THE KINETICS OF SENESCENCE.

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The question of why we grow old and die is gradually being answered with the accumulation of data.[1]

While this question is a very old one, the wide scientific interest in this subject dates from the time of Weismann's discussion on life and death.[2] Weismann popularized the fact first pointed out by Bütschli that unicellular organisms may be considered as immortal since they will live and multiply indefinitely in appropriate media which are frequently renewed.

The observation by Leo Loeb[3] that cancer cells, which are considered as merely modified somatic cells, can be grown indefinitely when transplanted successively from the old host to younger animals was the next contribution to this subject. This led to the conclusion that cancer cells must be considered immortal and he generalized this for all forms of somatic cells of multicellular animals. The proof of this was furnished by the experiments on tissue culture, as gradually developed by Leo Loeb,[4] Harrison,[5] Burrows,[5] and Carrel

[1] The literature on senescence was recently fully summarized in the following two monographs. Pearl, R., The biology of death, Monographs on experimental biology, New York and London, 1922. Robertson, T. B., The chemical basis of growth and senescence, Monographs on experimental biology, Philadelphia and London, 1923.

[2] Weismann, A., Ueber die Dauer des Lebens, Jena, 1882; Ueber Leben und Tod, Jena, 1884.

[3] Loeb, L., *J. Med. Research*, 1901, vi, 28.

[4] Loeb, L., Über die Entstehung von Bindegewebe, Leucocyten, und rothen Blutkörperchen aus Epithel und über eine Methode isolierte Gewebsteile zu züchten, Chicago, 1897. Quoted by Loeb, J., The organism as a whole from a physicochemical viewpoint, New York and London, 1916.

[5] Harrison, R. G., *J. Exp. Zool.*, 1910, ix, 787; *Tr. Cong. Am. Phys. and Surg.*, 1913, ix, 63. Burrows, M. T., *J. Exp. Zool.*, 1911, x, 63; *Tr. Cong. Am. Phys. and Surg.*, 1913, ix, 77.

and Burrows, and Carrel.[6] These modifications enabled Carrel,[6] and Carrel and Ebeling[14] and other collaborators to grow several types of tissues *in vitro* some of them for many years thus substantiating the suggestion of the potential immortality of somatic cells of higher organisms.

Moore[7] who, at the suggestion of Loeb, investigated the temperature coefficient for the duration of life for the hydranth of a tubularian, found the temperature coefficient to be of the order of a chemical reaction. The observations of Gudernatsch[8] that the duration of the tadpole stage can be controlled by thyroid feeding, and of Morse[9] that the same results may be obtained by feeding iodized amino-acids, add further support to the theory that a chemical substance may control the duration of life.[10]

Jacques Loeb started in 1908[11] an investigation on the temperature coefficient of the duration of life and the cause of natural death which was continued by him in collaboration with Northrop[12] on aseptic cultures of *Drosophila.* In these organisms all accidental causes of death were avoided and it could be shown that there is a temperature coefficient for the duration of life of these organisms which is of the order of magnitude of that of a chemical reaction. The duration of life of the aseptic flies of *Drosophila* was trebled when the temperature was lowered by 10°C. The authors arrived at the conclusion that the duration of life of organisms is the time required to complete a chemical reaction or a series of chemical reactions, resulting either in the production of toxic substances in sufficient

[6] Carrel, A., and Burrows, M. T., *Compt. rend. Soc. biol.*, 1910, lxix, 293, 298, 299, 328, 365; *J. Exp. Med.*, 1911, xiii, 387; 1911, xiv, 244. Carrel, A., *J. Exp. Zool.*, 1911, x, 63; *J. Exp. Med.*, 1911, xiii, 416; 1912, xv, 393, 516; 1913, xvii, 14; 1913, xviii, 287.

[7] Moore, A. R., *Arch. Entwcklngsmechn. Organ.*, 1910, xxix, 287.

[8] Gudernatsch, J. F., *Zentr. Physiol.*, 1912, xxvi, 323; *Arch. Entwcklngsmechn. Organ.*, 1912–13, xxxv, 457; *Am. J. Anat.*, 1913–14, xv, 431.

