

BIOLOGICAL BASIS OF STRESS-RELATED MORTALITY

PETER STERLING and JOE EYER

University of Pennsylvania, Philadelphia

Abstract—It is believed in primitive society that physical health depends on harmonious social relations and that sickness follows social disruption. The mortality patterns of adults in modern society support this view, but its biological basis is not widely appreciated. This essay reviews the mechanisms by which chronic psychological arousal produces chronic physiological arousal and, in turn, specific biological pathology.

The brain sets for the body a broad pattern of physiological and metabolic activity and enforces it by control over the autonomic and endocrine systems. Under conditions of arousal the brain sets a pattern of catabolism, mobilizing all the mechanisms that produce energy for "coping" and suppressing the mechanisms that store energy or use it for growth, repair, and surveillance against pathogens. As part of this adaptive response the brain mobilizes cardiac, vascular, and renal mechanisms to raise blood pressure. When arousal is chronic, the high pressure causes damage which, in interaction with a variety of arousal-induced chemical changes, leads to endstage diseases such as coronary heart disease, stroke, and kidney disease. The biological causes of cancer and diabetes are not fully known but seem to be powerfully influenced by arousal-induced endocrine patterns.

Treatment of arousal pathology at the end stages has been highly technological, of limited success, and very expensive. The leading alternative has been an attempt to prevent endstage disease by treating mild hypertension on a mass scale (23–60 million patients in U.S.) with potent drugs. As drugs block peripheral pressor mechanisms, the brain drives them to compensate and to require blocking by additional drugs. Over the decades of prophylaxis for which drugs are intended, their cumulative iatrogenic effects are likely to be serious. Psychosocial treatments for mild hypertension (including placebo, relaxation techniques, and social support) appear to be quite effective. These treatments appear to work by reducing chronic arousal, and tend not to evoke compensatory or iatrogenic responses. The extraordinary sensitivity of the brain and the neuro-endocrine system to psychosocial intervention suggests that in modern, as in primitive society, these are the treatments that will prove safest and most effective.

INTRODUCTION

The Iroquois Indians were, in 17th Century America, a society of agriculturists and warriors. The men were brave, self-reliant, and uncomplaining even when subjected to physical torture. Although it was not permitted among them to express openly any weakness or dependence, the Iroquois did dream. Their dreams were of rage—often directed against the French, and of pleasure—of feasting, of being cared for by friends, of orgiastic sex. Such dreams were entirely acceptable, and, as one account puts it, "without shame they received the fruits of their dreams and their souls were satisfied" [1, 2].

It was understood by the Iroquois centuries before Freud that dreams are expressions of unconscious wishes. These were not, as the Victorians believed, statements of infantile conflict, but rather expressions of pressing adult needs. The dreams were publicly discussed and interpreted, and it was for the community to fulfill the demands of the dream. The Iroquois believed that failure to respond to the dream and frustration of its expressed wishes would result in serious illness and death.

"The community rallied round the dreamer with gifts and ritual. The dreamer was fed, he was danced over, he was rubbed with ashes, he was sung to, he was given valuable presents..." [2]. When someone had a hostile dream, he was helped by the community to act out the hostility—either in reality, if the hos-

tility was directed outside the community—or symbolically if the object of anger was within the community. When a sick person dreamed about another person, it was understood that he wanted a friend. In such cases therapy included *giving* a friend in a special ceremony, following which the two treated each other as kin in a life-long relationship. In short, the Iroquois believed that disease could be prevented or cured by encouraging fierce warriors to be dependent, by helping members of the community to act out their fantasies, and by providing lonely people with friends.

This view of disease as primarily a social phenomenon, the result of an unfulfilled social or psychological need, is a very general one in primitive societies. It is also usual in such societies that an important part of therapy for existing disease involves restructuring social relationships to fulfill unmet needs. This may involve a relation between a "patient" and shaman or may, as in the Iroquois example, involve the whole community [3].

Only traces of this conception of disease and therapy as related to social interaction remain in modern society. It is acknowledged, of course, in the many forms of psychotherapy, and in the potent social interaction known as the "placebo effect". A placebo (L. "I shall please") is a pharmacologically inactive substance that is frequently almost as effective therapeutically as a pharmacologically active one. For example, a placebo relieves post-operative pain in 50% of patients while a standard dose of morphine, one of

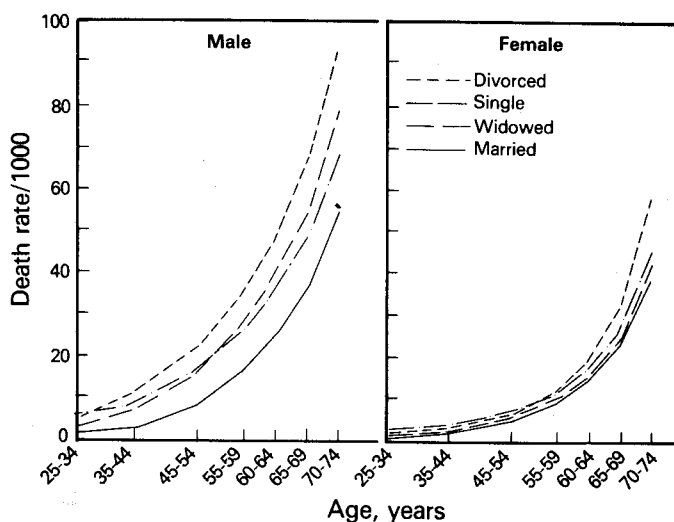


Fig. 1. Death rates, all causes, by marital status, United States. Redrawn from [8].

the most potent analgesics, relieves pain in only 70% [4]. Placebo surgery for anginal pain (from heart disease) is frequently as effective as real surgery—particularly when the surgeon expresses to the patient confidence in the outcome [5]. In modern medicine, however, use of the placebo is generally considered close to fraud [6]. The U.S.F.D.A. now routinely requires that the “efficacy” of new drugs be tested in “blind” comparisons with placebos to be sure that the public gets its pharmacological money’s worth. While the practice may be good from the point of view of “consumer protection”, it forces attention away from the clearly demonstrated healing power of psychosocial interaction revealed by the use of a harmless substance as placebo. It discourages “pleasing” the patient and encourages development of increasingly potent and, therefore, dangerous drugs [7].

Modern society does not generally recognize the importance to health of disruptions to intimate social relationships. Yet, such disruptions are associated with large elevations of morbidity and mortality. For example, the death rates for widowed and divorced are higher at all ages than for married [8] (Fig. 1). These differences hold for every leading cause of death as well as many minor ones (Fig. 2). The difference between married and divorced is much greater for men than for women probably reflecting the relatively greater nurturance American men receive in the marital relationship. On the other hand, the absolute death rates for men are much higher at all ages than for women, reflecting in various ways men’s “warrior” status.

The elevated mortality associated with disruption of intimate social relationships is seen in essentially every comparison between disrupted and less-disrupted populations [9]. Thus, urban death rates are higher than rural; migrant death rates are higher than native ones; black death rates higher than whites, and so on. These differences, too, hold for all ages and for all of the most significant causes. Perhaps one can begin to see in these statistics support for the Iroquois

belief that disease comes from excessive self-reliance and loneliness.

Modern thinking has not incorporated these striking data because disease is regarded not as a social phenomenon, but primarily as a dysfunction within the machinery of an individual body. The dysfunction is to be repaired as one would a machine, by chemical or mechanical intervention. This model of medicine arose in the 19th Century in part from the physiology of Claude Bernard who viewed the body as a self-regulating machine [10], and in part from the observations of microbiologists, such as Pasteur, and pathologists, such as Virchow, who focused attention on the specific toxic effects of infectious agents on our biochemical and cellular machinery [11]. This mechanical model of disease has now been extended as the fundamental one for *every* disease, including the mental illnesses and the addictions. For example, modern medicine considers that one of the most important causes of peptic ulcer is excessive acid secretion by the stomach. The treatment, therefore, involves neutralizing the acid with “anti-acids”, or neutralizing the nerves that stimulate acid secretion with “anti-cholinergic” drugs, or cutting the nerve, and, if all else fails, removing the acid-secreting part of the stomach [12].

Most physicians, once trained in this mechanical model of disease, have no way of incorporating data about the social causes of disease because the two kinds of analysis are on such different levels. Doctors come to regard evidence from the social model as vague, of uncertain importance, and in any case, outside their realm. Thus, despite the common folk knowledge about the emotional causes of ulcer, a major textbook of pathology currently regards the role of stress as controversial and concludes that the origins of peptic ulcers are “enigmas wrapped in mystery” [13]. Furthermore, even though it is widely known that simple hospitalization is a highly effective cure for ulcer [12], the obvious implication that removing a person from his normal tension-ridden

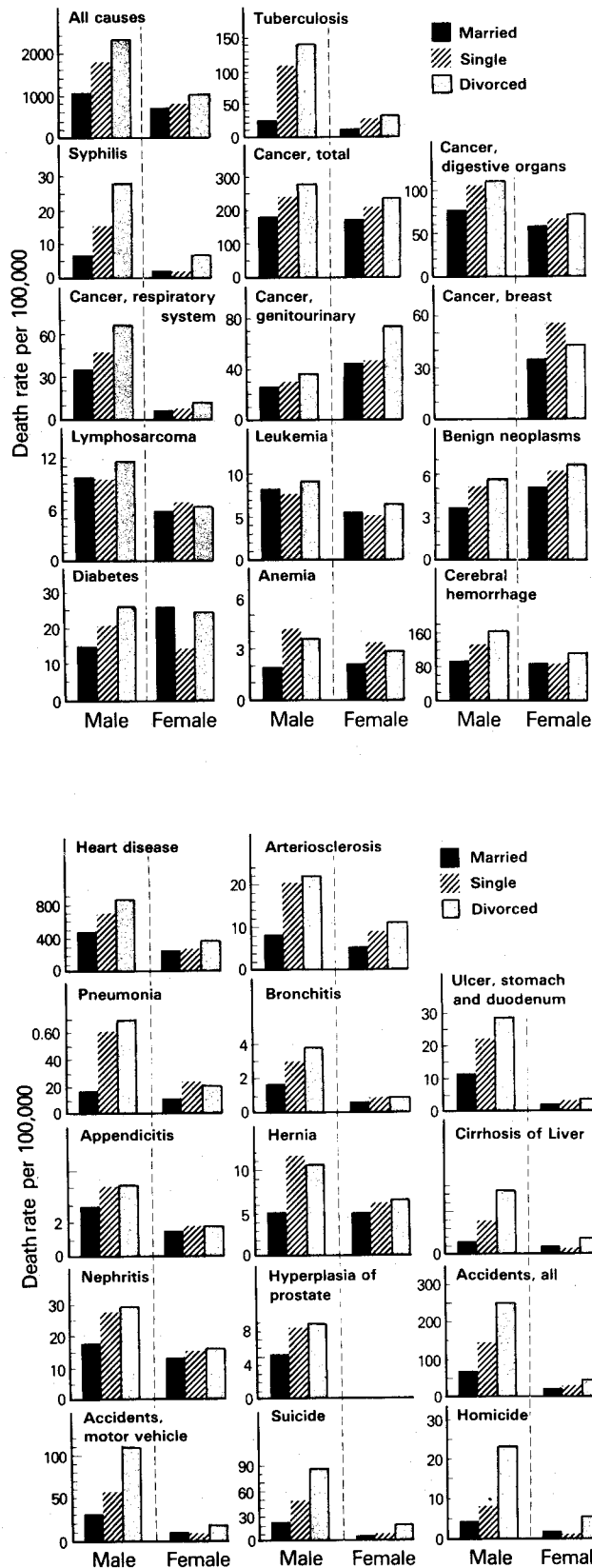


Fig. 2. Standardized death rates, specified classes of cause of death, United States. Redrawn from [8].

environment allows ulcers to heal, is rarely developed into a therapy. Drugs or surgery are preferred, even though they have no relative benefit and many deleterious effects [14].

The failure of doctors to unite both social and biological observations into a comprehensive theory of disease and therapy is not hard to understand. After all, one can *see* microbes under the microscope and clogged arteries in an angiogram. One can *measure* acid production, blood pressure, hormone levels, and so on. Social relationships, on the other hand, seem hard to grasp and even more difficult to manipulate therapeutically. This is not necessarily because of any intrinsic difficulty but rather because of the lack of systematic training in these skills. Thus, most modern physicians have not been taught what to do with a patient whose ulcer has healed in the hospital, beyond prescribing a diet or drugs. Recently, family therapy has begun to develop some of the possibilities for social treatments [15], but there is still a large contrast with primitive groups who take training in social therapeutic skills more seriously. Among the Senoi of Malaya, for example, children are encouraged to relate their dreams every morning at breakfast and are schooled by parents in their interpretation. The children are taught to recognize, even anticipate, social ruptures and how to heal them quickly [16].

There is much to learn about the causes and cures of disease from such thoughtful observations of human behavior as are made by primitive peoples. On the other hand, we are no longer innocent; given the power of our technology and the scientific method, we are bound to account for the specific mechanisms by which the social and psychological causes of disease are linked to the immediate biological causes. In an earlier essay [9] we argued from epidemiological evidence (of the sort mentioned briefly above) that modern development is accompanied by major disruptions of intimate human relations, that such disruptions cause chronic physiological arousal ("stress"), and that arousal is the major cause of death among adults in modern society. The specific physiological mechanisms that may be involved in death from chronic arousal were not treated in detail. Yet, without some plausible hypotheses about these mechanisms, we can neither be convincing nor can we test or illuminate the original argument. Fortunately, there has been in modern medicine an astonishing accumulation of technique and observations that permit one to begin to comprehend, in terms of endocrine and neural pathways, the effects on the body of social and psychological events [17].

In this essay we describe how the body's physiological mechanisms are controlled by the brain, how physiology is altered during arousal, and how chronically altered physiology leads to the major pathologies. The treatments devised by contemporary medicine for arousal-caused pathology are generally heroic. They commonly employ excessive force at the wrong points in the system and are only marginally successful. Among white males over age 30, for example, there has been hardly any increase in life expectancy since 1900 (Table 1).

Such inappropriate and misdirected force is also responsible for much iatrogenic (physician-caused) ill-

ness, the dehumanizing character of medical care, and its spiraling cost. Our analysis suggests that diseases now treated mainly at the end stage, and solely at the physiological level, can be prevented and treated by creating new social relationships. In short, we present hard data to support and explain in mechanistic terms the Iroquois view that the body can be treated by giving satisfaction to the soul [18].

THE BRAIN CONTROLS THE BODY'S PHYSIOLOGY

In this section we summarize relatively new evidence that the central nervous system exerts ultimate control over all aspects of body physiology. The facts to be presented are drawn from standard sources and are not in conflict with earlier evidence concerning physiological regulation. The overall view that emerges, however, does contrast sharply with prevalent medical belief. It is the common view that the body's physiological systems are held "constant" by simple, regulatory feedback loops. This belief in "internal constancy" leads physicians to view unusual elevations or depressions of body metabolites or hormones as "inappropriate" and to combat these changes by intervention with drugs or surgery. We shall show, however, that many of these metabolic alterations make sense as part of an individual's overall process of coping with the environment and that the metabolic changes are merely reflections of the brain's control over physiology. Both the coping and the accompanying metabolic changes are *entirely* appropriate to the social environment. If anything is inappropriate, it is the social environment which both stimulates and demands unremitting coping.

Autoregulation of the internal environment

Physiologists since Claude Bernard have emphasized that in order to exist a human or other mammal must closely regulate its internal environment to protect itself against the large fluctuations of the external world [19]. This means that the chemical composition of the blood, its concentration of salts, glucose, amino acids, etc. as well as its volume, pressure and temperature must all be controlled within certain limits. It has been recognized for 100 years that a failure in any of these regulatory processes can be an immediate cause of disease. If, for example, blood glucose rises too high, profound changes occur in carbohydrate metabolism and acid-base balance, leading

Table 1. Expectation of life (years), white males, United States, by year and age, 1900-1970

Age	Year				
	1900	1920	1940	1960	1970
0	52.8	60.3	65.4	67.4	67.7
5	59.9	62.4	64.3	64.4	64.4
20	47.9	49.1	50.1	50.1	50.1
30	39.6	40.8	40.9	40.9	40.9
40	31.2	31.7	31.7	31.7	31.7
50	23.1	23.2	23.2	23.2	23.2

Redrawn from [64], p. 29.

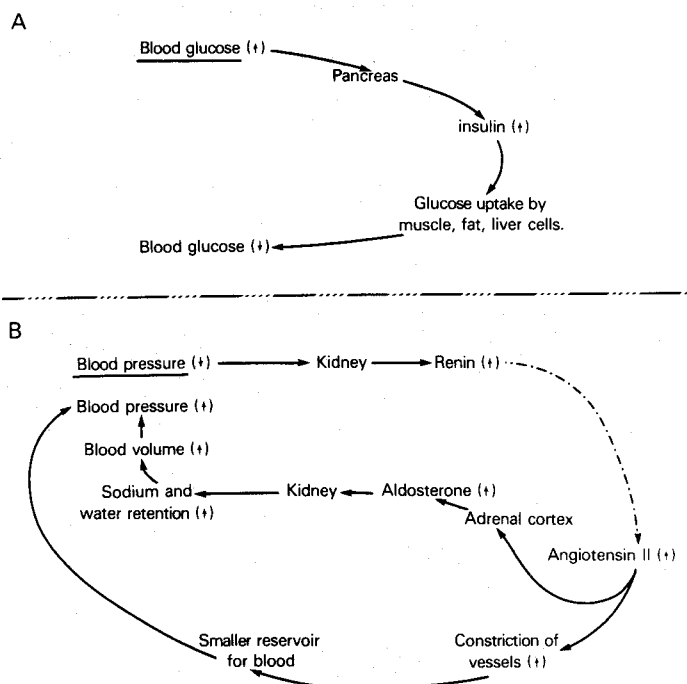


Fig. 3. Examples of local autoregulatory (negative feedback) mechanisms.

ultimately to coma. Similarly, a fall in blood pressure can lead to a loss of blood supply to the brain, fainting, and ultimately, coma.

