Physiological Limitations and Age

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THE PHYSIOLOGY of aging in man rather than age differences in disease incidence has been the chief concern of the Gerontology Branch of the Public Health Service's National Heart Institute. A large body of this latter information is available from other sources (*1*, *2*). In the course of our studies, we have found that aging does not affect all organ systems in the same way.

It is obviously difficult to define rigorously what should be called senescence as opposed to "disease." We can only hope to describe changes that occur with the passage of time in subjects for whom all diagnosable disease, which would affect the organ system under study, has been ruled out. To do this, we apply what we call "uniform subject selection criteria" so that other investigators will know what we mean by the phrase "healthy normal subject" and can judge the results accordingly.

The most basic principle of physiology is that the function of most organ systems is to maintain constancy of the internal environment. This is the principle of homeostasis as advanced by Bernard, Cannon, and others. We therefore require three types of information to characterize physiological age differences effectively.

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1. The resting state of the internal environment.
2. The resting organ functions that maintain this state.
3. The reserve or maximal capacities of these organ systems and their ability to defend the internal environment against displacements induced by stress.

The Internal Environment

Under resting conditions, the internal environment is surprisingly well preserved in the older individual as evidenced by lack of change in body temperature (*3*) and levels of various substances in the blood. Thus, Shock and Yiengst (*4*) found that the acid-base equilibrium of the blood is maintained within normal limits in the old man (fig. 1). A slight fall in pH does occur with corresponding, but not significant, changes in CO_2 tension and bicarbonate level.

Arterial fasting blood sugar does not change significantly with age (*5*), but there is some evidence suggesting a slightly higher fasting level in venous blood (*6*).

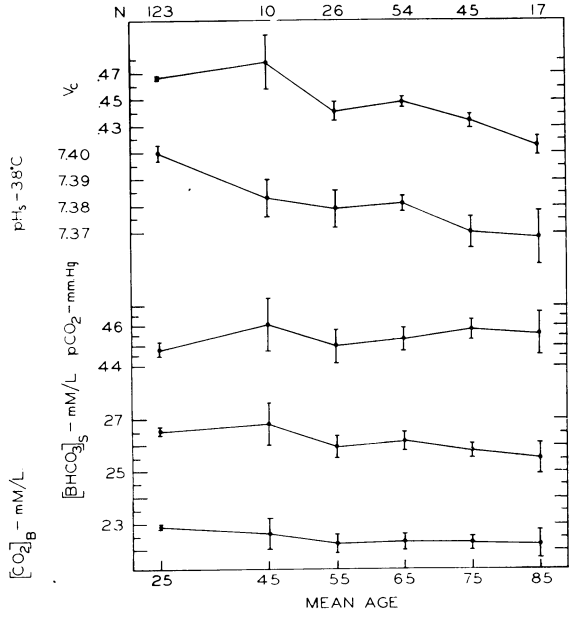
Hematological values of the blood are also well maintained in the aged. Shapleigh, Mayes, and Moore (*7*) determined these values in a series of 100 men and women 60–95 years of age and compared them with previously reported values for healthy young adults. Red cell counts, hemoglobin, and hematocrit values were slightly, and probably significantly, lower in the 60–95-year age group, with a smaller sex difference than in young individuals. Red cell

indexes and reticulocyte counts remained within the normal range, and no definite qualitative erythrocyte changes were seen microscopically. Total and differential leukocyte counts were also unchanged.

