AGEING, INVOLUTION, AND SENESCENCE*

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The clinical phenomena with which physicians are customarily concerned depend on pathological derangements of biological processes. In fact all medical training is directed towards the study of these states. The main thesis to be advanced here is that the biological processes, or morbid derangements thereof, which underlie these clinical phenomena acquire full significance in medicine only when their time sequence is considered with reference to a time scale in the human life-cycle called ageing.

The terms in the title of this article denote phases in the latter part of the life-cycle. However, the remarks which follow are even more applicable to early life, when the organism is growing and developing.

The ideas presented are intended to encourage the student and physician to adopt a new orientation of their knowledge of biological events around the different phases of the life-cycle. In doing so they will obtain a new vantage point from which to view more clearly the multifarious processes of disease.

MEDICAL SIGNIFICANCE OF AGE

To stress the importance of age (or time) may require a few words of justification, for it may seem to some readers a mere play on words—a vague abstraction—for is age not a mere convention for the dating of a series of events in organized development? Not so at all. It is my belief that its true significance goes far beyond this. Biologically, age confers on any category of development, whether normal or abnormal, an orientational as well as a quantitative dimension. A given age always represents a position in the growth scale from the medical viewpoint. Since all the main events in the life-cycle normally occur in orderly temporal sequences and are more or less age-constant for any given species, even one as complex as man, one of the clearest manifestations of disease is a displacement of the individual from the expected position in the chronology of his life-cycle. Usually this takes the form of a regression, i.e. the morbid process of disease either forces the organism backwards or retards its development so that its capacity for adaptation is less than would be expected for its age. What is pathological at any given moment may be appreciated only when comparison is made with normal standards for age.

But the consideration of age (or time) has also another meaning in medicine, for it has been shown that the susceptibility of an organ or system to a given disease is determined by its level of growth, development, and involution. Certain categories of disease are known to predominate in particular periods of life. Anomalies of development, genetically determined metabolic diseases, and certain of the more serious infective processes, for example, tend to declare themselves in infancy and childhood, whereas disease arising from neoplasia, vascular occlusion, atrophy and degeneration are peculiar to late adult life. And then, too, one learns in medicine that each disease, being itself a biological process, has its own temporal attributes. Some diseases evolve slowly, others rapidly; and some exhibit a tendency to inevitable progression whereas others regress spontaneously.

Thus, the medical status of a human organism at any one moment in its life-cycle is the product of its own growth potentialities, its variable capacity to react to disease, the time of action of a given disease, and the cumulative effects of all the injuries and diseases which have previously acted upon it. In a broad sense, tacit recognition is given to these facts in our separation of the specialties of paediatrics and geriatrics.

This critical use of age in medicine is not in any way meant to be restrictive or formalistic. Instead, it should encourage a point of view, and a quest for the natural trends of biological processes as a first step in identifying departures therefrom. It also places a premium on the determination of the range of individual differences among both normal and diseased individuals. The pathological thus takes on a statistical aspect, being defined as a deviation for a person of given age which exceeds the probable range of expected normal individual variation.

Many of these facts seem too obvious to dwell upon, but a moment's reflection brings to light a curious paradox. In paediatrics, standards of growth, development and maturation are recognized as providing the background against which every potential pathological process must be viewed. The accomplished paediatrician is expected to know, with reasonable certainty, the time of appearance and disappearance of a large range of reflex and automatic activities, perceptual abilities, language skill, and various cognitive phenomena. But at the other end of the life-cycle, perhaps because of man's irresponsible egotism or unconscious wish for immortality, there has been an unwillingness to accept involution and ageing as the natural and inevitable phases of life. Not a few medical scientists and physicians insist that all change at this time is but the cumulative effect of injury and disease.

The general effects of advancing age and the ways in which it alters organ function, susceptibility, and reaction to disease will be summarized.

THE MEASURE OF GROWTH AND AGEING

As a first generalization, it may be said that the natural length of life is an integral characteristic, built, in some mysterious way, into the organism. The rat is old at 2 years; the rhesus monkey survives for 20 - 25 years; the Galapagos tortoise lives to be 100 years old. Man, like the African elephant, may expect to continue for 70 - 75 years. The duration of animal and human life correlates roughly with the size of the brain. Despite all the publicity about medical science lengthening man's life, this has been only a statistical change brought about by controlling infant mortality and infectious disease. Thereby more people are enabled to reach the upper limit of life expectancy. In fact, since biblical times, when man was said to be allotted threescore and ten years, the span

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of human life has not lengthened greatly. As Tappel[1] remarks, the clock inevitably runs down for the average person before the 75th year, and it seems to make little difference whether he inhabits a luxurious urban apartment or a primitive hut. Only the exceptionally endowed person lives beyond this.

