Handbook of Life Stress, Cognition and Health

Edited by S. Fisher and J. Reason

34

Allostasis: A New Paradigm to Explain Arousal Pathology

PETER STERLING
and
JOSEPH EYER
University of Pennsylvania School of Medicine, Philadelphia

INTRODUCTION

This chapter summarizes our joint effort as epidemiologist (J.E.) and neurobiologist (P.S.) to understand the physiological basis for certain broad patterns of human morbidity and mortality. Age-specific death rates rise when intimate social relations are disrupted. This is observed in contemporary statistics, for example the mortality associated with bereavement, divorce, migration and overwork. It is also observed historically in the increased mortality of urban versus rural populations and in the rise of age-specific death rates that accompanies modern economic development. The increases in all these examples are large (two- to ten-fold) and are observed for essentially all causes, so they cannot be explained by any single environmental factor such as air pollution or nutrition (Berkson, 1962; Eyer and Sterling, 1977).

Disruptions to intimate social relations, including war, migration, and economic development, affect most strongly youth entering the labor market. The size of a particular birth cohort is especially important because this affects the competitive experience of that cohort throughout its lifecycle. A small cohort entering the labor market during an economic expansion experiences relatively mild competition and has lower death rates from all causes. A large cohort entering the labor market during an economic contraction experiences greater competition and social disruption and has correspondingly higher mortality (Eyer and Sterling, 1977).

The major causes of death shift as a cohort ages, but high mortality in youth from one set of causes presages high mortality later from another set. The large cohort born after World War II ('baby boom') entered the labor market in the 1960s at the end of a long cycle of economic expansion. It experienced elevated mortality at ages 15–24 from accidents, homicide, and suicide, and at ages 30–34

from liver cirrhosis (due to alcoholism). This cohort is now reaching the age at which the important causes of death become renal, cerebral, and cardiovascular disease (see Figure 10 in Sterling and Eyer, 1981), causes for which hypertension is the largest single contributor. Cancer, too, becomes an important cause of death, though its main impact comes somewhat later. Our historical studies predict for this cohort an increase in mortality from these causes (Eyer and Sterling, 1977).

Having discovered these patterns, we could find no explanation for them in textbooks of physiology. No text explains, for example, why in modern society blood pressure rises with age (Eyer, 1975). Nor do they explain why this rise starts at the age when children enter the environment of school (Figure 34.1; Blumenthal *et al.* 1977). Texts do not explain why blood pressure is highest and hypertension most prevalent where social disruption is greatest, e.g. among the unemployed and (in the US) among blacks. The most common form of hypertension is called in textbooks 'essential', meaning of unknown cause. In certain

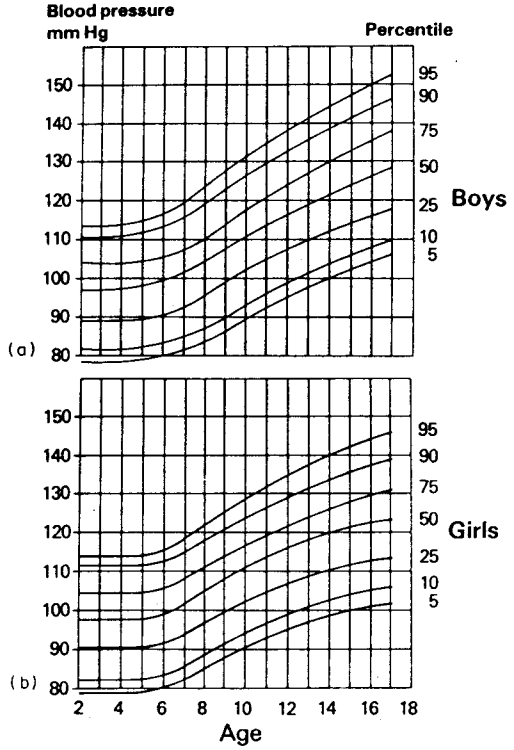

FIG. 34.1 Percentiles of diastolic blood pressure measurement (right arm, seated). (Reprinted from Blumenthal *et al.*, 1977.)

instances the epidemiological observations that we cite are acknowledged, but are given biological explanations that are unrelated to the social and psychological patterns. Thus, a standard explanation for elevated blood pressure in modern society is that salt consumption is excessive and beyond the kidney's capacity to excrete it. This is supposed to cause retention of excess salt water in the vascular system which causes the high blood pressure. Hypertension among blacks is commonly attributed to a genetic predisposition.

These explanations beg the questions *why* we eat so much salt and *why* the kidney fails to excrete it. Similarly, one needs to explain why the blood pressures of American and Caribbean blacks rise so much higher than those of the West Africans whose genes they share (Waldron, 1979). The only possible link between sociopsychological and physiological phenomena is the brain. Textbooks do not describe this link because the dominant conceptual model in physiology for a century has viewed the body as operating almost independently of the brain. Neurobiological studies of the 1960s and 1970s revealed many links between brain and soma, and appreciation of the richness of these links has accelerated in the 1980s. By now the evidence warrants abandoning the old conceptual model and adopting a new one in which the central nervous system is the pre-eminent regulatory influence on somatic physiology (Sterling and Eyer, 1981). Here, we review briefly the old model and present the new one, which accounts quite easily for the epidemiological findings.

HOMEOSTASIS VERSUS ALLOSTASIS

The principle of homeostasis is that to maintain stability an organism must hold all the parameters of its internal milieu constant (Bernard, 1865; Cannon, 1932). Deviations from normal are corrected automatically by local, 'negative feedback' mechanisms. Thus, normal blood sugar is about 80 mg/ml. A rise above this level can trigger release of insulin from the pancreas which leads to uptake of glucose by liver and muscle and restores blood glucose to normal. Similarly, normal blood pressure is about 110/70 mmHg. A rise above this level can trigger slowing of the heart, dilatation of the vessels, and excretion of salt and water by the kidneys. Those three factors—reduced cardiac output, enlarged vascular reservoir, and reduced blood volume—all contribute to restoring normal pressure.

The major thrust in physiological research for the last century has been to study isolated organs and tissues. It turns out that most organs function remarkably well when they are disconnected from the rest of the body and brain and placed in a dish. The pancreas releases insulin when glucose is added, and a slice of kidney pumps salt water. Consequently there has been great success in identifying the cellular and subcellular bases for local feedback control, and this has bolstered the idea that in the body the organs function autonomously.

On the other hand, when measurements of the internal milieu are made in an intact, unanesthetized organism, the results fit the homeostatic model very poorly. Consider Figure 34.2a, which is a continuous record of arterial blood pressure made from a normal adult human over a period of 24 hours (Bevan *et al.*, 1969). The pressure is by no means constant. Instead, there are many peaks and

