The Journal of Mind and Behavior
Spring 1980, Vol. 1, No. 1

Stress, Aging and Retirement

Hans Selye

International Institute of Stress

In dealing with stress, aging, and retirement, I first describe the scientifically established facts constituting the basis of that now-vast field of medicine concerning *stress*. Since the relationship of *aging* to stress is less fully known, however, my treatment of it will necessarily be more speculative and tentative (with a digression on the phenomenon of "calciphylaxis"), ending with a consideration of how to retard the processes of senescence and prolong life.

The topic of *retirement* is a behavioral issue, and I confine myself to the application of stress theory in coping with this great change of one's lifestyle. The principles involved are actually not much different from those required for day-to-day challenges; in fact, it is argued that a moral code for handling stress becomes even more relevant for the aged.

Stress

Stress is defined as *the nonspecific response of the body to any demand,* where "nonspecific" refers to those common changes produced by a variety of agents, or *stressors*. In everyday life we distinguish between two types of stress effects, namely *eustress* and *distress*, depending upon whether stress is associated with desirable or undesirable results. (For a discussion of problems of definition, see Selye, 1952, 1976a, 1976b).

Stress was first recognized by its characteristic triad of symptoms — adrenal stimulation, shrinkage of the lymphatic organs, and gastrointestinal ulcers — as well as by loss of body weight with certain alterations in the chemical composition of the body (Selye, 1936). It was later found to comprise many other changes all of which, taken together, form a syndrome — a set of manifestations occurring at the same time. This was called the *general adaptation syndrome* (G.A.S.), and develops in three stages (Selye, 1976b):

1. *Alarm Reaction.* This happens upon sudden exposure to any stimulus to which the organism is not adapted. The reaction has two phases:

a. *Shock phase,* the initial and immediate reaction to the agent; tachycardia, loss of muscle tone, decreased temperature and blood pressure are typical symptoms. The body's resistance is diminished and, if the stressor is strong enough, as in the case of severe burns or extremes

Requests for reprints should be sent to Hans Selye, M.D., Ph.D., D. Sc., International Institute of Stress, University of Montreal, 2900 Boul. Edouard-Montpetit, Montreal, Canada H3C 3J7.

of temperature, death will result. Here too the characteristic triad first appears.

b. *Countershock phase,* a rebound reaction marked by the mobilization of defensive forces. Most of the acute stress diseases correspond to these two phases of the alarm reaction.

2. *Stage of Resistance.* Resistance is achieved if continued exposure to the stressor is compatible with adaptation. The bodily signs of the alarm reaction have virtually disappeared, as increased adaptive responses successfully check the stress.

3. *Stage of Exhaustion.* If the stressor is severe and prolonged, the signs of the alarm reaction reappear, but now they are irreversible, and the individual dies.

The triphasic nature of the G.A.S. supplied the first indication that the body's adaptability, or *adaptation energy,* is finite. There seem to be two kinds of adaptation energy: the superficial kind, which is ready to use, and the deeper kind, which acts as a sort of frozen reserve. When superficial adaptation energy is exhausted during exertion, it can slowly be restored from a deeper store during rest. This protects us from wasting our resources too lavishly in certain foolish moments, because acute fatigue automatically stops us.

The precise nature of adaptation energy is still unknown. Whatever is lost during stress is not merely caloric energy, since even with sufficient food, exhaustion ensues. One would think that once adaptation occurred, and energy is amply available, resistance should go on indefinitely. But just as any inanimate machine gradually wears out, even if it has enough fuel, so does the human machine sooner or later become the victim of constant wear and tear. Because of this, it is tempting to view the G.A.S. as a kind of accelerated aging, and its three stages as analogous to the three stages of a man's life: childhood (with its typical low resistance and excessive responses to any kind of stimulus), adulthood (during which adaptation to most commonly encountered agents has occurred and resistance is increased) and finally, senility (characterized by irreversible loss of adaptability and eventual exhaustion) ending with death. We shall have more to say about this later, in connection with stress and aging.

Mechanisms. The stress response is mediated through extremely complex pathways. Apart from specific changes, the first effect of a stressor acting upon the body is to produce a nonspecific stimulus. This may be a nervous impulse, a chemical substance or lack of an indispensible metabolic factor, and is referred to simply as the *first mediator* because we know nothing about its nature. We are not even certain that it has to be an excess or deficiency of any particular substance; it is possible that various derangements of homeostasis can initiate the stress response. Undoubtedly, in humans, with their highly developed central nervous system, emotional arousal is one of the most frequent initiators of

somatic stress; yet it cannot be regarded as the only factor capable of causing stress, since stress reactions (that is, nonspecific responses common to all demands made upon a living organism) also occur in primitive animals lacking a nervous system. But even in humans, conscious psychic disturbances are not indispensible, since typical stress reactions can occur in patients exposed to stressors while under deep anesthesia. Indeed, anesthetics themselves are commonly used in experimental medicine to produce stress, and the stress of anesthesia is a serious problem in clinical surgery. (This issue, as well as many other sources of controversy about the stress concept, has been debated in Mason, 1975a, 1975b; Selye, 1975.)