With advancing age there is a steady, inexorable susceptibility to fatal disease. The probability doubles about every 8 years as one grows older. Susceptibility parallels decline in growth rate of the body. But the disease to which man ultimately succumbs, be it cancer, coronary occlusion, or some other malady, does not greatly alter his predetermined life-span. If he were fortunate enough to avoid such conditions his life would not be lengthened much beyond 10 years. Interestingly, delay in growth by undernutrition in childhood has been shown to delay ageing in animals and also the vulnerability to disease in their senescence. Whether overnutrition has the opposite effect is not known. It has also been observed that whole-body irradiation hastens ageing and increases susceptibility to disease and death.

For a long time the general process of ageing in the whole organism has been measured by calculation of the mortality rate, which correlates with age. This fact, derived more than a century ago from crude biological data by Gompertz,[2] states more specifically that the probability of death increases geometrically with time, a formulation which is found to apply to many species, including man. Expressed in mathematical terms, death rate (DR), meaning the number of individuals dying per unit time/survivors at the beginning of that unit of time is:

$DR = R_0 e + a t$,

where a = Gompertz's constant, t = age, and R_0 = extrapolated death rate at zero time.

Graphically the curve assumes the shape shown in Fig. 1.

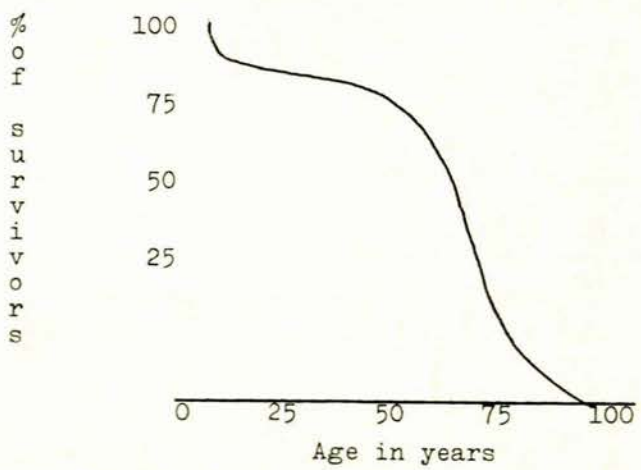

Fig. 1. Correlation of mortality rate and age.

But to the biologist and physician death, of course, is not the main consideration. What are more meaningful are indices of vitality, of resistance to disease and of organ efficiency. In point of fact senescence is defined in such terms, i.e. the decline of vitality, the progressive lowering of biological efficiency and the diminution of the capacity of the organism to maintain itself as an efficient machine. Early loss of certain functions is called involution; unexpected, premature decay of any given tissue or cell population has been termed abiotrophy.

The composite of overt bodily changes due to senescence such as the cessation of bodily growth, wrinkling of the skin, greyness of the hair, loss of teeth, involution of the sexual organs, loss of acuity of the senses, bent posture, weakening of muscular power and co-ordination, rigidity of mind, conservative views, and forgetfulness are known to every observant human. Many of these changes have been subjected to measurement by biological scientists. When considered one by one, it is evident that waning vitality or senescence has different times of onset and rates of progress in different organ systems. Measurements of visual and auditory acuity are said to reach their maximum at the age of 10 years and resistance to infection at 15 years, whereas intellectual power reaches its peak at about the 21st year, and muscular power and co-ordination at the 25th. Shock[3] has composed a table giving rough estimates of decline in the efficiency of various organs from the age of 30 to 75 years.

