Zeitschrift: Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche

Herausgeber: Schweizerische Akademie der Medizinischen Wissenschaften

Band: 24 (1968)

Artikel: Homeostatic disturbances and adaptations in aging

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DOI: https://doi.org/10.5169/seals-307734

D.C.: 612.67:612.017.2

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Homeostatic disturbances and adaptations in aging

N. W. Shock

The term homeostasis was first introduced into physiology by Cannon to describe the processes by which steady states are maintained in the body in the face of altering demands and displacements induced by environmental conditions [1]. It is well known that all cellular processes operate best under certain conditions of temperature, ionic strength, acidity, substrate concentrations, etc. Since life of the total animal depends on proper functioning of cells, it is clear that the internal environment of the body to which all cells are exposed must be maintained and regulated within fairly close limits. With increasing complexity of organization specialized functions are taken over by groups of cells with the development of various organ systems. However, the environment of cells of each organ which contributes to the overall maintenance of body equilibrium must also be maintained within optimal limits. Many of the organs of the body participate to varying degrees in these regulatory processes and much of current research in physiology is directed towards identifying the control mechanisms involved in this integrated activity. Although the nervous and endocrine systems play a primary role in regulatory mechanisms and the maintenance of homeostasis, other organ systems such as the lungs, kidneys, liver, and the gut are also involved [2].

Studies from our laboratory have shown that under resting conditions there is little or no change in the chemical composition of the blood with increasing age. As shown in Fig. 1 fasting blood sugar levels remain essentially unchanged throughout the life span in the human [3]. Similarly, the acidity and bicarbonate content of arterial blood are closely regulated even into advanced old age when observations are made under basal conditions [4]. However, when experimental displacements in blood sugar levels or bicarbonate content are induced the rate at which the body is able to readjust levels and bring them back to normal resting values is much slower in old subjects than in young.

The homeostatic ability to regulate blood sugar levels can be readily tested by administering glucose intravenously and following the rate of disappearance of the excess glucose from the blood [5]. 35 male subjects aged 23–86 years were selected on the

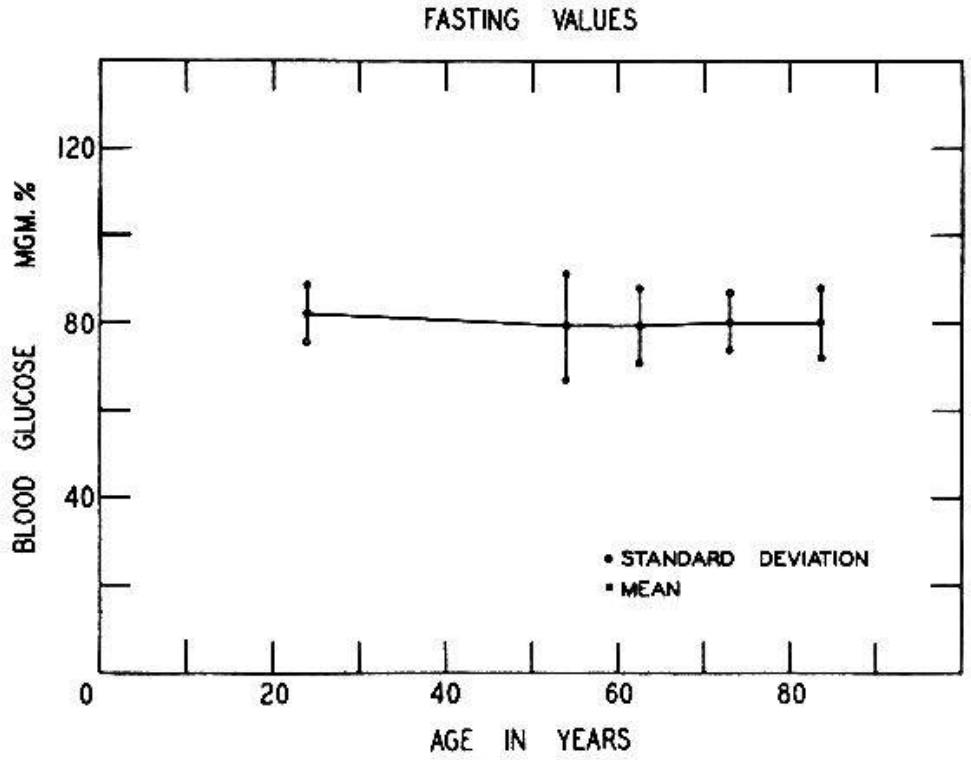

Fig. 1. Fasting glucose levels in arterial blood. Mean values by decades. The vertical line indicates ± 1 SD.

basis of a detailed history, physical examination, and a series of laboratory tests. Presence of any of the following served to exclude a subject from the study: a) history or known evidence of diabetes or glycosuria; b) severe alcoholism, hepatomegaly, cirrhosis or other liver disease; c) cardiac decompensation or edema; d) infections, temperature elevation, or acute chronic trauma within one week of the test; or e) the taking of steroid drugs. All were ambulatory in-patients on a routine hospital diet for at least one week.

Two experimental procedures were carried out in each subject under basal conditions separated by an interval of not less than one week. In the first test 0.38 g of glucose per kg body weight were administered intravenously (50 ml of 50% glucose in water over a period of 2 min), and blood samples were collected from a vein in the opposite arm at 5 min intervals for the first hour and at 20 min intervals during the second hour. In the second experiment the same procedure was followed except that 5 units of hyperglycemic factor free insulin per m^2 of body surface area were injected just preceding the administration of the glucose.

Plots of the log glucose concentration in the blood against time were constructed for each experiment and, since they were substantially linear, least squares fits were made to the observations and slope of the line K was used as the index of the rate of recovery. Fig. 2 illustrates the results from a 26-year-old subject on the left and an 86-year-old subject on the right. The upper lines of open circles represent the rate of recovery from the glucose load, whereas the lower lines illustrate the rate of recovery of blood sugar following the simultaneous administration of glucose and insulin.