[9] Morse, M., *J. Biol. Chem.*, 1914, xix, 421.

[10] *Cf.* also the recent interesting discussion on Amphibian metamorphosis, by Huxley, J., *J. Hered.*, 1922, xiii, 349; 1923, xiv, 3.

[11] Loeb, J., *Arch. ges. Physiol.*, 1908, cxxiv, 411.

[12] Loeb, J., and Northrop, J. H., *Proc. Nat. Acad. Sc.*, 1917, iii, 382; *J. Biol. Chem.*, 1917, xxxii, 103. Loeb, J., *Scient. Month.*, 1919, ix, 578.

quantity to make us grow old and ultimately kill us, or in the destruction of some needful substance, or both. The idea of Metchnikoff[13] that these substances are produced by bacteria in the intestine does not hold for these experiments, since the flies used were free from microorganisms.

Finally the latest support of Loeb's theory of senescence is furnished by the observations of Carrel and Ebeling[14] that blood serum from a young animal is a better nutrient medium for growth of tissues *in vitro* than serum from an older animal; and that diluting the serum from the old animal, that is decreasing the concentration of the hypothetical toxic substance or substances, improves it as a medium for the growth of the tissues *in vitro*.

Assuming the above conclusion, that senescence and death are due to the accumulation of a toxic substance or substances in the body represents the fact, then the most important problem relating to senescence is to determine the properties and manner of formation of this substance or of these substances.

An indirect method often employed by physical chemists and biologists in studies on the manner of formation and of the properties of a substance or substances limiting a process is to determine the kinetics, or time relations, of the process. This method has, for example, been found useful in the study of radioactive substances;[15] in the study of injury, recovery, and death of plant tissues;[16] and in the study of growth of plants and animals.[1] It may be that a knowledge of the kinetics of senescence will likewise prove useful in getting an insight into the process of senescence, and getting an idea concerning the nature of the agencies limiting the process of senescence. Thus, if the course of senescence is found to follow the course of chemical reactions *in vitro*, it may be considered to substantiate the theory that senescence is a physicochemical process limited by physicochemical agencies.

[13] Metchnikoff, E., The prolongation of life, New York, 1908.

[14] Carrel, A., and Ebeling, A. H., *J. Exp. Med.*, 1921, xxxiv, 599.

[15] *Cf.* Rutherford, E., Radioactive substances and their radiations, Cambridge, 1913.

[16] Osterhout, W. J. V., Injury, recovery, and death, in their relation to conductivity and permeability, Monographs on experimental biology, Philadelphia and London, 1922.

Data on the course of senescence, and their analyses from this physicochemical standpoint have already been presented as regards the factors limiting milk production with age in the dairy cow[17] and the factors limiting egg production with age in the domestic fowl.[18] It was shown that the decline in the speed of egg production with age in the domestic fowl may be represented by the same exponential relation which is used to represent the decline in the speed of a monomolecular chemical reaction with time

$$Y = Ae^{-kt} \tag{1}$$

in which Y represents the number of eggs laid per year, which is taken as an index of vitality, or reciprocal of senescence, of the fowl at the age, t. This equation is taken to represent the course of decline of vitality with age when not complicated by growth because the domestic fowl is thought to be sexually mature during her first laying year.

The case of change of milk production with age in the dairy cow[17] is somewhat different; milk secretion begins at about 2 years of age, while the cow does not reach full body weight until 8 or 9 years. Milk production at any age, is therefore taken to represent the resultant of two processes, growth and senescence. The speed of growth of the dairy cow after the age of 2 years was found to decline exponentially with age as represented by equation (1)[19] which, as pointed out, also represents the decline in vitality with age in the domestic fowl. It therefore appears that growth and senescence both follow the same exponential law—the law of monomolecular change in chemistry; and that the two processes are simultaneous and consecutive. It was in fact found[17] that the course of milk production with age in the dairy cow can be represented by the equation of two simultaneous consecutive reactions

[17] Brody, S., Ragsdale, A. C., and Turner, C. W., *J. Gen. Physiol.*, 1923–24, vi, 31.