TABLE I. PHYSIOLOGICAL DECLINE WITH AGE (FROM N.W. SHOCK)[3]

1. Brain weight—46%
2. Blood flow to brain—20%
3. Speed of return of blood acidity to equilibrium after exercise—83%
4. Cardiac output at rest—30%
5. Number of glomeruli in kidney—44%
6. Glomerular filtration rate—31%
7. Kidney plasma flow—50%
8. Number of fibres in nerves—37%
9. Nerve conditions velocity—10%
10. Number of tastebuds—64%
11. Maximum oxygen uptake (during exercise)—60%
12. Maximum ventilation volume (during exercise)—47%
13. Vital capacity—44%
14. Less adrenal activity
15. Less gonadal activity
16. Power of hand-grip—45%
17. Maximum work rate—30%
18. Basal metabolic rate—16%
19. Body water content—18%
20. Body-weight (males)—12%

Senescence appears, then, to be a diverse and complex process with manifestations in all the structures and functions of the body. The clinical problem set before the physician is to separate these declining forces of vitality from the effects imposed by the accidental impingement of injury and disease.

AGEING IN SPECIAL ORGANS AND TISSUES

The Nervous System

Of all the age-related changes in the various organ systems of the human body, those in the nervous system are of paramount importance. On the stage the actor, who caricatures the old man by portrayal of feeble action, idleness and seeming preoccupation, bent posture, short shuffling step, tremulous hands, soft voice, obstinacy and rigid conservative opinions and a tendency to reminisce, has selected some of the principal nervous effects of age on the nervous system. The lay and medical observer customarily interprets these changes as a kind of reversion to the ways of early life—the second childhood.

le troisieme enfance; 'old men are boys again', to use the words of Aristophanes. While roughly correct, this view of old age stems largely from certain resemblances, superficial at best, of the senile dement and the helpless infant.

The most consistent neurological abnormalities of octogenarians, described by Critchley and others,[4] include presbyopia, presbyacusis, reduced rates of activity, slowed reaction time, slowness and reduced range of perception (inapperception of the aged), small pupils with restricted pupillary light, and convergence reflexes, limited range of upward gaze, tendency to flexed posture of the trunk and limbs, diminution of vibratory and to a lesser extent other forms of sensation over feet, loss of fine co-ordination, weakening of muscle power, thinness of musculature, and reduced or absent Achilles reflexes.

But probably the most detailed information about changes in cerebral function comes from the study of the cognitive processes. Intelligence, perception, memory, mental efficiency and speed, which have been measured by psychological tests, reveal a decline in all these intellectual activities, starting in early adult life and progressing to the senium. On a large sample of the population the regression is linear, but the losses are anything but uniform and predictable. A few individuals of 90 years may retain mental competency and perform creative work. Lehman[5] notes instances of exceptional mental power persisting into the eighth and ninth decades of life. Verdi, for example, composed *Otello* at the age of 73 years and *Falstaff* at 79; Humboldt wrote the 5 volumes of his *Kosmos* between the ages of 76 and 89 years; Goethe produced the second part of *Faust* when he was more than 70 years old; Galileo and LaPlace went on making scientific contributions in their eighth decades. It must be pointed out, however, that most of these works were but continuations of studies that had occupied them when young. Indeed, little that is new and original is commenced after the fortieth year. Deterioration of the capacity to memorize, while retaining learnt material of the past, and the relative preservation of verbal skill characterizes many of the mental performances of the aged. High intelligence, well-organized habit patterns, and sound judgement compensate for many of these deficiencies.

Personality changes in the aged are less easily measured but nevertheless certain consistent trends have been observed, and they may seriously derange the life of the individual and those around him. Many old people become obstinate, self-centred, rigid and conservative, but the opposite qualities are observed in a few: undue pliancy, boastfulness, vacillation, and uncritical acceptance of ideas. Whereas environment appears to play a part in moulding these traits, Kallman's[6] studies of senescent, monozygotic twins suggest that genetic factors are the more important. Aggressive individuals with much energy and a diversity of interests and wide range of social interaction appear to preserve better their balance and adjustment and to resist the ravages of age than those with the opposite tendencies. But of even greater importance is the depressive mood, the attitude of mixed hopelessness, defiance, fear, worry, suspiciousness and distrust, which feature in a considerable proportion of ageing personalities and account for the 3-fold increase in the suicide rate in late middle life and old age. Involutional agitated depressive psychosis is the most frequent psychiatric illness of this period of life.

The morphological bases of these involutional changes in the nervous system have never been fully established. From early adult life to the senium the average male brain weight declines from 1,375 to 1,232 G—a loss of nearly 150 G. This is based on a loss of neurons and replacement gliosis, amounting to as much as 30 - 35% of the lumbar anterior horn cells, lumbosacral sensory ganglion cells, and Purkinje cells. An extreme degree of lipofuscin accumulation accompanies this loss, being especially prominent in thalamic and certain other neurons. Such changes are often termed 'arteriosclerotic', but there is no evidence that they depend on any recognized form of vascular disease.