Most elements of the internal environment are controlled by hormones which at first glance appear to have simple, "negative-feedback" relations with the products or processes that they regulate. A disturbance in some process stimulates hormonal secretion: the hormone corrects the disturbance and removes the stimulus for its own secretion. For example, a rise in the concentration of glucose in the blood stimulates the pancreas to secrete insulin. Insulin stimulates liver, muscle and fat cells to admit glucose, reducing its blood level and removing the stimulus for insulin secretion (Fig. 3A). In some cases a more complex cycle is involved, but the principle is the same. A fall in blood pressure, for example, stimulates the kidney to secrete the hormone, renin, which leads via a series of intermediate steps (Fig. 3B) to the secretion of the adrenal hormone, aldosterone. Aldosterone causes the kidney to excrete less sodium and water. This raises the total volume of blood in the vascular system which tends to restore the pressure and remove the stimulus for secretion.

In both of these examples the regulation can proceed quite independently of neural controls. Indeed, if the pancreas is removed from the body and placed in a dish, it secretes insulin vigorously when glucose is added. Similarly, the kidney still secretes renin when the blood pressure is lowered even if the nerves to the kidney are cut. For every other hormone there are similar local triggers that can act independently of the brain.

The brain controls endocrine mechanisms

In addition to these autonomous mechanisms every

hormone is also regulated by the brain, usually in several ways. First, the brain controls nerve cells located throughout the body, called collectively, the "autonomic nervous system". The autonomic system, which has two divisions, the "sympathetic" and "parasympathetic", has been known since the turn of the century to innervate the heart, muscles of the viscera, such as the gastrointestinal, respiratory, and cardiovascular systems. More recently, with the advent of electron microscopy, it was discovered that many hormone-secreting cells are also innervated by autonomic neurons. Thus, the pancreatic insulin cells are directly contacted both by sympathetic nerves which suppress and parasympathetic nerves which stimulate insulin secretion. Similarly, sympathetic neurons innervate the renin cells in the kidney and can evoke renin release; the adrenal cortex also receives sympathetic innervation which may directly influence aldosterone secretion. Table 2 lists all the endocrines known to receive direct innervation [20].

The brain also influences the body's hormones by means of its own hormones, produced within a special region called the "hypothalamus". About a dozen hypothalamic hormones are known, many of which have been discovered only in the last decade [21] (Table 3). Some act directly on peripheral tissues; others act on peripheral hormone-secreting cells, and still others act on the pituitary, which by means of its own hormones, controls both peripheral tissues and endocrines. Some hypothalamic hormones act in all these ways.

To continue with our examples, insulin secretion is directly suppressed by the hypothalamic hormone, "somatostatin", which also acts on the pituitary to suppress growth hormone release. Similarly, aldosterone release (from the adrenal) can be stimulated by a

Table 2. Direct innervation of the endocrines

Organ	Hormone (cell type)	Innervation
Pancreas	Glucagon (alpha)	+ (s↑, p↓)
	Insulin (beta)	+ (s↓, p↑)
	Somatostatin (delta)	+ (...)
Adrenal	Epinephrine (medulla)	+ (s↑)
	Norepinephrine (medulla)	+ (s↑)
	Cortisol (cortex)	+ (s?)
	Aldosterone (cortex)	+ (s?)
Kidney	Renin (juxtaglomerular)	+ (s↑)
	Renal erythropoietic factor (?)	?
	Somatomedin (?)	?
Thyroid	Thyroxin (follicular)	—
	Calcitonin (parafollicular)	+ (s↓)
Pineal	Melatonin (parenchymal)	+ (s↑, —)
Gut	Gastrin	+ (? , p↑)
	Cholecystokinin-pancreozymin	?
	Secretin	?
Parathyroid	Parathormone	—
Ovary	Estrogens, progesterone (follicular)	—
Testis	Testosterone (Leydig)	—
Liver	Angiotensinogen (?)	?
	Somatomedin (?)	?
	Erythropoietic globulin (?)	?
Thymus	Thymosin (?)	?

s = sympathetic; p = parasympathetic; ↑, ↓ = increase or decrease secretion.

chain of events that "begins" with the hypothalamic hormone, "ACTH-releasing hormone" [22]. The multiple neural controls over insulin and the renin-aldosterone cycle are summarized in Fig. 4A and B.

Functions of the neural controls

An important question arises concerning these new discoveries: what is the reason for having these central controls since the local, self-regulating mechanisms seem to function perfectly well without them? Part of the answer is that the neural controls permit hormonal changes to occur in *anticipation* of changes in the local feedback systems. Such anticipatory changes reduce the size and length of metabolic fluctuations that would otherwise occur. For example, insulin release can be triggered by the vagus nerve [23] and may occur as part of the well known pattern of digestive reflexes (secretion of saliva, acid, enzymes

in response to the sight or taste of food). Such anticipatory insulin release would contribute to the sequestration of glucose by the liver and would thus minimize both the rise of blood glucose and the amount of insulin required later. Failure of the early phase of insulin secretion is part of the pattern of adult-onset diabetes [24].

The second reason for the central controls, and the most important one for our argument, is that most processes in the body *cannot be kept constant*. Instead they must vary according to the demands of the environment on the organism. Fig. 5 illustrates the variations in blood pressure recorded over 24 hours in a normal individual [25]. Although the average pressure hovers around 110/70 ("normal"), there are many small peaks and troughs with 2 major peaks at 16 and 24 hours, followed by a prolonged fall and then a sustained rise.

Table 3. Hormones secreted by the brain

Vasopressin (anti-diuretic hormone, ADH)
Oxytocin
Corticotropin releasing hormone (CRH)
Thyrotropin releasing hormone (TRH)
Growth hormone releasing hormone (GH-RH)
Growth hormone release-inhibiting hormone (somatostatin, GH-RIH)
Prolactin releasing hormone (PRH)
Prolactin release inhibiting hormone (PIH)
Melanocyte stimulating hormone releasing hormone (MSH-RH)
Melanocyte stimulating hormone release-inhibiting hormone (MSH-RIH)
Gonadotropin releasing hormone (GnRH)

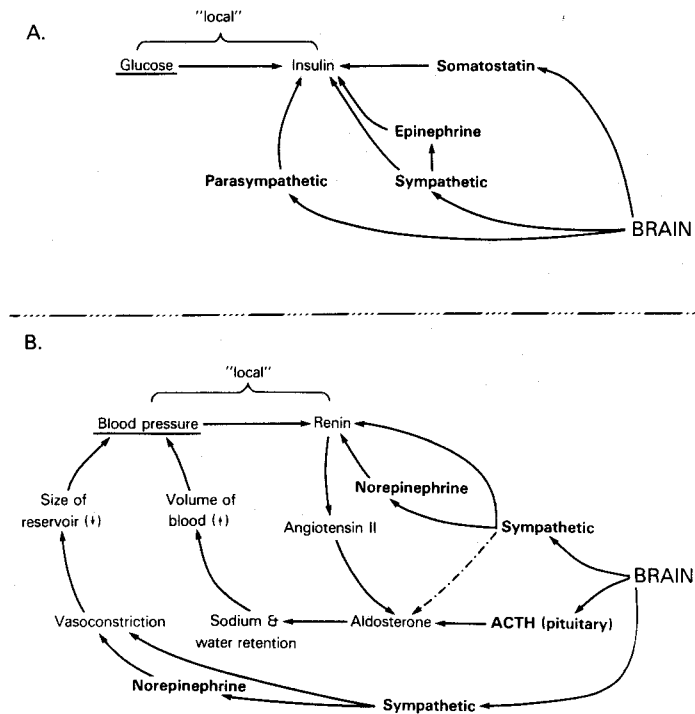


Fig. 4A & B. Examples of control by combined local, neural and neural-hormonal influences.

These shifts reflect alterations in the degree of the individual's arousal in response to environmental demands. During hours 15–16, he was dozing during a lecture and at hour 16 was jabbed with a pin. The blood pressure rose sharply but promptly returned to "normal". At hour 24 (midnight) the individual had intercourse which was accompanied by a sharp pressure rise followed by a profound and a sustained fall during sleep. The next morning (hour 08) the individual was rushing to ready his children for school and to prepare himself for work. His blood pressure rose to the preorgasmic heights of the previous night and remained there for 3 hours.

If the only controls over blood pressure were local negative feedbacks, it would be impossible to have such adaptive changes in blood pressure because every deviation from "normal" would be automati-

cally corrected. We illustrate this point in detail for regulation of blood pressure because of its importance in the later discussions of pathology, but the case can be made for regulation of blood glucose and every other process as well.

Every time blood pressure rises, three mechanisms are called into play that tend automatically to restore pressure to "normal" (Fig. 6). The first, already discussed, is the "volume" mechanism involving the renin-aldosterone cycle. A rise in pressure suppresses the renin-aldosterone mechanism. This stimulates transfer of sodium and water from the blood to the urine and thus tends to lower pressure. The second negative feedback mechanism involves a neural "reflex". A rise in pressure is detected by neural sensors, such as the carotid sinus. Using this information, the brain causes the heart via autonomic nerves to

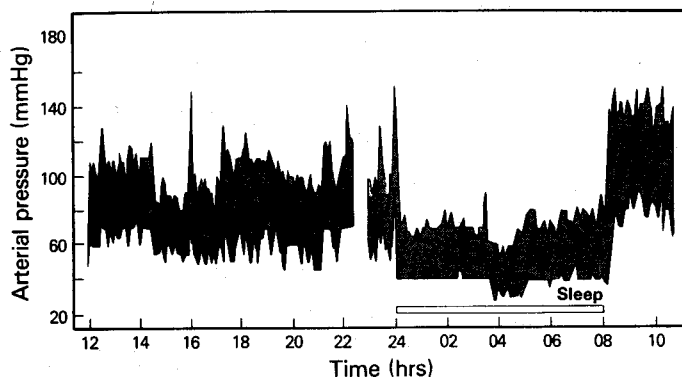


Fig. 5. Arterial pressure, plotted at 5 min intervals of subject A.B. Redrawn from [25].

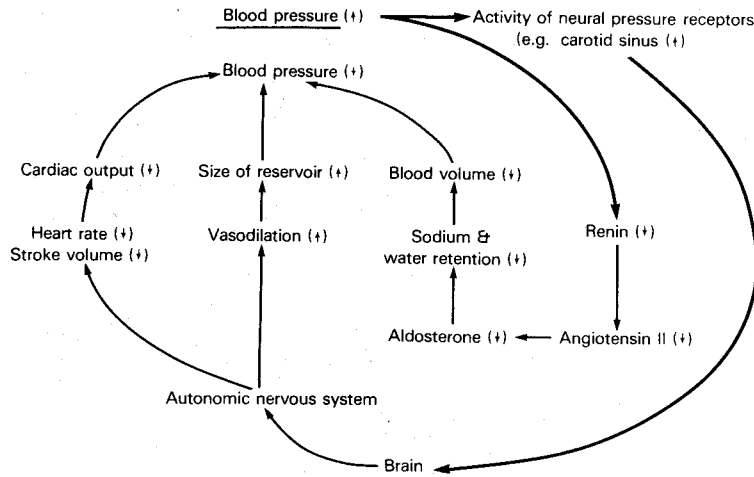


Fig. 6. Automatic (negative feedback) maintenance of constant blood pressure by local and "reflex" mechanisms.

decrease its output, both by beating more slowly and by ejecting less blood per beat (lower "stroke volume"). Third, the brain, via autonomic nerves, causes dilation of the blood vessels. The net result is that there is less fluid circulating more slowly in a larger reservoir—all of which tends to reduce the pressure to "normal". Clearly, if pressure is to remain elevated, such mechanisms must be opposed by some other process.

The sustained rises in blood pressure are in fact initiated by the brain through its control of *all* the relevant peripheral autoregulatory mechanisms. Without such total control, no change initiated by the brain could be sustained because it would invariably be compensated by the automatic mechanisms. Suppose, for example, the brain raised the blood pressure

by increases in cardiac output and vasoconstriction. If the renin cells in the kidney were permitted their autoregulatory response, blood pressure would gradually decrease by way of the "volume" mechanism. To prevent this, the autoregulatory control of renin secretion must be overridden or reset (like a thermostat) by the brain. Figure 7 summarizes the multiple, interlocking mechanisms by which the brain raises pressure [26].

BROAD PATTERNS OF HORMONAL AND METABOLIC RESPONSE

The elevations of blood pressure illustrated in Fig. 5 occurred when the person was aroused—by a painful stimulus, by making love, and by anticipation of

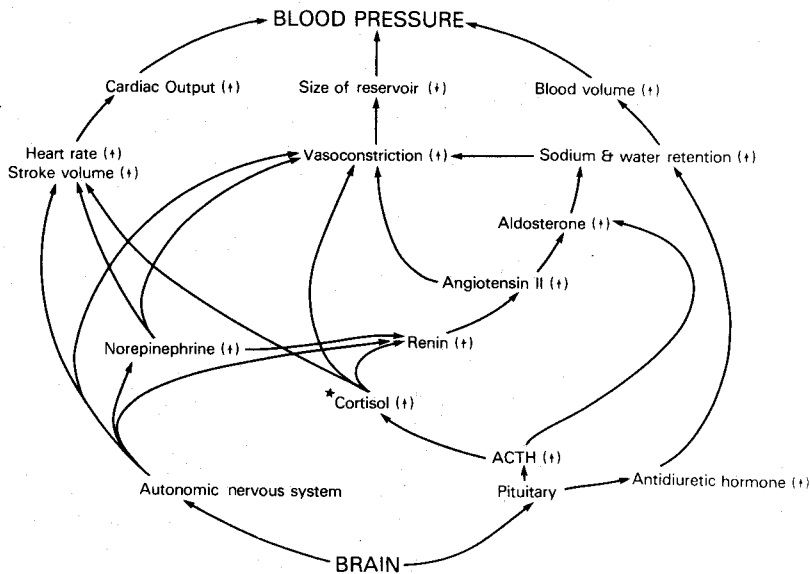


Fig. 7. Multiple, mutually-reinforcing mechanisms raise blood pressure during arousal. Negative feedbacks reset or overridden. *Indicates that cortisol acts indirectly through increasing the binding of norepinephrine to its receptors. See [26] for further detail.

work. These rises in blood pressure during arousal and the falls during periods of relaxation (Fig. 5, post-coital period, and sleep) are fragments of broader physiological patterns that are initiated by the brain as adaptations to particular environmental circumstances. Certain elements of the total pattern were recognized by W. B. Cannon [27] early in this century. He noted that during arousal, as in preparation for "fight or flight", there is not only an increase in blood pressure but also a change in the total pattern of blood flow in the body. More blood is delivered to the heart and skeletal muscle, less to the skin, gut and kidneys. Movements of the gut and all digestive secretions are halted. There is a mobilization of the body's energy stores; for example, glucose is poured into the blood by the liver. Cannon's work emphasized the role of the sympathetic nervous system and the adrenal hormone, epinephrine, in this "emergency" mobilization. Later, Selye [28] showed that another adrenal hormone, cortisol, is also secreted during arousal and makes an important contribution to this mobilization.

For many years it was impossible with the available technology to measure directly any of the hormones in the blood. The studies of Cannon, Selye, and others were limited to laborious indirect measurements of the particular hormones with which they were familiar. This limitation and the relative insensitivity of hormonal assays led them to study animals and people under extreme conditions of acute arousal such as rage, terror, utter frustration, etc. One of Selye's experiments, for example, was to tie a rat's legs together, a procedure that produces stomach ulcers after only 24 hours. It was natural, given the narrow range of substances measured and the narrow range of experimental conditions, that the sympathetic system, epinephrine, and cortisol would be viewed as the main components of a special "emergency" system superimposed on an otherwise "constant" internal environment.

Quite a different picture has emerged in the last decade for it has become possible to measure the blood levels of virtually every known hormone. The great sensitivity of the tests has encouraged studies of both animals and humans under life circumstances far milder and more commonly encountered [29] than the acute rage or terror of earlier studies. By 1968 John Mason [30] had measured, either directly or indirectly, a large number of hormones in individual

monkeys under a variety of relatively mild circumstances. In one situation an animal had to watch for a signal and then press a lever in order to avoid a shock. The task is simple for a monkey but requires attentiveness for long periods so as not to miss the signal. Under these circumstances Mason found increases in measures of a whole group of hormones: epinephrine, norepinephrine, cortisol, growth hormone, thyroxine, and antidiuretic hormone, and decreases in another group: insulin, testosterone, and estrogens. He found similar changes in hormonal patterns during the period when the animal was simply becoming adapted to the chair in which the task was to be performed. The available evidence from human studies also supports the concept that during arousal there are coordinated shifts in the total hormonal patterns including increases in epinephrine, norepinephrine, glucagon, cortisol, growth hormone, renin, angiotensin, aldosterone, and decreases in insulin, testosterone, and estrogen [30].