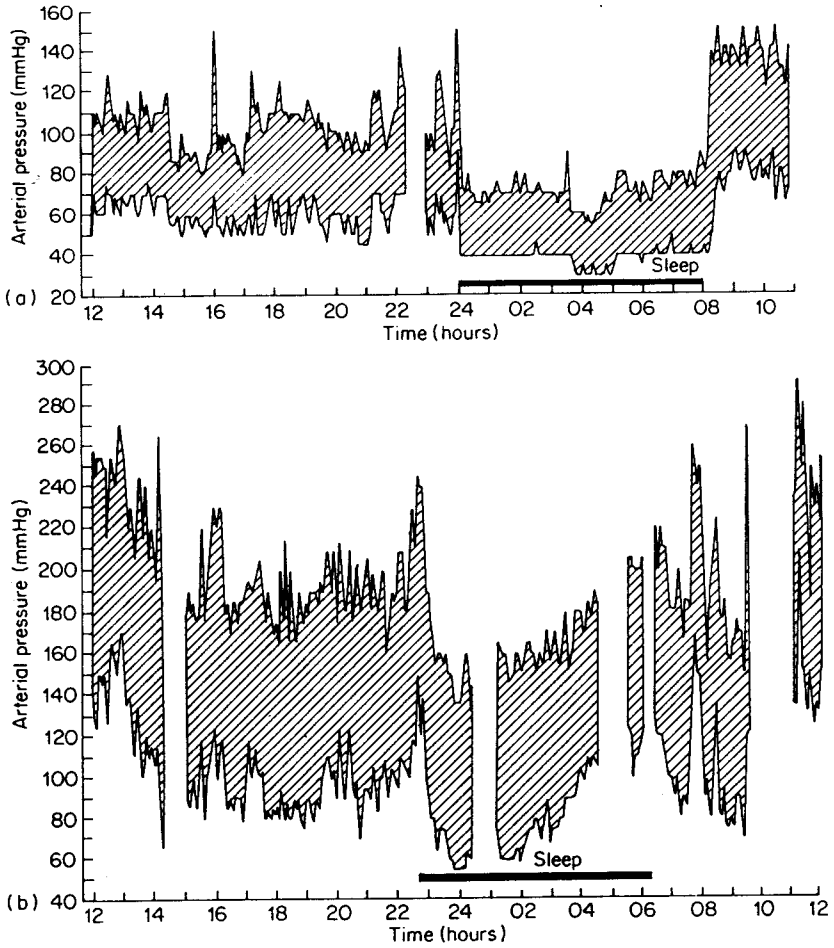

FIG. 34.2 (a) Arterial pressure from a normal subject plotted at 5-minute intervals. (b) Arterial pressure from a hypertensive subject. (Redrawn from Bevan *et al.*, 1969.)

troughs of varying size and duration. Some peaks are identified with specific behavioral states and environmental events. For example, the pressure fell between hours 15 and 16 when the subject was dozing in a lecture, and rose sharply at hour 16 when he awakened (briefly) to a jab from a pin. The pressure rose at hour 24 (midnight) when the subject engaged in sexual intercourse, and fell profoundly (as low as 50/30 mmHg) during sleep. At hour 08, when the subject was preparing to meet his work day, the pressure rose to the preorgasmic level of the previous night and remained there for hours.

It is obvious from this record that the idea of a 'normal' value toward which automatic mechanisms drive the blood pressure is a fiction. In one behavioral state the pressure is maintained low for a long period without restoration, and in another state it is held high for long periods, also without restoration. It makes no more sense to average the pressures from these different periods than it does to 'average' the states of sleep and wakefulness or the states of sexual arousal and satiety. Clearly, to achieve stability an organism must occupy each one of these different states and move flexibly between them. At each behavioral transition, the blood pressure must be reset to match the new state (see also Pickering *et al.*, 1986).

An aroused behavioral state in which an organism is preparing to respond with some form of 'coping' behavior to an environmental challenge generally requires a rise in blood pressure. The early studies by Cannon emphasized acute, intense arousal engendered by pain, fear, and rage (Cannon, 1929). Later studies by Selye emphasized aroused behavioral states of somewhat longer duration and milder conditions (Selye, 1956). Whereas Cannon had studied animals prepared for immediate 'fight or flight', Selye studied animals under conditions of chronic frustration, for example a rat with its legs tied together for 24 hours. A still milder paradigm was introduced by Mason and colleagues in which an animal could avoid an electrical shock by watching for a signal and then pressing a lever (Mason, 1968). An aroused state can also be engendered in animals by disrupting a socially stable community, for example among mice by introducing a strange male into an established colony (Henry *et al.*, 1967).

In all such animal models, when the acute or semichronic arousing stimulus is removed, the blood pressure falls. However, when the arousing stimulus is made chronic and removed only after a rather long period, the pressure may remain elevated. Thus, after many months of elevation in response to an avoidance conditioning paradigm, the high pressure in monkeys becomes sustained (Forsyth, 1969). Similarly, the elevated pressures evoked in rats as part of a 'defense response' by chronic brain stimulation also become sustained, even when the stimulation ceases (Folkow and Rubinstein, 1966). The elevated pressures in a mouse colony fall when the stranger is removed, but only if less then 6 months has elapsed; thereafter the pressure remains high even when the stranger is gone (Henry *et al.*, 1967).

The question arises as to what other physiological parameters besides blood pressure covary with behavioral state. The answer is, essentially *all* of them (Table 34.1; Mason 1968, 1971, 1972). As blood pressure rises during arousal, there is a dramatic shift in the pattern of blood flow: more to muscle, less to the gut, kidney, and skin. Correspondingly, there is a metabolic mobilization to increase energy production. Glucose, amino acids, and fatty acids are released from their macromolecular storage forms (glycogen, protein, and fat) and their blood levels rise. Synthesis of the storage forms is halted. Red blood cells and oxidative enzymes in the liver increase because these facilitate the energy mobilization. Other processes that use energy but that do not contribute to the metabolic mobilization are suppressed: the immune response declines as circulating white blood cells decrease and the thymus shrinks (Selye, 1956). Wound healing, bone growth and

Table 34.1 Catabolic state (arousal)

Increase
Blood pressure
Cardiac output
Retention of salt and water (to support blood pressure)
Blood to muscle
Breakdown of carbohydrate, fat, protein
Blood levels of glucose, fatty acids, amino acids
Circulating red cells
Production of red cells
Synthesis of oxidative enzymes (liver)
Decrease
Blood to kidney, skin, gut
Synthesis of glycogen, fat, protein
Repair, replacement, growth of bone
Replacement of cells with high turnover (gut, skin, etc.)
Production of cells for immune system (thymus, lymph nodes, bone marrow)
Sexual processes (endocrine, cellular, psychological, behavioural)

The *anabolic state* (relaxation) is accompanied by a reversal of the above pattern.

repair, replacement of the cellular lining of the gut, etc. all slow markedly. Thus, corresponding to the behavioral/psychological state of arousal there is a biochemical state of 'catabolism', that is, breakdown of metabolic compounds to produce energy. Corresponding to states of relaxation is a biochemical state of 'anabolism', that is, a rebuilding of energy stores, repair, and growth (Mason, 1972).

The catabolic mobilization accompanying arousal is accomplished by shifts in essentially all the known hormones. Catabolic hormones (those that promote energy production), e.g. epinephrine, norepinephrine, cortisol (glucocorticoids), growth hormone, glucagon, and thyroxine, increase. Anabolic hormones (those that promote growth and repair), e.g. insulin, estrogen, and testosterone, decrease. The timing of these changes is complex because certain hormones, such as epinephrine, cortisol, and growth hormone, serve the acute mobilization and rise almost instantaneously (seconds to minutes), while others, such as thyroxine and the sex hormones, have slower, modulatory roles and rise or fall over longer periods (hours to weeks). Other hormones that indirectly support energy production also change (Mason, 1968). For example, vasopressin (antidiuretic hormone), renin, angiotensin II, and aldosterone all increase (see Sterling and Eyer, 1981) and atripopeptin decreases (Eskay *et al.*, 1986). This pattern serves the aroused state by increasing the rate of circulation through the cardiovascular system (Fig. 34.3).

