# SOME PHYSIOLOGICAL ASPECTS OF AGING IN MAN*

*The Wesley M. Carpenter Lecture*†

N. W. SHOCK, Ph.D.

Chief, Section on Gerontology, National Heart Institute, National Institutes of Health, P.H.S., D.H.E. & W., Bethesda, Maryland and the Baltimore City Hospitals, Baltimore, Maryland

ALTHOUGH a precise definition of aging may offer semantic difficulties, it is a concept which all individuals recognize, particularly those who have attained the age of 50. Aging is a biological phenomenon which is common to all living organisms, and hence is a proper topic for investigations in comparative physiology. This evening's lecture will, however, be concerned with a discussion of the physiological aspects of aging in man. Since aging is a process which directly concerns all of us, we are interested primarily in a description of what happens to people with the passage of time. We all know that, with the passage of time, the incidence of disease increases and the probability of dying within the next year or five years is enhanced. This latter fact is illustrated graphically in Figure 1, A and B where the logarithm of the mortality rate is plotted against age. It may be seen that after the age of 40 or 50 years the plots are essentially straight lines with a constant slope.[1] Comparison of the curves for India, where mortality rates are high, with those of the United States,[2] indicates two major points: (a) the slopes of the curves are strikingly similar, and (b) the curve for the United States is displaced to the right. Thus, a given rate of mortality was attained in India at ages approximately 15 years younger than in the United States. Figure 1 B shows a similar relationship for mortality rates in the United States in 1900 as compared with 1950.[3] Here the displacement is approximately five years. These curves serve to illustrate the biological aspects of aging. The fundamental biological problem is to determine the factors that influence the slope of the curves—to find out why there is a systematic increase in the probability of death with increasing age. Changes in position of the mortality

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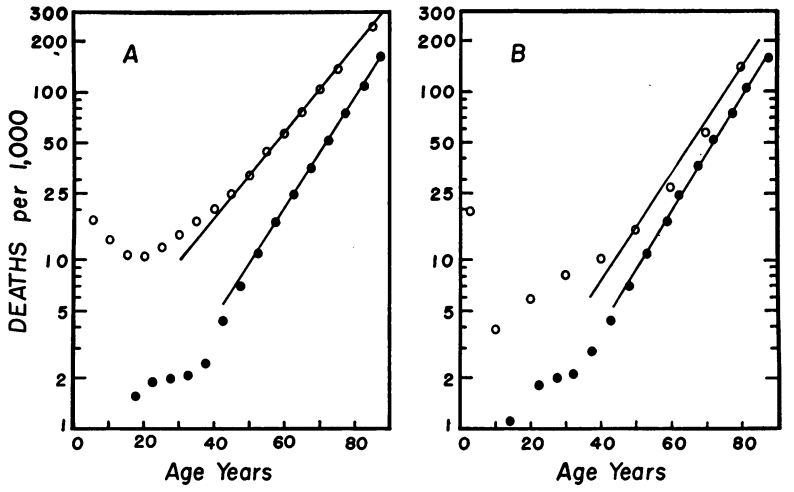


Figure 1—Log total mortality rates plotted against age. A. Comparison of mortality rates for India o—o and the United States •—•[2]. B. Improvement in mortality rates in the United States between 1900 o—o and 1951 •—•[3]. There is a displacement of the curves to the right, with little change in the slopes of the linear part of the curves.

curves, that is, the displacement of the curves toward the right, are influenced by environmental factors such as improved hygiene and the reduction in disease incidence. Consequently, part of the problem of aging is closely associated with the prevention of diseases such as cardiovascular diseases, cancer, arthritis and mental disease. Therefore, to consider aging of man in the "absence of disease" is an abstraction which has little possibility of full attainment. Research on the problems of cardiovascular diseases, cancer, etc. have a direct bearing on problems of aging. However, for the discussion this evening, we shall be concerned primarily with the description of changes which occur in the absence of diagnosable disease states; e.g., changes which at least at the present moment are not regarded as disease. It is well recognized that age changes as identified today may represent states of early pathology and, with a sharpening of diagnostic procedures in the future, many of the observed characteristics may prove to be the early stages of disease. For my own part, I regard aging as the changes which take place in the organism with the passage of time. Consideration of Figure 1 leads to another important generalization, namely, that the probability of death at any age is influenced by what has happened to an individual earlier in life. Thus, studies on aging must take into account the entire

life span, including the periods of growth and development if we are to understand the aging process. Ideally, we should be able to collect observations on the same individual throughout his life span. Practically, we are as yet unwilling to support long term studies of this kind. Hence, we must do what we can to describe the characteristics of different individuals who have reached different points on the curve of mortality. If we could choose sufficient numbers of subjects randomly from the population, it would be unnecessary to exclude subjects with specific disease states. However, most studies must be carried out on already selected populations where the probability of the occurrence of disease is greater than in the general population. Hence, it is desirable to exclude from aging studies those individuals where disease can be identified.