Statistical analyses were performed on K values obtained from the individual experiments and show that there was a significant age decrement in the rate of recovery of blood glucose levels under both conditions. Although the rate of disappearance of glucose was increased by the administration of insulin in both old and young subjects, the effect was substantially

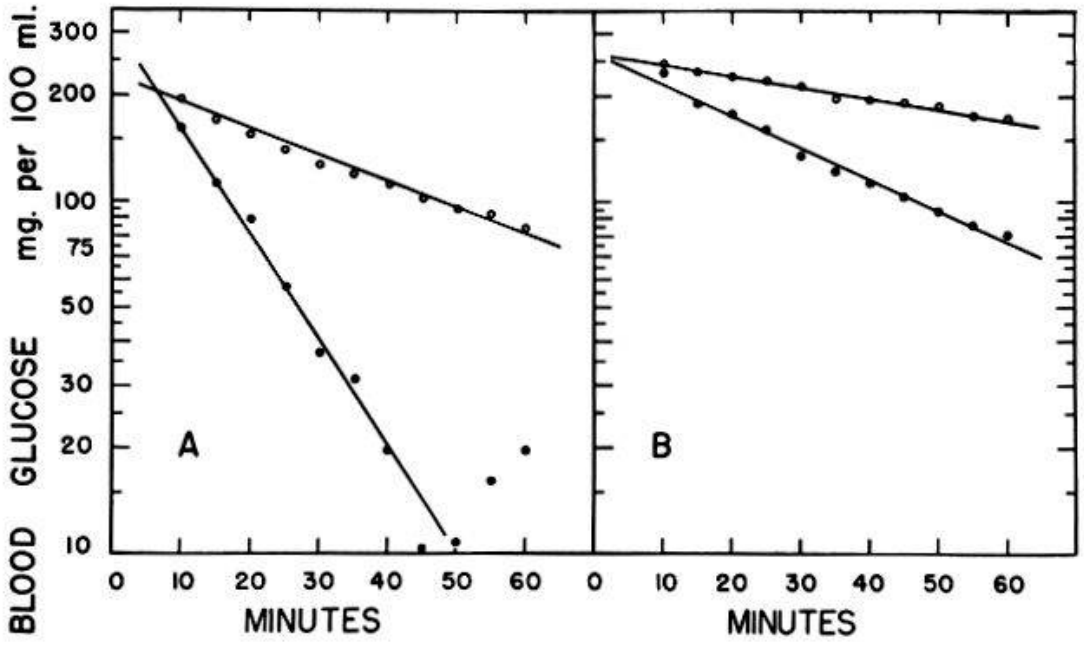

Fig. 2. Log glucose concentration in venous blood (mg/100 ml) plotted against time (min). A: 26-year-old male. B: 86-year-old male. Upper lines (open circles) represent observations following intravenous administration of 50 g glucose; lower lines (solid circles) represent observations following intravenous administration of 50 g glucose plus 5 units of insulin. – From SILVERSTONE et al. [5].

greater in the young subjects than in the old. These experiments show clearly an age impairment in the homeostatic mechanisms involved in the regulation of blood sugar levels, and that the sensitivity to a physiological stimulus, namely insulin, was diminished in the elderly subjects.

Subsequently, a similar experiment was carried out by Dr. ANDRES et al. on a group of highly educated active subjects ranging in age from 30 to 96 years with practically identical mean values of K for young (mean age 31 years), middle-aged (mean age 49 years), and old (mean age 79 years) subjects [6].

There were, of course, many differences between these two groups; differences in diets and nutritional status, presence of chronic illness, activity levels, and the stress of recent illness. The fact that the change in K values with age for these two widely different groups of subjects was so similar indicates that it is aging *per se* that is primarily responsible for the decline in glucose tolerance, and that we are dealing with the effects of age on the homeostatic mechanism.

Recently Dr. ANDRES et al. [6] have been able to obtain evidence that with increasing age there is a diminution in the sensitivity of the β-cells of the pancreas to respond to increased glucose concentration in the blood with the release of insulin. These studies required the development of a new experimental technique which permits the investigator to maintain a steady specified glucose concentration in the blood which perfuses the islets of the pancreas [7].

The principle of the method is that of a servo-control or negative feedback by which the rate of the intravenous infusion of glucose is frequently readjusted according to the

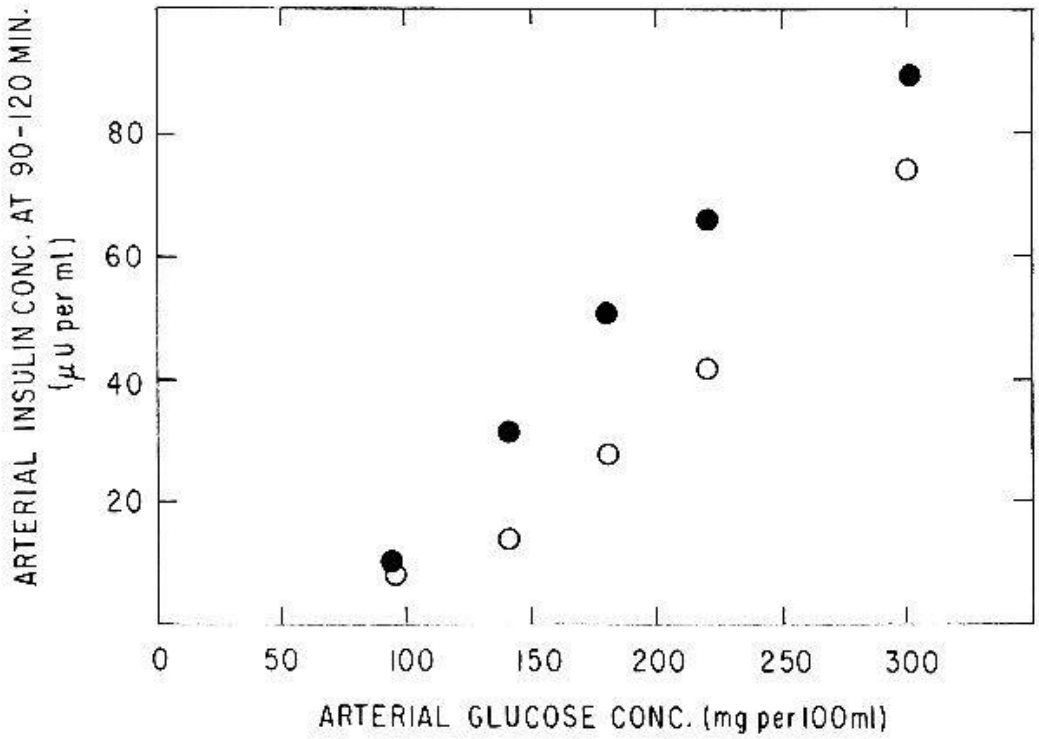

Fig. 3. Effect of age on the glucose-insulin dose-response curve. Mean values for young adult subjects are plotted as closed circles; old subjects are plotted as open circles. – From SHOCK and ANDRES [6].

difference in the actual level of arterial glucose and the desired level. By this technique arterial glucose concentration can be rapidly brought from the basal fasting level to a new steady state concentration and held there for long periods of time. Identical hyperglycemic stresses can be applied to old and young subjects.