Functional Measures

It must be emphasized again, however, that the data described so far tell us very little of function or reserve capacities of the system for meeting the stresses of daily living. For example, if an individual's daily urea production remains constant while some renal insult suddenly reduces urea clearance, his blood urea will gradually rise until the product of blood level and clearance is once more equal to this tissue production rate. This new steady state level of blood urea will then be evidence of impaired renal function. It is also evident, however, that this same individual, if placed on a low protein diet at the same instant as his renal damage, might show no elevation of blood

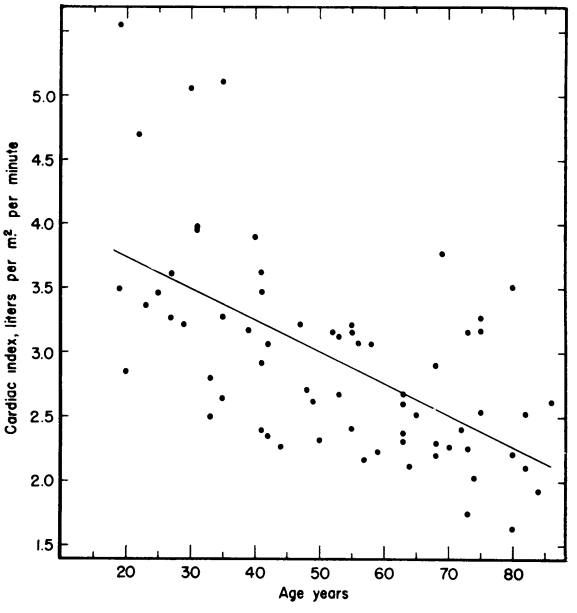
Figure 1. Trends in the acid-base equilibrium of the blood of men with increasing age.



Average curves from top to bottom include percentage of red cells, serum pH at 38° C., carbon dioxide tension expressed in millimeters of mercury, and serum bicarbonate and blood carbon dioxide content, both expressed in millimoles per liter. The vertical lines indicate ±1 standard error of the mean.

SOURCE: Reference 4.

Figure 2. The relation between basal cardiac index (liters per square meter per minute) and age (years) in 67 men without circulatory disorder.



SOURCE: Reference 9.

urea. Theoretically, then, physiological functions and reserve capacities can be reduced enormously without change in the internal environment, under resting conditions. In this regard, many of you will recall patients with a progressive downhill course and eventual death despite an impressive list of normal blood chemistries.

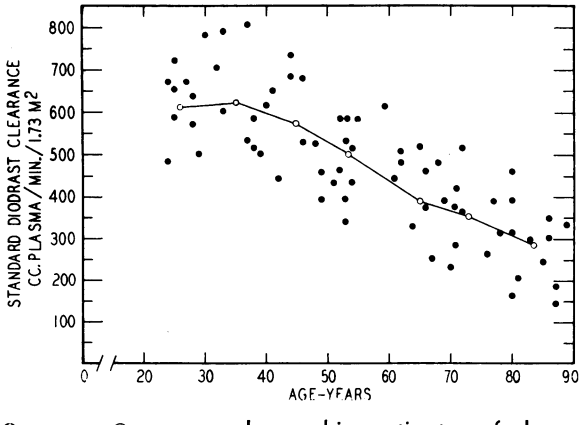
Among functional measures that can be employed, the basal metabolic rate (BMR) is of obvious interest in agewise comparisons. One often hears the suggestion that people "slow down" as they grow older, as evidenced by obvious changes in speech, gait, and cerebration. The ultimate energy source for all of these functions is, of course, oxidative metabolism. Without implying a causal relationship, one might ask if this overall metabolic rate also declines with age, at least under resting conditions. This appears to be the case. Shock and Yiengst (*8*) demonstrated a significant age decrement in basal O_2 consumption whether expressed as total oxygen uptake for the individual or per unit surface area. Expressed in calories per square meter per hour, the decline is from approximately 36 at age 40–49 to 30 at

age 80–89. This is not dramatically large, but it is highly significant and agrees quite well with most other data. Later, we will have reason to question the adequacy of calculated body surface area as an index of the amount of functioning tissue present in the individual. The fact to be emphasized at this point is that oxygen consumption per individual decreases with age.

A decline in resting cardiac output and cardiac index was found in a series of 67 men by Brandfonbrener, Landowne, and Shock (*9*), as shown in figure 2. This, of course, tells us nothing of the reserve capacity of the heart for increasing its output under conditions of exercise. We have recently initiated a study designed to give us this information, using exercise carried to exhaustion as the maximum stimulus to cardiac output.