Theories about the nature of aging have existed since our earliest records of history. Unlike other fields of science where a steady progression from a large number of speculative to one or two highly probable main hypotheses may be found, theories of aging can only be catalogued. These theories fall into two major groups: (a) those which regard aging as an inherent property of living matter, and (b) those which attempt to relate aging to impairments in specific physiological systems, of which the gonads have been most popular. Even now, we do not have enough information to choose between the hypothesis that aging is a biological phenomenon inherent in all animals which proceeds even in the absence of disease, or whether aging and death occur only as the accumulation of pathological processes. In the case of the human, the evidence is fairly clear that a good many years of longevity could be added to the human simply by reducing and minimizing the effects of disease. If there is a fundamental biological process which limits life span, surely few, if any, humans have ever approached this ceiling.

Our approach to the problem of aging has been to describe, as quantitatively as possible, changes in physiological functions in individuals who are free from clinical symptomatology of a disease state which would influence the organ system under study. Although the data presented may not meet the rigorous criteria of studies on aging, the data are descriptive of aging people. Furthermore, since we regard aging as a process, it is obvious that we must examine not only older people but also study individuals distributed over the entire life span.

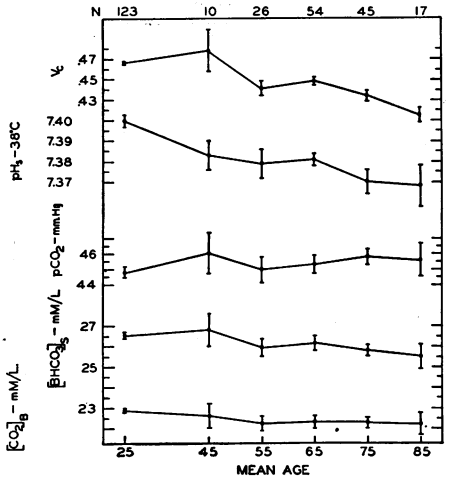


Figure 2—Trends in the acid-base equilibrium of the blood of males with increasing age. Average curves from top to bottom include per cent red cells, serum pH at 38 C., carbon dioxide tension expressed in millimeters of mercury, serum bicarbonate, and blood carbon dioxide content both expressed in millimoles per liter. The vertical lines indicate ± 1 standard error of the mean. From Shock and Yiengst[4] in *J. Gerontology* 5:1-4, 1950. Reprinted by permission.

Thus, in all of our studies, we have attempted to include, within the population tested, individuals ranging from ages 20 to 90.

All of the data, which I shall present tonight, have been taken from studies carried out in the laboratories of the Section on Gerontology. In these studies, we have had, over the past several years, the collaboration of Drs. Luther E. Smith, J. E. Cohn, Dean F. Davies, John H. Miller, David H. Solomon, Leroy E. Duncan, Roger K. McDonald, Morton D. Bogdonoff, Martin Brandfonbrener, Donald M. Watkin, Milton Landowne and Mr. Marvin J. Yiengst. Without the active collaboration and day-to-day operations of experiments by these investigators, this presentation would have been impossible.

Although it is commonly assumed that all physiological processes go down hill as we grow older, our laboratory investigations have shown that this is not always the case. For example, we have found that the regulation of the acid-base equilibrium of the blood does not change systematically with age.[4] Figure 2 shows the average values in 152 men distributed between the ages of 45 and 90 years, compared

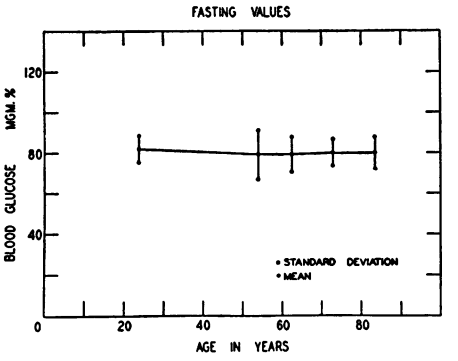


Figure 3—Average fasting glucose level in arterial blood of males. Vertical line indicates ± 1 standard error of the mean. Data from Smith and Shock.[6]