Fig. 3 shows the amount of insulin present in the blood at glucose levels of 140, 180, 220, and 300 ml of glucose per 100 ml in young and old subjects. It is clear from these results that the older subjects achieve a much lower insulin level in their blood in response to a given hyperglycemic stress than do the young subjects.

In summary, it has been shown that with increasing age there is impairment in the ability of the individual to readjust blood sugar levels and that a part of the impairment at least is due to a decreasing sensitivity of the islet tissue of the pancreas to respond to enhanced blood sugar levels with the release of insulin.

Regulation of the acid base equilibrium of the blood is effected primarily by two mechanisms. The first is through elimination of carbonic acid by the lungs or increased retention by reduced ventilation. These processes represent effective devices for rapid adjustment by altering carbonic acid content of the blood. When fixed acids are released into the blood, carbonic acid is displaced from the large pool of bicarbonate present and consequently tends to lower the bicarbonate concentration. The increased carbonic acid is readily eliminated under normal circumstances through the lungs and thus equilibrium is restored and the pH of the blood is restored to normal values.

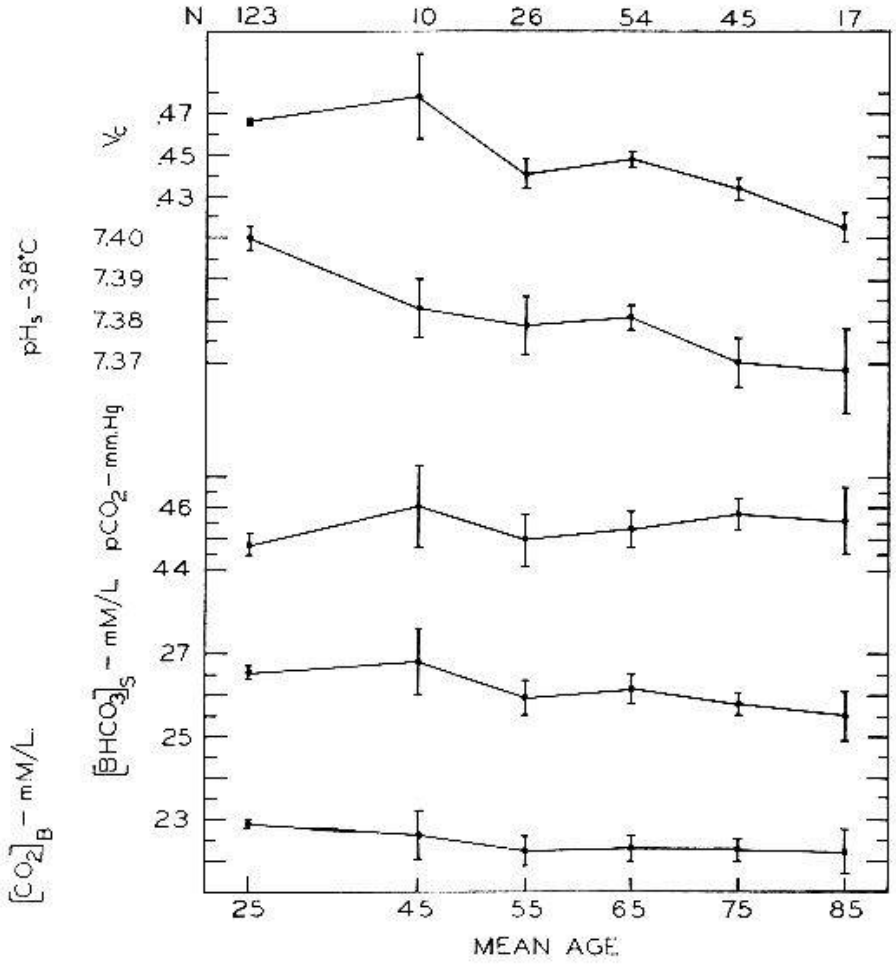

Fig. 4. Trends in the acid-base equilibrium of the blood of males with increasing age. Average curves from top to bottom include % red cells, serum pH at 38°C, carbon dioxide tension expressed in mm Hg, serum bicarbonate, and blood carbon dioxide content both expressed in mM/l. The vertical lines indicate +1 standard error of the mean. – From SHOCK N. W. and YIENGST M. J.: Age changes in acid-base equilibrium of the blood of males. J. Geront. *5*, 1–4 (1950).

On the other hand, conditions leading to accumulation of bicarbonate may be compensated temporarily by reduced ventilation and consequent piling up of CO_2 in the blood. Thus the ratio of bicarbonate to carbonic acid concentrations is restored and the pH is appropriately regulated.

The second mechanism of importance in regulating acid base equilibrium is through the action of the kidneys which eliminate excess base as bicarbonate and excess acid by the formation of additional ammonium ion. Adjustment by this mechanism requires considerably more time than adjustment through the carbonic acid mechanism. Both processes, of course, are dependent upon the adequacy of the blood supply to the kidneys and to the lungs and to the functional capabilities of both of these organs.

As previously pointed out, under resting conditions the pH and the bicarbonate content of the blood do not change significantly with increasing age [4] (Fig. 4). Tests of the effectiveness of the pulmonary system in adjusting to increased CO_2 tensions are difficult to carry out since the results are also influenced by the sensitivity of the respiratory center to alterations