Pulmonary function, in the aspects we have measured, changes markedly with age (*10*). Thus, total lung capacity (TLC) declines, but in our sample of 140 subjects this is paralleled by a decline in surface area. Total lung capacity corrected for surface area does not change. The compartments of total lung capacity change strikingly, however, with an increase in residual volume (RV) at the expense of vital capacity (VC) and its subdivisions. Thus, there is a shift from mobile to fixed lung spaces. The other large change we have found is in maximum breathing capacity. This falls from a mean of about 132 liters per minute at age 20–29 to 50 liters per minute at age 80–89. Most of this impairment seen in the older individual is a result of a relative inability to increase respiratory rate under the test conditions.

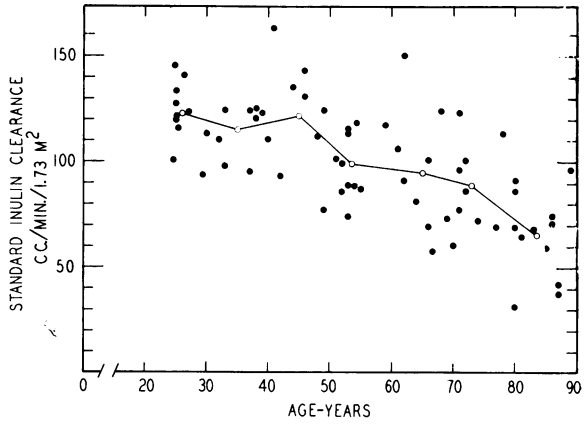
Figure 3. Change in standard diodrast clearance or effective renal plasma flow with age.



○———○ average values, cubic centimeters of plasma per minute per 1.73 m.² body surface area.

SOURCE: Reference 12.

Figure 4. Change in standard inulin clearance or glomerular filtration rate with age.



○———○ average values, cubic centimeters of filtrate per millimeter per 1.73 m.² body surface area.

SOURCE: Reference 12.

It may be suggested that our older subjects are suffering from emphysema. Certainly, we cannot distinguish these age changes from emphysema, particularly if an arbitrary value of the ratio of RV to TLC (or VC) is to be the clinical criterion, as it often is. We can only suggest that this common form of emphysema is a relatively constant age change and that the term "senile" emphysema is appropriate.

Of all organ systems maintaining the internal milieu, probably none bears a greater burden than the kidney. The arterial blood reaching the kidneys passes through the glomeruli; of this, about 20 percent is filtered through the glomerular membranes. About 99 percent of this filtrate water is actively reabsorbed by the kidney tubules, together with glucose, amino acids, and electrolytes, while waste products are excreted into the remaining filtrate volume by these same tubules. The external product is urine of variable composition; the internal component, blood plasma of constant composition. Thus, a complete estimate of renal integrity includes measures of the amount of blood or plasma perfusing the kidney, the proportion of plasma filtered, or the filtration

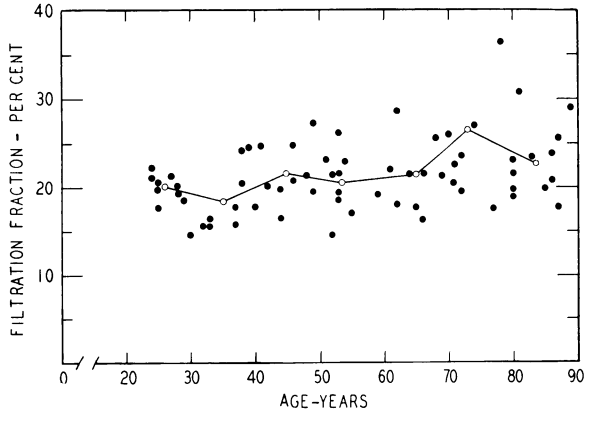
fraction, the amount of glomerular filtrate formed, and the maximum capacity of the tubules to reabsorb or excrete specific substances.