A list of some hormones associated with the catabolic and anabolic states is given in Table 34.2. It is notable that quite a few of them have been discovered only recently, e.g. the opiate hormones (enkephalin, dynorphin, and endorphin: Akil *et al.*, 1984), the cardiac hormone (atriopeptin: Manning *et al.*, 1985; Eskay *et al.*, 1986; Dillingham and Anderson,1986), and the immune system hormones (interleukins and thymosins: Goetzl, 1985). The discovery rate of new, physiologically active peptides increases as techniques in molecular biology advance. *All* physiologically active substances and processes discovered so far are regulated and therefore fluctuate with shifts in demand corresponding to shifts in behavioral

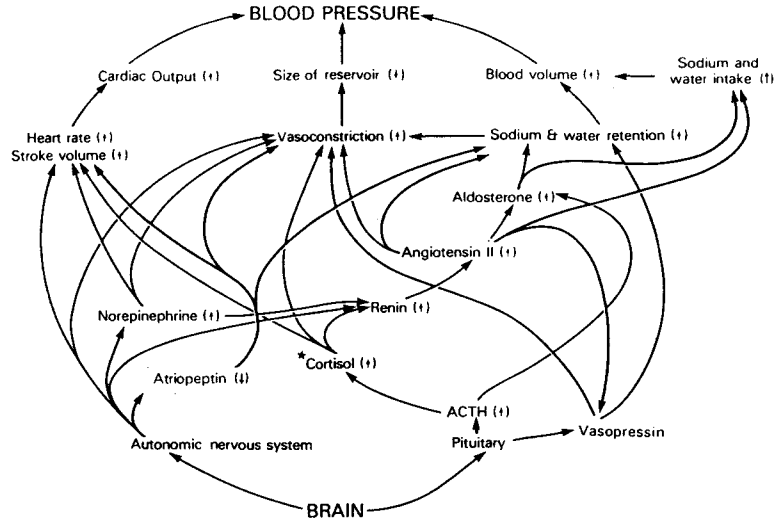

FIG. 34.3 Multiple, mutually reinforcing mechanisms to raise blood pressure during arousal. Negative feedbacks reset or overridden. (*Indicates that cortisol acts indirectly by enhancing receptor binding of norepinephrine.)

Table 34.2 Hormonal pattern during arousal

Catabolic hormones increase	Anabolic hormones decrease
Cortisol (glucocorticoids)	Insulin
Epinephrine	Calcitonin
Norepinephrine	Testosterone
Glucagon	Estrogen
Growth hormone	Prolactin
Antidiuretic hormone (vasopressin)	Luteininzing hormone
Renin	Follicle-stimulating hormone
Angiotensin	Gonadotrophin-releasing hormone (GnRH)
Aldosterone (mineralocorticoids)	Prolactin-releasing hormone (PRH)
Erythropoietin	Atriopeptin
Thyroxin	Thymosins
Parathormone	Lymphokines
Melatonin	Cytokines
Thyroid-releasing hormone (TRH)	
Adrenocorticotrophic hormone (ACTH)	
Enkephalin, Dynorphin, Endorphin } opiates	

and/or psychological state. Thus the contextual fluctuation of blood pressure illustrated in Figure 34.2 is not exceptional. Rather, it exemplifies a critical principle of physiology: to maintain stability an organism must *vary* all the parameters of its internal milieu and match them appropriately to environmental demands. We refer to this principle as allostasis, meaning 'stability through change'.

MECHANISMS OF ALLOSTASIS

To create allostatic fluctuations, connections are required from brain to soma. Such connections, elucidated in considerable detail by new methods introduced over the last few decades, are now known to be extremely rich. Electron microscopy permits nerve terminals to be visualized in direct contact with specific types of cell, and immunocytochemistry permits nerves to be visualized by the application of antibodies to specific neurochemicals. Such methods show that cells in most of the classical endocrine glands are contacted by nerves. Thus, cells in pancreas that secrete insulin, glucagon, and somatostatin are directly innervated; so are cells in thyroid that secrete calcitonin (see Sterling and Eyer, 1981). Organs not formerly considered to be endocrine are now recognized to contain special endocrine cells and these too are under neural control, for example cells in kidney that secrete renin (see Sterling and Eyer, 1981) and in heart that secrete atriopeptin (Eskay *et al.*, 1986). Tissues previously thought to be free of nerves, for example the metabolically active surfaces of bone (Hohmann *et al.*, 1986) and cells in tissues of the immune system such as spleen, thymus, and lymph nodes, are now known to be innervated (Felten *et al.*, 1985). All blood vessels, including those in the brain itself, are richly innervated. Thus, the brain has direct access through nerves to every tissue and especially to all the internal signalling systems such as the endocrines, blood vessels, and immune system.

The brain also synthesizes its own hormones which it releases into the blood; dozens are now identified, with the certainty that more are still to come. Each brain hormone acts at several levels, affecting (1) peripheral tissues and organs, (2) peripheral endocrine secretions that in turn affect tissues, and (3) pituitary secretion of hormones that alter both tissues and peripheral endocrines. For example, vasopressin released by the brain causes blood vessels to constrict, the kidney to decrease urine output, and the heart to increase blood output. It also stimulates aldosterone release from the adrenal, and ACTH release from pituitary. All these actions of vasopressin tend to increase blood pressure. Thus, neural control is multileveled, with the general form of a cascade (see Figure 34.3).

All the elements in the cascade tend to be mutually reinforcing and this provides the brain with powerful means to override local negative feedback mechanisms that would tend to oppose its commands. This can be appreciated in Figure 34.3, which summarizes the multiple mechanism for raising blood pressure. Clearly, if the brain raised pressure only be increasing cardiac output, pressure would tend to be reduced automatically by local mechanisms for vascular dilatation and renal excretion of salt and water. Similarly, if the brain raised pressure by suppressing salt-water excretion, cardiac output would be reduced automatically by local mechanisms. By controlling all the mechanisms simultaneously, the brain can enforce its command. Furthermore, it can effect the changes rapidly. The existence of these multiple, mutually reinforcing mechanisms is of great therapeutic significance, as we shall see.

The hormones and metabolites whose levels in allostasis are set by the brain also feed *back* to the brain, where they reinforce the original command. These feedbacks, like the feedforward mechanisms, also have the general form of a cascade. For example, the hormones angiotensin II and aldosterone, whose peripheral roles in raising blood pressure are shown in Figure 34.3, affect multiple regions in the brain. Angiotensin stimulates the area postrema in the medulla to cause further neural drive on the heart, vessels and kidney. Angiotensin also acts on the hypothalamus to increase release of vasopressin (Miselis, 1986). Most remarkably, angiotensin and aldosterone, the hormones that cause the kidney to save salt, act on the brain to increase the *appetite* for salt (Zhang *et al.*, 1983). This makes perfect sense since the same allostatic purpose is served by both mechanisms: increase the available salt in order to support the elevation of blood pressure. The newly discovered salt/water regulatory hormone, atriopeptin, is also found in the brain (Standaert *et al.*, 1986).

Allostasis, because it involves the whole brain and body rather than simply local feedbacks, is a far more complex form of regulation than homeostasis. Yet it offers definite advantages. One is that it permits a fine matching of resources to needs. In homeostasis, negative feedback mechanisms, uninformed as to need, force a parameter to a specific 'setpoint'. If blood pressure were actually determined in this way, that is, set to an average, 'normal' value, it would almost invariably be too high or too low for whatever was going on at the moment. Allostasis provides for continuous re-evaluation of need and for continuous readjustment of all parameters toward new setpoints. This makes the most effective use of the organism's resources.

Another advantage of allostasis is its design for *anticipating* altered need and achieving the necessary adjustments in advance. In homeostasis, when increased need creates an 'error' signal, negative feedback mechanisms may try to correct the error, but by then the required resources may be unavailable and the time needed for correction may be too long. Errors corrected by negative feedback can get dangerously large. For example, if one is called upon to leap into action from a sitting position, blood pressure to the head tends to fall as blood drains to the lower body by gravity. Homeostatic mechanisms would correct this, of course, but the error signal (fall in blood pressure to the head) would be associated with momentary dizziness. The most advantageous time for resetting is *before* one leaves the chair.