[18] Brody, S., Henderson, E. W., and Kempster, H. L., *J. Gen. Physiol.*, 1923–24, vi, 41.

[19] Brody, S., Ragsdale, A. C., and Turner, C. W., *J. Gen. Physiol.*, 1922–23, v, 445.

$$Y = Ae^{-k_1 t} - Be^{-k_2 t} \qquad (2)$$

in which Y is the milk production which is taken as an index of vitality at the age, t. The first term on the right side of the equation represents the course of decline of milk secretion with age due to the process of senescence; the second term represents the declining increase in vitality with age due to the process of growth. If the above premises and reasoning are correct, then equations (1) and (2) should represent respectively the course of vitality (reciprocal of senescence) when not complicated by growth, and vitality when complicated by growth. It is the purpose of this communication to test this idea by attempting to fit equations (1) and (2) to certain published data which are thought to indicate the course of vitality or senescence with age.

The most interesting data on the course of vitality with age are those obtained by Carrel and Ebeling[14] on the rate of growth, and the duration of life of fibroblasts cultivated *in vitro*, using plasma from the domestic fowl as a culture medium. They found that there was a definite relation between the age of the animal and the amount of new tissue produced in its plasma in a given time. The duration of life of the fibroblasts decreased in a similar way with the age of the fowl from which the plasma was used. While only a few experiments have been made, which may turn out to be statistically insufficient for drawing conclusions concerning the significance of the agreement between computed values as obtained from equation (1) and observed values, nevertheless, because of the importance of these data, it seemed worth while to attempt to roughly determine the mathematical relation connecting the duration of life of the fibroblasts *in vitro* and the decline in ovulation, with the age of the fowl from which plasma was used as a culture medium. Such a comparison was made, and it is shown in Fig. 1. In Fig. 1 it is seen that the course of duration of life of fibroblasts with age and also the course of ovulation with age follow the same course as represented by equation (1).

As pointed out in the same paper by Carrel and Ebeling[14] the relation between the age of an animal and the speed of healing of its wound is probably closely allied to the effect of age of the animal

from which the plasma is used as a culture medium, on the speed of growth of the fibroblasts. Both phenomena are probably ultimately dependent on the condition of the blood. Fig. 1 also shows that the curve of healing of a wound 40 sq. cm. in area as interpolated from Text-fig. 1 of the paper by du Noüy[20] also follows the course represented by equation (1).

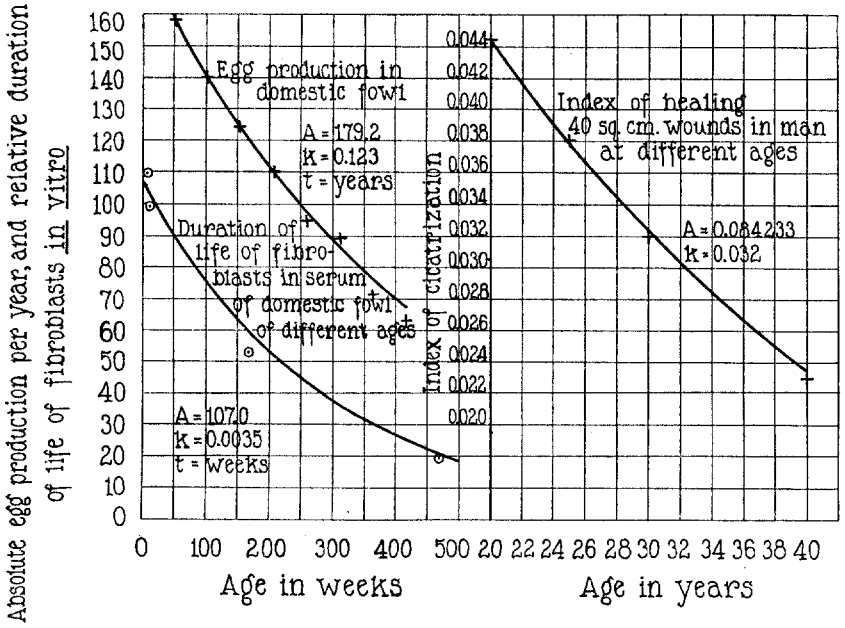

FIG. 1. The effect of age on the vitality of the domestic fowl as measured by the duration of life of fibroblasts in its serum and by its egg production; also the vitality of man as measured by the rate of healing of 40 sq. cm. wounds at different ages. The crosses and circles are the observed values; the curves represent the equation