It is found that renal plasma flow, as measured by diodrast clearance, decreases from about 600 cc. per minute in the 20–29-year age group to about 300 cc. per minute in the 80–89-year age group (*11*, *12*). Figure 3 shows a scatter plot of these individual values. It may be seen that some of the 80-year-old subjects have values at least as high as some individuals in the 40–50-year age group. One wonders what values these 80-year-old subjects would have shown in their youth. This variability is seen in many other functions and only stresses the need for longitudinal studies in aging since individuals might show stepwise decrements in function.

Glomerular filtration rate, as measured by inulin clearance, also declines with age as seen in figure 4 (*11*, *12*). This is slightly less than the decline in effective plasma flow so that the filtration fraction increases slightly, but significantly, as shown in figure 5.

From these data alone, we cannot say whether the reduced plasma flow results from loss of nephrons, reduced flow per nephron, or a combination of these two factors, but the increased filtration fraction would imply a relative increase of efferent to afferent arteriolar constriction. It would also appear that total renal resistance has increased more than total peripheral resistance, since the age decrement in

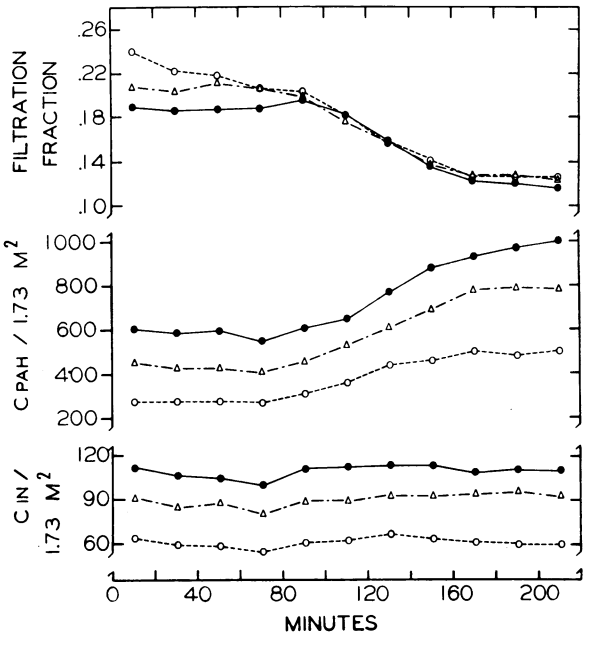
Figure 5. Change in filtration fraction with age.



○———○ average values, percent of plasma filtered.

SOURCE: Reference 12.

Figure 6. Changes in glomerular filtration rate (C_{IN}), effective renal plasma flow (C_{PAH}), and filtration fraction during the pyrogen reaction. Fifty million killed typhoid organisms were injected intravenously at zero time.



○----------○ mean values for 14 subjects aged 70–85 years (O groups).

△—·—·—△ mean values for 20 subjects aged 50–69 years (M group).

●———● mean values for 20 subjects aged 20–49 years (Y group).

SOURCE: Reference 13.

renal blood flow exceeds that in cardiac output (*9*) while mean blood pressure does not fall.

Are the apparent changes in the resistance of the kidney to blood flow the result of unalterable anatomic changes in the arterioles or can resistance be lowered by a physiological stimulus? To answer this question, McDonald, Solomon, and Shock (*12*, *13*) tested the effect of a bacterial pyrogen which increases effective plasma flow in young subjects. It was found that effective plasma flow could be increased significantly in all age groups, and that while the absolute baseline and magnitude of increase was smaller in the oldest group the percentage increment was similar to that of the young. The glomerular filtration rate was unchanged by the pyrogen while the filtration fraction necessarily declined significantly to become equal in all age

