recalling. Buffon claimed that the time required for an animal to grow to maturity could be multiplied by 6 or 7, and the resulting value would equal the life span. This law was discussed at intervals in the course of the eighteenth and nineteenth centuries. To-day it seems pretty well forgotten by the biologists. This law is interesting because it states that the life span is directly proportional to the growing period of a young animal. This law was devised from a consideration of the growth rates of various species such as

man, camel, horse, cow and dog. It was not based upon data concerning individuals within a given species. This law is interesting because it suggests a possible method of extending the life span of an individual. It also makes one aware of the many animals of widely different life spans that are available for experiments. Thus man is fortunate in having a much greater span of life than mice, rats, guinea pigs, chickens, rabbits, cockroaches and dogs. Within our reach is the possibility of determining the factors that set this limit to the life span or possibly to discover that the fixed life span is fictitious.

In order to test the assumption that an individual within a species that grows to maturity slowly will have a greater life span than one that grows rapidly, an experiment with white rats was designed. This species was selected because (1) its nutritional requirements are better defined than those of any other species. This has been the chief animal used in the laboratories for the past twenty years. (2) The white rat's span of life is about two years, normally. Therefore, an experiment would not need to extend over a period of more than five years. (3) The white rat is small enough so that large groups can be employed. Thus we can compensate for individuals that develop specific diseases that are not related to the experiment. (4) Numerous earlier studies had shown the white rat can be retarded in growth and still attain maturity. No marked stunting effect results from retarding the growth at least as far as any one has extended such retardation. (5) The white rat is similar to man in its nutrition and in the life spans of the opposite sexes. The female rat lives longer than the male. This is also true for the human species.

In planning the diet for this experiment it was desired to satisfy the nutritional requirements of the body in every respect, except that the body would have insufficient calories to permit growth when the food intake was restricted. We designed a diet that was adequate in vitamins, protein, inorganic salts and fats, even when the animal was restricted to a low level of intake each day. Thus for long periods the animals whose growth was retarded could be prevented from growing. At the same time the food ingested each day provided every recognized constituent to insure the health of the animal but not enough calories to permit growth. In such a case the real cause of the retardation of growth is probably due to the use of the protein for energy, since insufficient calories are allowed. Thus in final analysis the retardation may be due to protein in spite of a high level in the diet fed. This is analogous to an automobile in which the engine contains ample oil, the differential is well greased, the battery gives a good spark but only enough gas flows into the carburetor to permit the car to run 20 miles an hour. To make it run faster we feed the engine more calories. Likewise with the rat, the diet was adequate in every known respect. It was designed so that all that was needed to make the rat grow or to increase from its uniform rate was to feed it more calories. Sugar provides calories for the rat just as gasoline does for the automobile. No one expects "longevity" in an automobile without oil, grease and a few repair parts in addition to fuel. Likewise in the body of an animal we must have protein, inorganic material, vitamins and some fat. With these needs satisfied it was possible to control the rate of growth of the animals by calories alone.

In planning an experiment in which the growth of a young animal is retarded, it seems desirable to start as early as possible. In the case of the nursing young it is difficult to decrease the growth rate very much and still

TABLE I

LIFE SPANS OF RATS THAT MATURE SLOWLY COMPARED WITH THOSE MATURING RAPIDLY

Diet	Mean Life Span (Days) ♂	Mean Life Span (Days) ♀	Median Life Span (Days) ♂	Median Life Span (Days) ♀
I—Adequate calories (rapid growth)	509	801	522	820
II—Deficient calories (slow growth)*	(792)	(755)	797	904
III—Deficient calories (slow growth)*	(883)	(824)	919	894
Stock Diet (75) (rapid growth)†	503 ± 12		*Note:* Campbell discards early deaths while our data include them.	
Campbell‡ (A) (rapid growth)	576 ± 10	604		
Campbell‡ (B) (rapid growth)	635 ± 12.9	664		

* Values in parenthesis are still increasing, since the animals are alive.

† From unpublished data obtained from our rat colony five years ago.

‡ H. Louise Campbell, Thesis, Columbia University (1929).

keep the young alive and healthy. Furthermore, there is a transition period in which the animal is weaned and changed from milk to solid food. Retarding the growth during this period is also somewhat dangerous, since most species are very sensitive to changes during this time. In view of the difficulties in animal life immediately after weaning this experiment with rats was planned so that three groups were employed.

At the time of weaning 106 rats were divided into three groups, one containing 34 individuals and the other two 36 each. The members of one group were allowed to grow normally for two weeks they matured rapidly. The members of the second group were forced to grow very slowly by limiting their daily allowance of food from the time of weaning. The third group of rats was allowed to grow normally for two weeks after weaning. They were then restricted in their food allowance and forced to mature slowly. This restriction, providing all the necessary elements as we have stated, limited only the calories.