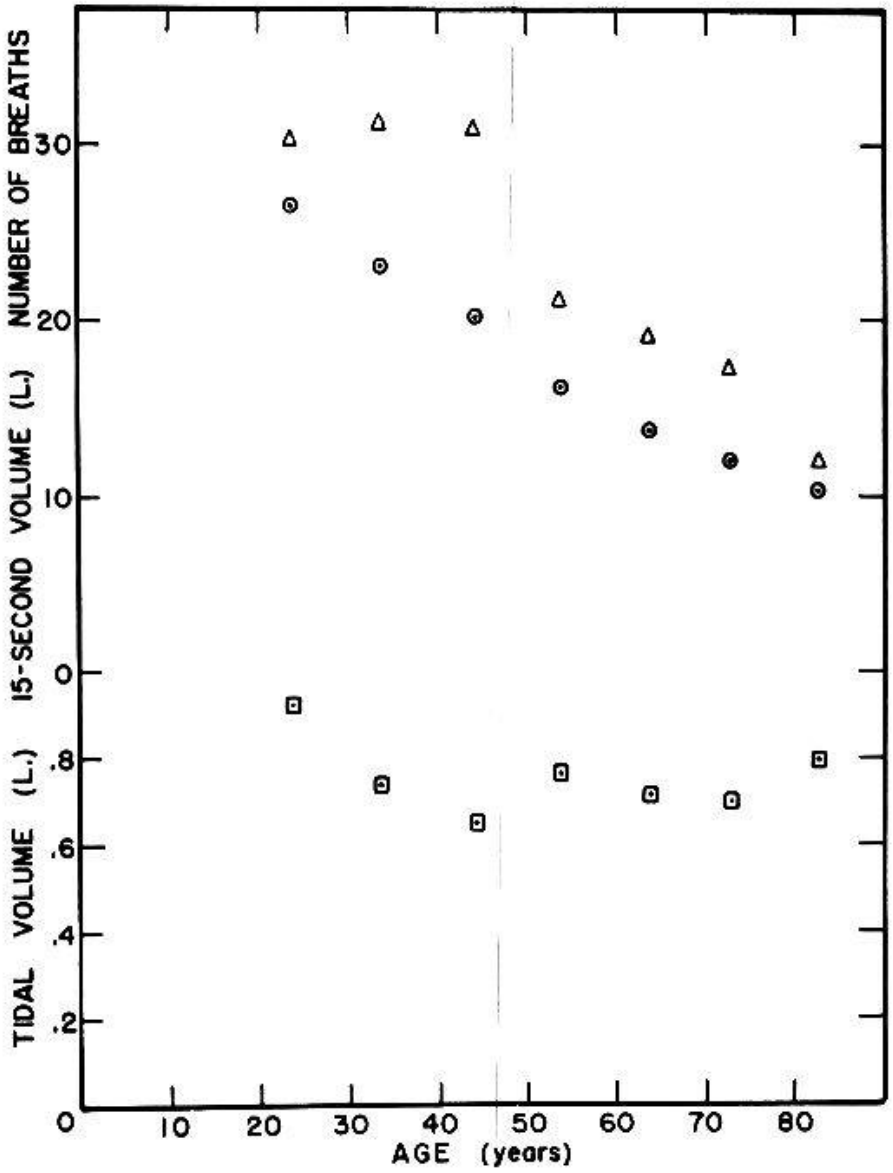

Fig. 5. Average values for tidal volume (⊡), total 15-sec volume (◉), and number of breaths (△), required for each of 6 trials by each individual in a subsample of 107 subjects are averaged and plotted by age decades. Total 15-sec volume and number of breaths are plotted on the same scale. – From NORRIS et al. [9].

in CO_2 tension. Experiments in animals and a few studies in humans have given presumptive evidence that the sensitivity of the respiratory center to carbon dioxide diminishes in old age [8]. It has also been shown that the maximum breathing capacity diminishes rather markedly with increasing age [9]. The defect in the elderly subjects lies entirely in their reduced ability to maintain the high rate of respiration. In fact, the tidal volumes under these conditions do not shift significantly with age (Fig. 5).

The two primary changes in the lung with increasing age is an increase in the unevenness of ventilation and perfusion and an increased stiffness primarily of the chest wall. Actually, recent studies on compliance of the human lung indicate that lungs in older people are more flabby than lungs in the young [10]. These results were based on functional measurements on intact

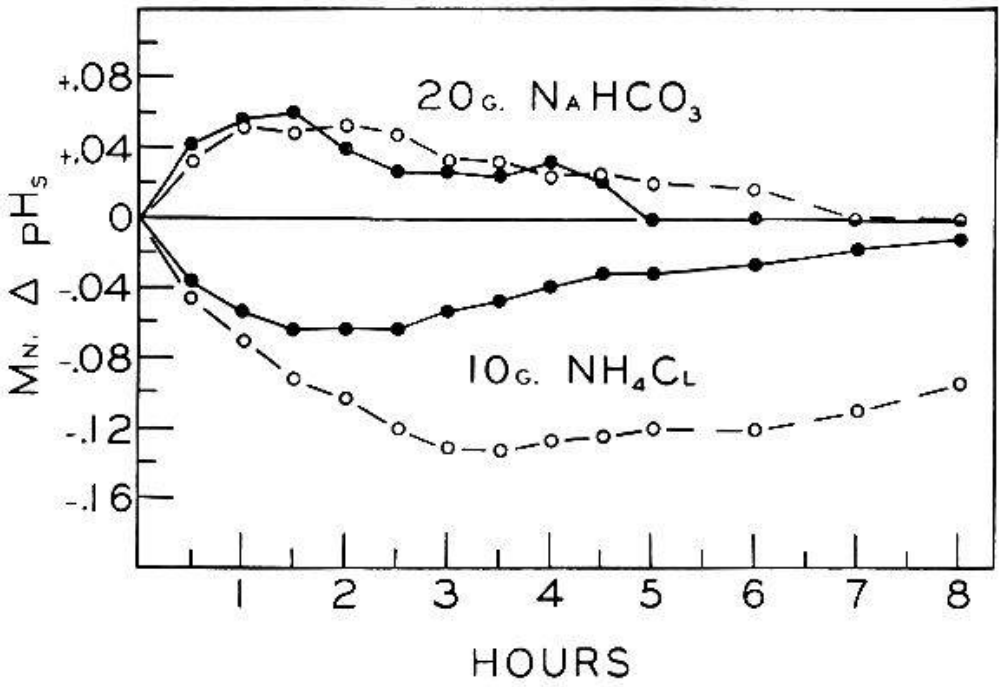

Fig. 6. Effect of oral administration of sodium bicarbonate (20 g) or ammonium chloride (10 g) on pH of arterial blood. ●—●—● = Mean curve, 20–25-year-old subjects. o o o = Mean curve, 75–85-year-old subjects. N = 10.

humans and are not in accord with the static measurements of lung compliance which have been carried out in animals and show an increase in stiffness of the lung itself.

Long term adjustments of the acid base equilibrium are effected through the kidney which excretes the excess acid or alkali.

To test the effectiveness of this homeostatic mechanism the direct approach would be to inject excess acid or alkali directly into the blood stream. Since this is impossible, displacements in the acid base equilibrium of the blood were induced experimentally by the oral ingestion of sodium bicarbonate or of ammonium chloride [4].