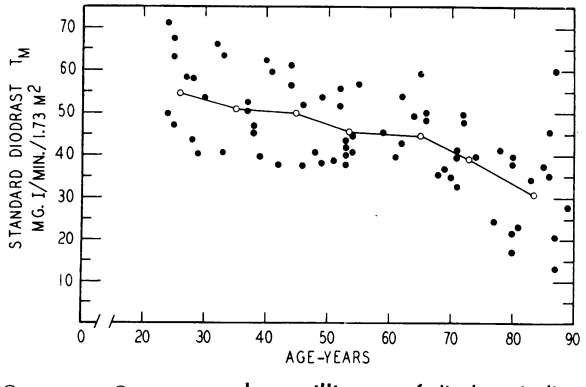
groups (fig. 6). This suggests that a large proportion of the total as well as relative efferent vasoconstriction present in an old kidney is reversible (*14*).

It was also found that tubular function, as estimated by maximum rates of diodrast excretion and glucose reabsorption, decreased with age, as shown in figures 7 and 8 (*11*, *12*, *15*). The magnitude of these decrements is similar to that of glomerular filtration rate (GFR), which suggests that nephrons lose function as a unit. Constancy of the ratio GFR: diodrast T_m is seen in figure 9. The decline in effective plasma flow, however, exceeds any of these decrements, suggesting that vascular impairment is primary rather than secondary to loss of nephron function (*11*, *12*). This relationship is illustrated in figure 10.

Possible Effects on Longevity

What do these changes mean with respect to health, vigor, and life expectancy? They are certainly never listed as cause of death. Yet we may ask if they are in some way related to the unfortunate contour of mortality curves—something happens to the individual with time so that probability of death at any moment is not constant but increases with age. This can be illustrated by the results of renal studies. It is known, for example, that urea and inulin are excreted by the kidney in a similar way except that some of the urea diffuses back into

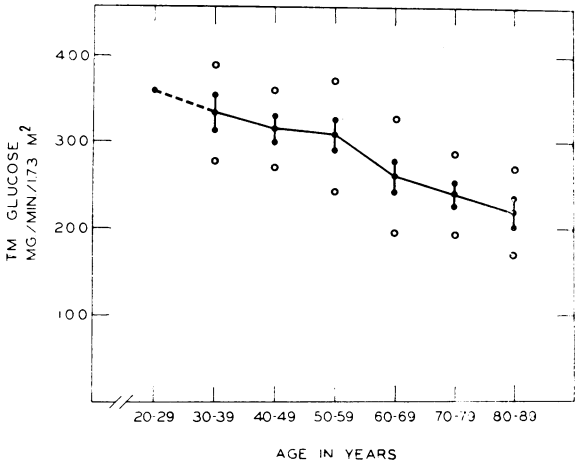
Figure 7. Change in standard diodrast T_m with age.



○———○ average values, milligrams of diodrast iodine per minute per 1.73 m² body surface area.

SOURCE: Reference 12.

Figure 8. Decrease in maximal tubular reabsorptive capacity with age.



The slope is drawn to connect the mean values for each decade. The vertical lines represent ± 1 standard error of the mean, while the open circles define the limits of ± 1 standard deviation of the distribution.

SOURCE: Reference 15.

the blood stream. Thus, we would expect urea clearance to show an age effect similar to that of the glomerular filtration rate and also to find some increase in blood urea nitrogen unless an older man's nitrogen catabolism is reduced in a parallel way.

Studies by Lewis and Alving (*16*) do show an age reduction of urea clearance of about the same magnitude as the fall in glomerular filtration rate as found in our laboratory. An older man's nitrogen catabolism is reduced, but only slightly, and this is not enough to prevent an increase of blood urea nitrogen from 10 mg. percent to 18 mg. percent over a 20–90-year age span. This relationship between blood level clearance rate and production of urea is a simple hyperbolic one, that is, successive constant decrements of urea clearance produce ever larger increments in blood urea.