Through the first mediator, the stressor eventually excites the hypothalamus, a complex bundle of nerve cells and fibers that acts as a bridge between the brain and the endocrine system as illustrated in Figure 1. The resulting nervous signals reach certain neuroendocrine cells in the median eminence (ME) of the hypothalamus, where they stimulate the secretion of CRF (corticotrophin-releasing factor), a chemical messenger. In this way a message is relayed to the pituitary, causing a discharge of ACTH (adrenocorticotropic hormone) into the general circulation.

Upon reaching the adrenal cortex, ACTH triggers the secretion of corticoids, mainly glucocorticoids, such as cortisol or corticosterone. These compounds liberate a readily available source of energy for the adaptive responses necessary to meet the demands made by the stressor agent. Some corticoids also facilitate various other enzyme reactions and suppress immune responses as well as inflammation, thereby helping the body to coexist with potential pathogens.

Usually secreted in lesser amounts are the pro-inflammatory corticoids, which stimulate the proliferative ability and reactivity of connective tissue, enhancing the "inflammatory potential." Thus, they help to put up a strong barricade of connective tissue which prevents the pathogenic stressor agent from spreading to other parts of the body. Because of their prominent effect upon salt and water metabolism, these hormones have also been referred to as *mineralocorticoids* (e.g., desoxycorticosterone, aldosterone). The somatotrophic (or "growth") hormone of the pituitary likewise stimulates inflammatory defense reactions.

This chain of events is cybernetically controlled by several feedback mechanisms. For instance, if there is a surplus of ACTH, a short-loop feedback returns some of it to the hypothalamus-pituitary axis, and this shuts off further ACTH production. In addition, through a long-loop feedback, a high blood level of certain corticoids similarly inhibits too much ACTH secretion.

While these events are taking place, another important pathway is utilized to mediate the stress response. Other stress hormones, such as catecholamines (e.g., adrenaline and noradrenaline), are liberated to

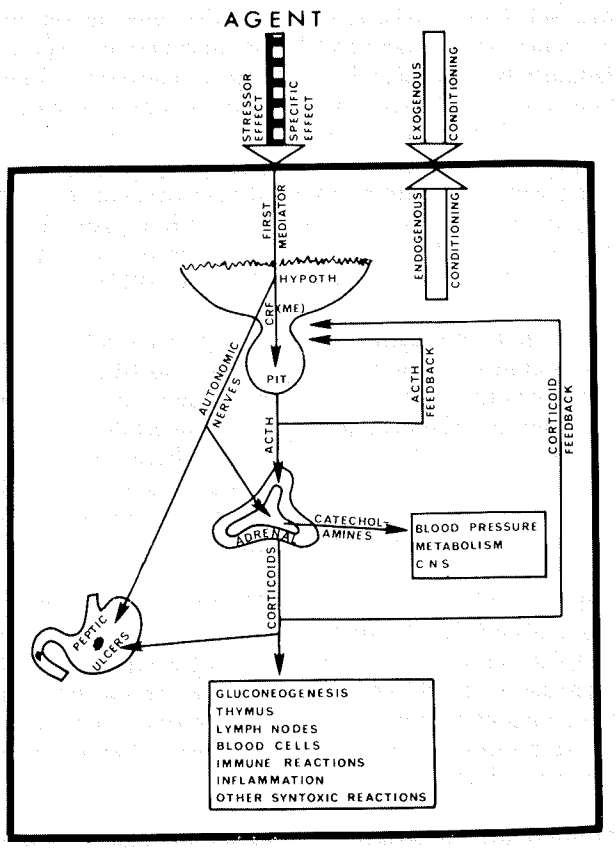

FIG. 1. *Principal pathways mediating the response to a stressor agent and the conditioning factors which modify its effect.* As soon as any agent acts upon the body (thick outer frame of the diagram), the resulting effect will depend upon three factors (broad vertical arrows pointing to the upper horizontal border of the frame). All agents possess both non-specific stressor effects (solid part of arrow) and specific properties (interrupted part of arrow). The latter are variable and characteristic of each individual agent; they are not discussed here other than to state that they are inseparably attached to the stressor effect and invariably modify it. The other two heavy vertical arrows pointing toward the upper border of the frame, represent exogenous and endogenous conditioning factors which largely determine the reactivity of the body. It is clear that since all stressors have some specific effects, they cannot elicit exactly the same response in all organs. Furthermore, even the same agent will act differently in different individuals, depending upon the internal and external conditioning factors which determine their reactivity. (Reprinted by courtesy of Butterworths, Reading, Mass., from H. Selye, Stress in Health and Disease, 1976).

activate mechanisms of general adaptation. Adrenaline in particular is secreted to make energy available, to accelerate the pulse rate, to elevate blood pressure and the rate of blood circulation in the muscles, and to stimulate the central nervous system. The blood coagulation mechanism is also enhanced as a protection against excessive bleeding if injuries are sustained in the encounter with the stressor.

The local response of any directly injured territory to nonspecific stressors is called the *local adaptation syndrome* (L.A.S.), and is mainly characterized by tissue death and reactive inflammation. The L.A.S. and the G.A.S. are closely coordinated. Alarm signals are sent out by the directly stressed tissues to the centers of coordination in the nervous system and hence to the endocrine glands, especially the pituitary and the adrenals. These produce adaptive hormones, which combat wear and tear in the body. Thus, the generalized response (G.A.S.) acts back upon the specific region where the L.A.S. originated (Selye, 1976a).