In the accompanying growth curves, the chart, we have selected curves for typical rats from each of the groups, and thus the course of growth is shown graphically. In rearing the retarded growth groups the practise has been followed of keeping them at a stationary weight for one to four months. A weight increase of about ten grams was then obtained by increasing the allowance of food. Part of these increases were made by feeding sugar only in addition to the regular allowance of food. At other times the step upward in the growth was induced by such rich sources of vitamins as beef liver. In each case the controls were also allowed the same additional and special foodstuffs, as the retarded growth groups during the same period of time.

In the accompanying chart the slow climb to maturity of the lucky rats or victims (as your philosophy dictates) can be seen. After more than 28 months all were allowed to mature. For the remainder of their lives they were allowed all the food they desired. Thirteen of these original rats were still alive after 1,200 days. All these were rats whose growth was retarded. This represents 18 per cent. of those from retarded growth groups and none of the rapidly maturing.

TABLE II

NUMBER OF EACH SEX OF RATS ALIVE AT THE BEGINNING AND AFTER 1,200 DAYS, SHOWING THE INCREASED LIFE SPAN AFTER RETARDED GROWTH

Diet	No. animals start			No. animals alive at 1,200 days		
	♂	♀	Total	♂	♀	Total
I—Adequate calories (rapid growth)	14	22	36	0	0	0
II—Deficient calories (slow growth)	13	23	36	3	5	8
III—Deficient calories (slow growth)	15	19	34	2	3	5
Total alive			106			13

In Table I is a summary of the mean and median life spans which was made at 1,191 days. From groups I, II and III the only fixed value at 1,191 days was that for animals of diet I. Late in the first year of this experiment some of the females of the retarded growth groups were lost during the hot summer of 1931. This tends to distort the data for the mean life span of the females. For this reason the data for the median, which is a truer picture in this case, are included.

These data as well as those of Dr. Campbell of Columbia, which we have inserted for comparison, show that the life span of the female rat which matures rapidly is longer than that of the male. It is worth noting that the mean life span of the female rat in our experiments, even with rapid growth, was about a fifth longer than that found at Columbia. One can think of several explanations for this difference, such as diet or heredity. Another difference is that Dr. Campbell's rats were bred and bore young regularly, while those in our experiments were not allowed to reproduce. In this table are also inserted the results of an earlier experiment in which 75 male rats were kept in our colony until the end of their lives. Their mean life span was 503 days, while in the present case the value was 509 days. In these cases the diets and the years in which the experiments were run were quite different, but the growth rates and the life spans were similar. This affords additional evidence that the rate of growth and the life span are related if the diet is complete qualitatively.

The data are clear in regard to the male rat. They are less clear in regard to the female, since there are animals alive in each group except one. Furthermore, this table was made at a time well outside the period of the normal life span of our male rats but just outside the span for the female animals. Since even female rats that matured rapidly lived about a fifth longer than those of Miss Campbell, there is the possibility that growth of young within the uterus may remove some essential from the body of the mother and thus shorten her life span.

In Table II is a summary of the number of each sex at the beginning and at the end of 1,200 days, slightly more than three years. At the present time this experiment has been running 1,200 days and there are 13 animals alive. Since the average male rat lives from 500 to 600 days and the average man lives from 50 to 60 years, ten days in the life of a male rat is equivalent roughly to a year in that of a man.

Most of the rats that are alive now are more or less blind and some have been so for about half of the period. Thus it

seems that the eye fails before other parts of the body. These old animals, like old men, seem to be susceptible to lung infections and these seem to be the immediate cause of some deaths. The hair of the animals retarded in growth remained fine and silky for many months after that of the rapidly growing animals had become coarse. In studies with animals it is customary to observe the hair, since its condition frequently reveals changes that are taking place within the animal body.

In summarizing, these data indicate:

(1) That the life span of the rat is extended if the growth of the animal is retarded by inadequate calories and if an adequate intake of other essential nutrients is insured.

(2) That the potential life span of an animal species is unknown and greater than we have believed.

(3) That the difference in growth rates of the opposite sexes within a species may account for the differences in life span.

(4) That the problems of longevity can be attacked profitably to-day by means available in most nutrition laboratories.

Finally, in order that we may not become over-enthusiastic concerning the worth of longevity studies, it may be worth recalling the well-known lines of Lucretius with which he closes Book III of the "Nature of Things."

> Verily, a sure end of life is ordained for mortals, nor can we avoid death, but we must meet it. Moreover, we spend our time amid the same things, nor by length of life is any new pleasure hammered out. But so long as we have not what we crave, it seems to surpass all else; afterward, when that is ours, we crave something else, and the same thirst for life besets us ever, openmouthed. It is uncertain too what fortune, time to come, may carry to us, or what chance may bring us or what issue is at hand. Nor in truth by prolonging life do we take away a jot from the time of death, nor can we subtract anything whereby we may be perchance less long dead. Therefore you may live on to close as many generations as you will: yet no whit the less that everlasting death will await you, nor will he for a less long time be no more, who has made an end of life with to-day's light.