Similarly, if blood pressure is to be elevated, the time to save salt and water to support the rise is at the moment of elevation and not after much salt and water has been lost to urine so that new supplies are required. Further, if the elevation is to be sustained, new supplies will be needed eventually and the time to seek them is before the body's supply is exhausted. Finally, there is no way for a homeostatic regulatory system to benefit from experience. One learns to get up from the chair slowly if dizziness is a problem and to bring supplies of water and salt to a dry

environment. All of these anticipatory regulations are achieved by allostatic mechanisms.

The insight provided by the allostatic model, that specific appetites serve anticipatory mechanisms for physiological regulation, is crucial. It makes comprehensible the relation between physiological need, diet, and pathology. An individual's tendency to eat salt and his kidney's tendency to save salt are driven in concert by the same hormones (aldosterone and angiotensin II; Figure 34.3) as part of an allostatic response to arousing stimuli. Because salt consumption and salt excretion are matched to the level of arousal by means of neuroendocrine mechanisms, they cannot logically be considered 'excessive'. If anything is to be considered 'excessive' in the sense that it leads to pathology, it must be the level of arousal itself.

ALLOSTATIC REGULATION OF THE IMMUNE RESPONSE

The organism's response to an infectious agent involves an extraordinary web of centrally organized, mutually reinforcing connections between the brain, endocrine, and immune systems. To fight a virus optimally requires: (1) recognizing it as foreign, (2) selectively producing white blood cells (leucocytes) to attack it specifically and not the body's own cells, (3) suppressing viral replication by raising body temperature, (4) redirecting metabolic energy to promote these activities, and (5) suppressing activities (and the hormones that promote them) that would compete with these needs. Thus, even though the immune system can initiate a response to the virus through local homeostatic mechanisms, the brain is required to develop full response. The brain needs information regarding the intensity of the infectious challenge so that it may weigh the seriousness of these demands. The brain also needs mechanisms to suppress the immune response in case other demands are more pressing (Kanigel, 1986; Goetzl, 1985).

It has been discovered recently that cells of the immune system secrete a host of chemical factors, called lymphokines and cytokines, that affect the brain (Figure 34.4; Hall *et al.*, 1985; Felten *et al.*, 1985). These include many peptide hormones that are also secreted by endocrine glands such as the adrenal and pituitary (Blalock *et al.*, 1985). For example, leucocytes can release ACTH (Smith *et al.*, 1986), endorphins (Smith *et al.*, 1985), enkephalin (Zurawski *et al.*, 1986), and thyroid-stimulating hormone (TSH; Geenan *et al.*, 1986). The amount of ACTH released is substantial—enough to evoke from the adrenal a rise in cortisol comparable to that produced by moderate arousal (Besedovsky *et al.*, 1986). There are additional factors secreted by leucocytes such as thymosins, interleukins, and interferons (Figure 34.4; Goetzl, 1985). All of these secreted factors, as in the case of hormones that control blood pressure, have local effects and also reinforcing effects on the brain. The details are far from completely clear, but the following examples may give some feeling for the broad organization.

The glucocorticoid hormones, whose secretions are evoked by leucocyte ACTH, suppress production of leucocytes except for those that specifically bind the infectious agent. Thus, these hormones play a key role in the development of selectivity in the immune response (Besedovsky *et al.*, 1985). ACTH, cortisol, and

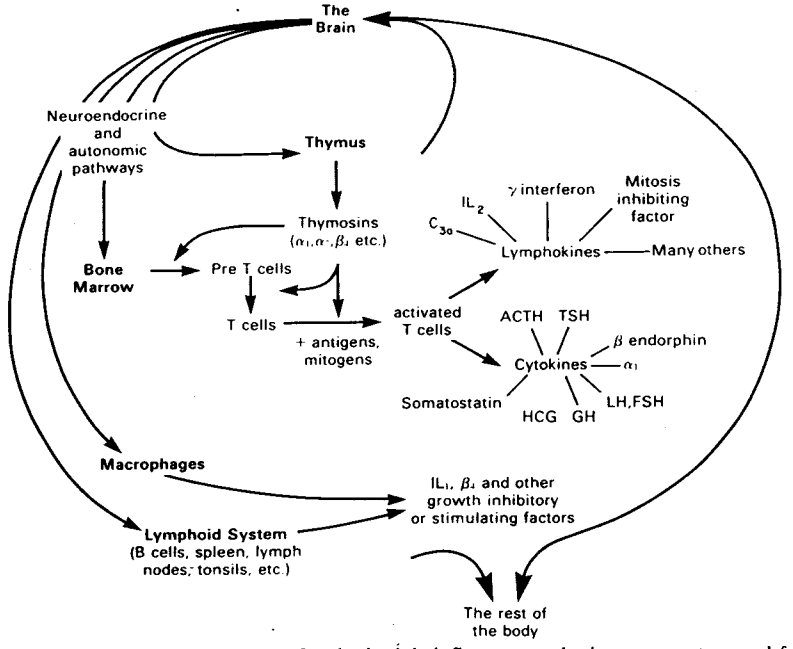

FIG. 34.4 Multiple pathways for the brain's influence on the immune system and for signals from the immune system to the brain. (See Goetzl (1985) for details.)

the opiate hormones also act on the brain to promote euphoria (Barnes, 1986; Shavit *et al.*, 1985). Interleukin IL1 binds to thermoregulatory neurons in the hypothalamus that promote a rise in metabolic rate (e.g. by promoting TSH secretion and thus activation of the thyroid) (Besedovsky *et al.*, 1986). IL1 also promotes sleep. Interferon acts peripherally to block viral replication and on the brain to cause lethargy. Thymosin B_4 promotes the development of the cellular immune response in the thymus and also binds in the hypothalamus to promote secretion of luteinizing hormone (LH). LH promotes elevation of sex hormones that in turn promote anabolic chemistry, mood, and behavior (Hall *et al.*, 1985). Thus, if the response to the virus were the only coping demand, the organism would tend to develop fever and go to sleep, accompanied by dreams of nurturance and pleasure that promote the endocrine state optimal for supporting its developing immune response.

On the other hand, if for some reason the level of arousal is very high, the brain will evoke secretion of much higher levels of ACTH, cortisol, and the other catabolic hormones (Bourne *et al.*, 1974). The immune system and the inflammatory response will be suppressed until the arousal resolves (Laudenslager *et al.*, 1983; Keller *et al.*, 1983; Schleiffer *et al.*, 1985). Then the body and brain can turn their attention once again to internal affairs and fight the infection. This general

scheme may help explain why one often falls ill immediately after a period of intense arousal. The internal challenge has already been present for some time but the symptoms have been suppressed. When the level of catabolism called forth by the brain falls to a certain level, the processes engaged by the system of lymphokines and cytokines are then asserted. Thus, as for the cardiovascular system, the critical reason for having feedforward connections from the immune system to the brain is to permit allostasis, enabling the brain to weigh the internal versus external demands and to allocate resources accordingly.

REGULATION OF AROUSAL

Weiss (1972) documented four factors that regulate arousal. He measured the extent of gastric ulceration in pairs of rats 24 hours following their exposure to the identical series of tail shocks. When the shocks were administered at random intervals, ulceration in both rats was severe. However, when one rat was provided with a warning signal before each shock, its ulcers were greatly reduced compared to the control rat which received the identical shocks. Similarly, when a rat could prevent some shocks by pressing a lever, its ulcers were fewer than in the control rat which received the identical number of shocks but for which all the shocks were inescapable. When, following a lever press, a signal was provided to indicate a correct response, ulcers declined still further. Thus, *predictability*, a sense of *control*, and *feedback* all permit the organism to reduce its level of arousal. However, when *demand*, that is, the rate of required response, is made very high, these factors are overridden and the ulcers increase.