Fig. 6 illustrates the effects of administering 20 g of sodium bicarbonate or 10 g of ammonium chloride to old and young subjects on the rate of displacement and recovery of the pH of arterial blood. In young adults recovery was effected within a period of 8–10 hours. In aged subjects, however, the rate of recovery was much slower and required as much as 24–48 hours.

In order to evaluate the basis of this marked age difference in homeostatic capabilities, detailed studies of renal function were conducted in normal males aged 20 90 years [11].

These subjects were carefully screened to eliminate any with clinical or laboratory signs of kidney disease, cardiac disease, edema, or hypertension. Estimates of resting renal plasma flow were made by determining the clearance of diodrast or PAH. For these determinations patients were well hydrated and in a fasting condition. Constant blood levels of inulin, diodrast or PAH were maintained by continuous intravenous infusion and catheterized urine specimens were obtained for three 10-min periods after equilibrium had been established. Glomerular filtration rate was estimated simultaneously by the inulin clearance technique and maximum tubular excretory capacity for PAH or diodrast was determined in three additional 10-min periods.

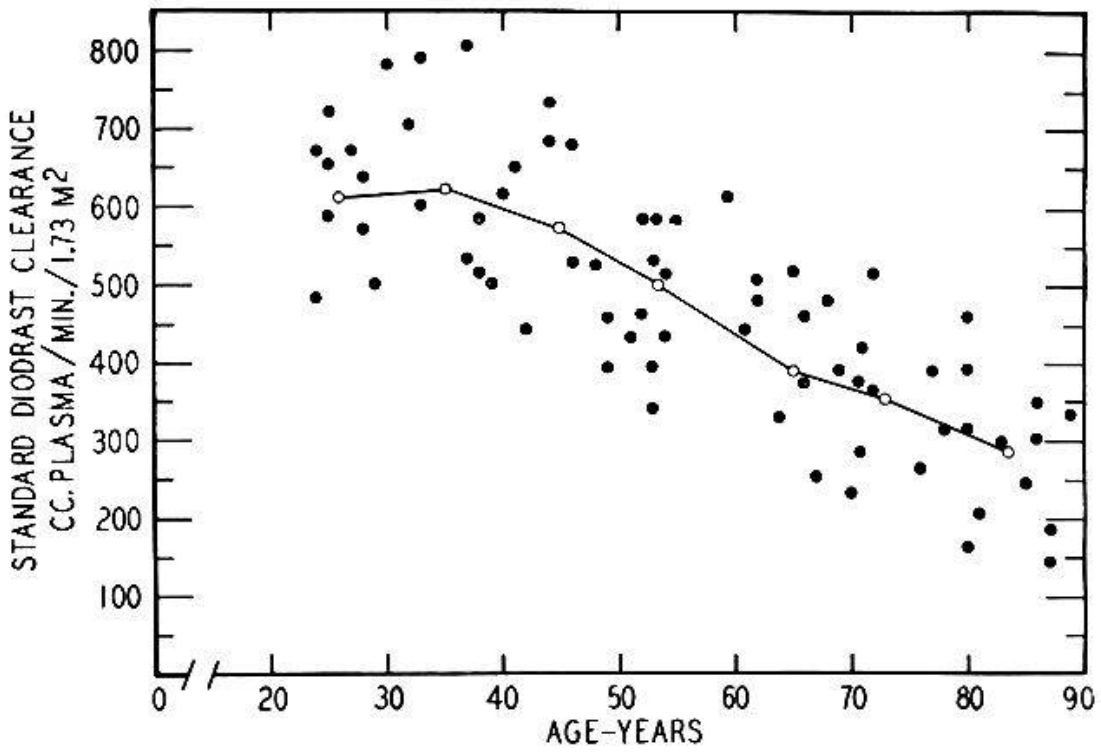

Fig. 7. Change in standard diodrast clearance or effective renal plasma flow with age. o—o = average values cm³ plasma/min/1.73 m² body surface area. – From Shock [12].

Fig. 7 shows that, although there were wide individual differences, there was a statistically significant decrement in resting renal plasma flow of approximately 6% per decade. Fig. 8 shows that the inulin clearance falls at practically the same proportional rate as the renal blood flow. Fig. 9 shows that the maximum rate of tubular excretion for diodrast also falls with age but at a slightly greater rate.

Examination of these results by the calculation of appropriate ratios indicated that the simplest explanation was the assumption that with increasing age there is a dropping out of entire nephrons. Thus, one of the factors involved in the reduced ability to excrete excess acid or alkali is undoubtedly associated with a loss of nephrons and a reduction in the amount of blood passing through the kidney [12].

Further experiments were conducted in order to see whether the reduction in renal blood flow was due to structural changes in the arterioles in the kidney or whether the reduced flow was due to a functional vasoconstriction.

Since it had been shown previously that the administration of a pyrogen to young subjects resulted in a marked vasodilatation of the arterioles of the kidney with an increase in blood flow, this method was applied to a group of 54 male subjects between the ages of 20 and 84 years [13]. In these experiments diodrast and inulin clearances were measured in eleven 20-min urine collection periods immediately following the intravenous administration of 50 million killed typhoid organisms (0.5 cm³ of TAB vaccine).

During the course of the pyrogen reaction in which a rise in body temperature was prevented by the oral administration of aminopyrine, no