Homeostasis and Heterostasis

It was the great French physiologist Claude Bernard who first pointed out that the *milieu intérieur* of living organisms is not merely a vehicle for carrying nourishment to cells but that "it is the fixity of this milieu intérieur which is the condition of free and independent life." Walter Cannon later suggested the designation homeostasis for "the coordinated physiological processes which maintain most of the steady states in the organism" — in short, the ability of the body to remain in equilibrium with itself.

There are many complex biochemical mechanisms which ensure the fixity of the milieu intérieur — such coordinated stabilizing responses are called homeostatic. Natural homeostatic mechanisms are usually sufficient to maintain a normal state of resistance; however, when the organism is faced with exceptionally heavy demands, ordinary homeostasis is not enough. The "thermostat of defense" must be raised to a higher level. For this process, I proposed the term *heterostasis* as the establishment of a new steady state by treatment with agents that stimulate the physiologic adaptive mechanisms through the development of normally dormant defensive tissue reactions. Both in homeostasis and in heterostasis, the milieu intérieur participates actively.

The production of natural protective agents can be stimulated by treatment with chemicals that augment the secretion of appropriate enzymes, or by immunization with bacterial products that increase the body's manufacture of antibodies to combat infections.

In homeostatic defense, the potential pathogen automatically activates usually adequate reactions; when these do not suffice to meet the demand, the strength of such responses can be increased by natural agents administered ready-made by the physician. Heterostasis depends upon treatment with artificial remedies that have no direct curative

action, but which can precipitate the production of unusually high amounts of the body's own defensive agents so as to achieve fixity of the milieu intérieur, despite abnormally high demands that could not be met without outside help.

The most important difference between homeostasis and heterostasis is that the former maintains a normal steady state by physiological means, whereas the latter "resets the thermostat" of resistance to a heightened defensive capacity by artificial interventions from the outside. By chemical treatment, this process induces the body to raise the production of its own nonspecific (multipurpose) remedies. However, each type of planned or enforced training of the body through outside interventions also raises resistance from the homeostatic to the heterostatic level.

Heterostasis differs essentially from treatment with drugs (for example, antibiotics, antacids, antidotes, pain killers) that act directly and specifically rather than by strengthening the body's own nonspecific defenses; in treatment with drugs, the milieu interieur is passive (Selye, 1976a).

Syntoxic and catatoxic reactions. The biochemical activity of the stress syndrome depends mainly upon two types of reactions — syntoxic and catatoxic. Apparently, in order to resist different stressors, the organism can regulate its own reactions through chemical messengers and nervous stimuli which either pacify or incite to fight. Syntoxic stimuli act as tissue tranquilizers, creating a state of tolerance which permits peaceful coexistence with aggressors. The catatoxic agents cause chemical changes, mainly through the induction of destructive enzymes, which lead to an active attack upon the pathogen, usually by accelerating its metabolic degradation.

Presumably, in the course of evolution, the body has learned to defend itself against all kinds of challengers, whether arising in the body or externally introduced, through these two basic mechanisms. Among the most effective syntoxic hormones are substances produced by the adrenal cortex, which I have called corticoids. The best known members of this group are the anti-inflammatory corticoids such as cortisone and related substances which inhibit inflammation and many essentially defensive immune reactions. These corticoids are being effectively used in the treatment of diseases in which inflammation itself is the major cause of trouble, such as inflammation of the joints, eyes, or respiratory passages. Likewise, they have a marked inhibitory effect on the active rejection of grafted foreign tissues (Selye, 1976a).

Direct and indirect pathogens. If a person accidentally puts a hand in strong acid, alkali, or boiling water, damage will occur regardless of vital reactions, because all of these are direct pathogens; they would cause injury even to the hand of a cadaver, which obviously could not put up any defense reactions. Indirect pathogens, on the other hand, cause damage only because they provoke exaggerated defensive responses.

Most common inflammatory irritants, including allergens, are essentially indirect pathogens.

During evolution, immunologic reactions which lead to destruction of microbes, grafts and other foreign tissues undoubtedly developed as useful defensive mechanisms against potentially dangerous foreign materials. However, when — as in the case of many allergens, heart transplants, etc. — the attack against the "foreign" agent is unnecessary or even harmful, one can improve upon nature by suppressing this hostility (Selye, 1976a).

Cross-resistance and cross-sensitization. Several stressors applied simultaneously can have a cumulative effect. For example, cold and hunger decrease resistance to almost any stressor, and concurrent application of various drugs and/or physical agents may result in the summation of their individual stressor potencies. In this case, it has become customary to speak of *cross-sensitization.* By contrast, during or immediately following an alarm reaction produced by one stressor, there may develop a *cross-resistance* against the damaging effect of another. Both these cross-effects depend on many factors, such as intensity and duration of the stressor, associated specific effects, genetic background, and species susceptibility.