These experiments have been repeated in rats using several measures of immune response with the same result. The random, inescapable shocks cause immune suppression. When there is predictability, control, and feedback with regard to the shocks, the immune suppression declines, but when the demand for bar pressing to prevent shocks is elevated, the immune system is once more suppressed (Schleiffer *et al.*, 1985; Keller *et al.*, 1983; Laudenslager *et al.*, 1983).

The Weiss experiments do not identify every factor controlling arousal in humans—for example, they omit the role of psychological defense mechanisms (see Wolff *et al.*, 1964)—but they make much intuitive sense. The biological purpose of the aroused state is to allow an organism to 'cope' physiologically, behaviorally, and emotionally with specific environmental demands. When the environmental demands are identified, predicted, and demonstrably met, that is, when coping has been successful, arousal must be followed by a period of relaxation. This allows anabolic hormones to flow, restoring blood pressure, energy stores, the immune system, gut lining, and so on. It also allows restoration of a relaxed subjective state so that intimate social relations and spiritual ties can be restored that tend to be disrupted by the agonistic moods and behavior accompanying arousal. (In this context, it must be appreciated that essentially all the catabolic hormones, including epinephrine, cortisol, ACTH, thyroxine, TRH, and the opiates, in addition to their metabolic effects, tend to elevate mood, suppress fatigue and pain, and promote agonistic behavior (see Nemeroff and Dunn, 1984).) From this point of view one might consider the Sabbath as a cultural adaptation to ensure regular periods of physiological, interpersonal, and spiritual anabolism. Its progressive corruption in modern society reflects the continued unrestricted expansion of arousing activities and the loss of a potentially important source of anabolic time.

When demand and thus arousal become chronic, the brain–body system adapts at essentially all levels of organization. The muscle in blood vessel walls thickens and so becomes more effective in raising blood pressure. On the other hand, when the muscle is maximally relaxed, it no longer lowers the pressure quite as much. Furthermore, since the vessels are now always more constricted, they require a higher blood pressure than formerly to maintain the same resting blood flow (Folkow and Neill, 1971; Lund-Johanson, 1984). The vascular system becomes in a sense 'addicted' to higher pressure.

Similarly, the body becomes addicted to its own catabolic hormones. Many hormones act by binding to specific protein 'receptors' on the surfaces of and inside cells. It is now appreciated that a hormone's potency depends on the number of its receptor molecules available for binding as well as on the quantity of the hormone. Chronic elevation of a hormone generally leads to downward regulation of its receptors (see Friedhoff and Miller, 1983). Therefore, to obtain a given effect eventually requires a larger dose of the hormone. To the extent that subjective states such as appetite and mood are regulated by hormones binding to receptors in the brain, there will tend to be addiction of subjective state to arousal. That is, the higher the chronic levels of one's own opiates, cortisol, ACTH, angiotensin, and so on, the more dependent one's mood may become on keeping them high. When the level of arousal has been high for a long period due to high demand, entry into a relaxed condition may create an unpleasant state of withdrawal from one's own catabolic hormones. This could provide a physiological basis for an individual's continuing to seek conditions of high demand ('workaholism', Type A behavior).

Another neurophysiological mechanism for adaptation to chronic arousal is that the brain tends to create fixed automatisms out of previously flexible anticipatory responses. Just as a bell that has come to presage food causes salivation and a rise in insulin, so do hosts of signals, previously neutral, come to presage arousing events and automatically reinforce the aroused endocrine and subjective states. One potential consequence of all the mechanisms mentioned is that specific genes whose activities are associated with arousal may be switched irreversibly into the active state (Reisine *et al.*, 1986; Yamamoto, 1985). If this were so for the genes controlling synthesis of any of the catabolic hormones or their receptors, the chronically aroused state could persist even in the absence of objectively arousing situations. Thus there are pathways at all levels from that of the genes, receptors, tissues, neural systems, subjective states, and the social system that tend through natural adaptive mechanisms to become addicted to chronic arousal and thereby make it permanent.

The tendency for the physiological consequences of chronic arousal to become self-maintaining is evident in the studies already cited. This includes the failure of blood pressure in monkeys, cats, and mice to return to normal when the chronically arousing stimuli are removed. It probably also explains, at least in

part, why blood pressure in humans that is first labile in response to arousal can become permanently regulated at much higher than normal levels long after the chronically arousing stimuli are gone. Figure 34.2b, a 24-hour recording from a hypertensive individual, gives some feeling for this point. It can be seen that the pressure is not fixed at a specific level, but is modulated over a considerable range, falling in sleep and rising by day, just as the normal individual whose record was shown in Figure 34.2a. There continues to be allostatic regulation, but the average setpoint is much higher than normal.

PATHOLOGY FROM CHRONIC AROUSAL

One may expect, because arousal alters the level of virtually every regulatory chemical in the body and affects the metabolism and function of every system, that chronic arousal would lead to a variety of pathologies. Figure 34.5 indicates some of the main pathologies of the renal–cerebral–cardiovascular system and how they arise in a cooperative manner from multiple mechanisms all driven by arousal. The main problems are that chronic hypertension damages blood vessels in every organ and that elevated cholesterol and other blood lipids cause atherosclerosis in damaged vessels. Add to that increased viscosity and clotting tendency of the blood, and the potential for rupture or occlusion of vessels in kidney, brain, and heart becomes significant. Chronic stimulation of the now compromised heart by continuing signals of arousal, as well as by drugs whose consumption tends to accompany arousal (e.g. nicotine and caffeine), increase the chances of sudden coronary death (see Sterling and Eyer, 1981).

Diabetes, the fifth leading cause of death in the US, is a condition in which regulation of carbohydrate, fat, and protein metabolism is abnormal. Its sequelae are accelerated atherosclerosis and other forms of cardiovascular deterioration, increased protein breakdown, reduced immunity, and usually hypertension. The hormonal pattern in childhood-onset diabetes, lowered insulin and elevated glucagon, resembles the hormonal pattern of arousal. This is not to say that arousal causes the disease, but it certainly exacerbates the symptoms. This has been shown clearly for diabetic children in families in which interparental conflict is discharged through the child (Minuchin *et al.*, 1978). In adult-onset diabetes, the timing of insulin secretion is abnormal so that the hormone is relatively ineffective and ultimately causes down regulation of its own receptors (Jacobs and Cuatrecasas, 1977). Chronic arousal would tend to exacerbate this conditon since the arousal hormones tend to antagonize insulin. Chronic arousal, because it tends to suppress insulin secretion, may also be one of the initiators of adult-onset diabetes. This disorder is especially prevalent among the obese. The prevalence of obesity is greatest in the most disrupted segments of the population, leading one to wonder whether the appetite for food, like salt, may be strongly driven by the catabolic hormones of chronic arousal.