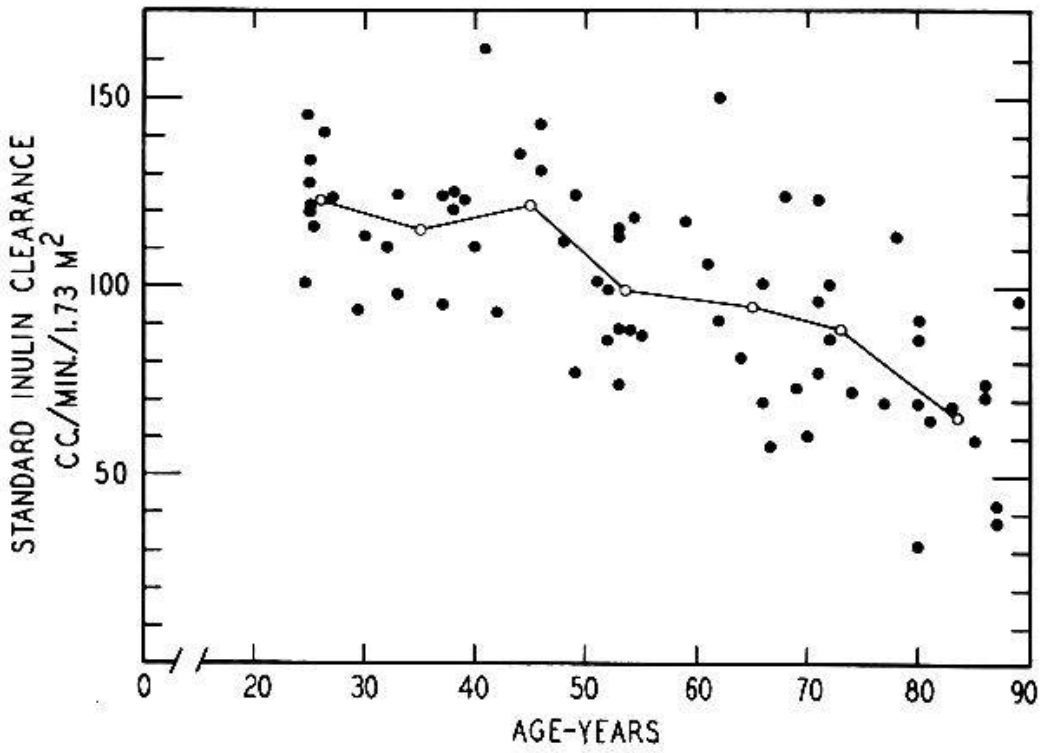

Fig. 8. Change in standard inulin clearance or glomerular filtration rate with age. o—o = average values cm³ filtrate/mm/1.73 m² body surface area. – From SHOCK [12].

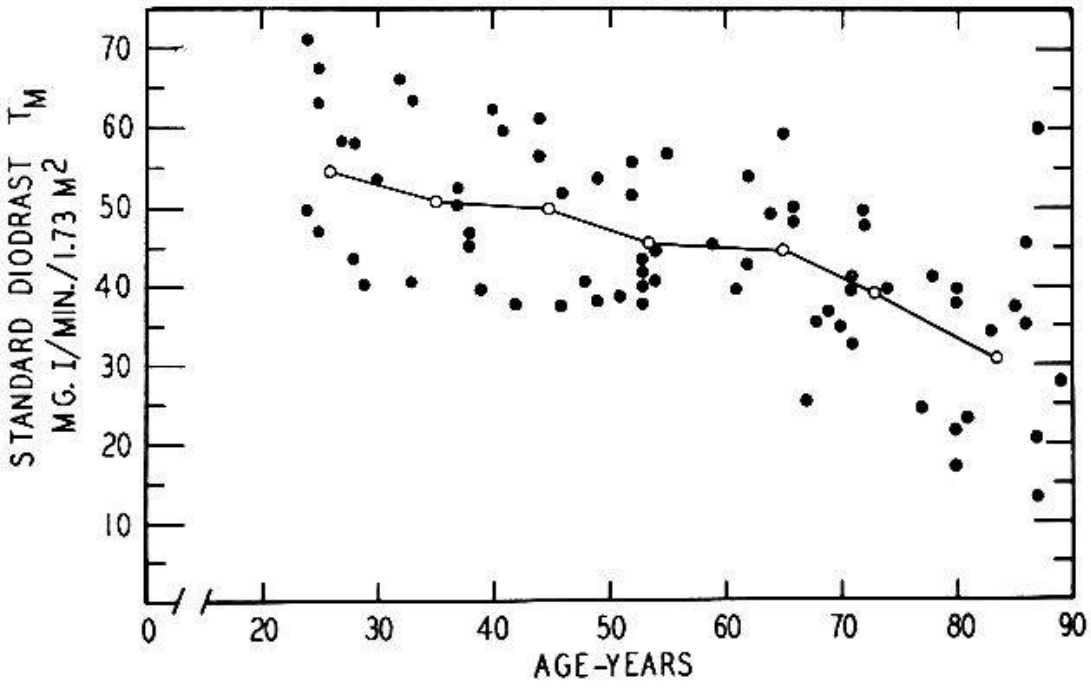

Fig. 9. Change in standard diodrast T_m with age. o—o = average values mg diodrast iodine/min/1.73 m² body surface area. – From SHOCK [12].

significant change in glomerular filtration rate was observed (Fig. 10). In contrast, a significant increase in the PAH clearance was observed in all age groups. Although the mean absolute increases were greater for the young than for the old, when the increments were expressed as % of base

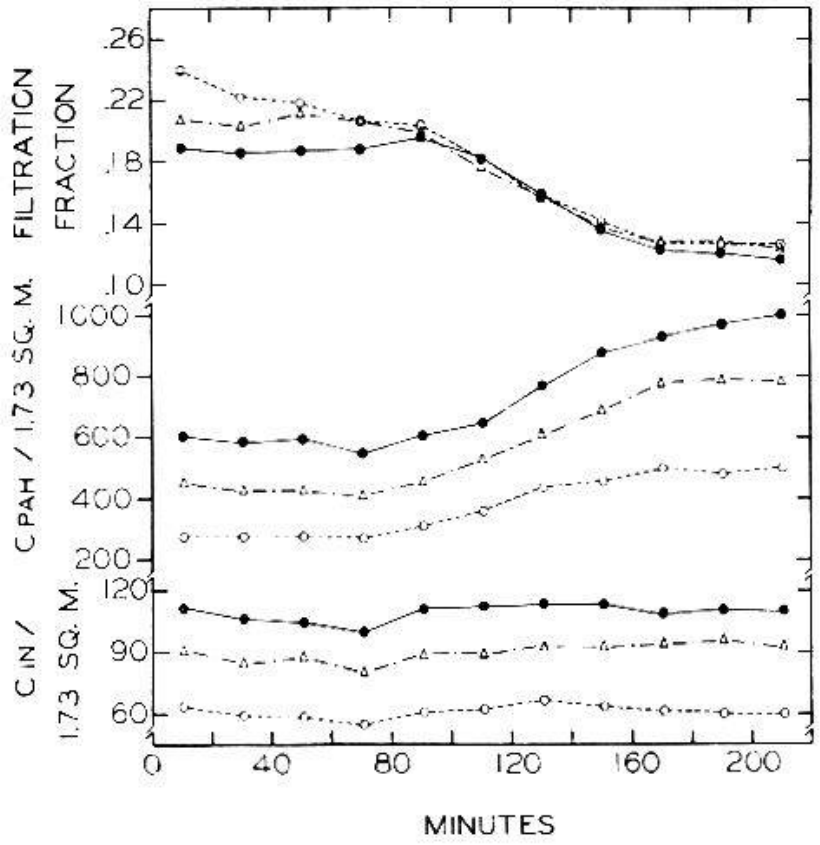

Fig. 10. Changes in C_{In}, C_{PAN}, and FF during pyrogen reaction. 50 million killed typhoid organisms were injected intravenously at 0 time. o---o = Mean value for 14 subjects in O group (70–85 yrs.), Δ·-·-Δ = Mean value for 20 subjects in M group (59–69 yrs.), ●—● = Mean value for 20 subjects in Y group (20–49 yrs.). – From McDonald [13].