$$y = Ae^{-kt}$$

The values A and k are indicated near the curves, the source of data is given in the text.

In addition to these data obtained under conditions which are more or less under control there are available statistical data which

[20] du Noüy, P. L., *J. Exp. Med.*, 1916, xxiv, 463.

seem suitable for measuring the course of senescence. The mortality data on man are of course the largest body of this type of data. It seems reasonable to assume, that other conditions being the same, the greater the degree of senescence, the greater would be the chances of breaking down of some vital organ-system due to a given unfavorable exposure. The course of mortality under such conditions should therefore form an index of the course of senescence. All other conditions are not, however, the same throughout life. Many types of mortality such as those due to occupational accidents and diseases; to the maternal state; to infectious diseases, as tuberculosis, which act selectively during the earlier years for reasons other than senescence, are of course independent of senescence as such. On the other hand there are types of mortality due to the breaking down of organ-systems subjected to approximately uniform environmental conditions throughout life and which seem to be closely associated with the degree of senescence. As examples of these latter types of mortality may be mentioned mortality due to cerebral hemorrhage and apoplexy; to diseases of the arteries; to Bright's disease; to cancer; and to certain infectious diseases to which the exposure is approximately the same throughout life, which do not develop an immunity, and which do not act cumulatively; for example, pneumonia. Of course the important factor of heredity must be left out in a study of statistical data on man. In spite of leaving out the factor of heredity and of other obvious defects of the data, the course of mortality due to these diseases follows rather closely an exponential course with age as shown in Fig. 2. The straightness of the mortality curves on this semilogarithmic paper indicates that the speed of mortality changes in geometrical progression with age which is the fact represented by equation (1).

The curves in Fig. 2 represent the specific mortality data only after about 15 years of age. Up to this age, the specific mortality decreases, which decrease is thought to be principally due to increasing vitality; for experience shows that the same child can withstand less favorable conditions at the age of 10 to 15 years than it could when it was younger, for example, between birth and 1 year of age. The whole life curve of vitality as measured by the reciprocal of mor-