Several additional hormones seem to fall into one of these 2 groups on the basis of indirect evidence. Calcitonin secretion is suppressed by its sympathetic innervation [31] and may, therefore, be expected to be suppressed during arousal when these nerves are active. Parathormone secretion is stimulated by cortisol and may be expected to increase during arousal when cortisol is elevated [32]. Erythropoietin is stimulated by ACTH, thyroxine, and growth hormone and may be expected to rise during arousal when these hormones are elevated [33]. Finally, synthesis and release of melatonin from the pineal is increased by sympathetic activity [34]. Table 4 summarizes the changes for which there is direct or indirect evidence.

The drama of these findings become clear when one considers the functions of the two groups of hormones. All of the hormones that are *suppressed* during arousal are ones that promote synthetic or "anabolic" processes requiring energy. Most of the hormones that increase during arousal are ones that promote degradative or "catabolic" processes directed at the immediate mobilization of energy [30].

Anabolism

The anabolic processes include energy storage, growth, renewal, repair, and maintenance of surveillance against infectious agents and the body's own malignant cells. In the anabolic state the body stores energy as glycogen, fat, and protein by polymerization

Table 4. Hormonal pattern during arousal

Catabolic hormones increase	Anabolic hormones decrease
Cortisol	Insulin
Epinephrine	Calcitonin
Glucagon	Testosterone
Growth hormone	Estrogen
Antidiuretic hormone	Prolactin
Renin	Luteinizing hormone
Angiotensin	Follicle stimulating hormone
Aldosterone	Gonadotropin releasing hormone (GnRH)
Erythropoietin	Prolactin releasing hormone (PRH)
Thyroxine	
Parathormone	
Melatonin	

Table 5. Anabolic and catabolic states

Anabolic state
Increased synthesis of protein, fat, carbohydrate (growth, energy storage)
Decreased breakdown of protein, fat, carbohydrate (growth, energy storage)
Increased production of cells for immune system (white blood cells of thymus and bone marrow)
Increased bone repair and growth
Increase in sexual processes (cellular, hormonal, psychological)
Catabolic state (arousal)
Halt in synthesis of protein, fat carbohydrate
Increased breakdown of protein, fat, carbohydrate (energy mobilization)
Elevated blood levels of glucose, free fatty acids, low density lipoprotein, cholesterol (for energy)
Increased production of red blood cells and liver enzymes for energy
Decreased repair and replacement of bone
Decreased repair and replacement of cells with normally high turnover (gut, skin, etc.)
Decreased production of cells for immune system (thymus shrinks, circulating white cells decrease)
Decreased sexual processes
Increased blood pressure, cardiac output
Increased salt and water retention

of glucose, fatty acids, and amino acids. These substances are also used to produce new cells to replace the ones that wear out continuously. The cells lining the gut, for example, are completely renewed every 24 hours. Bone is replaced and remodeled by reabsorption and redeposition of calcium salts. Wounds are healed by production of new cells, and by extracellular deposition of proteins. The immune system is maintained by continuous cell and antibody production in the bone marrow, lymphoid tissue, and thymus. Blood pressure in the anabolic state is relatively low, about 120/75 [35]. Blood cholesterol and fatty acid levels are also relatively low. Nevertheless, each organ receives the blood supply that it needs to carry out its contribution to these processes of synthesis and maintenance.

Among the hormones that promote anabolism, insulin promotes synthesis of glycogen, fat, and protein; testosterone also promotes synthesis of protein; calcitonin promotes bone formation. It is not, however, merely the presence of particular hormones that is crucial to anabolism, but also the overall hormonal balance. This is because each hormone has multiple actions; in certain combinations they may enhance, and in others, counteract each other's effects. For example, the anabolic effects of insulin are enhanced by the absence of growth hormone, epinephrine, glucagon, and cortisol, all of which tend to antagonize the effects of insulin. The bone forming effects of calcitonin are enhanced in the absence of parathormone.

Catabolism

The catabolic processes that are powerfully turned on during arousal have a much narrower focus. Energy must be mobilized and supplied to those organs that need it in the short run to deal with the environmental demands. Stores of fat, glycogen and protein are broken down into molecules such as free fatty acids and glucose that can be rapidly converted into energy. The blood levels of these substances, and

also cholesterol, rises. Synthesis of new stores is halted. The production of most kinds of cells is slowed. Bone repair and wound healing is slowed. The thymus shrinks, and the levels of antibodies and white cells in the blood fall [36]. In fact, the only synthetic processes that are maintained or stimulated are those that accelerate the catabolism. Thus, there is an elevation of protein synthesis in the liver, but these proteins are enzymes that accelerate glycogen breakdown. Production of blood cells increases—in order for the oxygen supply to keep pace with the accelerated metabolism. The adrenal gland increases in size—to produce the hormones required for catabolism.

The cardiovascular changes accompanying arousal, which Cannon noted, can now be seen as part of this larger pattern. The cardiac output and the blood pressure are increased, in order to speed extra blood to the tissues. The altered pattern of blood flow also makes sense: flow to muscle, heart and brain must be maintained or increased, but flow to the kidney, gut and skin is decreased because the blood is needed elsewhere.

Some of the hormones that rise during arousal contribute directly to energy production. Thus, epinephrine, growth hormone, glucagon, and cortisol all promote carbohydrate, fat, and protein breakdown. The suppression of the immune response, wound healing, etc. that occur in the presence of these hormones all appear to be a consequence of the need to fuel this energy production. Other hormones that rise during arousal seem to have accessory functions. Thus, ADH and aldosterone promote salt and water conservation to maintain elevated blood pressure and to conserve body water and salt lost in sweating during exertion. Renin, angiotensin, norepinephrine contribute in other ways, that we have described, to blood pressure elevation. Erythropoietin contributes to the catabolic pattern by stimulating red blood cell production, parathormone by mobilizing calcium at the expense of

bone. Melatonin may contribute indirectly to the catabolic pattern by suppressing release of the hormones that promote release of anabolic sex hormones [37].

The effects of this shift in overall hormonal pattern is all the more powerful because each hormone has multiple effects that reinforce the others. For example, cortisol not only increases protein breakdown but also reinforces the effects of epinephrine in breaking down fat and carbohydrate and the effects of norepinephrine in stimulating the heart and vasoconstriction. Similarly, norepinephrine in stimulating the renin-aldosterone cycle, leads to an elevation of angiotensin and sodium both of which cooperate with norepinephrine in constricting vessels and raising blood pressure. Renin, through angiotensin, not only stimulates the aldosterone cycle, but also stimulates drinking and ADH release [26].

In summary (Tables 4, 5), accompanying the shift from relaxation to arousal, there is a shift in the whole pattern of hormonal secretion. The endocrine pattern in arousal promotes the mobilization of energy at the expense of maintenance and repair processes. These catabolic processes are accompanied by auxiliary mobilization of the renovascular system for conservation of salts and water. All of these shifts are initiated by the brain via its control over autonomic and endocrine systems.

It is obvious for several reasons that these metabolic priorities must be set by the brain. First, the various organs, such as kidney, liver and heart, can respond via chemical signals to changes in internal environment but have no way, except via the brain, of assessing the demands of the external environment. Second, many of the changes we have described occur in *anticipation* of external demands; anticipation is a process that can only occur in the brain. Finally, many of the endocrine and metabolic changes that accompany arousal are in the opposite direction from what would be expected from the independent, autoregulatory processes. Thus, during arousal or exercise, glucose uptake by muscle rises while plasma insulin falls [38], a reversal of the usual autoregulatory pattern.

For a body to remain healthy periods of arousal must be balanced by periods of relaxation. Otherwise, there would be no replenishing of the resources exhausted by catabolism. There would be no repair of accumulated damage, no vigilance against pathogens. We must consider, therefore, what triggers and maintains arousal, what determines its intensity, and finally, what permits arousal to resolve into a state of relaxation.

TIPPING THE BALANCE: MULTIPLE DETERMINANTS OF AROUSAL AND RELAXATION

The function of arousal is to prepare the organism to "cope" with some environmental demand and to support such coping behavior while it is in progress. "Coping" is defined by the dictionary as "struggling" or "contending". It describes behavior involving special physical and, especially, emotional energy and attention that is required to deal with some difficult circumstance. When the environmental demand has

been removed by the coping behavior, arousal resolves into relaxation, and catabolic processes resolve into anabolic ones. At the simplest level, the sequence may be described in a negative feedback diagram:

ENVIRONMENTAL DEMAND → AROUSAL → COPING
RELAXATION ← ALTERED ENVIRONMENT

Objective determinants

Some concrete feeling for the objective determinants of arousal may be obtained by considering an experimental animal model which also provides a useful metaphor for understanding certain aspects of the human condition. When a rat is placed in a box and given intermittent electrical shocks, it rapidly (within 21 hours) develops stomach ulcers [39]. Selye and others have demonstrated that the ulcers are the consequence of intense arousal and are accompanied by the full pattern of catabolic responses such as inhibition of growth, elevated epinephrine and cortisol, shrunken thymus, and lowered white blood count [40]. It is possible, therefore, to use the amount of ulceration as a measure of the intensity of arousal and, by varying the conditions under which the shock is given, to identify some of the factors that affect the level of arousal. Recently, Jay Weiss developed an extremely sensitive way to perform such studies. He wired two rats together so that, no matter what happened in the experiment, both rats received the same number and intensity of shocks. Any differences in the amounts of ulceration between the two rats could be attributed to changes in arousal as a consequence of experimental manipulations [39].

Weiss identified 4 factors that affect the level of arousal under these circumstances. First, if a rat could predict when it would be shocked because of a warning buzzer, it developed fewer ulcers than its partner which was shocked without warning. Clearly, in novel or wholly unpredictable situations the arousal mechanism must remain on so as not to miss the anticipated environmental event. The possibility of predicting when an event will occur and what its nature will be, permits the organism to restrict the intensity and duration of anticipatory arousal to only that which will be needed for coping.

Second, Weiss found that ulcers were reduced when the rat was given some effective control over the situation. When the rat could prevent some of the shocks by pressing a lever, it developed fewer ulcers than its partner which received the same number of shocks but whose coping behavior was not effective. Third, the ulcers were even further reduced if the rat, after pressing the lever, was given a signal that it had performed the correct response, i.e. that the shock had been successfully prevented. In other words, reassuring "feedback" about the effectiveness of coping behavior reduces arousal.

Fourth, Weiss found that when the demand for performance was raised, that is, when the frequency with which the lever had to be pressed to prevent a shock was increased, the amount of ulceration rose. This occurred even though the rat was still able to prevent most of the shocks and even though it received "feedback". Apparently, when the demand for coping is too

intense, no amount of control or feedback can prevent arousal.

The measurements of physiological arousal made in non-human primates [41] and in humans under a variety of circumstances and over a variety of time periods all fit the conceptual framework established by Weiss' experiments. In the short run: patients entering a hospital for diagnostic tests show rises in epinephrine, norepinephrine, cortisol and growth hormone [42]. Such individuals are facing an unpredictable situation in which little effective coping behavior is possible and in which little reassuring feedback is usually given. Students during examination periods show rises in cortisol, growth hormone, epinephrine, norepinephrine, blood glucose, free fatty acids, serum cholesterol and blood pressure, and a fall in white blood cells [43]. Under this circumstance there is, of course, opportunity for effective coping, but the levels of unpredictability and demands for performance are high, and the level of immediate feedback is low. Experimental subjects show similar changes while performing "piece work" such as sorting ball-bearings of similar size under time pressure [44].

Over the middle run: it has been demonstrated that heart rate, palmar sweating (a measure of sympathetic activity) and cortisol excretion are typically elevated on weekdays, when demand is high, and lower on weekends [45]. Over a still longer run: individuals in basic training (23 weeks) at officer's candidate school show rises in cortisol and falls in testosterone in the early training stages and a reversal of this pattern by the end of successful completion of training [46]. In another example, it has been shown that tax accountants show large rises of blood cholesterol (independent of diet) and falls in blood clotting time (another indication of arousal) during long periods of intense work to meet tax deadlines [47] (Fig. 8). Finally, unemployed men show sustained rises in blood pressure from the time they are notified of their job loss until they are stably reincorporated into a new work situation [48]. In all of these situations all four of Weiss' factors are probably relevant.

One can appreciate from the Weiss experiments that arousal in humans can be triggered and sustained by a variety of mechanisms and that, as a consequence, arousal can be chronic in people differing widely in emotional constitution and life circumstance. Arousal will tend to be high, for example, among people with little control over life circumstances and little reassuring feedback—the poor. It will be high also among those upon whom there are great demands for performance even if they appear to have substantial control and feedback—rich executives.

The Weiss experiments also allow us to appreciate what we already know intuitively, that arousal may be associated with a variety of emotions, not all of which are negative or unpleasant. Arousal stemming from lack of control and feedback may be associated with fear or anger. "High demand" situations may be accompanied by anxiety, but also by pleasure, particularly if coping is successful. That pleasure is felt, however, does not mean that the arousal is less intense or that its metabolic costs to the body are less. The therapeutic implications of the Weiss experiments are that a change in any *single* determinant of chronic

arousal will have a limited effect. In particular, if the demand for coping remains high, a reduction in other sources of arousal will not be of much help. We shall return to these points later.

We noted earlier that the Weiss experiments are to be taken metaphorically. One reason is that the determinants of arousal which he can isolate experimentally in rats are usually mixed in various proportions in the more complex circumstances under which arousal is measured in humans. It is, for example, difficult to determine how much of the cortisol rise during hospitalization may be due to the unpredictability of the situation, how much to the lack of reassuring feedback.

Another reason for avoiding too literal and fixed an interpretation of these determinants is that one may anticipate some differences between humans and animals because of species differences in metabolism and coping styles. Thus, cortisol, norepinephrine and growth hormone all rise in monkeys and humans during arousal; rats show a similar pattern except that their growth hormone levels fall [49]. In addition, most individual studies on humans have so far employed only a limited number of arousal measures. Here, too, one would anticipate that different circumstances and coping styles would have somewhat different physiological requirements and that, as a consequence, the various components of the arousal response would behave somewhat differently. Thus, in humans, while cortisol seems invariably to rise during arousal, growth hormone may or may not rise. In one study growth hormone rose in parallel with cortisol when the individuals were anxious but "detached" but did not change when the individuals were anxious and "engaged" [50]. There are other examples in which norepinephrine rises but not epinephrine, vice versa, and so on [51].

Such observations probably explain why each hormone is influenced by multiple, partly independent central controls. Recall, for example, that insulin is controlled by both sympathetic and parasympathetic nerves, and also by the hypothalamic hormone, somatostatin. Multiple controls such as these would permit differential endocrine responsiveness where it is needed. Thus, insulin can be turned on alone by parasympathetic activity or it can be turned on in combination with growth hormone by turning off somatostatin which suppresses them both. We anticipate that the detailed meanings of the dissociation between various hormones under different circumstances of arousal will be a fascinating area for future research, especially as the measurements become easier and more economical. Information regarding the differential hormone responsiveness will undoubtedly enrich the basic concepts of patterned endocrine changes during arousal.

Subjective determinants of arousal and relaxation

The environmental demands discussed in the previous section are quite real. One only need experience the unpleasantness of electric shock, the pressure of a school examination, or the fear and discouragement of unemployment to know this. On the other hand, there is no isomorphism between "objective reality" and its representation in the brain. For this reason the diagram above is oversimplified. It omits, among

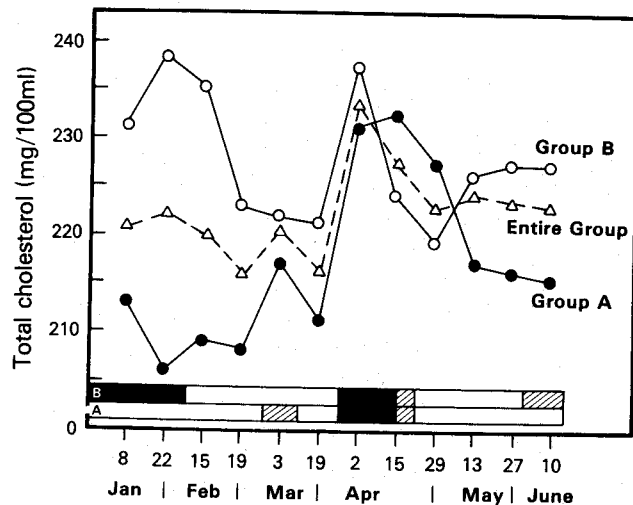


Fig. 8A. Serum cholesterol changes observed in two groups of accountants. Group B had a high stress period in January-February, in addition to the tax deadline shared by both groups in April. Redrawn from [47].

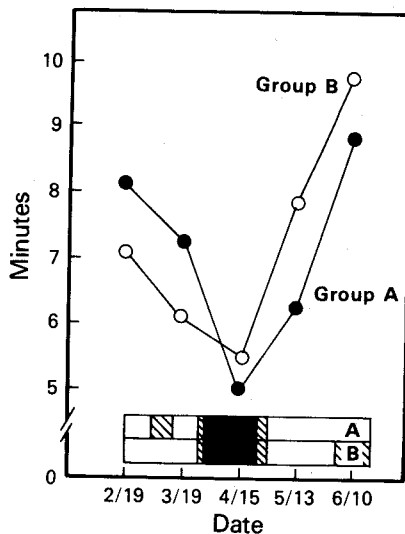


Fig. 8B. Average blood coagulation time in two groups of accountants going through the April deadline. Redrawn from [47].

other things, the fact that an objective demand must be *perceived* in order to be arousing and that an objective alteration of the environment accomplished by coping behavior must be perceived if arousal is to resolve into relaxation. In humans the objective nature of the demand, whether grave or trivial, can be irrelevant; frequently it is the translation to subjective reality that is critical.

