

KINETICS OF MUSCLE ATROPHY

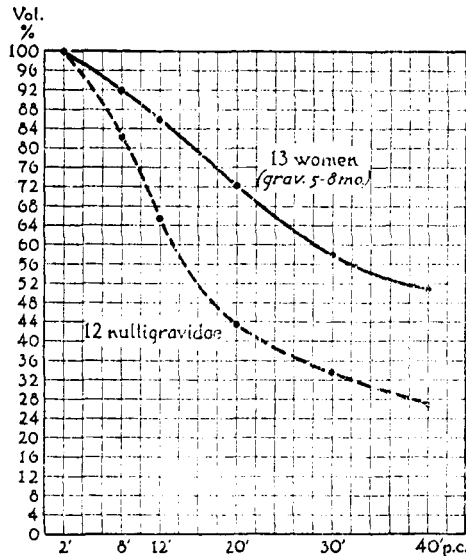


FIG. 1.

Mean curves of evacuation of gall bladder, after a standard meal of 4 egg yolks mixed in an equal volume of milk.

of bile salt-cholesterol ratios⁴ cannot be adequately discussed within the limits of this preliminary article. Suffice it to say that Westphal's pilocarpine experiments on pregnant women,⁵ pointing to a hypermotility of the Sphincter of Oddi during pregnancy, seems to afford the most promising line of investigation. Just when this delay in emptying becomes recognizable has not yet been determined. In the 4 individuals who were pregnant only 2 to 3 months the mean curve of evacuation of bile was only a little slower than normal—a difference that was not statistically significant.

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Kinetics of Muscle Atrophy in Different Species.

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It has long been known that when skeletal muscle of homotherms is denervated, an atrophy ensues. The muscle undergoes a progressive loss of weight which is directly proportional to lapse of time after denervation. Quantitative data concerning the percent

⁵ Westphal, Karl, *Z. f. Klin. Med.*, 1923, **96**, 95.

of weight lost by skeletal muscle at various periods of time after denervation have been reported by Langley and Kato,¹ Lipschütz and Audova,² and Chen, Meek, and Bradley.³ The last authors noted that the curve relating weight loss to time was of a logarithmic type. No precise definition of the relationship between weight loss and time has, however, been given. It was suggested by Hines and Knowlton⁴ that, in the rat, the loss of muscle weight in denervation atrophy follows very closely the curve of the equation for a reaction of the first order.

This idea has been tested on the results from experiments on rats, mice, guinea pigs, pigeons, and dogs. In each instance the gastrocnemius of one side was denervated and after designated periods of time the weights of the denervated and control muscles were determined. The weight loss of the denervated muscle was calculated on the basis of the assumption that the control muscle weight represented the initial weight of the denervated muscle.

It is immaterial whether the calculation is made on the basis of wet or dry weight since such slight alterations as occur in the water concentration of denervated muscle (Hines and Knowlton⁴) would not be of significance for these calculations.

The assumption of the identity in weight of 2 contralateral muscles from an animal is only true statistically. For any given animal it is not precisely true. Furthermore, this assumption is vitiated if the animal undergoes a significant change in body weight after denervation. If, however, the animals are fully grown and in a good nutritional state, the assumption is entirely justified.

With these facts in mind, the percent of weight lost during varying periods of atrophy was determined. The averages are shown in Table I. The test of fit of the individual weight loss data to the equation $k = 1/t \log_{10} A/(A-x)$ was made.

If the data fit the curve, "k" should be a constant characterizing the atrophy rate.

"t" is the atrophy time in days and is not equal to the time after denervation. Easily recognizable changes, such as fibrillary contractions, acetyl choline sensitivity, weight loss, and reduced glycogen concentration do not make their appearance until 48 to 72 hours after denervation. The peripheral stump of the cut nerve has lost its viability slightly earlier than this so that the atrophy time "t" is closely approximated by making it equal to the time, in days, after denervation minus $1\frac{1}{2}$.

¹ Langley, J. N., and Kato, T., *J. Physiol.*, 1914-15, **49**, 432.

² Lipschütz, A., and Audova, A., *J. Physiol.*, 1921, **55**, 300.

³ Chen, K. K., Meek, W., and Bradley, H. C., *J. Biol. Chem.*, 1924, **61**, 807.

⁴ Hines, H. M., and Knowlton, G. C., *Am. J. Physiol.*, 1933, **104**, 379.

TABLE I.

Days after Denervation	No. of Animals	Weight Loss %	k*
Rats.			
3	17	8.3	.030
5	10	16.4	.027
7	26	21.3	.023
14	22	48.3	.029
21	25	61.9	.030
28	23	72.3	.032
42	7	79.0	.029
	Total 130		Mean kt .029
Life Span ⁸ = 3.5 years.			P. E. .0005
Mice.			
3	19	6.3	.024
5	15	15.7	.025
7	19	22.5	.025
14	13	50.8	.032
21	12	68.4	.036
	Total 78		Mean kt .028
Life Span ⁹ = 2 years.			P. E. .0009
Guinea Pigs.			
7	6	18.4	.019
14	6	39.5	.022
21	4	54.3	.022
	Total 16		Mean kt .021
Life Span ⁸ = 6 years.			P. E. .0009
Dogs.			
28	4	29.8	.0071
42	5	17.3	.0025
118	5	40.0	.0024
132	7	54.8	.0036
	Total 21		Mean kt .0037
Life Span ⁸ = 15-20 years.			P. E. .0003
Pigeons.			
7	9	11.8	.012
14	9	28.8	.014
21	11	33.3	.011
28	4	37.0	.010
	Total 33		Mean kt .012
Life Span ⁸ = 12 years.			P. E. .0006

*k = $\frac{1}{t-1.5} \log_{10} \frac{85.5}{85.5-x}$; t = time, in days, after denervation; x = % weight lost. The values of k are calculated from individual data.