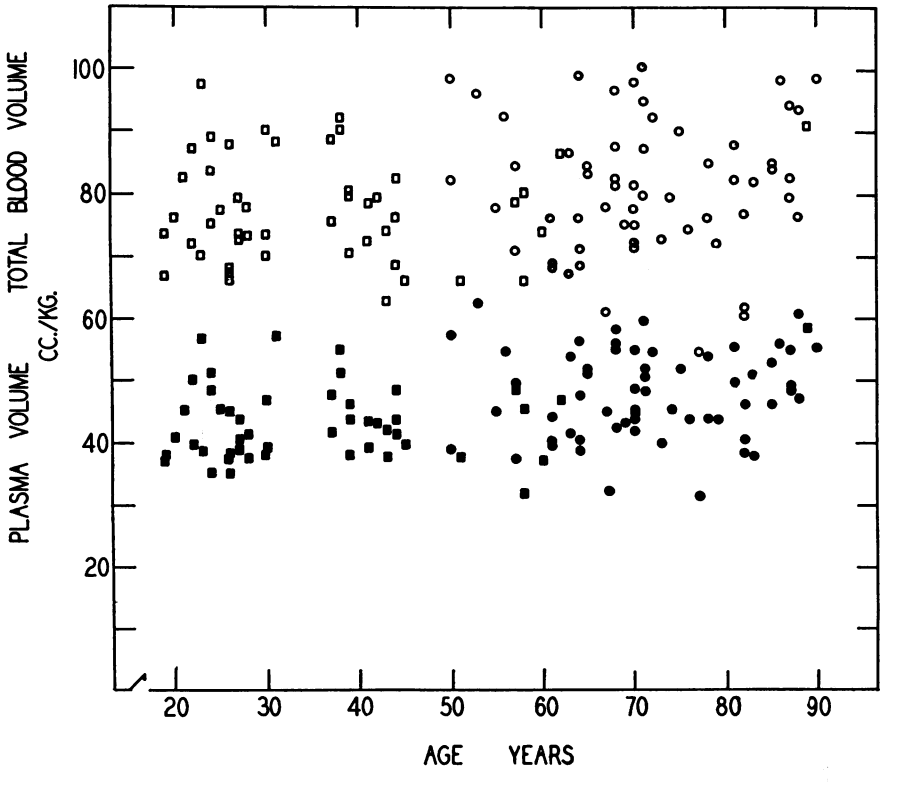


Figure 4—Total blood volumes, cc. per kg. and plasma volumes, cc. per kg. in 105 males. □ total blood volume determinations from Gibson and Evans[9]; ■ plasma volume (Gibson and Evans[9]); o total blood volume; ● plasma volume. From Cohn and Shock.[8] *Amer. J. med. Sci. 217*:388-91, 1949. Reprinted by permission of the publisher, Lea & Febiger.

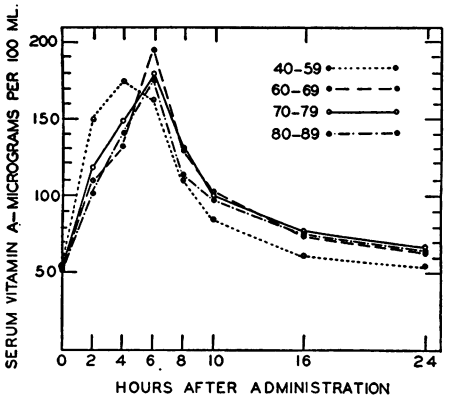


Figure 5—Vitamin A plasma levels in males of 4 age groups following oral administration of 100,000 units of vitamin A.

o - - - - o 13 subjects aged 40-59 years;
o — — o 15 subjects aged 60-69 years;
o ——— o 15 subjects aged 70-79 years;
o — - - — o 15 subjects aged 80-89 years.

From Yiengst and Shock,[10] in *J. Gerontology* 4:205-11, 1949. Reprinted by permission.