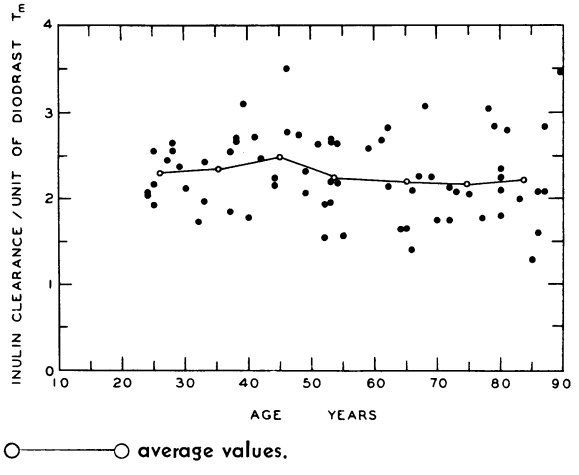
From this and from the Lewis and Alving data, we can make a simple prediction. Suppose that a 20-year-old man suffers some renal insult such as nephritis or ureteral occlusion which reduces his urea clearance by 25 percent. As a consequence his blood urea nitrogen will increase from approximately 10 to 13.3 mg. percent, or a rise of 3.3 mg. percent. This is still within the limits of normal. If, on the other hand, a 90-year-old man suffers the same fate,

his blood level will rise from 18 to 23.9 mg., an increase of 5.9 mg. percent, which is above the normal range. Further renal insults will serve to magnify this difference. Urea itself is relatively nontoxic, but impairment in reserve will make the accumulation of substances in the body more rapid, and the deleterious effects of toxic substances will be more marked in the old man.

It is more difficult to make predictions with respect to pulmonary function. Although the maximal breathing capacity is normally much higher than the ventilatory level attained with violent exercise, it is quite likely that there is a correlation between the two levels, and we have some preliminary findings which support this. However, by making a variety of assumptions with regard to dead space and tidal volume, it can be calculated that ventilation volume per se does not limit the oxygen uptake or exercise performance of an older man until values below 20 liters per minute are reached. As these calculations were designed to demonstrate the effect of ventilation alone, they assume perfect mixing of air in the lungs. Since mixing is not perfect, the age changes in lung compartments we have observed would tend to impair lung transport and thus produce arterial oxygen unsaturation and undue demands upon cardiac output at ventilation volumes higher than calculated. Thus, we see that an impairment in one physiological system places an added burden upon another system whose functional capacity may also be decreased with age. What we have observed so far is that the maximum work rate of an old man is reduced; we are now trying to discover the relative importance of pulmonary, cardiac, or muscular limitations.

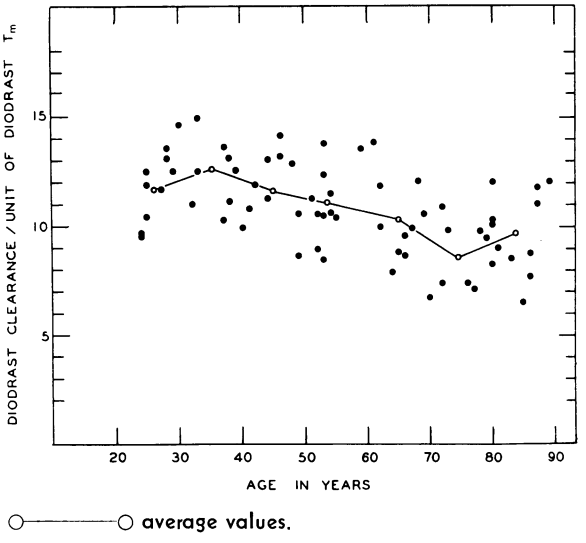
It is also not too difficult to imagine an adverse effect of pulmonary limitations upon life expectancy. For example, an older individual with reduced ventilatory capacity and mixing efficiency is in a far more precarious position with superimposed lobar pneumonia than is a young man.

Figure 9. Change in rate of glomerular filtration per unit of diodrast T_m.



SOURCE: Reference 12.

Figure 10. Change in effective renal plasma flow per unit of diodrast T_m.