The Musculature

The skeletal muscles also lose cells (fibres), and the reduction in their weight parallels that of the brain. This is expressed clinically by a diminution in peak power as well as endurance, and by a striking thinness. My own studies convince me that the wasting involves several processes, some primarily myopathic, others reflecting loss of motor neurons. The number of muscle cells diminishes with age, the lost fibres being gradually replaced by endomysial connective tissue and fat cells. But surviving fibres are thinner than normal (? disuse atrophy) and groups of fibres all in the same stage of atrophy undoubtedly manifest denervation from degeneration of anterior horn cells. Reduced conduction velocity of nerves is another index of this loss of motor and sensory axons.

The Lungs

As to respiratory function, maximum O_2 uptake, ventilation volume, and vital capacity progressively diminish with age—the last-mentioned from an average of 4·8 litres/min. at the age of 35 years to 3·5 litres at 65 years, according to Bates and Christie.[7] Coincidentally, lung volumes increase from 2·9 to 3·5 litres, due to diminution in elastic recoil. The efficiency of pulmonary function, as determined by evenness of mixing of inspired helium, falls from 75 to 54% in the same age periods. Oxygenation of blood, noted especially under conditions of stress, is also progressively reduced. No doubt the decline in O_2 absorption in part reflects reduced cardiac output, for less blood flows through the lungs of an older person in a given unit of time, but the absorptive surface of the lung is also altered.

The problem of emphysema remains unsettled. While obstructive bronchial disease and chronic cough favour its development during middle age, earlier in life these factors do not have this effect. This suggests that an age-linked change, perhaps the loss of elasticity, must be operative. A special form of purely senile emphysema, reflected in increased anteroposterior thoracic diameter and increase in respiratory rate with minimal physical exertion, seems also to parallel ageing.

Heart and Circulation

With respect to cardiac and circulatory activity it has been more difficult to separate out the effects of ageing and disease, particularly atherosclerosis and hypertension. Although the resting blood pressure in elderly individuals increases only slightly with age, a given amount of exer-

cise will raise the heart rate and blood pressure in old people more than it will in young individuals. Under conditions of maximal exertion the aged person cannot achieve as great an increase in cardiac output. This is the factor that limits work and muscular efficiency. The output falls from an average of 3·75 litres/100 sq.in. of body surface at the age of 30 years to 2·0 litres in the 80-year-old subject. In individuals who have escaped atherosclerosis and hypertension the heart gradually diminishes in weight with advancing years; the cardiac muscle cells undergo slight atrophy and accumulate 'wear and tear pigment'. Extreme atrophy of individual muscle fibres, with relative hypernucleation and mild fibrosis, completes the picture of 'brown atrophy'. The aortic valves also thicken and the mitral ring calcifies. Progressive deposition of calcium salts on the aortic valve, Mönckeberg's calcific valve change, leading often to stenosis and incompetency, appears more often to be the consequence of disease than of ageing. The vessel walls of arteries thicken slightly, the internal elastic lamina becomes reduplicated, and collagenous tissue may become hyalinized.

Kidneys

Between the third and eighth decades of life the blood flow through the kidney diminishes by 55%. The glomerular filtration rate and the maximum excretory capacity reabsorption rates decline to about the same extent. The number of functional units (nephrons) is reduced with age and there is a loss of both glomeruli and collecting tubules. On the other hand, the intrinsic capacity of one kidney to hypertrophy in the first 30 days after the removal of the other one does not seem to change significantly through the successive decades of late life. Nor does the increase in blood flow upon administration of a pyrogen. Having fewer functional units and less circulation, the ageing kidney takes more time to clear the blood of toxic agents. This is reflected by rising blood urea levels under all manner of conditions of systemic diseases; an abnormality which increases with age.

Skin and Supporting Tissues

In the skin and connective and elastic tissues the uniformity of ageing effects are well known and induce vain individuals to expend vast sums on cosmetics and beauty and health treatments in desperate attempts to counteract them. Fine wrinkling and looseness of skin, the increase in ectopic pressure lines, the prominence of temporal vessels, the greying and loss of scalp hair, the coarsening of the hair of the nostrils, and the female tendency to facial hirsutism, the tendency to slow wound healing and the formation of senile keratoses (warts) and increasing incidence of skin cancer on exposed surfaces represent the more frequent changes. Bean[8] and others point also to venous stars in the lower legs and thighs, and over the ribs; to cherry angiomas (ruby spots, DeMorgan spots); and to sublingual varicosities (caviar lesion), as having an unmistakable age relationship. Even in Osler's hereditary, haemorrhagic telangiectasis the vascular lesions of skin seldom appear (or bleed) before the third decade.