line values the rise for the young (aged 20–49, mean 36), middle aged (aged 50–59, mean 58.8), and old (aged 70–84, mean 76.9) groups was 76, 86, and 91% respectively. The filtration fraction (clearance of inulin over the clearance of PAH) diminished markedly in all subjects which indicated a fall in effective filtration pressure which would result from a greater vasodilatation of the efferent and the afferent site of the glomerulus if there was no change in blood pressure. These experiments lead to the conclusion that the renal arterioles in the aged kidney are capable of dilating and that the reduced renal blood flow observed in the aged is in part reversible and therefore not the result of structural changes in the renal vessels alone.

Regulation of the water content of the body depends on the response of the tubular cells of the kidney to diuretic and antidiuretic hormones. In order to assess age differences in responsiveness of the renal tubule cells to a physiological stimulus antidiuretic hormone was administered experimentally to groups of young, middle-aged, and old subjects in whom a maximum water diuresis had been induced [14].

In these experiments the clearance of inulin and PAH was measured continuously during a period of maximum water diuresis. Since urine volumes would be influenced by the number of nephrons functioning, the results of these experiments were examined in

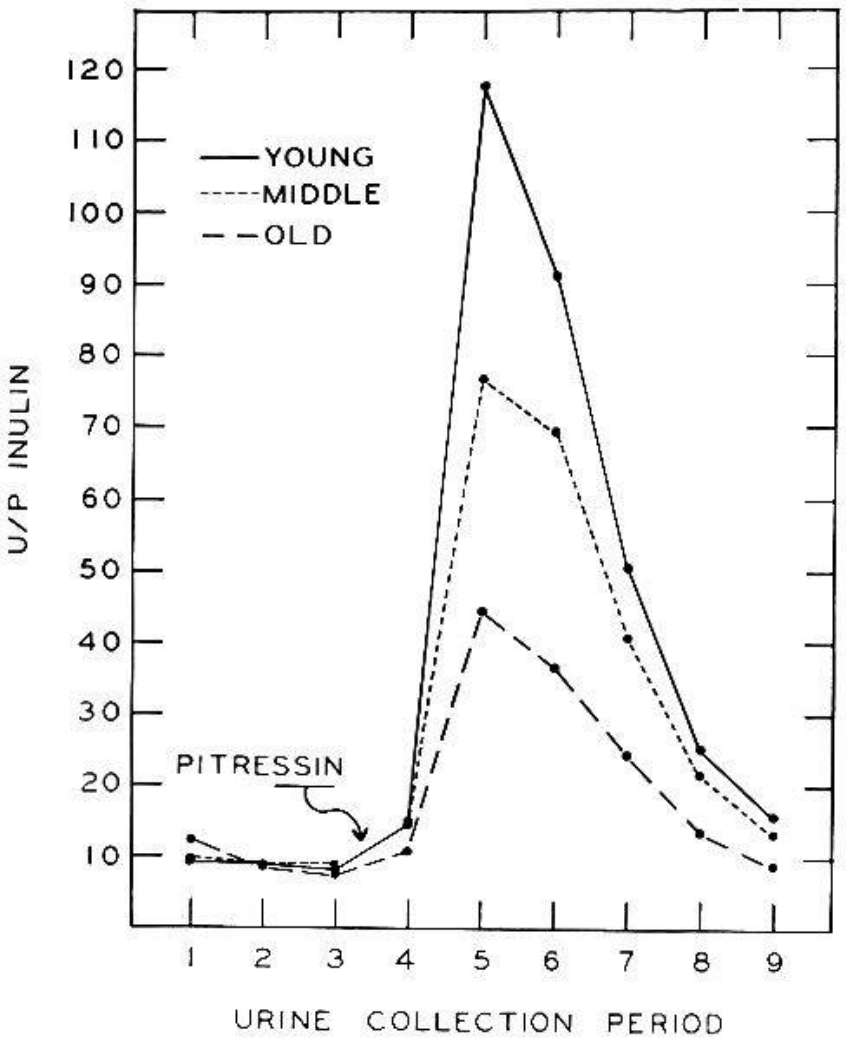

Fig. 11. Mean values of U/P inulin ratio for each of 3 age groups before and after the intravenous administration of pitressin (0.5 milliunits/kg body weight). Urine collection periods 1–9 represent 9 consecutive twelve minute periods. Pitressin was administered immediately after the conclusion of period 3. – From MILLER [14].

terms of the U/P ratio of inulin rather than in terms of urine volume. In this way the age difference in the number of nephrons present was eliminated.

As shown in Fig. 11, the U/P inulin ratio for all three age groups was the same during maximum water diuresis. At zero time, 0.05 units of pitressin were administered intravenously and the renal tubules responded by greatly increasing the amount of water absorbed from the glomerular filtrate, so that the U/P ratio for inulin increased substantially. As can be seen from the figure, the response of the young subjects was greatest, that of the middle-aged subjects intermediate, and of the old subjects considerably less. Thus, it is apparent that the tubular cells in the kidney of the aged subject could not respond to the antidiuretic hormone as effectively as those in young subjects.

In order to investigate further the mechanism of the impaired function of renal tubules in the elderly, experiments were conducted on excised kidney slices from young and senescent rats. Dr. BARROWS et al. have studied the

accumulation of PAH in kidney slices *in vitro* and have found a significant age reduction in the activities of enzyme systems essential for the production of energy required in renal transport mechanisms [15]. We are therefore able to show that aging has an influence on a basic cellular process which results finally in an impairment in a homeostatic mechanism required by the total animal.

Other studies have been conducted to identify age differences in the ability of the kidney to form ammonia which is essential in eliminating excess acid from the body [16].

In these experiments renal blood flow, glomerular filtration rate, and excretion of ammonia, acid, etc., were measured in old and young subjects following the oral ingestion of 10 g of ammonium chloride.

The elderly subjects excreted substantially less ammonia per unit of time than did the young subjects. However, since measurements of renal blood flow and filtration rate were also available, it was possible to show that the primary factor involved in this reduction in ammonia excretion was the fall in glomerular filtration rate. In fact, no evidence could be obtained to indicate that the mechanisms for ammonia formation were operating any less effectively in the old subjects than in the young.