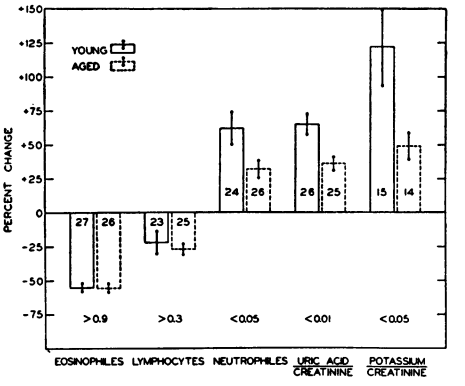


Figure 6—The responses of young and aged men to the intramuscular administration of 18 mg. of ACTH. The ordinate represents the per cent change from basal value during the four hours after ACTH administration. The bar ending each column indicates the mean; the circles indicate the standard error of the mean. The number of cases analyzed is shown within the columns. The probability of the chance occurrence of the observed difference is shown below each pair of columns. From Solomon and Shock,[11] in *J. Gerontology* 5:302-13, 1950. Reprinted by permission.

with observations on 123 students.[5] There is a slight diminution in the average pH of the blood in the older subjects, but the bicarbonate content and $CO_2$ tension of the plasma are maintained within normal limits. Thus, under resting conditions, the mechanisms available for regulation of acid-base balance are apparently adequate for the task, even in the 90 year old man.

Similarly, the fasting arterial blood sugar level is apparently unaffected by age,[6] as shown in Figure 3. There is, however, some evidence that venous blood sugar levels are slightly increased in the older subjects.[7] Estimates of blood volume, using the Evans-blue dye technique, have been made in 60 carefully selected subjects with results as shown in Figure 4.[8] Thus, elderly individuals, who are free from any clinical signs of fluid accumulation or edema, have approximately the same blood volume per unit of body weight as the young subjects studied by Gibson and Evans.[9]

In Figure 5, a comparison of the changes in blood vitamin A level, following the oral administration of 100,000 units of vitamin A, is

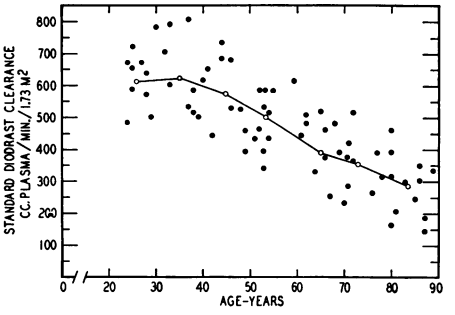


Figure 7—Change in standard diodrast clearance or effective renal plasma flow with age in males. o——o average values cc. plasma/min./1.73 sq. M. body surface area. From Shock,[13] in *Cowdry's problems of ageing,* 3.ed. (A. L. Lansing, ed.). Reprinted by permission of the publisher, The Williams & Wilkins Company.

shown for 126 males between the ages of 40 and 90 years.[10] Examination of this figure shows that, with the exception of an earlier peak response in 40 to 50 year old age groups, along with a somewhat more rapid return to resting values, there is little evidence for any significant differences between the older subjects and the 60 year old group. Thus, age does not seem to be an important factor in determining the absorption of vitamin A.

The eosinophile response to the intramuscular administration of ACTH was not significantly different between our young and old subjects (Figure 6).[11] Significant age changes were observed in the excretory measurements, i.e., the uric acid/creatinine and potassium/creatinine ratios in the urine were lower in the old than the young subjects. In view of the reduced renal function in older people which we have observed,[12, 13] it does not seem safe to ascribe the alterations in excretion to the responsiveness of the adrenal cortex to ACTH. In a number of extensive metabolic balance experiments, we have measured the ability of elderly males to retain nitrogen when placed on augmented protein intake.[14-17] In all of the experiments, we have found that the older individual is just as able to retain nitrogen as the young when offered increased amounts of protein in the diet. Thus, we have a whole array of physiological processes which show similarities, rather than differences, between the old and the young. These results show that, where a number of regulatory systems are involved, equilibrium

may be maintained in the old subjects as well as in the young. This is particularly true when subjects are tested under basal or resting conditions. When a physiological stress is placed upon the organism, the older individual usually shows a greater physiological response and a slower rate of return to basal or resting levels.