Since no two individuals are identical, it is not surprising that the same stressor may affect different people in different ways, and to different degrees. We all know that in the same room some people can feel too hot, others too cold, and yet others just right. There exist many endogenous and exogenous elements that can selectively enhance or inhibit a stress response. "Endogenous" refers to such internal factors as genetic predisposition, sex, age, and early training, and previous damage to specific organs; "exogenous" applies to the many external conditions operating at the time of the stress, such as treatment with drugs or hormones, dietary deficiencies, and the physical surroundings. Most exogenous conditioning agents may be regarded as acting through cross-resistance or cross-sensitization, as long as their effect is nonspecific (Selye, 1976a).

Diseases of Adaptation

Maladies in whose development the nonspecific stressor effects of the eliciting pathogen play a major role are called *diseases of adaptation* or stress diseases. However, just as there is no pure stressor (that is, an agent that causes only nonspecific responses and has no specific actions of its own), there are no pure diseases of adaptation. Some nonspecific components participate in the pathogenesis of every malady, but no disease is due to stress alone. The justification for placing a malady in this category is directly proportional to the importance that maladjustment to stress has in its development.

In some instances, as with peptic ulcers, hypertension, surgical shock,

and certain neuropsychiatric derangements, stress is by far the most significant pathogenic factor. However, in other cases (instantly lethal intoxications, traumatic injuries to the spinal cord, most congenital malformations) it plays little or no role, either because the damage is inflicted so rapidly that there is no time for any adaptive process, or because the pathogen is highly specific. In the latter event, whatever develops represents a secondary result and not the primary component of the pathogenic process.

In typical diseases of adaptation, insufficient, excessive or faulty reactions to stressors are at the root of the disturbance. Yet as I have said before, there is no disease attributable to maladaptation alone, since the cause of nonspecific responses will always be modified by various *conditioning factors* that enhance, diminish, or otherwise alter disease proneness. Most important among these are the specific effects of the primary pathogen, and the factors influencing the body's reactivity by endogenous or exogenous conditioners. Hence, diseases of adaptation cannot be ascribed to any one pathogen but to "pathogenic constellations"; they belong to what we have called the *pluricausal diseases* that depend upon the simultaneous effect of several potentially pathogenic factors, among which, sometimes, none alone would produce disease (Selye, 1976a).

An important part of the stress response is the secretion of certain defensive stress hormones such as cortisol and cortisol-like substances. By elucidating the mechanism of this stereotyped reaction to stress in general, we have learned a great deal not only about the way our body defends itself against stress, but also about the diseases of adaptation, which are largely due to derailments of the stress-defense mechanism.

The following essential points can be constructed from the model of stress described above:

1. *All life events cause some stress.* Physical, chemical and psychological agents, directly or indirectly (through the emotions they provoke, for instance), can elicit the stress reaction.

2. *Stress is not bad per se, but excessive or unnecessary stress (and especially distress) should be avoided whenever possible.* The body's capacity for nonspecific adaptation has developed over millions of years and has been preserved during the course of recent evolution, but adaptation is always required at a cost which has to be evaluated against the long-term survival value of adaptation.

3. *The stressor is the stimulus* eliciting the need for adaptation; *stress is the response* to the stimulus but it is not the total response of the body.

4. *The nonspecific aspects of the body's reaction to an agent may not be as obvious as the specific effects.* However, the same pathways of nonspecific adaptation can be mobilized dozens of times a day, without the individual being aware of this mobilization as he experiences diverse situations. Sometimes, only disease or dysfunction will make him realize

that he is under stress.

5. *Stress should be monitored through a battery of parameters;* however, the secretion of ACTH, corticoids and catecholamines are fairly reliable indicators of stress.

6. *Stress cannot be equated with ACTH, corticoid or catecholamine secretion.* These are but a few elements of a very complex scheme of modifications although they seem to be the main pathways of nonspecific adaptation.

7. *Removal of the stressor eliminates stress.* Since stress is part of the response to an agent, in some cases it can be dealt with most easily be avoiding the stimulus or resolving the conflict that it generates (see Selye, 1976a, 1976b; Tachē & Selye, 1978).

Stress and Aging

Aging appears to reflect the sum of all the stressors which have acted upon the body during a lifetime. Each period of stress, especially if it results from frustrating, unsuccessful struggles, leaves some irreversible chemical scars which accumulate to constitute the signs of tissue aging.

Frustration is usually due to the inability of attaining one's goals, which may lead to the feeling that nothing is worthwhile, and in many cases these emotional changes gradually lead to severe depression; but the successful attainment of a goal, for instance, winning a race, or being chosen for an award, also brings on "bouts" of stress. Therefore, in stress theory, the most important thing to remember is that *any* action or *any* stressful thought brings about an irreversible change in our system.

Athough it is difficult to prove that in animals every transient exposure to stress shortens the lifespan, several experiments have shown that this is so when stressors are continuously applied (Selye and Tuchweber, Note 1). When animals, forced to adapt to uninterrupted treatment with damaging agents (cold, forced muscular exercise, drugs), enter the stage of exhaustion, they become unusually sensitive to any additional damage. This nonspecific depletion of resistance is also characteristic of senile animals. The G.A.S. resembles an accelerated, "telescoped" version of the three stages typical of normal aging in these and other respects.