SOURCE: Reference 12.

Mechanisms of Aging

We have described some physiological age changes in man, with some possible consequences with respect to vigor and longevity. We must now ask how these changes come about. It is apparent that functional loss in an organ system implies either loss of active protoplasm or qualitative difference in the protoplasm. To estimate the relative importance of these two factors, we obviously need some good index of protoplasmic mass. There is quantitative histochemical evidence that, for a given tissue, protoplasmic composition is relatively constant with respect to water and electrolytes and does not change with age (*17*). Thus, intracellular

water, which can be estimated in intact animals, should serve as a better protoplasmic index than body weight or calculated surface area, which are obviously affected by such nonprotoplasmic materials as fat and edema fluid.

By using the antipyrine space as a measure of total body water and the thiocyanate space as an estimate of extracellular space, the intracellular water may be calculated as the difference between these two. Shock, Yiengst, and Watkin (*18*) found that total body water and intracellular water decrease significantly with age while the extracellular space does not change. Since these estimates were made for the same subjects used in studying the basal metabolic rate, they could be applied as BMR reference standards for each individual. It was found that basal O_2 consumption per unit of total body water or intracellular water does not change with age (fig. 11). This would suggest that, in terms of net metabolic activity, the protoplasm of an old man is unchanged; he simply has less protoplasm (*19*). Morphological studies of a variety of tissues in man support this viewpoint. Thus, a variable weight loss of many organs occurs with age, accompanied by widespread cell shrinkage, cell loss, and relative or absolute fibrosis (*20*).

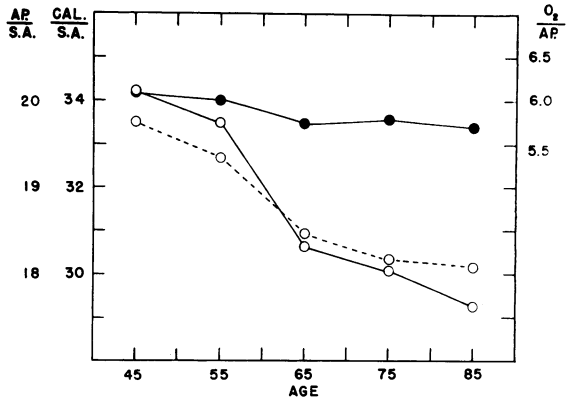
Qualitative cellular changes are equally interesting. Nuclear abnormalities (*21*, *22*) and vacuolated mitochondria (*21–24*) are observed as well as deposition of highly insoluble "age" pigments in heart, brain, and adrenal (*21*, *25*, *26*). Lansing (*27*) has summarized evidence for a loss of cell permeability accompanying increased calcium binding of the cell cortex. The implications of these changes, with respect to cell function, are intriguing, but can we say they are primary changes? We must ask another fundamental question posed by the overall histological appearance of old tissues: Does the intercellular material passively replace cells which shrink or die as they grow old or do the cells die only because they are literally strangled by connective tissue which ages and loses permeability? Or are both altered independently?

In some organs, such as the liver and adrenal, cell shrinkage and loss overshadows fibrosis and might, therefore, be considered a primary factor (*20*). However, the absence of dramatic morphological change in a tissue does not rule out the possibility that subtle alterations, such as reduction in blood flow or permeability, play an important role in aging. In other organs, such as the kidney, parenchymal changes may be secondary results of vascular lesions. It is possible that all of the renal age changes are secondary to progressive arteriolar change (*20*). The fact that the age decrement in renal plasma flow exceeds loss of tubular function would support this view although we can hardly cite it as proof. We cannot be sure that the nephrons would not eventually age in the absence of vascular changes. In short, we have no proof as to the primacy of either intracellular or extracellular changes as the basic cause of aging.

Lansing has summarized some evidence for the hypothesis that aging is a consequence of growth cessation (*27*). His own work shows that longevity of rotifers is inversely proportional to maternal age, that this effect is cumulative through successive generations, and that this progressive shortening of life span first appears when maternal age exceeds the growth phase of this organism. Lines of rotifer, with constant "old" maternal age, were termed "geriaclones" (*27*, *28*).