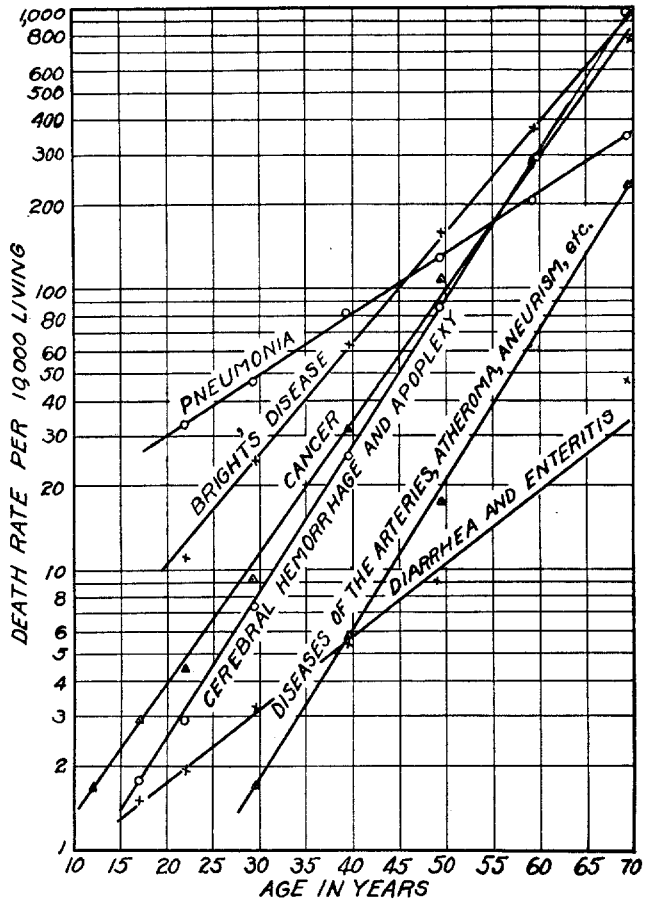

FIG. 2. The effect of age on the degree of senescence in man as measured by the specific death rates between 15 and 70 years. The data represent deaths per 10,000 persons exposed at the given ages which are based on the general male population of the United States Registration Area 1910–15 as given by Dublin and coworkers.[21] The straightness of the curves on this semilogarithmic paper shows that the course of mortality with age follows an exponential law. (From the curves, the mortalities due to cancer, to cerebral hemorrhage and apoplexy, and to diseases of the arteries, atheroma, aneurism, etc., are doubled about every 6 years; mortality due to Bright's disease is doubled about every 8 years; mortality due to enteritis and pneumonia are doubled, respectively, about every 12 and 14 years.)

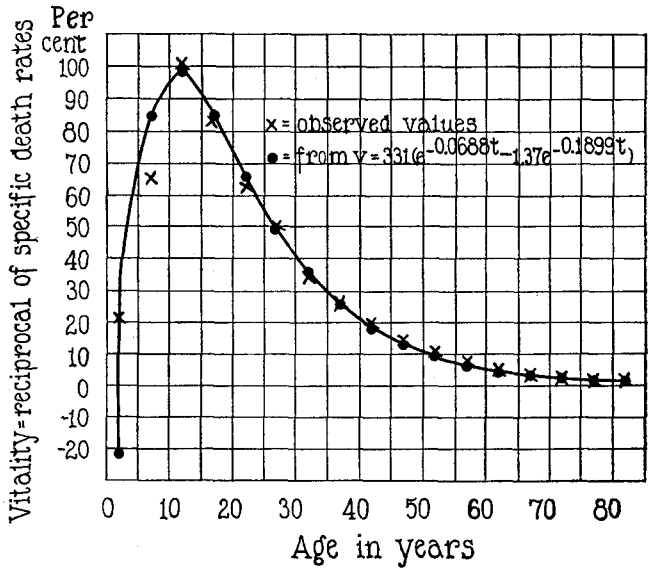

FIG. 3. The rising and declining course of vitality with age as measured by the reciprocals of specific death rates due to the breaking down of the nervous system and sense organs expressed in terms of percentage of maximum vitality. The values for vitality which are based on the mortality in the United States Registration Area exclusive of North Carolina in 1910 were computed from Group VII of Pearl's classification.. The original data are given in Table IX in Pearl's monograph,[1] × = observed values; ● = computed from $v = 331\ (e^{-0.0688t} - 1.37e^{-0.1899t})$.

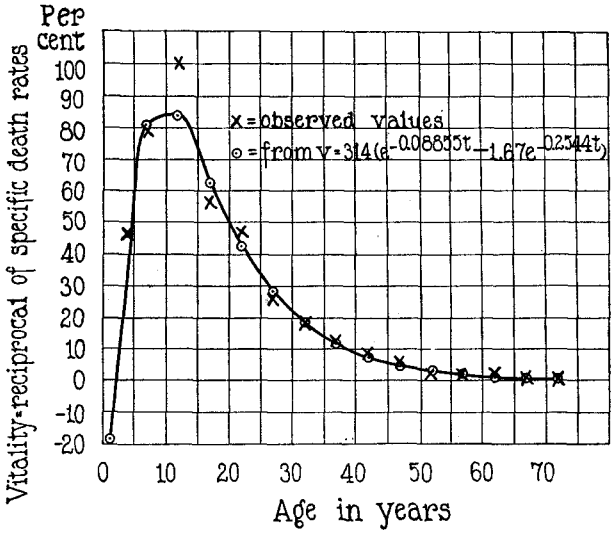

FIG. 4. The rising and declining course of vitality with age as measured by the reciprocals of specific death rates due to the breaking down of the kidney and related excretory organs (Group IV of Pearl's classification). For source of data see legend, Fig. 3. × = observed values; ⊙ = $v = 314\ (e^{-0.08855t} - 1.67e^{-0.2544t})$.