Cancer, another leading cause of death at older ages, is connected in several ways to arousal level. There are external factors such as drug consumption and diet. Thus smoking contributes to lung cancer and alcohol consumption to cancers of the liver and pancreas, while excess animal fat and deficiency of fiber apparent-

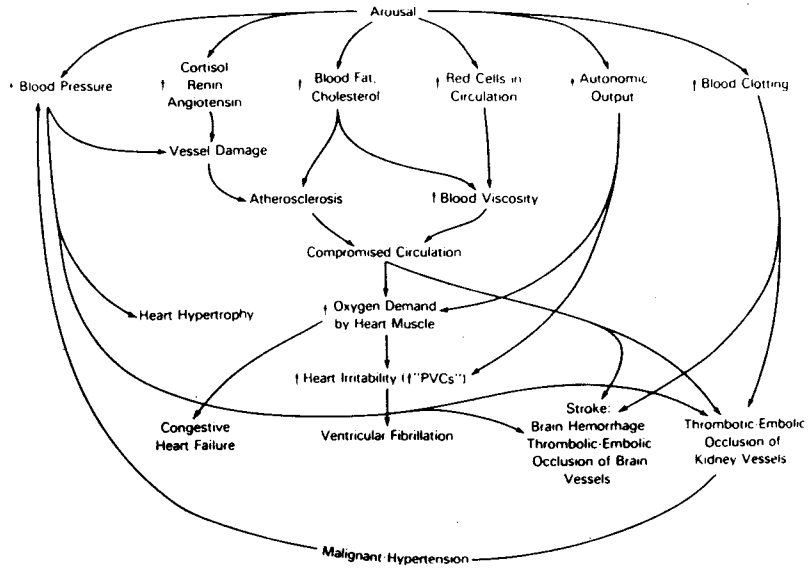

FIG. 34.5 Multiple mechanisms for renal, cerebral and cardiovascular pathology from chronic arousal. (Reprinted from Sterling and Eyer, 1981.)

ly contribute to colon cancer. The allostatic model suggests connections between appetite and physiological state; therefore, the modern craving for nicotine, alcohol, fat, and fiberless food may all be related to appetites driven by chronic arousal. The progressive contamination of our environment by asbestos, radiation, and organic chemicals is widely recognized to contribute to cancer. This is not linked to chronic arousal in any single individual; nevertheless, like the lapsing of the Sabbath already noted, it reflects a change of values that arises from and helps to reinforce chronic arousal as a societal pattern.

Cancers are also regulated by the body's immune and endocrine systems. Immunosuppressed humans and animals develop cancer at up to one hundred times the normal rate (Harris and Sinkovics, 1970). Female mice chronically aroused by handling and exposure to strangers show hypersecretion of cortisol, suppressed immune organs such as the thymus, and die at higher rates and earlier ages of virally evoked mammary tumors (Riley, 1975). In this case it appears that replication of the oncogenic virus is also directly stimulated by cortisol (Yamamoto, 1985). Rats subjected in the Weiss paradigm to inescapable and unpredictable shock develop tumors at higher rates than animals who can prevent or predict the shocks (Schleiffer *et al.*, 1985). Recently, specific genes have been discovered whose activities are related to the development of cancer. It has been learned that the proteins coded by at least two of these so-called oncogenes are identical in

structure to the receptor molecules for thyroid hormone and cortisol (Sap *et al.*, 1986; Weinberger *et al.*, 1986). Thus, some of the molecules that help determine whether cells become cancerous are direct targets for certain catabolic hormones.

DEFINITIONS OF HEALTH AND APPROACHES TO THERAPEUTICS

The homeostatic model defines health as a state in which all physiological parameters have 'normal' values. A value outside the normal range is said to be 'inappropriate', and thus a candidate for 'treatment'. The main treatment is to administer drugs that stimulate or suppress the somatic mechanisms that most directly control that parameter (Taylor and Caldwell, 1986). Thus, if blood pressure is above 140/90 mmHg, drugs are directed at the three basic mechanisms that raise the pressure: diuretics to reduce the volume of circulating salt water; vasodilators to increase the size of reservoir; antagonists of the beta-receptor to reduce the heart's output. To block one of these mechanisms is sometimes adequate, but frequently, as would be expected from the diagram in Figure 34.3, the brain uses the other mechanisms to compensate. Thus, a diuretic-induced reduction of blood volume may be compensated by an increase in cardiac output and by vasoconstriction; drug-induced vasodilatation is compensated by increased cardiac output, and so on (see Sterling and Eyer, 1981). When such compensations occur, additional drugs can be administered until all three mechanisms have been blocked. Another pharmacotherapy in the same spirit is to block the enzymatic conversion of angiotensin to its active form or to block the binding of this hormone to its receptors. These are potent treatments because angiotensin has many actions that affect all three of the somatic mechanisms for increasing pressure and many sites in the brain as well (see Figure 34.3). Further, in animals, blocking the central action of angiotensin is shown to reduce salt appetite (Weiss *et al.*, 1986; Moe *et al.*, 1984).

The pharmacological approach, despite its impressive ingenuity, contains an inherent tendency toward iatrogenesis. Because each hormone has multiple effects and each receptor type (alpha, beta, angiotensin, etc.) is widely distributed, every drug directed at restoring one parameter to normal necessarily causes other parameters to become 'inappropriately' high or low. For example, the diuretic treatment causes potassium to become inappropriately low and glucose, cholesterol and uric acid to become inappropriately high (Gifford, 1974). Consequently, the pharmacological reduction of blood pressure reduces the chances of a stroke, but the other effects *increase* the chances of a heart attack (Grimm, 1986; Leren and Helgeland, 1986). Additional drugs are commonly administered to restore these other parameters to normal (see Sterling and Eyer, 1981). Thus the therapeutic approach associated with the homeostatic model is inevitably associated with polypharmacy and iatrogenesis.

The other serious drawback is that the responsiveness of the organism is reduced. Pharmacological treatment that tries to clamp some parameter at its 'normal' value naturally prevents it from responding to increased demand at moments when that would be desirable. With blood pressure clamped low, the tolerance of a drug-treated hypertensive person for exercise is diminished, even though exercise might be therapeutic (Lund-Johanson, 1984). Further, the reduction of responsiveness is not limited (for reasons already noted) to the therapeutically targeted parameter. The drug treatments that reduce the tolerance of a hypertensive person for exercise may also render him lethargic and impotent (see Sterling and Eyer 1981).

The allostatic model defines health as a state of responsiveness. A parameter with values outside the normal range is not considered 'inappropriate' because every parameter is controlled by a multitude of mutally reinforcing signals. If a parameter has a value above or below normal, most likely there are multiple mechanisms forcing it there, and most likely the ultimate source of these signals is the brain. In this model, the elevated blood pressure of the hypertensive is considered to be entirely appropriate, and the question for exploration becomes 'appropriate to what?'.

The elevation of blood pressure may be appropriate to the arousing conditions of modern life. The chain of evidence linking the conditions of life to this disorder is now fairly complete. First, there is the epidemiological and behavioral evidence: (1) hypertension is greatest among human populations subjected to disruption of intimate social relations, (2) the pressure rise in the population to begins essentially at the moment children leave the family bosom and enter the uncertain and demanding environment of school, (3) hypertension can be produced experimentally in populations of animals by social disruption and in individual animals by arousing behavioral paradigms. Next, there is broad physiological evidence: (1) many neural and neuroendocrine mechanisms are available to elevate blood pressure and thus potentially to cause hypertension (see Figure 34.3), (2) chronic hypertension can be produced in animal models by stimulating the brain regions that activate these neural and neuroendocrine mechanisms, (3) these mechanisms are demonstrated to be active in the natural state under the arousing behavioral conditions associated with the development of hypertension, (4) pharmacological suppression of one mechanism for raising pressure is compensated by the other mechanisms, and this suggests that the target pressure is set by the brain.

Chronically elevated blood pressure is 'appropriate' in the allostatic model but it is certainly not healthy. When pressure is at high levels, there is no margin for responding to additional challenges or to opportunities for relaxation. Furthermore, high pressure leads inevitably to serious organic pathology (see Figure 34.5). Thus the allostatic model provides a scientific framework for recognizing the obvious, that health requires a decent balance between catabolism and anabolism.