Experience with tissue culture tends to reinforce this concept, but in a less definite manner. Thus, many cell types show unlimited

Figure 11. Age changes in basal heat production



●———● basal oxygen uptake, cubic centimeters per minute per liter total body water.

○———○ basal metabolism, calories per square meter per hour.

○----------○ total body water, liters per square meter.

SOURCE: Reference 19.

growth potential in vitro (*29*). Even adult human neurones have not entirely lost the capacity for mitosis, as shown by Murray and Stout (*30*). It is of interest that only neurones relatively free of age pigments were observed in mitosis. However, the experience with neurones and other cultures reveals a general antagonism between growth rate and tissue organization (*29–31*). Cell lines with high growth rates may survive indefinitely but show poor differentiation, while slowly growing cultures show more organization but are difficult to maintain. In fact, nonmitotic cells in culture generally live only a fraction of their survival time in vivo so we cannot yet say that they "age" as a consequence of growth lack; they simply do not survive or have not been observed for a sufficient length of time (*29*). Perhaps culture methods can be improved to the point where we can actually decide whether such cells inevitably age in the absence of their normal connective tissue environment. Obviously, this could be most easily tested with cultures from short-lived animals. Neurones from rat and man are morphologically alike, yet their normal life spans differ by a factor of 30. How would their survival times compare in vitro? So far, all we can say is that in vitro the price of immortality is chaos.

Research Needs

The question of primary causes of aging can be answered only by further research on both the human animal and lower life forms. We have studied many aspects of aging in man in the Gerontology Branch, but this field is far from exhausted. As a single example, we have seen that hematological values are only slightly altered with age, but we need information on the rate of replacement of plasma proteins, red cells, and leukocytes. We would also like to know the factors producing the great individual variability we have observed. Why do some 80-year-old men have the physiological reserve of men 30 or 40 years their junior? In this variability lies hope, if we can discern its cause. Longitudinal studies are pertinent to this question. The Gerontology Branch has existed long enough so that we are beginning to gather some of these data on both patients and investigators.

There is, however, information that can only be obtained by animal experimentation, as for example, age changes in tissue composition and enzymatic activity. Such studies on the rat are now in progress in the Gerontology Branch. Some other fundamental researches are best applied to invertebrates, many of which have the twin virtues of uniform genetic composition and very short life spans. The utility of such organisms is illustrated by such excellent studies as that of MacArthur and Baillie (*32*) on the temperature dependence of life span in *Daphnia magna* or by Lansing's work on rotifers (*27, 28*). These two studies jointly raise a curious question. The geriaclone rotifers show, in addition to shortened life span, earlier sexual maturity and accelerated growth rate but smaller final size. These are precisely the four effects seen in *Daphnia* raised at high temperatures. Why this should be so we have no idea, but it is obviously an important clue. It is problems like these which urgently require solution. The questions that face us are difficult, but there is no real reason to believe that they are unanswerable.

Summary

Examination of experimental studies on physiological changes with age indicate that, under resting conditions, the aged human is usually able to maintain uniformity of the internal environment. However, when increased demands are placed on a number of organ systems, impairment of function can often be detected. Thus, the primary characteristic of the older individual is a reduction in reserve capacities which makes him more vulnerable to stresses of even daily living than the young. These changes take place gradually over the entire adult life span and may, in part, be attributed to a loss of functioning tissue. The causes of this loss have not been identified. One of the outstanding characteristics of age change is the striking difference in vulnerability among individuals. At the present stage of research, we cannot identify the factors that determine these individual differences. It is not yet possible to determine the relative importance of loss of functioning tissue and alterations in cellular metabolism in producing the age changes in

physiological function which have been observed. Extensive research, including biochemical, physiological, and histological studies on species other than man will be required to answer these important questions.

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