There are obviously many other physiological processes such as the regulation of body temperature, blood pressure, response to exercise, etc., which call into play homeostatic mechanisms. There is also the broad area of the regulatory aspects of endocrine and neural functions which has been studied extensively by FROLKIS et al. [17] in the Soviet Union. Unfortunately time will not permit a detailed review of this literature but I hope that I have been able to present examples which will illustrate the general principles of gerontological research. We are a long way from understanding the detailed mechanisms of aging but it is only by detailed analytical studies where we can make progress. I hope I have illustrated the fact that, although many of the problems of aging originate in studies on the human, an understanding of the mechanisms of these processes requires an experimental approach which must often utilize other animal species and other systems. However, the goal of experimental gerontology is to understand aging and thus to deal rationally with the problems of elderly people.

Summary

One of the primary functions of many organs of the body is to maintain the internal environment within fairly close limits. Aging has little effect on the ability of the individual to maintain the constancy of the internal environment under resting or basal conditions. However, when displacements occur in the internal environment (blood) more time is required by old than by young subjects to readjust the blood to normal values. Thus aging is associated with an impairment of homeostatic mechanisms. In some organ systems such as the kidney, the age impairment is associated with the

loss of functioning elements (nephrons). In other systems, such as regulation of blood sugar levels, the age impairment is associated with the decrease in the sensitivity of control mechanisms. Further studies of the effect of age on a variety of physiological control systems represent an important area of research for gerontology. Although many of the problems of aging originate in studies on humans, an understanding of the mechanisms of age changes requires an experimental approach which must often utilize animals other than humans. However, the goal of experimental gerontology is to understand aging and thus to be able to deal rationally with the problems of elderly people.

Zusammenfassung

Eine der grundlegendsten Funktionen vieler Organe des Körpers besteht im Aufrechterhalten des «inneren Milieus» innerhalb ziemlich enger Grenzen. Der Alterungsprozeß beeinflußt die Fähigkeit des Individuums zur Erhaltung der Konstanz des inneren Milieus unter unveränderten oder fundamentalen Bedingungen nur wenig. Falls aber im inneren Milieu (z. B. im Blut) Veränderungen vorkommen, dann ist bei älteren Leuten zur Wiederherstellung normaler Werte mehr Zeit erforderlich als bei jungen.

Altern ist demnach mit einer Schwächung der homöostatischen Mechanismen verbunden. In einigen Organsystemen, wie z. B. der Niere, geht diese Schwächung Hand in Hand mit dem Verlust bestimmter Elemente der Funktion (Nephronen). In anderen Systemen, wie z. B. bei der Regulation des Blutzuckerspiegels, ist die Verminderung im Alter mit einer Abnahme der Empfindlichkeit der Kontrollmechanismen verbunden.

Weitere Studien über die Wirkung des Alterns auf verschiedene physiologische Kontrollsysteme bilden ein wichtiges Forschungsfeld der Gerontologie. Obwohl die Kenntnis mancher Probleme des Alterns auf Untersuchungen am Menschen beruht, benötigt man, um den Mechanismus der Alterungsprozesse zu verstehen, ein experimentelles Vorgehen, das meistens auf die Verwendung von Tieren angewiesen ist und nur selten am Menschen selber ausgeführt werden kann. Wie dem auch sei, das Ziel der experimentellen Gerontologie liegt im Verstehen der Alterungsvorgänge und in der Fähigkeit, die Probleme älterer Menschen rationell zu behandeln.

Résumé

L'une des principales fonctions de plusieurs organes de notre organisme est de maintenir les conditions du milieu interne dans des limites très étroites. La vieillesse n'altère pas sensiblement cette faculté de maintenir à l'état constant ce milieu interne dans des conditions inaltérées ou fondamentales. Toutefois, lorsqu'il arrive un changement dans le milieu interne (par ex. dans le sang), les personnes âgées ont besoin de plus de temps pour réajuster les valeurs à la normale.

La vieillesse va ainsi de pair avec une certaine déficience dans les méca-

nismes homéostatiques. Dans certains types d'organes comme le rein, la déficience due à la vieillesse est liée à la disparition d'éléments fonctionnels, comme le néphron. Dans un autre ordre de système de régulation, comme le maintien de la glycémie, c'est une diminution de la sensibilité des mécanismes de contrôle qui s'accentue avec l'âge.

D'autres études sur les effets de l'âge dans un grand nombre de systèmes de contrôle physiologiques représentent une part importante des recherches en gérontologie. Quoique bien des problèmes de gérontologie aient commencé par l'étude de l'être humain, il est nécessaire pour comprendre les mécanismes du vieillissement de faire appel à l'expérimentation sur l'animal. Le but de la gérontologie expérimentale est de mieux comprendre le phénomène du vieillissement et ainsi d'être capable de résoudre plus rationnellement les problèmes qui se posent aux personnes âgées.

Riassunto

Una delle funzioni fondamentali di molti organi del corpo consiste nel mantenere «l'ambiente interno» entro limiti abbastanza stretti. Il processo di senescenza influenza poco la facoltà dell'individuo di mantenere costante l'ambiente interno a condizioni immutate o fondamentali. Tuttavia, quando nell'ambiente interno (per esempio nel sangue) avvengono dei cambiamenti, le persone anziane hanno bisogno di maggior tempo per raggiungere nuovamente i valori sanguigni normali che non i giovani. La senescenza è quindi accompagnata da un indebolimento dei meccanismi omeostatici. In certi organi, come per esempio nei reni, questo indebolimento si produce contemporaneamente alla perdita di alcuni elementi funzionali (nefroni). In altri sistemi, come per esempio nel caso della regolazione del tasso glicemico, la diminuazione dovuta alla senescenza è collegata alla perdita di sensibilità dei meccanismi di controllo. Ulteriori studi riguardanti l'azione della senescenza sui diversi sistemi fisiologici di controllo rappresentano un campo di ricerca importante della gerontologia.

Quantunque la conoscenza di molti problemi della senescenza si basi su ricerche fatte sull'uomo, per comprendere il meccanismo dei processi dovuti all'invecchiamento, abbiamo bisogno di una procedura sperimentale che in generale deve servirsi degli animali e solo raramente può essere fatta sull'uomo. Comunque sia, lo scopo della gerontologia sperimentale sta nella comprensione dei processi di senescenza e nella capacità di curare in maniera razionale i problemi delle persone anziane.

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