The physiological patterns of people watching a film, for example, are highly responsive to its content. Physiological arousal, including rises in cortisol, epinephrine, and norepinephrine, occurs in response to "adventure" films; and physiological relaxation

occurs in response to Disney "nature" films [52]. Obviously, there is no objective demand for coping in the first case nor an objective basis for relaxation in the second. People merely respond empathetically, as though they were part of the situation.

Under other circumstances, the opposite phenomenon can occur: people can defend against the most grave objective reality and respond physiologically to the subjective circumstances created by their defenses. The most dramatic examples are the cortisol excretion patterns measured in parents of children fatally ill with leukemia [53]. Among those parents who responded to the reality of the situation and coped as best they could, cortisol levels were high. The cortisol levels were low, however, among parents who in one way or another, defended themselves against the reality. The psychological defenses were quite varied. Some parents flatly denied the reality and continued to make plans for the child's future. Others employed the defense of resignation and detachment, accepting the illness as God's will, or focussing on the remaining good things in their lives: "I am lucky to have as much as I do..." Some parents defended by avoiding contact with their children; still others defended by expressing intense affect focussed on themselves.

This study was particularly powerful methodologically in that it predicted the precise numerical values of cortisol levels in each parent, based on behavioral observations and on a brief interview. The correlation between predicted and measured levels of cortisol excretion were extremely high, 0.8 (fathers) and 0.58 (mothers). Perhaps the most dramatic observation was that cortisol excretion rose sharply among low excretors when their psychological defenses were temporarily abandoned. Examples are shown in Fig. 9.

A follow-up study [54] found that parents who had been "high-excretors" during the period of their child's illness showed low cortisol excretion following the death. In contrast, the parents who had been "low-excretors" while defending against recognition of

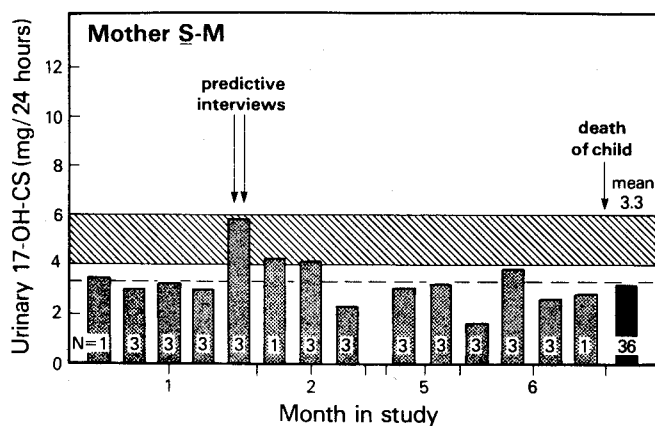


Fig. 9A. 17-OHCS excretion (a measure of cortisol secretion) of mother with low mean excretion rate whose primary defense was "detachment". Diagonally shaded area represents middle range of values for all mothers (4.1–6.0 mg/24 hr). Black bar represents total mean excretion rate. Shaded bars represent individual determinations. Numbers in bars represent number of collection days included in determination. When detachment became impossible during the interviews, cortisol secretion rose. Redrawn from [53].

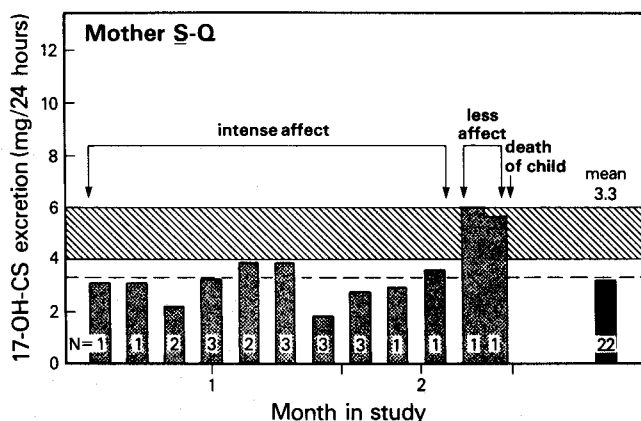


Fig. 9B. 17-OHCS excretion of mother with low mean excretion rate who used "affect" (crying, expressions of anger and complaint) defense. When this defense was abandoned immediately prior to the child's death, her cortisol excretion rose sharply.

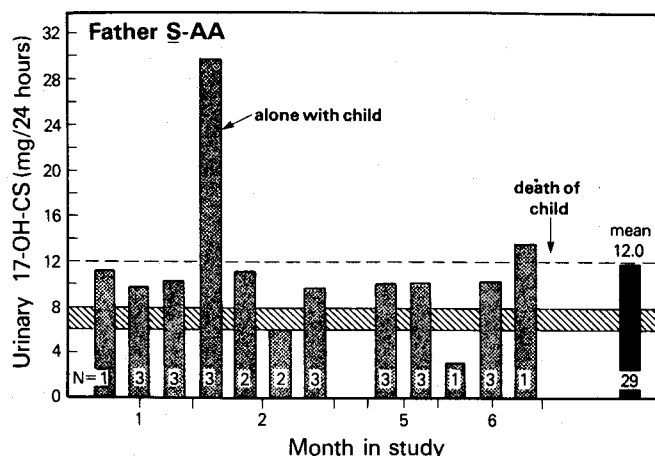


Fig. 9C. 17-OHCS excretion of father with high mean excretion rate whose major defense was avoidance. Diagonally shaded area represents middle range of values for all fathers (6.1–8.0 mg/24 hr). When it was impossible to avoid the child, his cortisol levels rose.

the illness, showed elevated cortisol excretion for long periods following the death [55]. One might conclude that psychological "defense mechanisms" do not render healthy people permanently unresponsive to objective reality. Instead, defenses permit people to digest "reality" and recast it into a form and time frame in which they can cope with it. In the case of a death, the work involves reshaping both one's feelings and also the intimate social network in order to supply the supports and to balance the tensions to which the dead person was central. This study is particularly important in emphasizing that arousal goes *not* with "objective" demand *per se*, but rather with the "recast" version of reality that elicits coping behavior.

CHRONIC AROUSAL FROM SOCIALLY DETERMINED SUBJECTIVE REALITY: TYPE A BEHAVIOR

The time course of arousal in humans depends very much on social outcome, for this determines to a large extent what is reassuring. If arousal is accompanied by behavior that leads to resolution of tensions and a growth in intimacy between people, it resolves into relaxation. Recall, for example, the profound fall in blood pressure following sexual arousal (Fig. 5). Recall, too, the therapeutic behavior of the Iroquois described in the Introduction. In contrast, struggle which leads to wider and more serious conflict with other people is bound to involve chronic, high level arousal because potential sources for social support are destroyed and the demands for coping multiplied. This is true even when the goal of the coping appears attractive to the individual involved.

One sees this clearly in the "Type A" or "Coronary prone" behavior pattern. It is characterized by "extremes of competitiveness, striving for achievement, aggressiveness (sometimes stringently repressed), haste, impatience, restlessness, hyperalertness, explosiveness of speech, and feelings of being under the pressure of time and under the challenge of responsibility". Type A individuals behave as though "engaged in a... *chronic struggle* to obtain an *unlimited* number of poorly defined things from their environment in the *shortest period of time* and, if necessary, against the opposing efforts of other things or persons..." [56]. This pattern of relentless coping behavior, accompanied by extremes of chronic physiological arousal, is associated in numerous prospective studies with 2-fold increases in the risk of a coronary heart disease [57]. It is, therefore, a major public health problem.

Such behavior might be expected of an individual trapped in the Weiss paradigm, where intense coping is objectively required under threat of punishment. As we have described elsewhere, the transformation of work in the 20th Century has made such situations common [58], and it is perhaps in the development of regimented mass-production labor that the Type A behavior originates. On the other hand, the Type A individual behaves the same way on vacation and at home. Every moment is scheduled and filled with tasks that "must" be done.

Type A individuals remain chronically aroused because the feedbacks that should, from an objective

point of view, be reassuring are "recast" into subjective forms that can be discounted. Thus, job promotions, economic success, control over the work situation do not lead to relaxation. Paradoxically, the only relative comfort lies in coping with *new* situations where predictability and control are low and demand is high.

Objectively, of course, no one *has* to live this way. Yet, it is useless to attribute this behavior pattern to individual personality quirks since roughly half of the adults in industrialized societies exhibit it. Furthermore, since Type A behavior is a rare and deviant pattern in pre-industrial societies [59], one must conclude that there are powerful social mechanisms for generating and maintaining it. These social mechanisms reflect our beliefs in the moral importance of work (coping), in the importance of "progress" (continuous change which produces new unpredictability and demand for coping), and in our contempt for the relaxation that follows establishment of successful control and feedback ("resting on one's laurels"). In short, we tend to recast objective reality to fit socially shared beliefs. In our society the recasting leads naturally to chronic arousal.

A paradox of Type A behavior is that it is an accepted and even idealized pattern of male performance in modern society, yet it has a high risk of ischemic heart disease. Since Type A behavior corresponds to one stereotype of what is needed for upward mobility and is mutually accepted by co-competitors in this stereotype, Type As are successful socially. However, Type A men often have great difficulties with their wives and children. One of the items in the diagnostic interview for Type A asks whether in playing competitive games with children, an adult always insists on winning. This is a sample of the attitudes which make Type As difficult to get along with for people who are not economic cocompetitors.

Type As commonly display determination and unrelenting positive thinking, in which pains, difficulties, and minor sicknesses go unnoticed. One might consider this merely as enthusiasm, but it bears some resemblance to mania, especially since ignoring pain and sickness through positive thinking contributes to the shortened lifespan of Type As. Thus, a Type A typically has as his first cardiac event a sudden, severe heart attack, whereas a Type B first enters the medical system in response to mild angina. These differences between men of Type A and B are the same as those between men and women in modern society, and are unquestionably involved in the differential lifespans in each case [60].

BIOLOGICAL MECHANISMS OF AROUSAL PATHOLOGY

Cardiovascular, renovascular, and cerebrovascular disease accounts for 55% of the total annual deaths in the United States (see Fig. 10) [61]. It is now widely recognized, as a result of large scale prospective studies, that hypertension is the single most important "physical" risk factor in this family of diseases [62]. The Framingham Study, for example, finds hypertension involved in over 80% of all cardiovascular

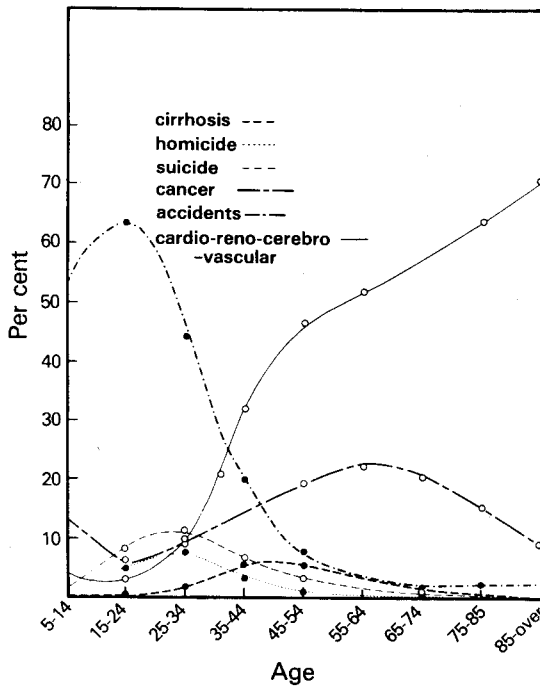


Fig. 10. Causes of death as percentages of total deaths at specific ages. U.S. White Males (1970), from Vital Statistics of the U.S., 1970.

deaths and at least twice as strong a predictor as smoking or blood cholesterol levels [63].

Hypertension is generally defined as an elevation of blood pressure to 140/90 mm Hg or higher. Between 23–60 million Americans aged 18–79 are considered by such a criterion to have hypertension [64]. This underestimates, however, the contribution of elevated blood pressure to mortality. Both prospective and actuarial studies show that the risk of cardiovascular disease rises continuously and exponentially as blood pressure rises beyond 100/60 [65]. The figure of 140/90 is merely an arbitrary level above which drug treatment is often recommended to lower the pressure.

There is recent evidence that blood pressure begins to rise in Americans quite early in childhood (Fig. 11). From birth until age 5 the mean pressure for the male population is about 94/63, and only 5% have pressures of 114/78 or higher. After age five, at about the time most children enter our competitive school system, pressures rise sharply. By age 13 the mean pressure for males has risen to about 119/73 and 5% have pressures of about 140/90 or higher. By age 18 the mean pressure for boys is about 132/81 and 10% have pressures of 145/90 or above [66].

Causes of hypertension

There exist only three mechanical possibilities for raising blood pressure. The body can: (1) increase the amount of salt water in the vascular system (by action of the kidney); (2) decrease the volume of the vascular system (by constriction of vessels); (3) increase the rate at which fluid is pumped through the system (by increasing output of the heart). To determine the "cause" of hypertension, it should be necessary only

to determine which of these mechanical changes can account for the rise in pressure and then determine which of the multiple neural and hormonal influences is driving the mechanical system.

In about 5% of the cases a specific pathology can be identified. A pheochromocytoma (adrenal tumor), for example, may produce abnormally large amounts

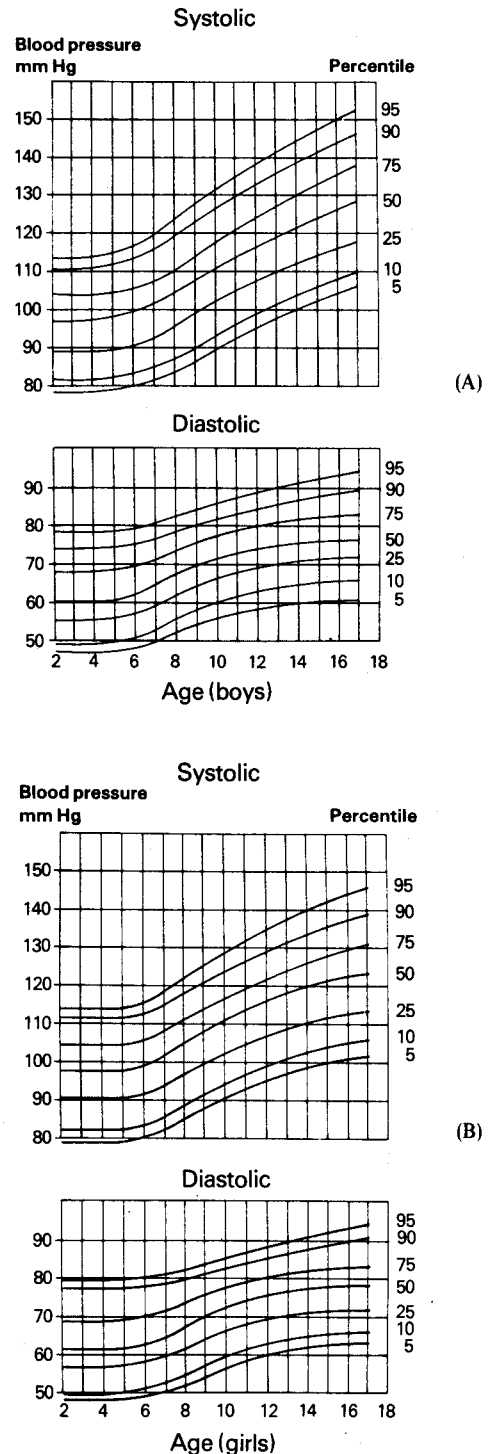


Fig. 11A & B. Percentiles of blood pressure measurement in boys and girls (right arm, seated). Reprinted from [66].

of norepinephrine which stimulates all three mechanical systems. Similarly, a constriction in the renal artery may cause excessive secretion of renin which, via the angiotensin-aldosterone systems, stimulates the salt water and vasoconstrictor mechanisms (see Fig. 7). In the remaining 95% of the cases, however, the blood pressure elevation cannot be attributed to any such specific pathology. In these cases the diagnosis is "essential hypertension", meaning that the cause is unknown.

There are, of course, many competing theories. One emphasizes the importance of the "volume" mechanism and postulates as the cause of essential hypertension a subtle defect in the kidney's excretion of sodium [67]. Another theory, noting the correlation between blood pressure and plasma levels of norepinephrine, urges the importance of norepinephrine in stimulating the various pressor mechanisms [68]. Still another, noting that plasma renin is high in some hypertensive patients, urges the overriding importance of the renin-angiotensin-aldosterone system [69]. No theory that emphasizes the defective behavior of one particular organ or hormone has been successful in explaining the phenomena of essential hypertension.

On the other hand, when the major observations cited by each school are assembled, they fit remarkably well with the picture of chronic arousal we have described. It appears that essential hypertension can be understood as part of a broad physiological pattern set by the brain. It is the brain, first of all, that determines what the blood pressure "should" be. This must be so because only the brain can recognize and anticipate the multiplicity of environmental demands that require changes in blood pressure (Fig. 5). The kidney helps set blood pressure via the "volume" mechanism [67], but it must do so under the brain's control because the kidney is ignorant of environmental demands. The brain, having set the goal, can force pressure in the appropriate direction by means of its control over all the multiple, interlocking systems that determine pressure (Fig. 7). Were pressure not set and enforced in this concerted way by the brain, all the various negative feedback mechanisms (Fig. 3) would return the pressure toward "normal".

Predictably, hypertension is associated with the broad hormonal pattern of arousal. During the acute arousal elicited in primates by avoidance conditioning, blood pressure rises in concert with the catabolic hormones [70]. Acute hypertension also accompanies the rises in cortisol, norepinephrine, and renin that in mice follow disruption of stable community organization [71]. Similarly, hypothalamic stimulation that in rats evokes acute behavioral arousal ("the defense response") also evokes acute hypertension [72].