tality therefore follows a rising and falling course. This rising and falling course may in many cases be represented by equation (2). As has been pointed out, equation (2) represents the course of two simultaneous consecutive monomolecular chemical reactions, and that this equation was found to satisfactorily represent the course of milk secretion with age in the dairy cow.[17] The agreement between observed and computed values as shown in Figs. 3, 4, and 5 is only

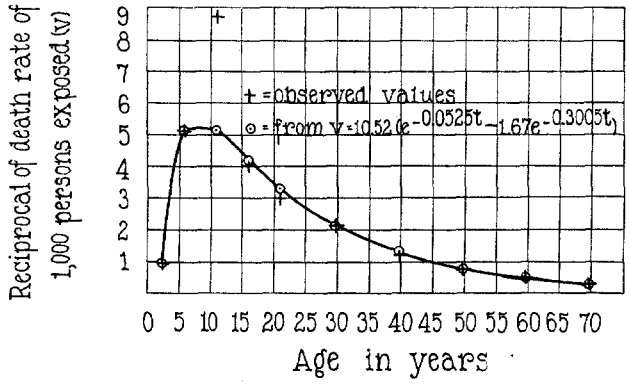

FIG. 5. The rising and declining course of vitality with age as measured by the reciprocals of specific death rates due to pneumonia computed from the general population experience (male) of expanding United States Registration Area 1910–15 as given by Dublin.[21]

approximate for reasons explained in a preceding communication,[17] and because of other disturbing elements ordinarily associated with infant and child mortality, as for example, mortality due to selective action on the weaker infants, the excessive mortality due to certain unfavorable environmental conditions prevalent among certain classes of the population which are especially dangerous during infancy;[22] and to mortality probably due to the undeveloped defensive or immune mechanism resulting in high mortality of the so called children's diseases.

[21] Dublin, L. I., Mortality statistics of insured wage earners and their families, New York, 1919.

[22] *Cf.* Rochester, A., Infant mortality results of a field study in Baltimore, Md. Based on births in one year, *U. S. Dept. Labor, Children's Bureau, Pub. No. 119*, 1923. *Cf.* also Holmes, S. J., and Goff, J. C., Eugenics in race and state, *2nd Internat. Cong. Eugenics, 1921*, 1923, ii, 233.

In addition to mortality data on man, data are available on the mortality of *Drosophila*. The life tables for *Drosophila* recently published by Pearl and Parker[23] while based on a relatively small population as compared to the mortality data on man are, nevertheless, even more valuable from the standpoint under consideration than the data on man because of the uniform and favorable condi-

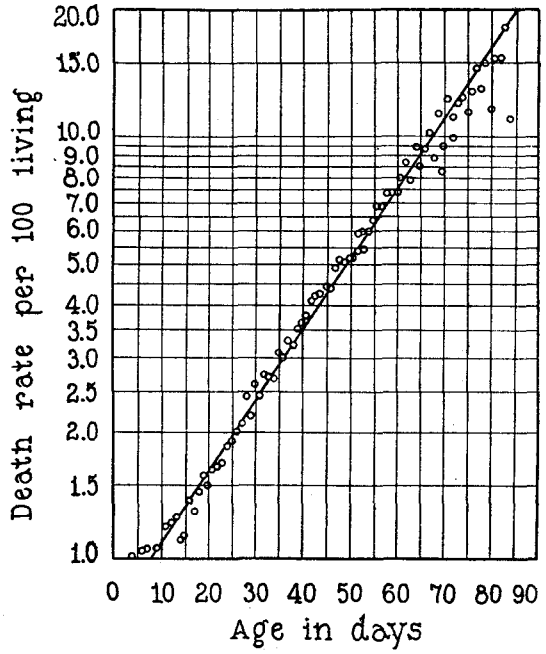

FIG. 6. The effect of age on the degree of senescence in *Drosophila* as measured by the specific death rates. The data represent the mortality of females computed (by the method explained in the text) from Table III of the paper by Pearl and Parker.[23] The straightness of the curve on this semilogarithmic paper shows that the curve of mortality with age follows an exponential law. (The mortality is doubled about every 18 days.)