There are, however, a number of physiological functions which show definite age differences even under basal or resting conditions. For example, there is a progressive diminution in renal plasma flow with increasing age.[12, 13] Figure 7 shows a scatter plot of values obtained in a series of carefully selected subjects. No subjects with clinical evidence or history of renal disease were included in the series. Subjects were also excluded if they had a blood pressure greater than 140/90. Thus, the changes in plasma flow, as indicated in the figure, represent changes that at least, at the present, can not be regarded as evidence of renal disease. It is important to note, first of all, the wide individual differences, and secondly, the gradual decrement in the mean values beginning at the age of 30 to 40. It may be seen that some of the 80 year old subjects had renal plasma flows as large as the mean value of the 40 year old group. The wide individual differences observed in renal function are equally true in the case of other measurements we have performed. A similar reduction in glomerular filtration rate, as well as the maximum rate of excretion of diodrast, and the maximum rate of reabsorption of glucose, has been found. In fact, the average decrement in all of these functions is percentage-wise about the same; i.e., the reduction is uniform in all of these functions at a rate of approximately 6 per cent per decade. In order to determine whether the vascular bed in the kidney of the aged had lost its functional capacity to respond to physiological stimuli, a series of experiments was carried out on which renal function was measured during the administration of a vasodilator.[18] In these experiments, renal vasodilatation was induced by the injection of 50,000,000 killed typhoid organisms (0.05 cc. TAB vaccine). Results of these experiments are plotted as average curves for the young, middle and old subjects in Figure 8. Following the administration of the renal vasodilator, a gradual increase in renal blood flow was observed in all age groups. On a percentage basis, the increase in flow was as great in the old as in the young subjects. The reduction in filtration fraction, which is apparent for all three age groups, is evidence that the renal vasculature in the old subjects was

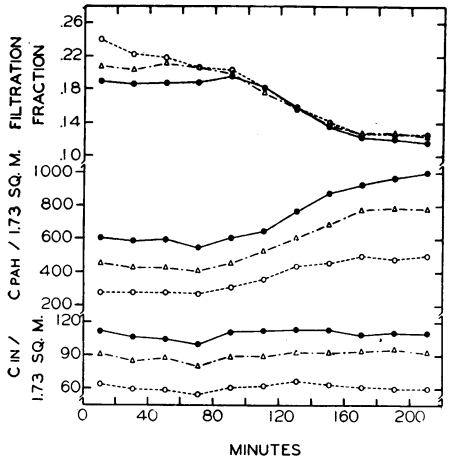


Figure 8—Changes in Cin, Cpah, and FF during pyrogen reaction. Fifty million killed typhoid organisms were injected intravenously at o time — male subjects.

o——o mean value for 14 subjects in O group (70-85 yrs.)

Δ-----Δ mean value for 20 subjects in M group (50-69 yrs.)

•———• mean value for 20 subjects in Y group (20-49 yrs.)

From McDonald, Solomon and Shock,[18] in *J. clin. Investigation, 30*:457-62, 1951. Reprinted by permission.

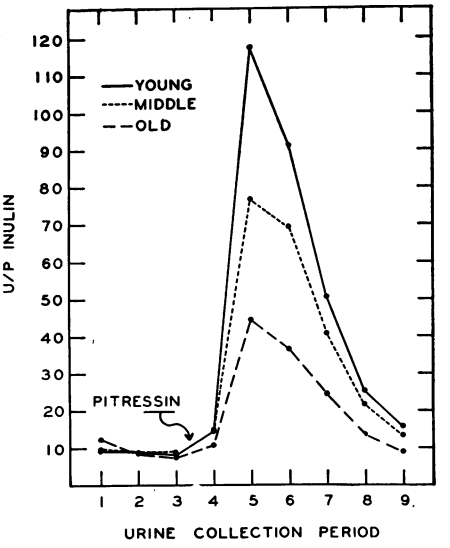


Figure 9—Mean values of U/P inulin ratio for each of 3 age groups before and after the intravenous administration of pitressin. Urine collection periods 1-9 represent 9 consecutive twelve minute periods. Pitressin was administered immediately after the conclusion of period 3. Inhibition of water diuresis is indicated by a rise in U/P inulin ratio. From Miller and Shock,[19] in *J. Gerontology, 8*:446-50, 1953. Reprinted by permission.

capable of responding to the physiological stimulus since this response is not related to the number of functioning nephrons present in the kidney.