Studies of collagen from skin and other organs disclose a decreasing solubility with age, and an increasing number of reticulin fibrils and a density of collagen fibres. As the collagen fibres degenerate they take on some of the staining properties of elastic tissue. In the arteries a similar series of changes occur, i.e. the medial elastic tissue splits, is duplicated, and calcifies with age. There is disagreement as to whether senile elastosis of the skin is due to degeneration of collagen or elastin.

Endocrines

Here gonadal deterioration is one of the most constant and inevitable marks of ageing. In the woman the arrival of menopause marks the end of her reproductive period, and this fortunately or unfortunately happens long before ageing effects are evident in other organs and tissues. In the male sexual vigour also diminishes, but, as all recent studies have shown, it persists for longer than was formerly believed possible. The number of ova in the ovaries and the number of spermatogonia and Leydig cells in the testis diminish with age. Gonadal atrophy is associated with uninhibited overactivity of the FSH production in the pituitary, and in the female this is of sufficient degree to cause vasomotor instability (hot flushes).

The basal metabolic rate falls slowly with age. Total urinary corticoid and 17-ketosteroid excretion decrease with increasing age. To cite one study, Pincus[9] and his associates found reduction in both 17-ketosteroids and corticoids, the former more than the latter. Methods which separate urinary and adrenal steroids show both to be affected, in the male and in the female. Stimulation of adrenals by ACTH diminishes with age.

Pituitary stimulation from failure of various endocrine glands results in the hyperplasia of certain cellular elements, with increasing tendency to adenoma formation.

THE CELLULAR BASIS OF AGEING

Many mechanisms are presumed to underlie the effects of age on the cellular constituents of the aforementioned organ systems. Recent investigative efforts have been directed along 3 lines: (*i*) the decline in the functional efficiency and finally the deterioration and death of highly specialized, non-dividing cells such as the muscle fibre, neuron, etc.; (*ii*) the failure of cell multiplication and of the process of mitosis in tissues composed of dividing cells; and (*iii*) the progressive alteration with age of the structural proteins (collagen) which constitute about one-third of the body protein and bind together elements of skin, muscle fibres, bones and blood-vessels, and elastin.

The Life-span and Ageing of Specialized Cells

Nerve and muscle cells which cease to divide early and must last the lifetime of the organism are known to have a variable life-span. If accidentally destroyed by disease, of course, they are never replaced. But in the absence of disease there is a steady fall-off which begins at about the end of the period of growth and maturation and continues at an accelerated pace into the senium. Functional deficits in organs such as the brain are in large measure to be ascribed to cell loss. Here emerges the fact that each organ is endowed with a safety factor, i.e. a protective excess of cells that must be surpassed before symptoms appear. Whether cells begin to falter functionally before their final disintegration is unknown.

The cytological events leading to death of non-dividing cells are little understood. In man as well as animals accumulation of lipofuscin in the cytoplasm of these cells

is a constant phenomenon of such predictability that it can be used as the most reliable cytological index of age. Called 'wear and tear' pigment, lipochrome or lipofuscin, these yellow granules form in the cytoplasm of nerve and muscle cells, being derived in all probability from lysosomes, or possibly mitochondria. Simultaneously with their formation the cell diminishes in volume, due presumably to loss of other cytoplasmic components such as Nissl bodies (the main cytoplasmic RNA in nerve cells) and mitochondria. The nucleus also becomes smaller, with infolding of the nuclear membrane and alteration of the nucleolus. Histochemical stains reveal a depletion of oxidative as well as phosphorylative enzymes. All of these changes have been verified in tissue culture.

Some of the speculations as to the mechanism of these morphological changes are of interest. Comfort[10] attributes them to progressive exhaustion of cell catalysts (enzymes and coenzymes), but this explanation does no more than restate the problem in a vague biochemical formulation. Tappel[1] has imaginatively ascribed them to the effects of cosmic radiation, which are believed to act on the unsaturated lipids of cell membranes, thereby initiating 'a process of peroxidation'. He picturesquely writes of the molecular havoc wreaked by the release of lysosomal enzymes and refers to the residual lysosomal granules as 'clinkers'. Biological anti-oxidants such as vitamins C and E, glutathione, cysteine, and sulph-hydryl proteins are said to counteract the process.