The most important mechanism for raising blood pressure during acute arousal is an increase in cardiac output. The vasoconstriction mechanism shows little net change because the vasoconstriction that decreases blood flow to organs such as gut and kidney is offset by the vasodilation that increases flow to cardiac and skeletal muscle. The volume mechanism during acute hypertension maintains roughly normal levels of salt and water; i.e., there is no compensatory diuresis to offset the pressure rise from increased cardiac output. When acute arousal terminates, the

normal cardiovascular pattern is promptly resumed (Fig. 5).

When arousal is maintained for long periods, the elevation of blood pressure tends to be sustained even when the arousing stimulus is removed. This is true in the monkey avoidance training [73], in the brain stimulation experiments [74], and also in the experiments with mice [71]. Thus, the hypertension produced in a colony of female mice by introducing a strange male resolves to normal only if the disruptive male is removed before six months have elapsed [75]. Thereafter, hypertension is sustained, even though the stimulus for it is gone. At this stage, the hypertension is sustained not primarily by elevated cardiac output, which tends to return to normal, but by increases in vascular resistance (vasoconstriction). There is clear and growing evidence that both the vessels and the brain itself undergo structural and functional changes as adaptations to life at high pressure.

The smooth muscles of the arterioles change. It is the arterioles across which occurs most of the pressure drop from the heart to the veins, and their smooth muscle cells are responsive to neural and hormonal stimuli. These muscles grow thicker when high pressure is sustained, and bulge into the inside ("lumen") of the vessel. The bulge, even when the muscle is maximally relaxed, imparts to the arteriole a higher resistance to blood flow. More importantly, when the muscles shorten in response to neural or hormonal stimulation, they bulge still further into the lumen and provide a much greater than normal resistance to flow for an equivalent amount of stimulation. This increased resistance produces, for the equivalent blood flow, an elevated pressure [76]. In response to local stretching at high pressure, collagen synthesis also increases and contributes additionally to the structural hypertrophy of the vessels [77].

During chronic hypertension information sent to the brain regarding the precise level of blood pressure is altered because of changes in the structure and sensitivity of the baroreceptors. Their threshold is raised so that they fail to discharge nerve impulses until higher than normal pressures are reached. They also fail to increase their activity sharply as they normally would to increments of pressure [78]. To the extent that the brain measures blood pressure by reading baroreceptor activity, it will have the mistaken impression that the pressure is low. The brain will therefore tend to stimulate all the peripheral mechanisms to raise the pressure.

Recent evidence points to a hormone-brain-diet link that may also contribute to sustaining hypertension during chronic arousal. Antidiuretic hormone, aldosterone, and angiotensin all stimulate mechanisms of thirst and sodium appetite by *direct action on the brain* independently of the changes they produce by other means in the body fluids [80]. For example, angiotensin stimulates a structure in the brain called the "subfornical organ" which in turn causes animals to drink salty water. Such evidence suggests that the strong appetite for salt in modern society, which certainly contributes to hypertension, is not an independent variable, but a consequence of the chronic arousal mechanisms that mobilize these hormones. A dietary tendency that begins as a hormonally stimulated drive can assume a life of its own (become a

"habit") and contribute independently to chronic hypertension.

Hypertension in humans typically develops under life circumstances associated with chronic arousal. Thus, its prevalence is higher in modern than in primitive society, higher among migrants than natives, higher in stressful occupations (air traffic control), and so on [81]. The catabolic hormones, norepinephrine [82], renin, angiotensin, and aldosterone are commonly elevated in association with hypertension [83]. Although other catabolic hormones such as cortisol and ADH have not been systematically measured in hypertensives, we predict that they would be elevated and the anabolic hormones depressed, at least in the early stages of hypertension before the vascular and baroreceptor changes described above become self-sustaining.

The developmental pattern of human hypertension, as far as it is known, fits the arousal model described above. In younger people pressure tends to be "labile", elevated into the hypertensive range at one reading and "normal" at another reading a few days or months later. The mechanism responsible for such elevations seems to be primarily the one associated with arousal, i.e. high cardiac output with no net change in vascular resistance. Among older people, hypertension tends to be "fixed" or "established", that is, consistently elevated from one reading to the next. At this stage increased vascular resistance accounts for much of the pressure elevation, and cardiac output may have returned to normal [84]. Not only is the total resistance of the vascular system increased at this stage, but vasoconstriction can be observed in regions where it did not earlier occur, for example, in the vessels supplying the retina [85].

Blood pressure in "fixed" hypertension is not truly fixed, but can vary widely from moment-to-moment and over months or years. Thus, as illustrated in Fig. 12, the systolic pressure of an "established" hypertensive can vary by more than 150 mmHg in the course of a day. The pressure falls markedly with

sleep (compare to Fig. 5). That the pressure during sleep fails to fall entirely to normal is not surprising since the resistance of the hypertrophied vasculature, even at maximal relaxation, never returns wholly to normal [86]. The extensive overlap between the pressure ranges of normal and hypertensive people (Fig. 13) illustrates the essential plasticity and responsiveness of the system even in established hypertension. It is obvious from this figure that it is physiologically possible for pressure to be low even in individuals with "fixed" hypertension.

Established hypertension and the anatomical and physiological adaptations that sustain it are reversible. In animals hypertrophied vessel walls become thinner when arterial pressure is reduced, and baroreceptor sensitivity return to normal [86]. In humans fragmentary longitudinal data suggests that pressures can fluctuate widely over a period of years and can fall as well as rise. Hypertension, which appears to be "established" by numerous readings over a period of months, simply "lapses" in a substantial fraction of cases [87].

Sustained pressure reductions in "established" hypertension can be achieved by treatments that avoid direct intervention in the renal and cardiovascular systems. A placebo procedure has been effective in which patients were led to believe that they were being treated with a powerful electronic device [88]. People can also learn to bring their pressures down with "biofeedback" and with relaxation techniques such as Transcendental Meditation [89]. When, in one study, pressures in hypertensives were reduced with meditation, the fall was accompanied by decreases in the arousal hormones norepinephrine and renin [90]. This suggests that when relaxation techniques lower blood pressure, they may do it by reducing chronic arousal. The contrast between this approach to treatment of hypertension and the conventional pharmacological methods is discussed below.

In summary, acute hypertension is part of the acute

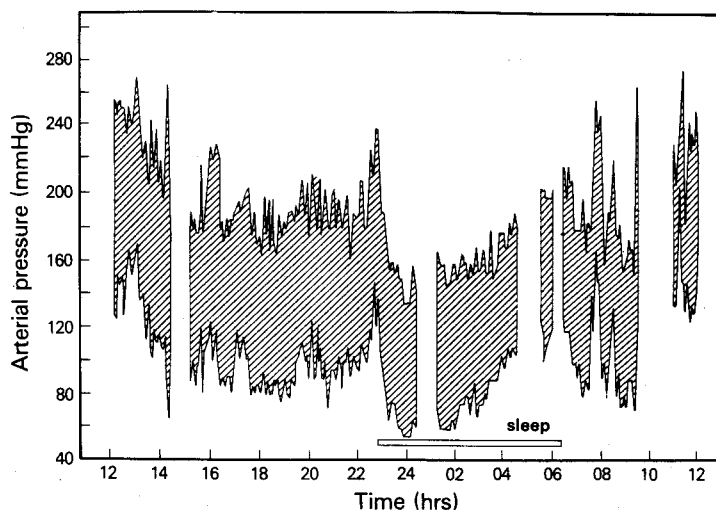


Fig. 12. Arterial pressure, plotted at 5 min intervals, of a hypertensive subject. Redrawn from [25]. Compare to Fig. 5.

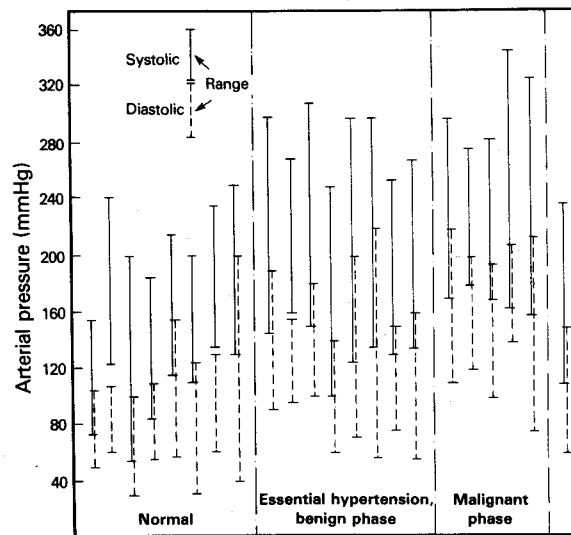


Fig. 13. Ranges of arterial pressure recorded for individuals over a 24 hour period. The top bar of each range represents the average pressure during the highest recorded hour. The bottom bar represents the average during the lowest recorded hour. Note the tremendous range of pressures experienced by individuals with essential hypertension and the great overlap with normals. Redrawn from [25].

arousal response. When arousal is chronic, the body adapts to the prolonged pressure elevation so as to sustain the hypertension even when the primary stimulus for it slackens. We shall see in the next section that as the individual spends progressively more time at high pressures, pathology begins to develop.

Pathology from hypertension

The damage from hypertension begins with small cracks and tears in the lining of the blood vessels. Damage is greatest at the sites of the highest pressure and, therefore, occurs primarily in arteries, rather than veins [91]. Damage is exacerbated by the leakage of angiotensin and renin into the vessel walls [92]. Although a tear is repaired, the resultant scar forms a focus for deposition of cholesterol and other substances to form an atherosclerotic plaque. Atherosclerosis is, therefore, a cooperative process that depends on both vascular damage and elevated cholesterol [93] which, as already noted, rises with arousal. Seventy percent of healthy American men have significant coronary artery atherosclerosis by age 20 [94].

Atheromatous plaques progressively occlude the arteries supplying the heart, brain, and kidney and, in combination with continued high pressure, set the stage for several kinds of disease. The heart enlarges over the years to pump against the elevated blood pressure, but its supply of nutrients and oxygen cannot keep pace especially when there is partial atherosclerotic occlusion of coronary vessels. As the heart begins to fail, blood backs up in the veins and fluid accumulates in the body, making work still more difficult for the heart until its failure is complete. In this syndrome, called "congestive heart failure", 50% of the patients die within 5 years of diagnosis [95].

The various parts of the heart contract in a carefully-timed rhythmic sequence in order for it to function effectively as a pump. Disruption of the rhythmic sequence can throw the heart into utterly disorganized writhing called "ventricular fibrillation". Death occurs in this condition because no blood can be pumped to the brain or any other part of the body.

Ventricular fibrillation can be precipitated during acute arousal in healthy hearts from excessive stimulation by the autonomic nervous system that produces "ventricular premature beats" [96]. Fibrillation is also caused by local changes in irritability within the heart itself as the result of the anoxia caused by inadequate coronary blood supply. The anoxia, in turn, can be precipitated in several ways. First, the coronary supply is already compromised by atherosclerosis. During acute arousal it may be impossible to deliver extra blood the heart requires through the partially occluded vessels. Second, blood viscosity increases during acute arousal [97] and the thickened blood can pass less easily through the narrowed vessels. Third, anoxia can be precipitated by acute, occlusive spasm of a coronary artery. Such spasms can be triggered by neural and hormonal activation of α -adrenergic receptors and especially easily in atherosclerotic vessels [98]. In summary, a heart whose blood supply is absolutely compromised by atherosclerosis or spasm, or relatively compromised by its hypertrophy from pumping at high pressure, is particularly vulnerable to any increase in demand, especially when the demand is accompanied by increases in blood viscosity and in the frequency of ventricular premature beats.

The atherosclerotic kidney and brain are prey to essentially the same kind of disaster—tissue death from anoxia. In these organs elevated pressure can cause vessels to rupture and bleed into the tissue

which becomes anoxic and dies in the region of hemorrhage. Such bleedings commonly occur within atherosclerotic plaques themselves. Blood clots form readily at these sites, particularly during arousal when clotting is accelerated. A clot may finally occlude the vessel where it is formed and cause local damage, or it may break free into the circulation and lodge in narrowed vessels elsewhere in the body. When such an event occurs in the brain it is called a "stroke" (300,000 per year in U.S.) [99]. Kidney damage that occurs in this way may not be immediately fatal, but the damage tends to trigger the renin-angiotensin system. This further elevates pressure which does still more damage. This process, called "malignant hypertension", invariably terminates in total kidney failure, stroke, or heart attack. All of these mechanisms are summarized in Fig. 14.

Diabetes

Diabetes is the fifth leading cause of death by disease in the U.S. and the second leading cause of blindness. About 1.25 million Americans have the "juvenile-onset" form of the disease while about 3.75 million have the "maturity-onset" form. Since 1950 the number of diabetics has increased more than 300% and the number of new cases is growing by about one million every three years [100]. Diabetes' major contribution to mortality is through acceleration of atherosclerosis and other forms of cardiovascular deterioration. There is also increased protein breakdown, reduced immunity and, in up to 80% of adult diabetics, hypertension [101]. Chronic arousal may have potent effects in both forms of the disease.

The hormonal pattern in juvenile-onset diabetes is one of lowered insulin and elevated glucagon se-

cretion [102], a pattern similar to the hormonal pattern of arousal. This is not to say that arousal causes the disease but that arousal can exacerbate its symptoms and sequelae. For example, during arousal, glucose and free fatty acids are mobilized from their storage forms by epinephrine. Since excesses of these metabolites are part of the problem in diabetes, their increase during arousal tends to throw the diabetic out of a metabolic balance whose restoration requires administration of larger than usual amounts of insulin. The consequent hyperglycemia, hyperlipidemia, and hyperinsulinemia all accelerate the progress of pathology [103]. A dramatic example of this effect has been demonstrated directly in diabetic children living in disturbed families. Such children, despite regular insulin treatments, are regularly brought to the hospital in diabetic acidosis. Typically, in such families conflict between parents is discharged through the child. In a "stress interview" the child's free fatty acid levels (a measure of arousal) rise and remain high while the parents' fatty acid levels fall. In such cases when the family system is restructured so that the child is no longer the mediator of conflict, the diabetes comes under control [104].

The problem in adult-onset diabetes is not a lack of insulin, for it is secreted in normal or greater than normal amounts. The timing of the secretion is off—it is delayed so that larger than usual amounts of insulin are required. Normally insulin is effective in small amounts because it is secreted while glucose is passing from the gut into the portal vein that carries blood to the liver. In the presence of insulin the liver absorbs much of this glucose and also stops releasing glucose into the blood. The result is that the rise in blood sugar following a meal is relatively modest. When in

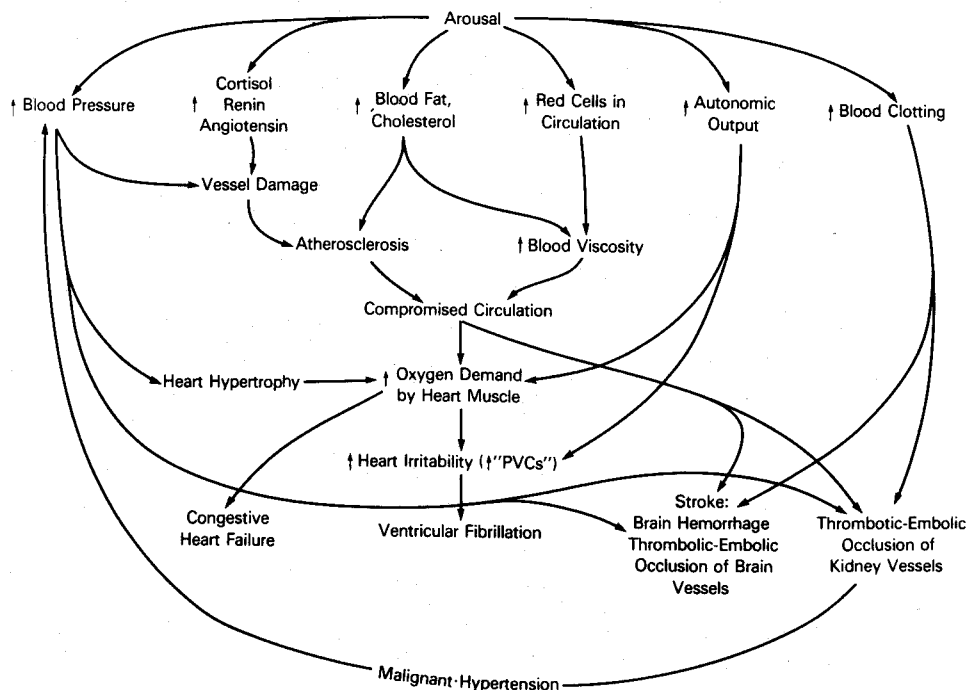


Fig. 14. Reno-cardiovascular pathology from chronic arousal.

adult-onset diabetes this early insulin secretion fails to occur, glucose passes through the liver into the general circulation and the rise in blood glucose is abnormally large and prolonged. The late insulin secretion must then be abnormally large to compensate for the glucose elevation [105]. The hyperinsulinemia over the long run appears also to suppress the production of insulin receptors on the membranes of muscle and fat cells, requiring still larger amounts of insulin for an adequate regulation of blood glucose [106].