Other experiments have shown that with increasing age there is a progressive loss in the ability of the renal tubular cell to perform osmotic work.[19] In these experiments, carefully selected subjects were hydrated and infused with a solution of inulin to permit the estimation of the glomerular filtration rate. Since this substance is filtered at the glomerulus and passes without reabsorption down the tubule, calculation of the ratio of inulin in the urine to that in the plasma offers a measure of water excretion or absorption. After a series of control observations, pitressin (.5 milliunits/kilogram body weight) was administered intravenously. Figure 9 illustrates the average results for groups of young, age 24 to 45; middle aged 46 to 65, and old, 66 to 86

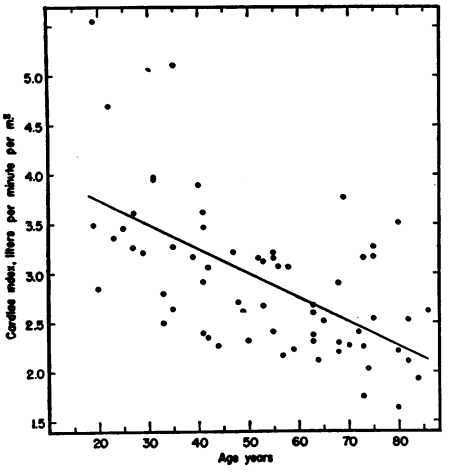


Figure 10—The relation between basal cardiac index and age in 67 males without circulatory disorder. Each point represents the average of 2 measurements in 49 subjects, of 3 measurements in 4 subjects, and a single measurement in 14 subjects. The line indicates the simple linear regression for the data. From Brandfonbrener, Landowne and Shock,[20] in *Circulation, 12*:557-76, 1955. Reprinted by permission of the publisher, Grune & Stratton, Inc.

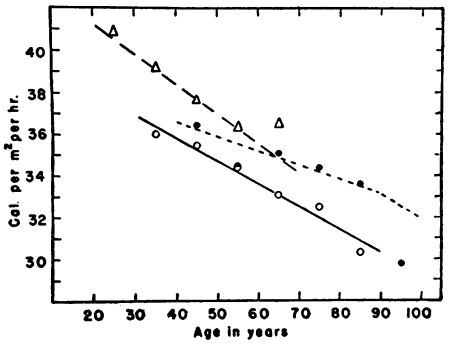


Figure 11—Linear regression of basal heat production of males on age. Mean values by decades are shown as individual points.

Δ——Δ data of Boothby, Berkson and Dunn[21];

• - - - - • data of Lewis[22];

o——o composite values for subjects (age 30-90).

From Shock and Yiengst,[23] in *J. Gerontology, 10*:31-40, 1955. Reprinted by permission.

years. Although the urine flow during the control periods was slightly less in the older group, there was no significant age difference in the U/P inulin ratios. Following the administration of pitressin, prompt antidiuresis was noted in all three groups as evidenced by a rise in the U/P inulin ratio. It may be seen that the young subjects responded with a marked inhibition of the diuresis when pitressin was administered, in contrast to the aged group where the effect, though present, was greatly diminished in extent.

Using the dye injection technique, we have also been able to demonstrate a significant diminution in the resting cardiac output with increasing age.[20] Subjects for these experiments were carefully screened to exclude any individuals with clinical signs of heart disease. Figure 10 shows the overall change in cardiac output with increasing age. Although a part of the diminution in output can be ascribed to a slight reduction in heart rate with age, and a small proportion can be attributed to a reduction in body size, there remains a significant reduction in stroke index with increasing age.

The gradual fall in basal heat production, per square meter of surface area over the age span of 20 to 60 years, reported by Boothby, Berkson and Dunn,[21] has been projected in setting standards for metabolism at higher ages. However, when older subjects were studied by Lewis,[22] the rate of fall in BMR with increasing age was somewhat less than that predicted from the earlier data. We have determined basal metabolism in 152 males between the ages of 40 and 90 years.[23] The data from our studies, as well as those of Kountz, Chieffi and Kirk[24] are summarized in Figure 11. Although the calculated surface area of individuals diminishes slightly with increasing age, the basal heat production, or oxygen uptake, falls at an even greater rate so that basal metabolism per unit of surface area shows a gradual decline. The rate of decline is almost identical for studies made on residents in old peoples' homes in Baltimore and St. Louis. It is of interest that the rate of decline in basal metabolism was apparently less among the community residing subjects tested by Lewis.