Loss of the Capacity for Cell Growth and Multiplication

The studies of Hayflick[11] and his colleagues on the innate capacity of cells to divide in tissue culture may shed light on this problem. They found—contrary to the original experiments of Alexis Carrel,[12] which showed that cells removed from the animal body and properly sustained and nourished in tissue culture could continue to live and divide for ever—that each fibroblast is destined to divide only a certain number of times. Fibroblasts from a human infant divide about 50 times; those of a 20-year-old about 30 times; and those from an 80-year-old person about 20 times. Towards the end of the life-cycle of the cell chromosomal aberrations and peculiarities of cell division begin to appear. Only if a special neoplastic type of change takes place, with the cells becoming 'mixoploid' (50 - 350 chromosomes per cell), many of which are abnormally formed, do the cells attain the immortality postulated by Carrel. Male and female cells behave alike, whether grown singly or together. Probably leucocytes and liver cells also possess a genetically determined capacity of limited mitosis.

What underlies the diminishing capacity of cells to divide? Wide variations in the tissue culture technique, mixing clones of young and old cells, exclude noxious agents in the cell environment. It is an intrinsic property of the cells themselves. Hayflick[11] sees it as a deterioration of the 'genetic program that orchestrates the development of cells'. Perhaps with the passage of time the DNA molecules of the dividing cell become deformed with an ever-increasing number of copying errors. Or, perhaps, depletion with age of certain enzymes involved in the transcription of DNA for the synthesis of proteins may occur. At all events these studies trace the secret of ageing in dividing cells back to some obscure degeneration of inherited information-containing molecules in the cell nucleus which provides the final control of cell division. Of course, one must not overlook the possibility that cells may behave differently in tissue culture than *in vivo*.

The Ageing of Collagen

Constituting 40% of all the protein in the body and undergoing certain consistent alterations in skin, muscles, bones and joints and blood-vessels, it is only natural that biologists should look at this substance for clues to the ageing process. Once the fibres of collagen are laid down they are not renewed. Labelled constituents of collagen show no 'turnover'. The long chains of amino-acid units that make up collagen are synthesized by fibroblasts. The chains, which consist of about one-third proline and glycine in a ratio of 2 : 1, are extruded from the cells into the ground substance of mucopolysaccharides and mucoproteins. These precollagen elements undergo a unique transformation wherein the proline becomes hydroxyproline by the attachment of OH sidechains. The latter figure in the formation of a left-handed alpha helix, which in turn coils with two right-handed helices, thus composing the basic tropocollagen units which are joined end-to-end as collagen.

Verzár and his associates[13] find that ageing collagen contracts more strongly when heated (tensile strength and elasticity increase), due possibly to the formation of more H bonds along the sides of the collagen strands between tropocollagen molecules. They have also discovered a lesser degree of solubility of the amino acids of ageing collagen, particularly of hydroxyproline. A diminishing amount of extractable elastin also runs parallel to age, but the change is less marked than in collagen. Chemical analyses have shown the aspartic- and glutamic-acid components of elastic tissue and amide nitrogen content to increase with age, whereas glycine, proline and valine decrease. To date there is no information on why these changes in ageing collagen and elastin occur.

AGE-RELATED DISEASES

In the aged and infirm the usual listed causes of death are tumour, infection (chiefly pulmonary), fractures of the hip, and vascular diseases of heart and brain. These conditions are also linked to advancing age, but the relationship is anything but specific.

That most tumours occur with increasing frequency in middle and late adult life there can be no doubt. Only in the most advanced ages does the incidence tend to fall. The cytological events that lead to neoplasia are unknown. One evidence of this tendency has been observed in experimental animals exposed to gamma-radiation which increases the incidence of tumours of many organs; a linear relationship has been shown between intensity of exposure and frequency of tumour. One class of endocrine tumours appear to form during periods of intensified functional demands, e.g. pituitary adenomas with atrophy of the gonads and adrenals. The increasing number of chromosomal aberrations observed in the later divisions of fibroblasts may be the basis of the increasing disposition to neoplasia.