Chronic arousal can contribute to this condition in two ways. The increases in catabolic hormones such as epinephrine, cortisol, growth hormone and glucagon, antagonize the actions of insulin and exacerbate the diabetes by further mobilizing glucose, fatty acids, and protein breakdown. Glucagon and norepinephrine, furthermore, act directly to suppress the secretion of insulin [107]. Arousal may also have a primary role in generating the adult-onset diabetes by contributing to the suppression of the early phase of insulin secretion. During arousal many of the secretory processes required for digestion are inhibited by the brain via the autonomic nervous system [108]. It would not be surprising, in view of the known neural control over insulin secretion [109], to learn that the normal, early phase of its secretion is one of the casualties of chronic arousal.

Cancer

Cancer accounts for 16% of the total annual deaths in the United States, and for 19% of the total in males over 30 [110]. Many studies, including several recent WHO reports, indicate that 60–90% of all cancers are initially generated by environmental agents including chemical carcinogens, radiation, and viruses [111]. Malignant cells generated by these agents seem to be, for the most part, eliminated from the body by the routine functioning of the immune system. This is evident, for example, in patients whose immune systems have been suppressed in order to permit acceptance of organ transplants. Such patients show 100-fold increase in cancer rates compared to operated controls [112]. The immune system may also be important in controlling cancer viruses.

The immune system is, as we have noted, an early casualty of arousal. Perhaps the clearest example of the interaction between virally stimulated cancer and arousal is in mammary tumors of mice. Female mice of strain C3H/HE are known to carry several viruses that under normal circumstances cause mammary tumors in 80–100% of the mice within 8–18 months after birth. "Normal circumstances" for these mice means that they are handled frequently and bled several times per week. Reared in open cages in a large animal room, they are subject not only to their own arousal but also to the signals of hundreds of other aroused mice carried by sound and by special odors called 'pheromones'. When the same mice, with the same viruses, are reared with minimal handling in special cages that isolate them from the sounds and smells of the large population, their cortisol levels fall from more than 700 ng/ml to about 40 ng/ml. The incidence of tumors at 400 days falls from 92% to 7% [113].

In summary, we have seen that the catabolic pro-

cesses accompanying chronic arousal contribute in many direct ways to the pathologies that underlie the leading causes of adult, particularly male, deaths. Important causes that remain are accidents, suicide, homicide, cirrhosis of the liver (due to alcoholism) and ulcer. Although there is much to be said about these causes, their relation to the chronic arousal that accompanies fear, anger, anxiety, and loneliness is so obvious that they are often used as direct measures of social and psychological malaise [114].

MEDICAL TREATMENT FOR AROUSAL PATHOLOGY

Endstage treatments

A huge proportion of the total medical effort is currently devoted to treating the end stages of disease. The problems of treating major pathology at the end stage without disrupting normal processes and provoking additional pathology are enormous. For example, treatment of metastatic cancer takes advantage of the relative sensitivity of cancer cells over normal ones to radiation or chemotherapy. Such differences in sensitivity are only marginal, however; in most cases the extension of the life-span is brief, and the suffering accompanying treatment is intense.

Some concrete feeling for the problem was given by Crosby who noted that in a group of 71 patients treated for acute leukemia with cytosine arabinoside, 71% died during the initial period of drug administration; the median survival of all patients was 2 1/2 weeks. He concluded: "The extension of time spent in toxic reactions to chemotherapy is the aspect of the aggressive treatment of leukemia which has become truly repellent. . . . By stepping up the aggressiveness of the therapy, the injury and agony of the patient are intensified and prolonged: the infections, the bleeding, the transfusion reactions, the isolation on Life Island" [115].

The 5-year survival of cancer patients improved significantly between 1935 and 1955, when antibiotics were introduced in surgery. Since 1955, however, the overall 5-year survival time for all treated cancers combined has remained constant despite massive and accelerating use of surgery, radiation and chemotherapy. The survival rate improved for uterine cancer and for some relatively rare cancers such as acute lymphatic leukemia in children (about 0.2% of all cancers) and Hodgkin's disease (about 1.0% of all cancers). These have been outweighed by increases in frequency of lung and other major cancers, for which therapy is ineffective and survival short [116].

The problem in endstage kidney failure is in certain respects similar. The technical approaches, dialysis or transplant, have extended the life span of patients an average of several years, in many cases under favorable terms. Yet, the mortality of patients on chronic dialysis is between 8–22% per year [117], and their lives are not normal. Diet must be rigidly controlled and life must be organized around the rhythm of dialysis. The balance of salts, metabolites, hormones, and waste products in their blood undergoes large fluctuations that would normally be controlled by the kidney. Patients begin to feel poorly as wastes build up, but feel poorly (cramps, confusion, exhaustion) as well for at least a day after dialysis because of the

metabolic disruptions. Impotence, probably from both physiological and psychological causes is common. One concrete measure of the inadequacy of the treatment is that the suicide rate among dialysis patients is 400 times greater than in the general population [118]. Kidney transplants are a better solution when they work, but compatible donors are rare, and with cadaver transplants only 50% are still functioning after two years [117]. Rejection of the transplanted kidney requires surgery for its removal and a return to dialysis.

Attempts at a surgical solution for severe atherosclerotic heart disease have also developed rapidly over the last decade. When coronary arteries are occluded by atherosclerotic plaques, the heart muscle becomes chronically anoxic, causing pain (angina) either at rest or at the slightest exertion. The threat of fatal heart attack is, of course, serious. By introducing a radio-opaque substance into the heart via a catheter and taking X-rays, the sites of occlusion are determined (angiography). Segments of vein are removed from the leg and grafted onto the heart to form shunts that permit blood to flow around the clogged regions of the coronary arteries.

Following such "coronary artery bypass grafts" (CABG) most patients initially have significant relief of pain [119]. The relief may be somewhat greater and more prolonged than that following sham surgery (placebo) [5], but this has not been clearly determined. Certainly the placebo effect in CABG surgery is large since many patients experience initial relief even when their grafts are wholly occluded [120]. In about one-third of the cases the grafts are occluded by the end of a year [121]; the atherosclerotic process continues in the unoperated vessels and is often accelerated by the surgery [122].

CABG produces very little improvement in objective measures of the heart's condition, such as ventricular function, or in control of arrhythmias [123], and there is almost no difference in long term survival between CABG patients and those treated medically [124]. The fundamental logic of the procedure seems called into question by recent pathological studies. Paradoxically, these showed healthy heart muscle in regions where the grafts were occluded and dead tissue where the grafts were patent [125].

The last two decades have also seen the rise of the "coronary intensive care units" where a patient is brought following a heart attack. A trained nursing staff continuously monitors the EKG. Oxygen, drugs and resuscitation equipment are available, and every attempt is made to prevent the development of dangerous arrhythmias. Yet, in a British study [126], when men were randomly assigned either to such a unit or to home care, there was little difference in outcome. Among the groups with the most severe heart attacks, mortality in the first month was 46.7% in the hospital and 44.4% at home. Among the less severely affected patients, mortality was 11% in the hospital and 7.9% at home. The authors of this study note that "coronary care unit psychosis" is a common phenomenon arising from the fearful atmosphere created by the social isolation, deaths of other patients, strange machines, and disruption of the normal sleep cycle. They raise the ironic possibility that the psychological state induced by the hospital en-

vironment may contribute to the development of arrhythmias that the technology is designed to treat. This study has been recently been repeated with a better design and on a larger scale—with the same results [127].

The financial costs of these technological treatments are huge because they are being offered not for rare diseases but for endemic ones. It is estimated that more than 70,000 CABGs were performed in 1977 at a cost of close to one billion dollars [128]. This does not include what Braunwald calls the "more insidious problem", that an "industry is being built around this operation: the creation of facilities in community hospitals... proliferation of catheterization and angiography suites.... This rapidly growing enterprise is developing a momentum and a constituency of its own.... If the notion that this operation does indeed prolong life is generally accepted, logical corollaries would be the performance of coronary arteriographic examinations on the several million asymptomatic or mildly symptomatic persons at high risk of having severe obstructive coronary-artery disease, followed by CABG on the many hundreds of thousands in whom such disease would surely be discovered. This course would escalate the annual national cost into many billions of dollars..." [128]. A similar problem exists for renal dialysis, which in 1980 will treat 50,000 patients at a cost of \$1.3 billion [129].

At the endstage of chronic disease, the technologies of diagnosis and intervention, no matter how daring, are marginally effective. One measure of this is that the life expectancy of adult, white males has hardly changed at all since 1900 (Table 1). Even though the technologies and surgical skills will improve with further experience, their contributions are likely to remain marginal because the body is already badly and irreversibly damaged. The interventions tend, furthermore, to be iatrogenic, partly because of their direct effects on normal biological processes (as in cancer chemotherapy) but also because of the additional acute arousal which they engender (as in the coronary care unit). Their financial costs are staggering and account for part of the rapid rise in cost of medical care.

The medical community is sensitive to these issues and almost universally recognizes the importance of prevention, or at least, early treatment. Thus, Kannel and Sorlie conclude their recent report on the Framingham Study [63]:

Despite truly spectacular progress in cardiology over the past quarter century cardiovascular mortality continues to take its huge annual toll.... Once infarcted neither the brain nor the myocardium can be restored by any means, nor can a kidney which has used up all its reserve and compensatory mechanisms be resurrected. The nature of cardiovascular disease is such that treatment directed only at already symptomatic disease, no matter how ingenious or successful, can not achieve a substantial reduction in cardiovascular morbidity and mortality. Only a preventive approach correcting precursors which lead to organ damage can have a substantial impact. Chief among these contributors requiring attention is hypertension.

Medical treatment of essential hypertension

At present, there is no accepted program for genuine prevention of essential hypertension because

there is so little agreement among physicians as to cause. The conviction is strong, however, that hypertension, once detected, should be treated vigorously with drugs for indefinitely long periods. The potential treatment population has expanded with every advance in understanding of the risk associated with high blood pressure and now includes up to 60 million adults [130]. Over 80% (48 million) are people with pressures in the "mild" hypertensive pressure range from (diastolic 90–104 mmHg). In New York and other large urban centers, primary care physicians already prescribe drug prophylaxis for the vast majority of these mild hypertensives [130].

Physicians usually refer to the Veterans' Administration cooperative studies [144] of the antihypertensive drugs in justifying this practice. These studies were done on 380 men in the 1960s for periods between one and four years. After careful sifting of potential participants from the VA clinics, patients were randomly assigned to placebo or drug treatment and followed in a double-blind fashion. Results were reported in several strata according to initial blood pressure level and cardiovascular risk. In the higher pressure ranges (diastolic 105–129 mmHg) and for people with preexisting heart or vessel damage, drug treatment lowered pressure (20–30 mmHg diastolic) and markedly reduced mortality from stroke, congestive heart failure, and kidney damage, as well as overall mortality, in comparison to the placebo control. Among men with mild hypertension, however, blood pressure reductions were smaller (about 15 mmHg diastolic). There was little mortality difference from control and "relatively little benefit from treatment unless they had CVR abnormalities at entry or were over 50 years of age" [144].

The U.S. Public Health Service conducted another large-scale, placebo controlled trial at about the same time, focusing on the possible benefits of drug treatment for mild, uncomplicated hypertension. Three hundred and eighty-nine men and women, young to middle age, were followed for 7–10 years. Once again the drug-treated group showed no mortality difference from the placebo group. The current U.S. program attempting to place up to 48 million mild hypertensives on permanent drug prophylaxis is not well supported by these findings.

The principal reason for the failure of drugs to have significant mortality impact was the failure to reduce mortality from coronary heart disease. As we will show in the next section, the mechanisms by which the antihypertensive drugs act may potentiate coronary heart disease. In longer term studies of these drugs, coronary heart disease may even increase. This hazard of the drugs needs to be understood in depth, because the prospect for treatment of mild hypertensives is one of decades of drug consumption starting in young adulthood and extending into old age.

From our description of how the drugs work it will become clear that the experience with drug treatment provides another important source of confirmatory evidence for a chronic arousal hypothesis of hypertension. Drug treatment has generally been designed to alter one or another peripheral pressor mechanism. When a drug is used in this way, a whole network of compensatory responses is aroused which tends to reestablish pressure at hypertensive levels. These com-

pensatory responses require additional drugs to suppress other parts of the regulatory network. The size and richness of these compensatory mechanisms is compatible with the idea that blood pressure is regulated by the brain and that in essential hypertension the whole network of peripheral mechanisms is being driven by the brain to maintain a high pressure.

Mechanisms of action of antihypertensive drugs

Each of the three peripheral mechanisms for raising blood pressure can be blocked by drugs. The volume mechanism can be blocked by administration of a diuretic, commonly a sulfonamide such as chlorothiazide. This compound stimulates excretion of salt and water, thereby creating a tendency for lower blood volume. Vasoconstriction can be decreased either by drugs such as hydralazine which directly relax vascular muscles, or by drugs such as α -methyl dopa which block neural activation of vascular muscle. Cardiac output can be decreased by drugs such as propranolol which block transmission of neural excitation to the heart. Many of these drugs simultaneously affect several systems. Thus, propranolol, in addition to its effect on the heart, prevents sympathetic activation of the renin-angiotensin system. By reducing angiotensin levels, propranolol acts both on the volume mechanisms (via aldosterone) and on the vasoconstrictor system (see Fig. 4) [131].

It is predictable, because the pressor mechanisms are instruments through which the brain urges pressure toward its set goal, that blocking one mechanism with a drug will evoke compensatory changes in all. Thus, diuretic stimulation of salt and water excretion evokes compensatory increases in secretion of renin, angiotensin, aldosterone, and antidiuretic hormone [132]. These tend to compensate for the diuretic's action by stimulating the kidney to try to save sodium and water, by stimulating the behavioral appetite for salt and water [80], and by stimulating the vasoconstrictor mechanisms to compensate for lower plasma volume. As the brain detects a lowering of blood volume by the diuretic, it directs further compensation by vasoconstriction and an increase in cardiac output.

In order to achieve a sustained reduction in pressure, it may be necessary to oppose these tendencies by the administration of additional drugs. Hydralazine is given to block the vasoconstriction but this stimulates *additional* compensatory responses, including an increase in the salt-water hormones and in cardiac output. The pulse rate may rise from 70 to 120 [133]. To block these compensatory responses propranolol may be added to the drug regimen [134]. Propranolol, of course, evokes compensatory responses in the volume and vasoconstrictor mechanisms, causing fluid accumulation [135] and vasoconstriction [134]. Ultimately, with the proper combination and dosages of drugs, it is possible to block the ability of the whole system to compensate, permitting the pressure to be controlled, finally, by the physician.

Each of the drugs employed to treat hypertension causes undesirable physiological imbalances either by their direct actions or by the compensatory responses they evoke. Some of these imbalances require treatment with additional drugs which in turn have their own "side effects". Other imbalances are not treatable,

and for many of these the long term effects are unknown. There is thus a tendency to establish a long cycle of iatrogenesis: the treatment of one pathology produces others which must be treated in turn. One of the most serious concerns is that the ultimate expressions of both the primary "side effects" and of the iatrogenic cycle is in elevated morbidity and mortality for diseases that are already so prevalent that their gradual increase in the population may go undetected.

Iatrogenic effects

Diuretics. The diuretic drugs, in exerting their intended effects, cause chronic, partial dehydration [136] which is superimposed upon the already subnormal plasma volume present in about three-quarters of the hypertensive population [137]. This leads to increased blood viscosity and to a smaller plasma pool which is normally drawn upon during changes in posture.

The partial dehydration also stimulates compensatory increases in renin, angiotensin, and aldosterone. Such endocrine disturbances alter the balance of various substances in the blood: levels of potassium and magnesium commonly fall while calcium, uric acid, and glucose commonly rise [138] (Table 6). The dehydration and electrolyte disturbances can account for the common symptoms of gastrointestinal irritation, weakness, lethargy, and postural hypotension (fainting during a shift in posture from lying to standing). The increased blood viscosity tends to decrease blood flow through vessels clogged by atherosclerosis, contributing to a local tissue anoxia and its symptoms, such as angina. Elevated blood viscosity also increases the chances for formation of blood clots and their dissemination as emboli to heart, kidney, brain. The high levels of angiotensin contribute to vascular damage and so accelerate atherosclerosis [139]. Loss of potassium can cause development of cardiac arrhythmias, including fatal ventricular fibrillation; in the long run it can cause necrosis of heart muscle [140]. Low magnesium can cause spasms of the coronary arteries and has recently been implicated in sudden death from ischemic heart disease [141].

A rise in calcium may have long term effects by accelerating calcium deposition in atherosclerotic plaques and in joints (complaints of arthritis are common—see Table 6). The rise in ratio of calcium to magnesium may increase the release of neural transmitter substances. This would have complex, but presently unrecognized, effects on the peripheral and possibly the central nervous system. Diuretics also cause in some patients irreversible pathology of the parathyroid, a gland critical in regulating blood levels of calcium and phosphorus; parathyroid surgery is sometimes necessary. The rise in uric acid can and does cause painful gout [138]. The sustained elevation of blood glucose and glucose intolerance is common (see Table 6) [142] and serious, since it can contribute to vascular deterioration and atherosclerosis and can develop into frank diabetes.

If a patient on a diuretic is receiving conscientious care, his physician will monitor these physiological parameters. When they become imbalanced, he will treat with additional agents, increasing still further the potential for iatrogenesis. Thus, a rise in uric acid

may require treatment with allopurinol or probenecid; a rise in blood glucose may require treatment for diabetes.

Similarly, potassium loss (hypokalemia) must be treated, usually with dietary supplements but patients are not easily induced to eat potassium because of its bad taste. Potassium tablets, even the slow-release variety, can cause small bowel obstruction and ulcers [143], so sometimes a second diuretic, spironolactone, is added to the regimen to help preserve potassium. However, in patients with elevated blood levels of ammonia (common in kidney impairment associated with hypertension), there is danger of inducing a fatal excess of potassium [138]. Therefore, blood potassium levels of patients on this drug must be monitored with extreme regularity and care. Finally, it appears that though blood potassium can be monitored, it is not a reliable measure of the degree of potassium restoration to the heart [140].