On the basis of the evidence presented, we may conclude that not all physiological processes show a diminution with age, and that those which do, show gradual changes extending over the life span without evidence for any sudden changes at a given chronological age, with respect to the average. This, of course, is not to say that periods of rapid change may not occur in individuals. However, before a definitive answer can be given to this question, it is necessary to have repeated observations in the same individual over his entire life span. Such data are not available at the present time, with the exception of a few subjects who have worked in the field of metabolism and have had estimates of basal metabolism made at various periods in their life span. It is interesting that the decrement per ten year period in most of these six individuals was approximately the same as that reported in our mean curves.[25] It may also be concluded that there are wide individual differences in the physiological changes that take place with age, i.e., there are factors other than age which play a large role in influencing decrements within an individual. This is indeed a hopeful sign and one which offers opportunity for maintenance of physiological status in older people if we can identify the other factors of the environment which are producing decrements in function.

How then can these age changes be explained? On the basis of histological evidence, we know that, with increasing age, there is a reduction in the amount of active protoplasm in a good many organs.[26] Thus,

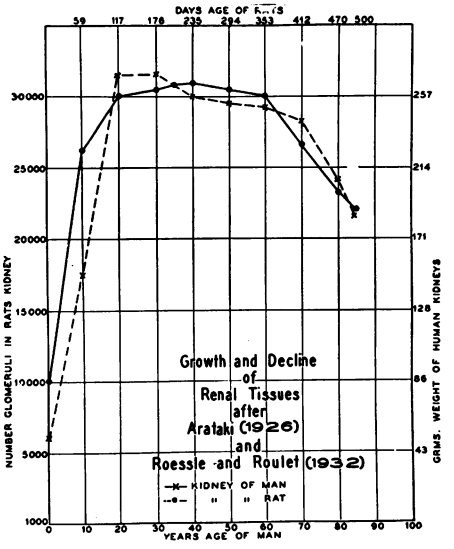


Figure 12—The growth and decline of the renal tissues after Arataki[27] and Roessle and Roulet.[28] From article by Oliver,[29] in *Cowdry's problems of ageing,* 3.ed. (ed. by A. I. Lansing). Reprinted by permission of the publisher, The Williams & Wilkins Co.

for example, the number of nephrons which could be counted in the kidney in the rat[27] and the kidney weight in man[28] show a gradual reduction with age (Figure 12).[29] Similar reductions in active protoplasm have been reported in a variety of other tissues. What we really want to know is how much of the age changes which are observed in the functional capacities of the total animal can be explained on the basis of a simple loss of tissue or protoplasm and how much must be ascribed to a reduced function in the protoplasm remaining. This question can obviously be answered only if we have some index of the amount of protoplasm in the body. Because of the increase in fat and water and other substances that replace active protoplasm as the animal ages, the use of body weight, or calculated surface area, is not an adequate index. In view of the findings of Lowry and Hastings[30] for example, that the intracellular water content of protoplasm is constant and does not change with increasing age, it is possible that the determination of the amount of intracellular fluid in the intact animal might offer a better index of the amount of protoplasm than either weight or calculated surface area. Although methods for estimating the extracellular water content in the intact animal leave much to be desired, the utilization of

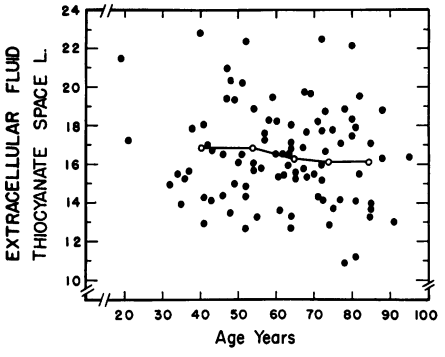


Figure 13—Relationship between extracellular fluid space (thiocyanate space) and age in males.

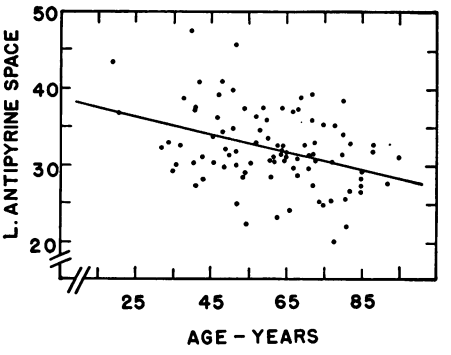


Figure 14—Age changes in total body water in males (measured by antipyrine space).