Due to the great advances made by classic medicine during the last half century, death caused by specific disease producers, such as microbes or malnutrition, has declined at a phenomenal rate. As a result, the average human lifespan increased in the United States from 48 years in 1900 to about 72 years by 1979. It is important to understand, nevertheless, that life has not been prolonged; premature death has simply been stopped. Greater numbers of individuals are being killed by maladies which cannot be eliminated using traditional medicine — by the so-called wear and tear diseases, diseases of civilization, or degenerative diseases, which are primarily due to stress.

It has long been assumed that the phenomena of aging must have a specific cause and that if we could only discover what this is, it should be possible to stop the clock and perhaps even to turn it back. Attractive though it may sound, there is no evidence to support this assumption. As far as we know, our reserve of adaptation energy is an inherited finite amount, which cannot be regenerated.

In chemical terms one might view adaptation energy as the ability to remove the chemical scars of life. Each biologic process leads to some chemical changes whose end-products are usually soluble or subject to destruction and elimination. Whenever this form of restoration is rapid, and recovery complete, our tissues undergo little change and we remain "young." However, an infintesimally small percentage of all biologic reaction-products are insoluble, or at least less rapidly removable than their rate of deposition. The so-called "aging pigments," calcium deposits, cross-linked proteins, and many other products of biologic activity belong to this class. Excessive accumulation of these products suffices to block waste-clearing processes. Such accumulation could induce the changes we consider characteristic of aging by the mere presence of ever larger amounts of inert waste products and the consequent inability to produce indispensible vital ingredients at the proper rate. Such processes largely account for the progressive hardening of aging blood vessels. As these lose their elasticity, the blood pressure must rise to maintain circulation through them despite their stiffness and narrowing. The resulting hypertension, in turn, causes a predisposition to cardiovascular accidents, particularly strokes (Selye, 1976a).

Another mechanism that leads to the final exhaustion of adaptability during senility is the cumulative effect of continuously losing small bits of irreplaceable tissue (in the brain, heart, etc.), usually due to injuries or minor vascular ruptures. In the young, these defects are readily compensated by the ample supply of remaining healthy tissue, but in the course of a long life, our tissue reserves are all used up. In the aged, these losses are replaced by actual connective scar tissues. They are added to the "chemical scars" of the piled-up metabolic debris which — as previously mentioned — cannot be eliminated.

Although there is little reason to suspect that an all-embracing concept of aging could ever be formulated, we might yet succeed in clarifying the biochemical basis of chronic fatigue that sooner or later affects all living tissues and becomes increasingly less amenable to restoration either through rest or through the caloric energy of food. In the meantime, the only practical approach to this type of study appears to be the stimulation and acceleration of diverse vital activities by exposing experimental animals to constant stress. This experimentation enables us to determine objectively the effect of wear and tear upon longevity as well as upon the structure and chemical composition of tissues. It also gives us an experimental model on which to test the influence of potentially protective agents (Selye, 1966).

Although I have performed over one thousand autopsies, I have never seen a person who has died of old age. In fact, I do not think anyone has ever died of old age. To permit an individual to die of old age would be the ideal accomplishment of medical research (if we discount the unlikely event of someone discovering how to regenerate adaptation energy). To die of old age would mean that all the organs of the body had worn out proportionally, merely by having been used too long. This is never the case. Death invariably occurs because one vital part has worn out too early in proportion to the rest of the body. Life, the biologic chain that holds our parts together, is only as strong as its weakest vital link. When this breaks — no matter which vital link it might be — our parts can no longer be held together as a single living being.

Note that I did not say "our parts die," because this is not necessarily so. In tissue cultures, isolated cells of a human being can go on living for a long time after the body as a whole has died. It is only the complex organization of all our cells into a single individual that necessarily dies when one indispensible part breaks down. An old man may die because one worn-out, hardened artery breaks in his brain, or because his kidneys can no longer wash out the metabolic wastes from his blood, or because his heart muscle is damaged by excessive work. But there is always one part which wears out first and wrecks the whole human machinery, merely because the other parts cannot function without it.

People, then, do not die of old age but rather of the diseases incident to it. Life develops according to a definite program which is undoubtedly coded in the genes of the individual somatic cells. But at the same time, deterioration takes place in the body at an ever-increasing rate. At present, there is no clear separation of the pthologic conditions accompanying old age from the normal process of senescence (Selye and Tuchweber, Note 1).

Parameters of Aging

Among the most reliable parameters used to assess aging are lifespan, changes in the physical and biochemical properties of connective tissue, and the capacity for adaptation. Associated with these is an increased susceptibility to chronic and especially malignant diseases. It is not possible to distinguish between the changes produced by age as such and those caused by previous diseases. According to the stress theory of aging, there is no clear distinction between the two groups of phenomena, because every stressful episode is a fundamental component of the aging process.

Some of the hypotheses relating aging to stress originated from observations of individuals in stressful circumstances. If one looks at photographs of people from concentration camps, one can see an expression resembling that of an old person. Probably severe stress elicted the prematurely aged condition. Moreover, older people entering the con-

centration camps withstood the stress far less adequately than did the younger people.

There is considerable experimental evidence to support the view that adaptability to changed environments declines with age. It has been proven that age influences the adaptability of rats to cold and mechanical trauma. The mechanisms responsible for the decreased adaptability of old rats are not yet fully understood, but it is known that neurohumoral factors, especially the pituitary-adrenocortical axis, are involved in adaptation to both cold and trauma.