The therapy suggested by the allostatic model is to reduce arousal. A prime objective, following the Weiss paradigm, would be to reduce demand by encouraging people to rest and play in proportion to their work and striving and to increase predictability, control, and feedback in their lives. Such steps would reduce *all* the neural and neuroendocrine drives on the multiple mechanisms for raising blood pressure. In contrast to pharmacotherapy, where blocking one mechanism evokes compensatory increases in others, reducing arousal would reduce pressure by the concerted action of multiple mechanisms.

Prevention and treatment of hypertension directed at the social and psychological levels are widely considered impractical compared to pharmocotherapy.

Yet, the experience of several decades with mass drug treatment for hypertension has raised doubts regarding its true practicality. Long-term drug treatment for mild and moderate hypertension reduces mortality from stroke but increases mortality from heart disease (Grimm, 1986; Leren, 1986; Freis, 1986a). Furthermore, the various unpleasant and iatrogenic effects of drug treatment cause enough patient non-compliance that pressure in the population remains uncontrolled. In fact, blood pressures in the large (baby boom) cohort that has experienced increased competition and chronic arousal since youth are higher than they were in the preceding small cohort at the corresponding age despite the wide availability of antihypertensive drugs (Eyer, 1980). Physicians enthusiastic about drug treatment for 20 years have sharply moderated their claims and are now recommending for mild hypertension simple follow-up visits and possibly relaxation training, diet and exercise (Chesney *et al.*, 1986; Freis, 1986a; 1986b).

The highly technological treatments for the end-stages of disease related to chronic arousal are also proving to be of dubious practicality. Coronary artery bypass grafts (CABG) successfully reduce pain from angina but contribute hardly at all to longevity (see Sterling and Eyer, 1981; Chaitman *et al.*, 1986; Cameron *et al.*, 1986). Kidney dialysis and transplantation prolong life but at great psychological cost to the patient (Abrams *et al.*, 1972). Treatments for the major cancers have been largely unsuccessful (Kolata, 1986). The technological approach is also very expensive. There are now about 250 000 CABGs per year in the US, at a cost of nearly $8 billion (Rimm *et al.*, 1986). When the large cohort comes of age for this surgery, these figures might easily double. The cost of medical care now absorbs about 12% of the US GNP, and still grows. To continue on this path of highly technological treatment will progressively limit the possibilities for other uses of the social product. What proves practical in the long run may not be technology but rather investment in social structures and activities that rebuild and enrich communal life, that reduce demand and enhance predictability, control and feedback.

SUMMARY AND CONCLUSIONS

'Homeostasis', the central model in physiology and therapeutics for 100 years, is superseded by a new model, 'allostasis', that emerges from recent studies in neurobiology. Homeostasis emphasized that the body's internal environment is held constant by the self-correcting (negative feedback) actions of its constituent organs. Allostasis emphasizes that the internal milieu varies to meet perceived and anticipated demand. This variation is achieved by multiple, mutually reinforcing neural and neuroendocrine mechanisms that override the homeostatic mechanisms. The allostatic model, in emphasizing the subordination of local feedbacks to control by the brain, provides a strong conceptual framework to explain social and psychological modulation of physiology and pathology.

Acknowledgements

We thank Professor Charles Kahn for suggesting the term 'allostasis', Dr Noga Vardi for reading the manuscript, and Ms Judy Jackson for typing.

REFERENCES

Abrams, H. *et al.* (1972). Suicidal behavior in chronic dialysis patients. *American Journal of Psychiatry, 127*, 1199.

Akil, H., Watson, S.J., Young, E., Lewis, M.E., Katchaturian, H., & Walker, M.J. (1984). Endogenous opioids: biology and function. *Annual Review of Neuroscience, 7*, 223–255.

Barnes, D. (1986). Steroids may influence changes in mood. *Science, 232*, 1344.

Berkson, J. (1962). Mortality and marital status. *American Journal of Public Health, 52*, 1318.

Bernard, C. (1865). *An introduction to the study of experimental medicine*. New York: Dover Publications. (Published 1957.)

Besedovsky, H. *et al.* (1985). Immune-neuro-endocrine interactions. *Journal of immunology, 135(2)*, Suppl., 750–754.

Besedovsky, H. *et al.* (1986). Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science, 233*, 652–654.

Bevan, A.T. *et al.* (1969). Direct arterial pressure recording in unrestricted man. *Clinical Science, 369*, 329.

Blalock, J. *et al.* (1985). Peptide hormones shared by the neuroendocrine and immunologic systems. *Journal of Immunology, 135*(2), Suppl., 858–861.

Blumenthal, S. *et al.* (1977). Report on the task force on blood pressure control in children. *Pediatrics, 59*, Suppl., 797.

Bourne, H.R. *et al.* (1974). Modulation of inflammation and immunity by cyclic AMP. *Science, 184*, 19.

Cameron, A. *et al.* (1986). Bypass surgery with the internal mammary artery graft: 15-year followup. *Circulation, 74* (Suppl. III), III-17.

Cannon, W.B. (1929). *Bodily changes in pain, hunger, fear and rage: An account of recent researchers into the function of emotional excitement*, 2nd edn. New York: Appleton.

Cannon, W.B. (1932). *The wisdom of the body*. New York: W.W. Norton.

Chaitman, B.R. *et al.* (1986). The role of coronary bypass surgery for 'left main equivalent' coronary disease: the CASS registry. *Circulation, 74*, (Suppl. III). III-30.

Chesney, M.A. *et al.* (1986). Behavioral treatment of borderline hypertension. *Cardiovascular Journal of Pharmacology, 8*, (Suppl. 5), 557–563.

Dillingham, M.A., & Anderson, R.J. (1986). Inhibition of vasopressin action by atrial natiuretic factor. *Science, 231*, 1572–1573.

Eskay, R., Zukowska-Grojec, Z., Haass, M., Dave, J.R., & Zamir, N. (1986). Circulating atrial natiuretic peptides in conscious rats: regulation of release by multiple factors. *Science, 2321*, 636–638.

Eyer, J. (1975). Hypertension as a disease of modern society. *International Journal of Health Services, 5*, 539.

Eyer, J. (1980). Social causes of coronary heart disease. *Psychotherapy and Psychosomatics, 34*, 75–87.

Eyer, J., & Sterling, P. (1977). Stress-related mortality and social organization. *Review of Radical Political Economics, 9*, 1–16.

Felten, D. *et al.* (1985). Noradrenergic and peptidergic innervation of lymphoid tissue. *Journal of Immunology, 135*(2), Suppl., 755–765.

Folkow, B., & Neill, E. (1971). *Circulation*. London: Oxford University Press.

Folkow, B., & Rubinstein, E.H. (1966). Cardiovascular effects of acute and chronic stimulation of the hypothalamic defense area in the rat. *Acta Physiologica Scandinavica, 68*, 48.

Forsyth, R.P. (1969). Blood pressure responses to long-term avoidance schedules in the unrestrained rhesus monkey. *Psychosomatic Medicine, 31*, 300.

Freis, E.D. (1986a). Borderline mild systemic hypertension: should it be treated? *American Journal of Cardiology, 58*,(7), 642–645.

Freis, E.D. (ed.) (1986b). Symposium on borderline hypertension. *Journal of Cardiovascular Pharmacology 8*, Suppl. 5.