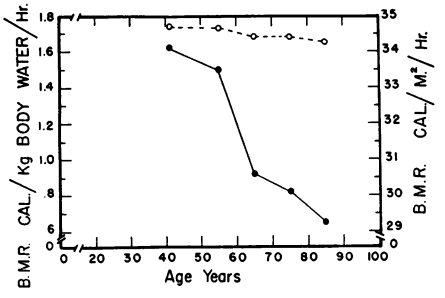


Figure 15—Age changes in basal heat production and basal oxygen consumption in males.

o - - - - o basal heat production, cal./M²/hr.

•———• basal oxygen consumption, cc. $O_2$/liter antipyrine space.

When expressed in terms of body water, the age change in basal metabolism disappears. Data from Shock.[33]

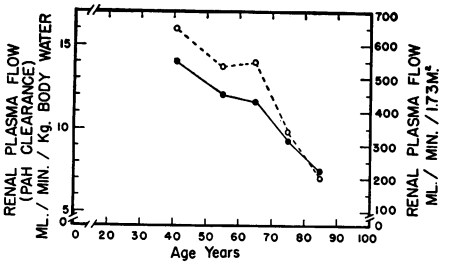


Figure 16—Renal plasma flow (cc./min.) expressed in terms of total body water (antipyrine space). The age decrement in renal function remains.

antipyrine for the determination of total body water offers some promise.[31] We have made simultaneous estimations of thiocyanate and antipyrine spaces in a series of individuals between the ages of 20 and 90 years.[32,33] In these experiments, an intravenous infusion containing 1 gram of antipyrine and 1 gram of thiocyanate ion in 50 millimeters of physiological saline was administered to each subject under basal conditions, following the withdrawal of the control blood sample. Additional bloods were drawn at ½, 1, 2, 3, 5 and 7 hours after the beginning of

the infusion. Each of the fluid spaces was calculated by estimating the concentration at zero time by extrapolating the straight line obtained when the logarithm of the concentration was plotted against time. The average values for extracellular water or thiocyanate space did not change with age (Figure 13), but there was a significant reduction in antipyrine space or total body water (Figure 14).

Since basal metabolism determinations were done on the same group of subjects on whom the fluid spaces were estimated, it was possible for us to calculate the basal oxygen uptake per kilogram of body water. When these calculations were made, it was found that the basal oxygen uptake per kilogram of body water, did not change significantly with age (Figure 15).[33] Thus, if we are willing to accept either total body water or intracellular water as an index of the amount of functioning protoplasm in the intact animal, we are forced to conclude that the oxygen uptake in functioning cells in old animals is no different from that in young animals under resting conditions; i.e., the age decrement in basal oxygen uptake may be explained completely on the basis of reduced amount of functioning protoplasm. However, not all of the changes, described above, can be attributed to a loss of total body protoplasm alone. For example, renal function measurements were made in 63 of the subjects on whom determinations of fluid spaces were made.[34] In these subjects, calculations of renal function, per unit of body water, did not remove the reduction apparent with increasing age. This, of course, does not say that the reduced renal function may not be due to a reduction in the number of functioning units in the kidney. It simply says that, if this is true, the rate of decline in the amount of renal tissue is greater than the overall decline in the total body (Figure 16).

As is often the case, these experiments raise more questions than they answer. For example, we would like to know to what extent the total oxygen uptake in the animal is related to the oxygen uptake of specific tissues. Such questions can obviously be answered only in animal experiments where sacrifice is possible. Although there are studies on the oxygen uptake of tissues from lower animals, the data are controversial and it cannot be said that a reduction in oxygen uptake has been demonstrated in the tissues of older animals.[25] Although it seems reasonable to suppose that there are metabolic changes in a cell that must precede its disintegration and disappearance, we must admit that this is one of the challenges for future research.

Thus, it is clear that, although a part of the diminution in physiological function of various organ systems may be ascribed to the loss of functioning tissue, some functions show changes which cannot be accounted for on this basis alone. The problems of aging offer a challenge to future research. First of all, we need to identify quantitative alterations in a specific organ system performance. Secondly, we need studies of the integrated performance to find out how organ systems work together to meet bodily stresses. The application of new research techniques, to characterize the responses of old and young animals, offers an opportunity for increasing our understanding of aging in the human animal.

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