The molecular basis for age-changes has been discussed by many theorists. Alterations of DNA, protein synthesis, membranes, and RNA have been invoked as factors of early change. Studies of cellular lifespan in cell culture have assumed great importance in recent years. The belief that the number of divisions of somatic cells is limited has received ample confirmation and represents a model of aging *in vitro*.

Nevertheless, we can assume that the relevant age-changes depend also on structural relationships among extracellular material, blood vessels and cells, and such a system is nonexistent in *in vitro* studies. In other words, the primary changes resulting in impaired cell function may occur in the extracellular material.

The pattern and rate of aging may be modified by pharmacologic agents and by altering endocrine balance or environment. In experimental animals, retardation of growth by restriction of dietary intake prolongs their lifespan and decreases the incidence of many chronic diseases. On the other hand, a number of environmental stresses, especially ionizing radiation, shorten lifespan and increase the rate of aging.

The observation that animals exposed to ionizing radiation die at an early age, with a syndrome of premature senility, attracted considerable attention. It was proposed that aging is the consequence of the cumulative effect of mutations in somatic cells. These take place in the genes and in their regulators so that errors of protein synthesis ensue. The evidence for this somatic mutation theory has been widely discussed in recent years, but it has not led to agreement among those who consider mutation only as a factor accompanying the aging process (Selye and Tuchweber, Note 1). It remains to be seen to what extent animal experiments will help us combat spontaneous aging, but there can be no doubt that really significant progress concerning the problems of the aged will only come through basic research into the fundamental phenomenon of senescence.

Calciphylaxis: A Clue to Aging?

A direct attack upon the problems of aging has become possible through the concept of calciphylaxis, which is a recently discovered biologic mechanism through which the body can selectively send calcium to certain organs or prevent the calcification of tissues, depending upon

conditions.

It has long been known that, in old people, there is some derangement in the distribution of calcium. The bones become brittle and lose calcium, while various soft tissues attract calcium salts and thereby become hardened. Thus calcium may accumulate in the arteries (arteriosclerosis), in the crystalline lens of the eye (cataract), around the joints, in tendons, and in many other tissues. Among the many factors that can interfere with calciphylactic responses is the exposure to systemic stress prior to sensitization. Local stress, on the other hand, may produce calcification under certain well-established conditions. If a rat is calciphylactically sensitized by the oral administration of a single dose of the vitamin-D derivative dihydrotachysterol (DHT), simultaneous application of trauma to various tissues will not cause any local calcinosis. But if a critical period (in this case, 24 hours) is allowed to elapse and then hair is plucked out over a small area, this mild trauma produces massive petrification of the epilated region. If, after similar sensitization, the shoulder or hip joint is traumatized, for example by extreme rotatory movements, periarticular calcium deposition results and motion in the affected joints becomes very limited and painful.

It had been assumed as a self-evident fact that the calcium deposition must be secondary to some "dystrophic" tissue damage that characterized aging. However, in the course of our work on calciphylaxis we noted that, in young animals, the induction of certain types of calcium metabolism disturbances may result in a variety of changes typical of aging, such as a generalized calcification of the arterial system, loss of elasticity and wrinkling of the skin, loss of hair, thymicolymphatic involution, atrophy of the skeletal muscles and the sex organs, dental anomalies and occasional cataracts (all similar to those seen in senile animals).

This "progeria-like syndrome" (progeria is a rare congenital disease whose symptoms resemble many of the features of aging) can be totally prevented if the animals are previously given small doses of calciphylactic challengers, such as certain metallic salts. These observations suggest that the experimental "aging" of the progeria-like syndrome is not the cause but the consequence of a disturbed calcium metabolism and can be prevented by agents which counteract such a disturbance. However, we still cannot state with certainty whether this syndrome is fundamentally related to the process of aging, because we have no way of diagnosing premature aging except through its resemblance to natural senility (Selye, 1965a, 1968).

Longevity

All said, there is no authenticated record of anyone living longer than about 120 years. This figure might indeed be regarded as the optimum lifespan of a single person, the age which he or she might attain by living

in perfect harmony with natural laws. There are many factors at work, of course, and I am far from saying that by following a healthy lifestyle, one automatically lives that long. We are not yet exactly sure what such a lifestyle would be, let alone know how to achieve it, nor even whether its achievement would be possible. Yet there is little doubt that the average human lifetime is capable of being considerably prolonged.

The basic question is really whether the spring in life's clock can or cannot be rewound after birth. This question cannot yet be answered, but it seems to me that with the knowledge of stress now available, much more can be done to protect the spring and prolong its usefulness. I shall have more to say about this in the next section, where, in connection with the problems of retirement, I describe a scientifically-based code of ethics.

Retirement

Evidently at this point we can only assume an intimate relationship between aging and adaptability (i.e., the effectiveness of the stress mechanism in preserving homeostasis). Yet even on this broad basis, I think it is possible to arrive at helpful conclusions about how to handle many of the problems occasioned by one's own aging and the decision or necessity to retire.