Hypokalemia and hyperuricemia occurred in many diuretic-treated patients in the VA [144] and PHS [145] studies. The special monitoring and care received by these patients prevented these conditions from becoming serious. In general practice, however, equal attention and safety cannot be assumed. It has been reported, for example, that of patients presenting with acute myocardial infarction and ventricular fibrillation, 87% of those receiving thiazide diuretics had hypokalemia, while only 2.6% of those not receiving thiazides had this predisposing cause of ventricular fibrillation [146]. Such evidence indicates that the hypokalemia common in all the large trials of diuretics may be a serious risk in mass drug prophylaxis of mild hypertension. The trials cannot estimate the size of this risk because hypokalemia is treated in the trial more carefully than can be expected in typical practice.

This combination of untoward effects on the cardiovascular system may help explain the reports of increases in myocardial infarction and "sudden death" in patients treated with antihypertensive drugs over periods of up to 8 years [140]. It may also explain why none of the large scale, controlled trials of antihypertensive drugs have shown decreases in death from myocardial infarction: the beneficial effects of lowered pressure may have been offset by these iatrogenic effects. In the long run the most damaging effects of diuretics may result from the chronic compensatory responses they evoke. By artificially stimulating the loss of sodium and water, they cause aldosterone cells of the adrenal, renin cells of the kidney and the ADH cells of the brain to work overtime. Whether this will cause their exhaustion and premature death, only time will tell.

Antivasoconstrictors. Vasoconstriction is treated by any of a host of drugs [138] including hydralazine, reserpine, alpha methyl dopa, and guanethidine, each of which has serious effects that often require additional treatment. We discuss in detail only hydralazine [133] whose mechanism of action was described earlier.

The therapeutic effect of this drug in causing vascular relaxation and a fall in pressure leads to compensatory increases in the renin-angiotensin-aldosterone system and in cardiac output. The increased output by a compromised heart can "cause anginal attacks

and...myocardial ischemia. The drug (hydralazine) has been implicated in myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease" [147]. The meaning of this warning is difficult to grasp since among the hypertensives who would be treated with hydralazine coronary artery disease is both common and often undiagnosed.

Chronic administration of hydralazine can lead to rheumatoid arthritis and to another condition resembling the serious disease, lupus erythematosus. This occurs through stimulation of the immune system and it is recommended that regular blood counts and antibody measurements accompany chronic hydralazine therapy. The frequency of these effects are proportional to the dosage and duration of exposure to the drug. Clearly, however, if hypertension is to be treated on a mass scale, the duration of exposure will be long. The lupus syndrome may be reversible, but often requires long term treatment with steroids whose multiple, serious effects are notorious. In addition to these effects of hydralazine, there are common unpleasant effects such as fever, skin eruptions, peripheral neuropathy (manifested by numbness in the extremities), flushing, nasal congestion, headache, dizziness and palpitation [133].*

Beta-blockers. The compensatory increases evoked by diuretics and anti-vasoconstrictors must be suppressed to prevent restoration of high pressure and increased strain on the heart. This is accomplished by drugs, such as propranolol, that block "beta-receptors" for epinephrine and norepinephrine. These receptors exist not only on the renin cells and on the heart but also on insulin cells, liver and fat cells, and on the muscle cells of blood vessels and the respiratory system. Propranolol attenuates the ability of all of these cells to respond to sympathetic stimulation. The drug is, therefore, dangerous under conditions where an individual may need such stimulation acutely. A person whose heart has been weakened by hypertension, needs sympathetic stimulation of the heart and may experience congestive heart failure when it is blocked by propranolol. This occurs even when care is taken to exclude obviously borderline patients. When such failure is precipitated, digitalis must be given. In some cases, depression of the heart rate must be treated by artificial pacemaker [134].

Similarly, during acute arousal glucose must be mobilized as part of the general catabolic response. This generally occurs through the breakdown of liver glycogen in response to epinephrine. When this process is attenuated, hypoglycemia can result. This can be particularly serious for diabetics taking propranolol because the usual signs of hypoglycemia, such as a rise in heart rate, are blocked as well. A recent review notes, "propranolol has not been reported to cause serious hypoglycemia in the unstressed, healthy human being" [134]. On the other hand, it is precisely the stressed, unhealthy humans who are likely to be receiving the drug.

Propranolol also precipitates acute bronchospasm (a closing of the airways) in up to 10% of patients, even after those with a history of asthma or other respiratory problems have been excluded. This effect is a straightforward consequence of the loss of sympathetic stimulation to the muscles that dilate the respiratory passages. It also means that the airways cannot enlarge, as they normally do, during arousal. Such acute respiratory crises are treated with norepinephrine [134].

Another common effect of propranolol when given alone for hypertension is to worsen the peripheral circulation. This occurs because the beta-receptors for vasodilation are blocked, permitting the alpha-receptors for vasoconstriction to act without opposition. The vasoconstriction can cause a fall in renal perfusion with an accompanying deterioration of kidney function. Coronary artery spasms may be precipitated by the same mechanism and lead to myocardial ischemia [98]. Finally, propranolol has acute effects on the central nervous system that are poorly understood but can be accompanied by insomnia, nightmares, hallucinations, fatigue, depression, paresthesia, ataxia (staggering) and dizziness [134].

The long term effects of propranolol are completely unknown, but there are several reasons for concern. First, propranolol may interfere with the complex and critical regulation of carbohydrate and fat metabolism. Epinephrine, whose beta-receptors are blocked by propranolol, regulates glycogen breakdown, stimulates release of free fatty acids from fat cells, and has a role in insulin release. In some cases, propranolol can block the latter and cause hyperglycemia. The long term effect of this iatrogenic diabetes may be an acceleration of atherosclerosis. Second, long term administration of propranolol may turn out to cause heart atrophy. This possibility must be suspected because neuromuscular blockage of skeletal muscle can lead to atrophy. The possibility of atrophy over the long term was conceded by an expert whom we consulted. It is already clear that "in patients without a history of cardiac failure, continued depression of the myocardium can, in some cases, lead to cardiac failure. In rare cases this has been observed during Inderal (propranolol) therapy" [148]. Whether these instances will remain rare as the duration of treatment extends into decades is a matter of conjecture. Certainly there are enough examples of therapies with disastrous long term effects to dampen optimism in the present case [149]. Prolonged administration of propranolol to heart muscle in tissue culture causes fibrosis in the tissue, apparently by altering the biochemistry of collagen synthesis [150]. Such an event *in vivo* could also promote cardiac failure. Finally, that propranolol reaches the central nervous system and exerts the acute effects noted above, raises questions regarding its long term effects on the brain [151].

Frequency and significance of iatrogenic drug effects

The VA studies analyzed for undesirable drug effects only the group with the lowest pressures (diastolic 90-114 mmHg) who received the fewest drugs at the lowest doses. Patients in this group were followed for an average of only 3.3 years. Even so, biochemical abnormalities occurred in one-fourth to one-third of this group (Table 6). It may be anticipated that in a

* Note added in proof: Hydralazine has recently been shown to be mutagenic and carcinogenic (Williams G. M., Mazze G., McQueen C. A. and Shimada T. Genotoxicity of the antihypertensive drugs hydralazine and dihydralazine. *Science* 210, 329, 1980).

Table 6. Incidence of iatrogenic effects accompanying drug treatment of hypertension†

Abnormality	Incidence before treatment		Incidence during treatment	
	Placebo	"Active" drug	Placebo	"Active" drug
Low potassium	1%	2%	2%	23%*
Elevated uric acid	13%	11%	16%	30%*
Elevated blood sugar	15%	15%	17%	30%†
Lethargy or weakness	0	0	26%	39%
Nasal stuffiness	0	0	29%	35%
Impotence	0	0	28%	29%
Arthritis	0	0	38%	27%
Headache	0	0	34%	25%
Angina	0	0	24%	13%
Ulcer symptoms	0	0	9%	12%
Skin rash	0	0	9%	8%
Depression	0	0	9%	9%
Nightmare	0	0	12%	6%
Other complaints	0	0	43%	43%
Any complaint	0	0	67%	82%

* Values at end of first year; some patients in drug group treated with additional agents.

† Values at end of second year.

‡ Data from V.A. Cooperative Study; *op. cit.* [144].

younger and healthier group the incidence of such effects will be lower at the beginning of treatment. Use of the drugs over decades, however, may ultimately generate an even greater incidence of serious abnormalities.

There was a high incidence in this group of patients of what the VA studies termed "subjective side effects", including weakness (39%), impotence (29%), arthritis (27%), and headache (25%) (Table 6). Eighty-two percent of the patients reported some difficulties that they had not experienced prior to the study. The VA studies and many physicians since then have tended to treat these "subjective" effects lightly because the data was collected by asking each patient which symptoms on a check list he had experienced. The placebo group with this procedure reported as many symptoms as the "active" drug group so the active drugs were considered safe.

This interpretation seems to us incorrect. It is not that the drugs are safe, but that the placebo under the conditions of the VA studies was dangerous. The check list was developed in the first place because the symptoms had been widely and spontaneously reported during earlier experience with the drugs. Other studies that did not use such a suggestive check list found marked side effects only for drug-treated patients and not for controls [152]. Furthermore, many of the "subjective" symptoms are to be anticipated from the known physiological effects of the drugs. Thus, postural hypotension would be an anticipated consequence of reduced plasma volume and reduced sympathetic response. Weakness and lethargy (often termed coolly by physicians, "exercise intolerance") would be anticipated with the full combination of antipressor drugs because the body is left with no substantial means of directly activating the cardiovascular system. This experience was summarized vividly by a hypertensive physician who ignores his prescribed medications: "When I do take them, I can't walk up a hill!"

This physician went on to express anger at relinquishing control over his body and at being reminded of it 4 times daily by swallowing his pills. There is no direct measure in Table 6 of such anger because the patients were not asked how they felt about their treatment. It seems likely, however, that the high incidence of symptoms in the placebo group is an indirect expression of the negative feelings that accompany this treatment modality. The impotence, for example, reported by 28% of the placebo group certainly makes sense when viewed as an expression of surrender. Since all of these "subjective" symptoms can be cured by placebo under circumstances of positive suggestion, it is hard to understand their genesis in any other way. In summary, there is a paradox in the drug treatment of hypertension. When a potent drug is given, the physician is ethically bound to warn the patient of possible symptoms. Such a warning, on the other hand, is also a powerful suggestion for the patient to experience the symptoms [153], particularly if he already has reason to feel angry.

The reduction of physiological responsiveness caused by the drugs, the unpleasant physical effects, and the resistance to permanently transferring control over major bodily functions to a physician seriously erodes "patient compliance", that is, the faithfulness with which the drugs are taken. That compliance is a serious problem is suggested by the rigid, multi-stage selection procedure employed in the VA studies. Initially all patients were excluded who would be unable to attend clinic regularly and also those who were considered "poorly motivated or otherwise uncooperative or unreliable", including alcoholics and vagrants. The study does not report what fraction of the population was excluded on this basis, but it was probably substantial given the high incidence of such behavior in the VA population. Patients admitted to the second stage were given placebos for 2-4 months. Their urines were checked at each monthly visit for the presence of the placebo, and their pills were

counted. Nearly half of the patients were excluded at this stage because of failure to pass these tests of reliability. As additional motivating factors each patient saw the same physician throughout the study; the visits and the drugs were free. Despite the rigid selection for high motivation, 8–15% of the patients dropped out after an average period of 17.6 months in the study.

There is little reason to believe, therefore, on the basis of the VA studies that the average patient would take 2–3 drugs 3–4 times a day for decades, particularly in view of the high incidence of unpleasant "subjective" side effects. Nor is it likely that they would go regularly to a doctor for expensive physiological monitoring. In general medical practice this careful monitoring, so necessary to the use of the drugs, is the exception, not the rule. One recent study of hypertension clinics found that only 1/3 of the patients who began treatment were still in the program after 8 months even though they received special reminders on the day before their appointment. Only 10% had normal blood pressure. Most patients, therefore, were not taking their drugs, or at least not in adequate doses. The study noted that the average waiting time was 2.5 hours to see the doctor and 1.8 hours at the pharmacy. The average time spent with the physician was 7.8 minutes [154].

Nor is it likely that a purely educational effort will solve the problem of compliance. In Framingham, Massachusetts a large sample of adults is examined biannually as part of the Framingham prospective heart disease study. Blood pressure findings are reported to the physician, and people with elevated pressures are urged to see their doctors for treatment. As in the United States generally, antihypertensive drugs are now commonly used in the Framingham population. Comparison of the blood pressures of those on drug treatment in the Framingham population with untreated individuals shows an average 6 mmHg decline in systolic pressure and lesser diastolic decline, over a ten-year period. This decline was insufficient to reverse the rise of blood pressure with age in treated individuals, and could produce at most only a very small reduction in cardiovascular mortality [63]. Hence, even in a community with a long history of education in the prevention of heart disease, drug treatment has been unsuccessful. Though Kannel and his co-workers in Framingham have not positively identified the cause of this failure, they suspect it is due to the failure of patients to take the drugs. From what we have described of the iatrogenic effects, this result is to be expected and in fact may represent a useful folk wisdom.

Psychosocial treatment of mild hypertension

Recently clinicians and researchers have made large efforts to increase compliance and in this have achieved some success [155]. Careful reading of the reports reveals that the increase in compliance occurs when the programs create new social support networks. The decreases of blood pressure, morbidity, and mortality demonstrated in these recent studies cannot be understood without explicit analysis of these social effects. In this section we present the evidence that psychosocial intervention in medical and nonmedical settings can generate large and sustained

blood pressure reductions in hypertensives, and conclude with a reappraisal of the recent drug studies from this point of view.

As one would predict if essential hypertension were psychosocially generated, simple changes at the level of people's objective and subjective experience can reduce chronic arousal and permit the brain to reset the average blood pressure to a lower level. It was found, for example, that one-third of a group of 40 men with established hypertension showed declines to normal over a 6–7 year period without intervention of any kind. The pressure elevations and falls were associated with "stressful and less stressful" periods in the men's lives [156]. In still another study, reassurance by treatment with placebo (an electronic gizmo) was effective in lowering blood pressures of clinic patients with established hypertension [157].

Psychological relaxation techniques are also effective in reducing blood pressure [158]. In one recent study, falls in pressure induced by meditation were accompanied by falls in norepinephrine and renin secretion [159], and in another trial there was a corresponding decline in serum cholesterol [160]. These studies seem particularly telling, for they suggest that the relaxation, in contrast to the drug treatment, does not evoke compensatory responses of the neuroendocrine system. Instead, as the whole organism relaxes, the neural drive on the adrenal cortex, renin cells, and other organs of catabolism is also reduced. This is a treatment which goes to the heart of the matter.

These small scale studies constitute only part of the evidence for the effectiveness of psychosocial intervention in mild hypertension. Additional evidence is provided by the placebo effect observed in all of the large-scale double-blind trials. In the Medical Research Council trial now underway in Britain, and a parallel trial in Australia, the blood pressure decline of those placed on placebo is two-thirds that of hypertensives treated with the drugs. This decline, like the drug effect, occurs in the first few weeks and is then sustained throughout the first year [161]. The first year's experience is all that has been published so far, but other subsequent comments and reports from these groups clearly suggest that the blood pressure decline on placebo is sustained and results, as one might expect, in significant mortality reductions [162].

In the MRC and Australian trials all initially screened participants were directly randomized into placebo and drug treatment groups and the double-blind trial begun. In the VA and PHS trials, all potential participants were first given placebo for a period of about three months. Those whose blood pressure declined below 90 mmHg (diastolic) during this time were excluded from the subsequent double-blind trials, in which the placebo group showed no average change in blood pressure over time [144,145]. Clearly, the VA and PHS studies demonstrated a significant placebo effect on blood pressure, but reported the results in a way that makes it appear as though there were no placebo effect. Both the VA and PHS authors note in various places that they intend to follow the experience with the excluded placebo responders, but they have nowhere published these outcomes.

The VA and PHS studies do provide enough infor-

mation to calculate roughly how large this placebo effect really was. In the PHS study, depending on which parts of the placebo effect one chooses to include, the average blood pressure decline of the whole initial group placed on placebo ranges between 6.4 and 9.6 mmHg (diastolic). This compares with a 10 mmHg (diastolic) average decline subsequently reported for the drugs versus placebo group in the double-blind trial [163]. The published information for the VA studies on this point is very fragmentary but a similar story can be pieced together [164]. Thus, it appears that the American trials broadly show the same placebo effect as that found in the MRC and Australian trials, but they design and report the studies so as to eliminate from the main analysis the very large group of placebo responders.

Besides the prior elimination of the placebo responders, the VA and to a lesser extent the PHS studies have yet another reason for showing no change in average blood pressure in the group on placebo in the double-blind trial. The final composition of the placebo groups included many patients who had been taking antihypertensive drugs before entering the study and being switched to placebo. Since blood pressure commonly shows a rebound rise following withdrawal of drugs [165], it is predictable that many of these patients would show a pressure rise. This rebound rise cannot properly be attributed to the inefficacy of the placebo.

Despite the weighty biases against the placebo regimen in the VA trials, nevertheless over 40% of those placed on placebo in the formal trial showed blood pressure decline over the course of the study. The VA authors have stratified the drug treatment group results into those showing greater or lesser blood pressure declines and published the resulting analysis long ago [166]. These authors have also said that they were conducting a parallel analysis of those whose blood pressure declined on placebo in the double-blind trial [167] but have, after 6 years, nowhere published the results.