†k calculated from the individual data.

⁸ Abderhalden, *Handbuch der Biologischen Arbeitsmethoden*, Vol. V, Part 3 C.

⁹ Robertson, T. B., and Ray, L. A., *J. Biol. Chem.*, 1920, **42**, 71.

"A" is the percent of the original muscle weight which can be lost in atrophy and is taken as 85.5. There is no way to quantitatively determine "A", but all reports have indicated that the connective tissue, blood vessels, etc. (non-loseable portion) of muscle are between 10 and 20% of the total weight. The first estimate was taken as 85% for loseable weight and in testing the rat data to the equation, the fit was apparent. Applying the method of least squares,

it was found that 85.5% gave a better fit than 85%. This figure (85.5%) was then used throughout the calculations.

"x" represents the percent of original weight lost in time "t".

It should be noted that the values for "k" given in Table I are the means of the "k's" calculated from the individual weight loss data and are not calculated from the mean weight loss. Likewise, the mean "k" for a species is calculated from the array of individual "k's".

It is clear that the data, within a species, give a reasonably close fit to the curve suggested as evidenced by the constancy of "k" after different periods of atrophy (Table I). "k" seems to have a characteristic value for a given species. The only exception is the data on the dog.

Apparently a genetic factor is of importance in determining the atrophy rate. This probably accounts, in part, for the lack of uniformity in the results from dogs. The dogs used did not represent a genetically homogeneous sample. The other species groups did. Another factor in the dog is the slower atrophy rate of the muscle, thus giving more opportunity for a regeneration of nerve so that continuity is often reestablished, even after the removal of a fairly long nerve section, before marked atrophy occurs. All animals in which this regeneration had proceeded to the point of giving a functional nerve were of course discarded. However, the question arises as to the possible "trophic" effect of the embryonic type of tissue first produced in the regeneration of motor nerve.

With these mitigating factors present in the dog, it seems justified to disregard the data on this animal for the time being and conclude that the mean rate of denervation atrophy in a homogeneous population of homotherms is defined by the equation of the curve for a reaction of the first order.

It seemed of interest to attempt to relate the absolute index of atrophy rate, "k", to some other characteristics of an animal. Changes in metabolic rate due to different levels of thyroxinization have been shown to alter the rate of denervation atrophy weight loss in the rat (Hines and Knowlton⁵). Metabolic rate changes due to differences in environmental temperature did not alter the atrophy rate in the rat (Hines and Knowlton⁶). That differences in metabolic rate do not account for the different atrophy rates in different species is shown by a comparison of the "k" for mice and rats. The effective metabolic rate would, of course, be that per

⁵ Hines, H. M., and Knowlton, G. C., *PROC. SOC. EXP. BIOL. AND MED.*, 1934, **31**, 1029.

⁶ Hines, H. M., and Knowlton, G. C., *Am. J. Physiol.*, 1934, **110**, 8.

gram of muscle. The mouse and rat have about the same metabolic rate per unit surface area, but the volume-to-area ratio is about 3 times as great in the rat as in the mouse. This means that the metabolic rate per gram of muscle must be about 3 times as great for the mouse as for the rat. In spite of this large difference, the atrophy rates are the same.

Logically, one might expect denervation atrophy rate to be related to growth rate. A comparison between rats and mice shows the same atrophy rate and approximately the same growth rate. Such a comparison between the other species of this series is not so simple because the physiological age at birth or hatching of rats, mice, guinea pigs, and pigeons varies considerably (Brody and Ragsdale⁷). Thus, their growth rates immediately after birth and at the times from birth to maturity vary to some extent merely on the basis of development at birth.

Another characteristic, related to growth rate and far enough removed from birth to make differences in development at birth of less importance, is the life span. On comparing the life span with the atrophy rate "k" (Table I), it will be seen that the longer life span is, in general, associated with a slower rate of denervation atrophy. It seems useless, at the present time, to attempt any more precise correlation between the life span and atrophy rate. Before that could be done, life tables for each of the species would have to be available. The populations of these experiments do not represent an average species group, since only adult individuals were used. Thus the life span should be greater for these animals than the average life span of the species.

It does seem, however, as if the specific denervation atrophy rate, "k" is an hereditary characteristic of a species, possibly related to the genetic factors associated with determinaters of growth rate.

Summary. The relationship of the rate of weight loss in denervation atrophy to time has been found to be defined by the equation

$$k = \frac{1}{t} \log_{10} \frac{A}{A-x}$$

where "k" is a constant characteristic of the species and probably related to growth rate, "t" is the time from loss of nerve viability, "A" is the percent of the original weight which is loseable in atrophy, and "x" is the percent of total weight lost at time "t".

⁷ Brody, S., and Ragsdale, A. C., *J. Gen. Physiol.*, 1922, **5**, 205.