It is generally recognized that medicine has made tremendous progress during the last three decades; this shows itself clearly in the statistically demonstrable great increase in life expectancy. A recent census indicated that there are about fifty million people in the United States above the age of sixty-five. This means that the problems of the elderly assume even greater importance.

The more medicine progresses, the more the proportion of older people in the general population will increase. The value of prolonging life is self-evident; yet I heartily agree with the *Journal of Gerontology,* which on its masthead describes its objectives as: "To add life to years, not just years to life."

There is, furthermore, a great difference between biologic and chronologic age. Chronologic age is easy to understand and determine in quantitative terms; biologic age is a less precise but much more important concept. There are many people who, at forty-five, have the mentality and motivation customarily associated with advanced age; they would prefer to retire from their jobs and should, provided they have the means to do so. Others still adore life at eighty and are perfectly able to act in a manner which makes them useful to themselves and to society; in this regard we need only think of the achievements in old age of Thomas Mann, Michelangelo Buonaroti, Pablo Picasso, Arturo Toscanini, and Bertrand Russell.

Successful activity, no matter how intense, leaves you with comparatively few aging scars. It causes stress but little, if any, distress. On

the contrary, it provides you with the exhilarating feeling of youthful strength, even at a very advanced age. Work wears you out mainly through the frustration of failure. Many of the most eminent among the hard workers in almost any field live a long life. They overcome inevitable frustrations by the great preponderance of success.

Of course, none of these men "worked" in the sense of work as something one has to do to earn a living but does not enjoy. Rather, one might say that they lived a life of constant leisure by always working at what they liked to do.

It is true that few people belong to this category of the creative elite; admittedly, their success in meeting the challenge of stress cannot serve as a basis for a general code of behavior. But one can live longer and more happily by working hard along modest lines if one has found the proper job and is reasonably successful at it.

Aging, we must realize, is inevitable, and if we can adapt to new conditions as they present themselves, we can be content with our lives, no matter what our age. Nature has endowed us with numerous compensatory mechanisms, and when one channel is blocked, we learn to develop another.

For activity and rest to be judiciously balanced, every person must find his own characteristic requirments for rest and activity. To lie motionless in bed all day is no relaxation for an active person; nor is retirement a reward for someone who likes to work. With advancing years, most people require increasingly more rest, but the process of aging does not progress at the same speed in everybody. Many a valuable person, who could still have given several years of useful work to society, has been made physically ill and prematurely senile by enforced retirement at an age when his requirements and abilities for activity were still high. This psychosomatic illness is so common that it has been given a name: *retirement disease.*

All work and no play is certainly harmful for anyone at any age; but then, what is work and what is play? Fishing is relaxing play for the business executive, but it is hard work for the professional fisherman. The former can go fishing to unwind, but the latter will have to do something else, or simply take a rest, in order to relax.

With most psychosomatic diseases it is the philosophy of life, the code of behavior of the patient, that is really at fault. He must either learn to adopt a "syntoxic" attitude — that is to say, he has to learn to live with the people responsible for his troubles if it is not worth his while to fight; or, if he is convinced he can and must win, he should behave in a "catatoxic" manner and force a showdown. In any event, the conflict has to be terminated. Although these concepts of "syntoxic" and "catatoxic" manners are here being applied to interpersonal relations, it was actually observations on tissue reactions to "syntoxic" and "catatoxic" chemicals (particularly hormones) that called my attention to this law governing human behavior.

Broadly speaking, coping with stress — including the stress of aging — can be accomplished at four levels: 1) by removing stressors from our lives; 2) by not allowing certain neutral events to become stressors; 3) by developing a proficiency in dealing with conditions we do not want to avoid; and 4) by relaxation or diversion from stressful demands (Tachē and Selye, 1978).

It would seem also that one of the most fundamental laws regulating the activities of complex living beings is that no single part of the body be disproportionately overworked for a long time. Systemic stress seems to be the great equalizer of activities within a person; it helps to prevent one-sided overexertion.

A large part — if not the major part — of violence, wars, revolts, alcoholism, drug addiction and other destructive behaviors is due to a loss of the stabilizing support of constructive goals. It appears that individuals have difficulty finding suitable substitutes for the traditional aims; they used to, but can no longer, believe in such values as religious loyalty, the integrity of political leaders and parties, and sanctity of the family or even the alleged security offered by accumulating a large amount of money.

I believe that science has destroyed the credibility of the strongest traditional aims by showing that most of them do not stand up to the rigid exigencies of scientific proof. All were based on absolute faith in an allegedly infallible authority which only too often proved to be fallible or even nonexistent.

In drawing up a balance sheet of the past, I am convinced that a scientifically acceptable code of ethics, a new philosophy of behavior, could do much more good to humanity than any discovery a scientist could make. Since the most important thing we must do is to live happily, each of us needs to develop a code of behavior that helps to achieve this. There are general principles which, following the laws of nature, appear to hold for everyone. These principles, derived from a lifetime of biological research, I have summarized as follows (Selye, 1974):

1. *Find your own natural predilections and stress level.* People differ with regard to the amount and kind of work they consider worth doing to meet the demands of daily life and to assure their future security and happiness. In this respect, all of us are influenced by hereditary predispositions and the expectations of our society. Only through planned self-analysis can we establish what we really want; too many people suffer all their lives because they are too conservative to risk a radical change and break with traditions.