As to the aged person's intolerance to infection, it may well relate to the failure of the ageing organism to adapt to environmental changes, rather than to any failure of

the normal process. Old animals are slower in adjusting to high and low atmospheric temperatures, whereas the levels of antibodies, the quantity of gamma- or immune globulins (and other plasma proteins) and the production of leucocytes are all surprisingly well preserved in old age. Pathologists are inclined to stress the atrophy of the adrenals and the germinal centres of lymph nodes and the thymus as indications of the incompetence of stress mechanisms, but the basis of the increased mortality in infection is probably more subtle. In every major illness in the elderly the exigencies of disease cannot be met because of a combination of organ inadequacies, no one of which is sufficient to become manifest during the healthy state. The sum total of all these organ deficits constitute a kind of *gestalt* of senility; the seemingly endless list of diseases found in the elderly at autopsy reflect the universality of both disease and age effects. But the latter, being relatively inapparent, are overlooked, which is the reason one is so often prompted to ask, during the autopsy of an elderly person: 'What was the cause of death?'

THE OBJECTIVES OF GERONTOLOGY

Is age as inevitable as our exposition of this subject implies? Can the immutable running down of cells and their increasing disposition to neoplastic change be altered? These are some of the basic biological considerations that await solution.

But until answers are secured the group of physicians concerned with diseases of the ageing human population known as geriatrics must be satisfied with the attainment of lesser objectives. They must reach an understanding of the common diseases of the senium with the idea of prevention and more effective therapeutic control. Since ageing does not occur simultaneously in all tissues and organs, and the patient often seeks help with certain of its effects at a time when most organs are relatively intact, many of the common restricted involutional losses may be corrected—the greying hair can be dyed, the long hairs of ears and nostrils clipped and the bald head wigged with a toupee. Others can be turned to assets—the faulty memory of the aged and their deafness excuse much and spare effort and annoyance. Finally, some of the chemical involutions can be corrected. Those which cause pernicious anaemia and subacute combined degeneration of the spinal cord are effectively treated with vitamin B_{12}; senile heart failure is responsive to digitalis; presbyopia is corrected by eyeglasses, etc.

Some physicians hesitate to diagnose disease as due to involution until after threescore years and ten, or avoid the diagnosis altogether because it suggests an incurable condition. Both reasons are incorrect. Many involutions, like presbyopia, can be demonstrated in their larval stages in the twenties and by the mid-forties failing visual accommodation is almost universal; and the disorders of uric acid metabolism called gout are manifest before the age of 40 years in an appreciable percentage of all those finally recognized. Many involutions or abiotrophies, after rapid progress for a few years, become arrested and compensated for in many ways.

The central issue in training for geriatric medicine is to learn as much as possible about the various diseases to which the aged are disposed and to learn how they interrelate to the ageing process. Experience in this field teaches one how energetically to press matters of prevention and treatment under different conditions of disability.

One of the great tragedies of urban civilization that hamper the treatment of elderly people slipping into second childhood, is the inadequacy of institutions for medical care and for independent living; one treats old people as if they were insane. In rural and primitive cultures, such individuals are cared for by their relatives in the familiar environment of their homes. This has become impossible in small apartments. There should be orphan asylums and foundling homes to provide for unwanted people in their second childhood as well as in their first. Psychiatric treatment does not help them. They are upset by the strange environment of the hospital or asylum where they deteriorate rapidly under sedative and antidepressive therapy.

This problem will grow as science brings arterial disease and neoplasia under control. By removing ageing people these diseases have traditionally served an important biological purpose, creating opportunity and removing burdens of the care of the aged from those in the child-rearing age. During the 19th century, when pneumonia killed more people, Sir William Osler called it 'the old man's friend', for, like Ecclesiasticus, he considered death kind to the old and feeble. Inheritance of resistance to involution, arterial disease, and cancer is evident in many families, but this biological blessing is paid for by the necessity of having to live with and support aged relatives. In an urban society such obligations favour late marriage and few or no children. Success in eradicating arteriosclerosis, cancer and rapid ageing will tend to be frustrated by natural selection and the survival of more grandchildren with fewer living grandparents. Atherosclerosis and neoplasm are now the chief factors in preventing our decline into second childhood and overstaying our biologically allotted span of life too long. As O. W. Holmes observed:

'Little of all we value here
Wakes on the morn of its hundredth year
Without both feeling and looking queer.
In fact there's nothing that keeps its youth,
So far as I know, except trees and truth.'

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