tions under which the animals were kept throughout life, and because of the homogeneity of the population. The specific mortalities for *Drosophila* were obtained by dividing the number of deaths during each day as given in Table III of the paper by Pearl and Parker[23]

[23] Pearl, R., and Parker, S. L., *Am. Naturalist*, 1921, lv, 481.

by the number living at the beginning of the day interval. The results shown in Fig. 6 are seen to follow an exponential course as represented by equation (1). The deviations of the observed values from the straight line during the first few days is probably due to the increase in vitality as explained in the preceding paragraph.

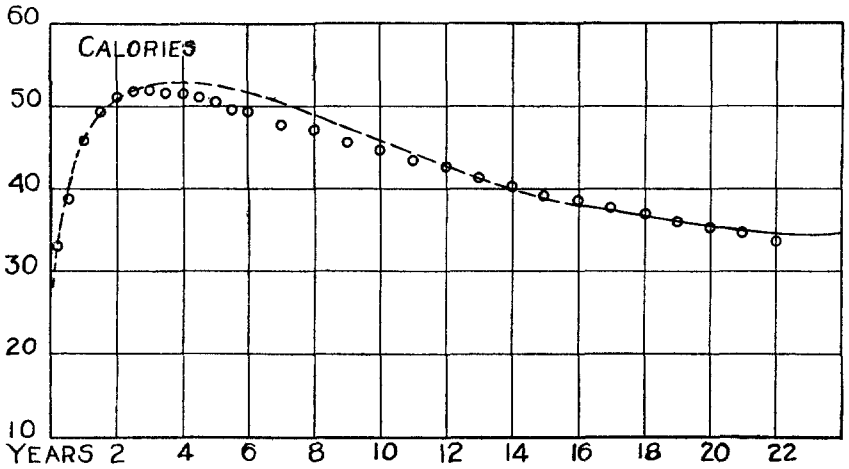

FIG. 7. "Variation of basal metabolism with age; calories per hour per square meter of body surface—Meeh's formula. Dash line shows average for males." Figure traced and legend quoted from Chart 2 of paper by Du Bois.[24] The circles represent the equations

$$y = 56.7e^{-0.024t} - 32e^{-1.224t}$$

if intrauterine period of growth is not considered;

$$y = 57.8e^{-0.024(t+0.78)} - 83e^{-1.224(t+0.78)}$$

if the intrauterine period of growth is considered, and if it is assumed that the duration of the intrauterine period of growth is 0.78 year.

An interesting if less satisfactory set of data from a statistical point of view is that published by Du Bois[24] on the course of basal metabolism with age expressed in terms of calories per square meter of body surface as determined by Meeh's formula. The agreement between observed and computed values as shown in Fig. 7 appears to be satisfactory considering the paucity of the data and the magnitude of experimental errors involved in the data.

[24] Du Bois, E. F., *Arch. Int. Med.*, 1916, xvii, 887.

SUMMARY.

The course of decline of vitality with age due to the process of senescence, when not complicated by the process of growth, follows a simple exponential law; that is the degree of vitality or of senescence (defining vitality as the reciprocal of senescence) at any moment is, regardless of age, a constant percentage of the degree of vitality or senescence of the preceding moment. This exponential law is the same as the law of monomolecular change in chemistry.

During the actively growing period of life the index of vitality rises, due to the process of growth and the course of vitality in the case when the growing period is included in the vitality curve, follows a rising and falling course. This rising and falling course may often be represented by an equation containing two exponential terms which is practically the equation used to represent the course of accumulation and disappearance of a substance as the result of two simultaneous consecutive monomolecular chemical reactions.