2. *Altruistic egoism.* The "selfish" hoarding of the goodwill, respect, esteem, support, and love of our neighbor is the most efficient way to give vent to our pent-up energy and create enjoyable, beautiful or useful things.

3. *EARN thy neighbor's love.* This motto, unlike "Love thy neighbor

as thyself," is compatible with man's biological structure, and although it is based on altruistic egoism, it could hardly be attacked as unethical. Who would blame the individual who wants to assure psychological homeostasis and happiness by accumulating the treasure of other people's benevolence? Yet this makes one virtually unassailable, for nobody wants to attack and destroy those upon whom one depends.

Even those who accept the value of this code as a means of facing the adversities inflicted by psychological reactions to stress often doubt that it can be applied to extreme situations — for instance, coping with incurable disease or advanced age. Yet from personal experience with these problems, I believe that altruistic egoism can be just as useful in dealing with life's worst crises as in handling everyday problems (Selye, 1979).

Retirement is a good example. A very old man may be unhappy, bitter, and a burden to those close to him because of his constant complaints, or he may always be radiating optimism and anxious to be useful to his relatives and friends by sharing with them the fruits of his long experience. Retirement may be the end of one's constructive life, or merely the beginning of another chapter. There are many reasons why people retire: for some, age or failing health makes it a necessity; for others, enjoyment of leisure or the pursuit of other activities is the motivator. Retirement as such is neither good nor bad; as with so many other things, how it affects us may depend largely on how we take it, and what we make of it. It is certainly a great change which, until we are adjusted to it, involves considerable stress. But here too it is not wholly beyond our control whether this stress acts upon us for better or worse.

For one who has never retired, to express such a view on retirement may seem presupposing. However, retirement is little different from many other periods of our lives to which we must adjust. In each of these the same principles apply: be necessary to others. Find a purpose for yourself, in keeping with your own natural inclinations and abilities. In essence this means to *Fight for the highest attainable aim. But do not put up resistance in vain* (as I have often summarized it). For young people, the "highest aim" is often a demanding career, and this may even be true of exceptional old people. But for many, the goal may simply be to get the most out of life, both qualitatively and quantitatively. Stress research, I think, can show us how to achieve both.[1]

[1] Those who are interested in a code of behavior based on stress research may wish to know that this was the topic of my presidential address at the 2nd International Symposium on the Management of Stress (November 18-22, Monte Carlo, Monaco), the largest such meeting ever held. (Among the main speakers were several Nobel laureates: Sir Hans Krebs, Christian de Duve, Linus Pauling, and my former student, Roger Guillemin — as well as Jonas Salk, Mauricio Rocha e Silva, and William R. Barclay, Chief Editor of J.A.M.A.) Future annual conventions are now being planned for the cities of Marrakesh, Cairo, Tokyo, and Montreal, among others. The proceedings of all these congresses are to be published in the newly-formed "Stress: the official journal of the International Institute of Stress and its affiliates." I will be contributing a brief editorial to each issue.

Reference Note

Selye, H., & Tuchweber, B. *Stress and aging.* Paper presented at the Symposium on Society, Stress and Disease, Stockholm, June 1976.

References

Mason, J. W. A historical view of the stress field. Part I. *Journal of Human Stress,* 1975, *1,* 6-12. (a)

Mason, J. W. A historical view of the stress field. Part II. *Journal of Human Stress,* 1975, *1,* 22-36. (b)

Selye, H. A syndrome produced by diverse nocuous agents. *Nature,* 1936, *138,* 32.

Selye, H. *The story of the adaptation syndrome.* Montreal: Acta, Inc., 1952.

Selye, H. Calciphylaxis: the key to aging? *Norden News,* 1965, *40,* 6. (a)

Selye, H. Man after 65: resource or burden? *Medical Opinion and Review,* 1965, *1,* 80. (b)

Selye, H. The future for aging research. In N.W. Shock (Ed.), *Perspectives in experimental gerontology.* Springfield, Ill.: Charles C Thomas, 1966.

Selye, H. Calciphylaxis and aging. *Archives of Otolaryngology,* 1968, *88,* 294.

Selye, H. *Stress without distress.* New York: Lippincott, 1974.

Selye, H. Confusion and controversy in the stress field. *Journal of Human Stress,* 1975, *1,* 37-44.

Selye, H. *Stress in health and disease.* Reading, Mass.: Butterworths, 1976. (a)

Selye, H. *The stress of life* (Rev. ed.). New York: McGraw-Hill, 1976. (b)

Selye, H. *The stress of my life.* New York: Van Nostrand Reinhold, 1979.

Tache, J., & Selye, H. On stress and coping mechanisms. In C.D. Spielberger (Ed.), *Stress and anxiety* (Vol. 5). Washington, D.C.: Hemisphere Publishing Corp., 1978.

Thompson, G. B. Work versus leisure roles: an investigation of morale among employed and retired men. *Journal of Gerontology,* 1973, *28,* 339-344.

Trujillo, T. T., Spalding, J. F., & Langham, W. H. A study of radiation-induced aging: response of irradiated and nonirradiated mice to cold stress. *Radiation Research,* 1962, *16,* 144-150.