Friedhoff, A.J., & Miller, J.C. (1983). Clinical implications of receptor sensitivity modification. *Annual Review of Neuroscience, 6*, 121–148.
Geenan, V. *et al.* (1986). The neuroendocrine thymus: coexistence of oxytocin and neurophysin in the human thymus. *Science, 232*, 508.
Gifford, R.W. (1974). A practical guide to management. In *The hypertension handbook* (p. 83). West Point: Merck, Sharpe and Dohme.
Goetzl, E.J. (ed.) (1985). Proceedings of the conference on neuromodulation of immunity and hypersentivity. *Journal of Immunology, 135*(2), Suppl.
Grimm, R.H. (1986). The drug treatment of mild hypertension in the multiple risk factor intervention trial: a review. Proceedings of a symposium on treatment of hypertension and primary prevention of coronary heart disease. *Drugs, 31*, Suppl. 1, 13–21.
Hall, N.R. *et al.* (1985). Evidence that thymosins and other biologic response modifiers can function as neuroactive immunotransmitters. *Journal of Immunology, 135*(2), Suppl., 806–811.
Harris, J., & Sinkovics, J. (1970). *The immunology of malignant disease*. St Louis, Miss.: Mosby.
Henry, J.P., Meehan, J.P., & Stephens, P.M. (1967). The use of psychosocial stimuli to induce prolonged systolic hypertension in mice. *Psychosomatic Medicine, 29*, 408.
Hohmann, E.L., Elde, R.P., Rysavy, J.A., Einzig, S., & Gebhard, R.L. (1986). Innervation of periosteum and bone by sympathetic vasoactive intestinal peptide-containing nerve fibers. *Science, 232*, 868–871.
Jacobs, S. & Cuatrecasas, P. (1977). Cell receptors in disease. *New England of Medicine, 297*, 1383.
Kanigel, R. (1986). Where mind and body meet. *Mosaic, 17*, 52–60.
Keller, S.E., Weiss, J.M., Miller, N.E. & Stein, M. (1983). Stress-induced suppression of immunity in adrenalectomized rats. *Science, 221*, 1301–1304.
Kolata, G. (1986). Cancer progression data challenged. *Science, 232*, 932–933.
Laudenslager, M.L., Ryan, S.M., Drugan, R.C., Hyson, R.L., & Maier, S.E. (1983). Coping and immunosuppression: inescapable but not escapable shock suppresses lymphocyte proliferation. *Science, 221*, 568–570.
Leren, P., & Helgeland, A. (1986). The Oslo Hypertension Study. Proceedings of a symposium on treatment of hypertension and primary prevention of coronary heart disease. *Drugs, 31*, Suppl. 1, 40–49.
Lund-Johanson, P. (1984). Hemodynamic concepts in essential hypertension. *Triangle, 23*, No. 1. 13–24 (Sandoz).
Manning, P.T., Schwartz, D., Katsuvbe, N.C., Holmberg, S.W., & Needleman, P. (1985). Vasopressin-stimulated release of atriopeptin: endocrine antagonists in fluid homeostatis. *Science, 229*, 395–397.
Mason, J.W. (1968). Organization of endocrine mechanisms. *Psychosomatic Medicine, 30*, 565.
Mason, J.W. (1971). A reevaluation of the concept of 'nonspecificity' in stress theory. *Journal of Psychiatric Research, 8*, 323.
Mason, J.W. (1972). Organization of psychoendocrine mechanisms. In N.S. Greenfield & R.A. Sternbach (eds), *Handbook of psychophysiology*. New York: Holt, Rhinehart and Winston.
Minuchin, S., Rosman, B., & Baker, L. (1978). *Psychosomatic families. Anorexia nervosa in context*. Cambridge, Mass.: Harvard University Press.
Miselis, R. (1986). The visceral neuraxis in thirst and renal function. In G. de Caro, A.N. Epstein & M. Massi (eds), *The physiology of thirst and sodium appetite*. Plenum.
Moe. K.E., Weiss, M.L., & Epstein, A.N. (1984). Sodium appetite during captopril blockage of endogenous angiotensin II formation. *American Journal of Physiology, 247*, 356–R365.
Nemeroff, C.B., & Dunn, A.J. (eds) (1984). *Peptides, hormones, and behavior*. Spectrum.
Pickering, T.G. *et al.* (1986). Behavioral determinants of 24-hour blood pressure patterns in borderline hypertension. *Journal of Cardiovascular Pharmacology, 8*. Suppl. 5, 589–592.
Reisine, T., Affolter, H.-A., Rougon, G., & Barbet, J. (1986). New insights into the molecular mechanisms of stress. *Trends in Neuro Science, 9*, 574–579.
Riley, V. (1975). Mouse mammary tumors: alteration of incidence as apparent function of stress. *Science, 189*, 465.
Rimm, A.A. *et al.* (1986). Trends in coronary surgery. *Journal of the American Medical Association, 255*, 229–233.
Sap, J. *et al.* (1986). The c-erb-A protein is a high-affinity receptor for thyroid hormone. *Nature 324*, 635–640.
Schleiffer, S. *et al.* (1985). Stress and immunomodulation: the role of depression and neuroendocrine function. *Journal of Immunology, 135*(2), Suppl., 827.
Selye, H. (1956). *The stress of life*. New York: McGraw-Hill.
Shavit, Y. et al. (1985). Stress, opioid peptides, the immune system and cancer. *Journal of Immunology, 135*, Suppl., 834.
Smith, E. *et al.* (1985). Lymphocyte production of endorphins and endorphin-mediated immunoregulatory activity. *Journal of Immunology, 135*(2), Suppl., 779–782.
Smith, E. *et al.* (1986). Cortiocotropin releasing factor induction of leukocyte-derived immunoreactive ACTH and endorphins. *Nature, 321*, 881–882.
Standaert, D.G., Needleman, P., & Saper, C.B. (1986). Organization of atrio-peptin-like immunoreactive neurons in the central nervous system of the rat. *Journal of Comparative Neurology, 253*, 315–341.
Sterling, P., & Eyer, J. (1981). Biological basis of stress-related mortality. *Social Science and Medicine, 15E*, 3–42.
Taylor, S., & Calwell, A. (eds) (1986). Proceedings of a symposium on treatment of hypertension and primary prevention of coronary heart disease. *Drugs, 31*, Suppl., 1.
Waldron, I. (1979). A quantitative analysis of cross-cultural variation in blood pressure and serum cholesterol. *Psychosomatic Medicine, 41*, 582.
Weinberger, C. *et al.* (1986). The *c-erb-A* gene encodes a thyroid hormone receptor. *Nature, 324*, 641–646.
Weiss, M.L., Moe, K.E., & Epstein, A.N. (1986). Interference with central actions of angiotensin II suppresses sodium appetite. *American Journal of Physiology, 250*, R250–R259.
Weiss, J.M. (1972). Psychological factors in stress and disease. *Scientific American, 226*, 104.
Wolff, C.T., Friedman, S.B., Hofer, M.A., & Mason, J.W. (1964). Relationship between psychological defenses and mean urinary 17-hydroxycorticosteroid excretion rates. I. A predictive study of parents of fatally ill children. *Psychosomatic Medicine, 26*, 574–591.
Yamamoto, K.R. (1985). Steroid receptor regulated transcription of specific genes and gene networks. *Annual Review of Genetics, 19*, 209–252.
Zhang, D.-M., Stellar, E., & Epstein, A.N. (1983). Together intracranial angiotensin and systemic mineralocorticoid produce avidity for salt in the rat. *Physiology and Behaviour, 32*, 677–681.
Zurawski, G. *et al.* (1986). Activation of mouse T-helper cells induces abundant preproenkephalin mRNA synthesis. *Science, 232*, 772–775.

KEY WORDS

Stress, allostasis, homeostasis, hypertension, arousal, psychoneuriommunology, iatrogenesis, health.