The importance of social and psychological interventions in lowering blood pressure and mortality risk among mild hypertensives is also suggested by another large U.S. trial recently reported by the Hypertension Detection and Follow-up Program Cooperative Group (HDFP) [155]. In this study "the HDFP investigators agreed that the results of the VA trial made it inappropriate to use placebos in large numbers of hypertensives", despite the fact that 70% of HDFP participants were in the blood pressure range (90–104 diastolic) in which VA and PHS studies had shown no relative mortality benefit, even in very biased comparisons with placebo treatment. Instead, intensive medicosocial interaction for one group of drug-treated patients (the "stepped care" group) was compared to simply telling control patients (the "referred care" group) that they had a very serious condition and should see their doctors.

The "stepped care" group in the HDFP study received, in addition to drugs, extensive psychosocial attention and support. This included encouragement to attend clinics frequently (5 times a year was the minimum), not merely for drug treatment follow-up, but also for general medical treatment, health education, and social support groups for reducing risk

factors such as obesity and smoking. All of these services, as well as transportation, were provided free. If this incentive to participate was not enough, an extensive staff of field workers constantly went out to persuade and bring in the tardy and the dropout, that is, the individuals usually at highest risk in any study who would most benefit from support and treatment. The comparison in this study was not a placebo control but a "referred care" group sent to physicians in the community without this encouragement or support. While there was a marginal difference in the *prescribing* of drugs to the stepped-care versus referred-care groups (no information was recorded or reported that allows comparison of how extensively the drugs were actually *taken*), it is very hard to follow the HDFP authors in attributing the 20% reduction in mortality found in the stepped care group over 5 years, compared to control, to a difference in drug use.

In the absence of a placebo control, as the MRC trial authors have been quick to note [162], the effect of drug treatment cannot be distinguished from the effect of psychosocial support. Since the effect of drugs on mortality of mild hypertensives in both the VA and PHS studies was nil, it is unlikely that the drugs in the HDFP study are responsible for the mortality differential. More likely it is the extensive psychosocial support provided to the stepped-care group. This would help explain why blacks from poverty areas normally lacking in medical and psychosocial support showed far greater benefit in reduced mortality than whites in the study who already had adequate support. Since the HDFP was conducted at 14 different centers, with the same drug treatment regimen but greatly varying patient populations and support programs at the different centers, it should be possible to separate statistically the effect of psychosocial support from that of drugs in the basic data.

Though the large and consistent placebo effects in the controlled trials are the strongest evidence for psychosocial intervention in mild hypertension, it would be a mistake to suppose that placebo treatment is the best that can be done. If social support is the key element in the medical placebo effect, far more community network support is possible than can occur in the expensive and relatively infrequent hospital or clinic visit. The horizon of possibility is indicated by the study of Berkman and Syme, who demonstrate 200–300% prospective mortality differences over 8 years between people having and lacking social support networks in a California community [168].

WHERE TO INTERVENE?

We have described some of the interlocking, mutually reinforcing mechanisms by which the brain controls the body, omitting discussion of the numerous small molecules, such as peptides and prostaglandins, new species of which are identified almost weekly and which probably provide additional pathways for control. It appears that in our society the brain asks a great deal of the body and maintains it, often relentlessly, in an aroused state at high cost in chronic disease. One can now understand the general mechanism, though not the details, by which loneliness and unfulfilled dreams cause illness.

In conventional medicine there are other points of view about the "causes" of chronic disease. There is, for example, a growing focus on its genetic basis. Undoubtedly, there is a "genetic component" to every disease: ulcer, hypertension, diabetes, cancer, schizophrenia, alcoholism, and so on. This means that each person inherits his own pattern of structural, physiological, and psychological vulnerability. Our bodies and minds crack in different places and after varying amounts of strain. It means that one family is likely, under chronic arousal, to suffer a different chronic disease than another. Genetics should not distract us, however, from recognizing that if as a people we were not so chronically aroused, we would have less disease despite the same level of genetic vulnerability.

Another focus in general medicine is on the "behavioral" causes of chronic disease. It is said that we have cancer because we smoke too much, hypertension because we eat too much salt, heart disease from too much fat and too little exercise, obesity from overeating, and alcoholism (cirrhosis) from too much drinking. The partial truth of these observations cannot be denied. But it is an error to think that these "behavioral" causes are independent of the physiology of the aroused state. We have pointed out that several of the hormones that increase during chronic arousal stimulate the brain in ways that specifically increase the drive for salt and water. It is not surprising then that salty foods are popular in a chronically aroused population. As long as the salt-seeking drive is stimulated by powerful hormonal effects on the brain, admonitions about the undesirable effects of salt will be as effective as were admonitions against sex in the Victorian era.

In regard to other "behavioral" causes of chronic disease we note that many primitive peoples share the same behaviors but generally not our excesses. Thus, many groups produce and enjoy tobacco, alcohol, and other psychoactive drugs, but as long as their social organization remains undisrupted, they have virtually no problems with chronic abuse. Per capita consumption of alcohol, tobacco and most other drugs rises dramatically with modern social transformation. Per capita tobacco smoking, for example, rises over one hundredfold, and is correlated with the rise of high pressure, mass production forms of work [169].

The same can be said for eating. The brain contains mechanisms that match caloric intake to energy expenditure. It must; otherwise one's body weight would not be stable. We eat relatively more in relation to our energy expenditures than do primitive peoples (even when their food is plentiful) and so regulate our weights at a higher level. Why? One might suspect that some of the catabolic hormones that accompany chronic arousal stimulate brain mechanisms responsible for food intake. This would make homeostatic sense in that hormones involved in burning the fuel would be part of the anticipatory mechanism to replenish. Each behavioral act, and particularly eating, has, of course, symbolic as well as neuroendocrine significance. Thus, we may tend to overfeed ourselves in attempting to gratify the desire, felt also by the Iroquois, that others should feed us. The point we wish not to lose track of is that the behavioral contributions to chronic disease are not

independent causes but are intimately related to the psychology and physiology of the aroused state.

Our cultural style in dealing with most problems has been to seek a technical solution and to apply it with maximum enthusiasm and force but with little insight into the true complexity of the matter. The result is sometimes a spectacular success. It is usually only temporary though, because in a richly interconnected system, application of a large force at a single point evokes compensatory responses that reverberate throughout the system. These tend to restore it to its original condition or else change it to a new but unpredictable state [170]. For example, massive application of DDT was stunningly effective in suppressing agricultural pests and mosquitoes. It did not eradicate them, however, but generated resistant strains and a host of new ecological problems that will continue for generations. We have learned bitterly that even in war a richly interconnected system is not easily defeated by the mechanical application of force.

The same is true of the extremely circumscribed therapeutic successes of technological medicine. It seems improbable that much will be gained by further development of agents whose terminology could have come from the Department of Defense: anti-tumor agents, anti-arrhythmics, anti-coagulants, and anti-hypertensives. The more sub-systems of the body that are blocked the more compensatory responses will be evoked, and the less responsive and flexible will be the body as a whole.

The appropriate points to intervene in arousal-caused disease are not primarily at the physiological level, for the brain itself has the most delicate and rich systems for control at this level [171]. It makes more sense, and will ultimately be far more effective, to intervene at the level of people's objective and subjective experience. It is necessary to understand what it is in their experience that generates and sustains chronic arousal. We noted in the previous section some of the evidence that psychosocial intervention can be effective. Not everyone who is treated at these levels will be able to escape the objective and subjective pressures that create their chronic arousal. Nor will every doctor have the skill and patience to make interventions on the levels where technology is relatively useless. It would be astonishing, however, if the record could not be improved.

The contributions of chronic arousal to mortality cannot be mitigated solely within a medical framework because the forces that generate arousal are powerful and deeply ingrained in our social structure and culture. Nor could we, even if it were desirable, return to a primitive life-style. We can and must, however, move toward a more reasonable balance between work and play, striving and loving, individuality and interdependency. At least this is what the radio-immune assays and chromatograms seem to be telling us.

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REFERENCES

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 18. See also Henry J. P. and Stephens P. M. *Stress, Health, and the Social Environment. A Sociobiologic Approach to Medicine*. Springer-Verlag, New York, 1978.
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 20. The following papers document the direct innervation of various endocrine organs. Note that most of the evidence is recent, going back only 10 years. Partly for this reason and also because there is no theoretical framework to accommodate it, the evidence is not discussed in textbooks. Nor is the evidence complete; the cells that secrete certain hormones: somatomedin and renal erythropoietic factor (kidney) and angiotensinogen I, erythropoietic globulin, somatomedin (liver), for example, have not yet been identified. Therefore, it is as yet impossible to say whether they are innervated. Both kidney and liver contain nerves, however, so it will not be surprising if these cells are discovered to be under neural control. In other cases, the negative results are so well documented that they are probably correct. Thus, though in birds the testosterone secreting cells are innervated, in mammals they do not appear to be, nor are the thyroxin, parathyroid, or estrogen cells.
- Pancreas**
- Shorr S. S. and Bloom F. E. Fine structure of islet-cell innervation in the pancreas of normal and alloxan-treated rats. *Z. Zellforsch. Mikrosk. Anat.* **103**, 12, 1970; Esterhuizen A. C., Spriggs T. L. B. and Lever J. D. Nature of islet cell innervation in the cat pancreas. *Diabetes* **17**, 33, 1968; Legg P. G. The fine structure and innervation of the beta and delta cells of the islets of Langerhans in the cat. *Z. Zellforsch. Mikrosk. Anat.* **80**, 307, 1967; Watari N. Fine structure of nervous elements in the pancreas of some vertebrates. *Z. Zellforsch. Mikrosk. Anat.* **85**, 291, 1968.
- W. F. Ganong (*Review of Medical Physiology*. Lange Medical, Los Altos, 1977) points out that the delta cells in the pancreas (see Legg, *op. cit.*) contain somatostatin and notes the effects of stimulation of the sympathetic and parasympathetic nerves to the alpha and beta cells.
- Adrenal**
- Innervation of the adrenal medulla is well known—see [19]. Innervation of the adrenal cortex: Unsicker K. Zur Innervatuin der Nebennierenrinde vom Gold hamster. Eine Fluoreszenz-und-electronenmikroskopische Studie. *Z. Zellforsch. Mikrosk. Anat.* **95**, 608, 1969; Unsicker K. On the innervation of the rat and pig adrenal cortex. *Z. Zellforsch. Mikrosk. Anat.* **116**, 151, 1971; Mikhail Y. and Amin F. Intrinsic innervation of the human adrenal gland. *Acta Anat.* **72**, 25, 1969; Ciaranello R. D., Wooten G. F. and Axelrod J. Regulation of rat dopamine B-hydroxylase. II. Receptor interaction in the regulation of enzyme synthesis and degradation. *Brain Res.* **113**, 349, 1976; Henry J. P., Kross M. E., Stephens P. M. and Watson F. M. C. Evidence that differing psychosocial stimuli lead to adrenal cortical stimulation by autonomic and endocrine pathways. In *Catecholamines and Stress* (Edited by Usdin E., Kvetnansky R. and Kopin I. J.), pp. 457–468. Pergamon Press, Oxford, 1976; Paul M. I., Kvetnansky R., Cramer H., Silbergeld S. and Kopin K. J. Immobilization stress induced changes in adrenocortical and medullary cyclic AMP content in the rat. *Endocrinology* **88**, 338, 1971; Henry J. P. and Stephens P. M., The social environment and essential hypertension in mice: Possible role of the innervation of the adrenal cortex. *Prog. Brain Res.* **47**, 263, 1977.

Kidney (renin cells)

Bunag R. D., Page I. H. and McCaffin J. W. Neural stimulation of the release of renin. *Circ. Res.* **19**, 851, 1966; Gomba S. Z., Bostelmann W., Szokaly V. und Soltesz M. B. Histochemische Untersuchung der adrenergen Innervation des juxtaglomerularen Apparates. *Acta Biol. Germ.* **22**, 387, 1969.

Thyroid (calcitonin cells)

Robertson D. R. The ultimobranchial body in *Rana pipiens*. VII. Cellular responses in denervated glands in autoplasmic transplants. *Z. Zellforsch. Mikrosk. Anat.* **126**, 182, 1972; Young B. A. and Harrison R. J., Ultrastructure of light cells in the dolphin thyroid. *Z. Zellforsch. Mikrosk. Anat.* **96**, 222, 1969.

Intestine

Neural control of gastrin secretion is well known, see [19].

Pineal (melatonin)

Ariens-Kappers J. A. The development, topographical relations and innervations of the epiphysis cerebri in the albino rat. *Z. Zellforsch. Mikrosk. Anat.* **52**, 163, 1960.

21. Schally A. V., Kastin A. J. and Arimura A. Hypothalamic hormones: the link between brain and body. *Am. Scient.* **65**, 712, 1977. It cannot be overemphasized that each hormone in the table probably acts at several levels and has multiple functions. Some of these have been elucidated for certain hormones such as somatostatin (GH-RIH)—see Table 3—but multiple functions have not yet been studied systematically for most of the brain hormones. Furthermore, many of these hormones exist not only in the hypothalamus from which they are released into the circulation, but in many other parts of the brain as well. See, for example, Winokur A. and Utiger R. D. Thyrotropin-releasing hormone: regional distribution in rat brain. *Science* **135**, 265, 1974. Finally, it should be appreciated that hormones from the periphery such as cortisol, sex hormones, insulin, etc. enter the brain and influence neural activity and behavior. See, for example, McEwen B. S. Interactions between hormones and nerve tissue. *Scient. Am.* **235**(1), 48, 1976. This whole area of neuroendocrinology is developing rapidly because of technical advances, and the next decade promises to strengthen our appreciation of the brain-body connections.
22. Other "relatives" of aldosterone, mineralocorticoids such as deoxycorticosterone, are even more sensitive to ACTH than aldosterone itself. See [74].
23. Frohman L. A., Ezdinli E. Z. and David R. Effect of vagotomy and vagal stimulation on insulin secretion. *Diabetes* **16**, 443, 1967; Kaneto A., Kosaka K. and Nakao K. Effects of stimulation of the vagus nerve on insulin secretion. *Endocrinology* **80**, 530, 1967. See also [109].
24. Felig P. The liver in glucose homeostasis in normal man and in diabetes. In *Diabetes—Its Physiological and Biochemical Basis* (Edited by Vallance-Owen J.), MTP Press, Lancaster, 1975.
25. Bevan A. T., Honour A. J. and Stott F. H. Direct arterial pressure recording in unrestricted man. *Clin. Sci.* **36**, 329, 1969.
26. Each component in this diagram is described in standard textbooks (e.g. [19]), though the components are not usually assembled so as to emphasize the overriding importance of the brain in setting blood pressure. What the diagram cannot adequately convey is that each element has many additional effects at different levels, all of which are mutually reinforcing. Thus, cortisol increases cardiac output, vasoconstriction, and renin release by increasing the binding of norepinephrine to β -receptors. Cortisol also contributes

to the production of angiotensin II by stimulating the production of angiotensin converting enzyme by macrophages. Friedland J., Setton C. and Silverstein E. Angiotensin converting enzyme: induction by steroids in rabbit alveolar macrophages in culture. *Science* **197**, 64, 1977. Cortisol also acts on the adrenal medulla, stimulating production of the enzyme phenylethanolamine-N-methyl transferase (PNMT), thereby elevating production of epinephrine: Wurtman R. J. Neuroendocrine transducer cells in mammals. *The Neurosciences Second Study Program*, (F. O. Schmitt, editor-in-chief,) pp. 530–538. Rockefeller Univ. Press, New York, 1970. Cortisol also induces sympathetic neurons in the superior cervical ganglion to produce more of the enzyme, tyrosine hydroxylase, which in turn increases the synthesis of norepinephrine: Hanbauer I., Lovenberg W. and Guidotti A. Role of cholinergic and glucocorticosteroid receptors in the tyrosine hydroxylase induction elicited by reserpine in superior cervical ganglion. *Brain Res.* **96**, 197, 1975. All of these actions are mutually-reinforcing. Angiotensin II, shown in the diagram to have only 2 effects, actually has at least 13 actions, all of which tend to raise blood pressure! (1) Vasoconstriction by direct action on arteriolar muscle. Angiotensin II enhances sympathetic activity at multiple levels: (2) Action on sympathetic nerve endings, causing increased release of norepinephrine. (3) Stimulation of autonomic ganglia. (4) Stimulation of catecholamine release from the adrenal medulla. (5) Stimulation of pressor reflexes by action on the area postrema of the brain. Angiotensin II also enhances the secretion of other hormones that cause retention of salt and water: (6) Stimulation of aldosterone secretion by direct action on the adrenal cortex. (7) Stimulation of ACTH release by direct action on the brain. (8) Stimulation of ADH release by direct action on neurons in the supraoptic region of the brain. Angiotensin II also has direct effects on kidney and gut: (9) Increases (at low doses) renal vasoconstriction, decreasing loss of sodium and water to urine. (10) Direct action within the kidney to retain more salt and water. (11) Stimulation of net fluid absorption from the intestine. Angiotensin and aldosterone also affect the appetite for salt and water: (12) Increases thirst and (13) increases sodium appetite by direct action on the subfornical organ and the organum vasculosum of the lamina terminalis of the brain. Finally, it is worth noting that derangements in one part of the pressor system (Fig. 7) may be compensated by changes in other parts. Thus, pathological hypertrophy of the renin cells in the kidney (Barter's syndrome) leads to elevation of angiotensin II and aldosterone. These changes are not followed by elevated blood pressure, presumably because the brain can reset other parts of the system (Ganong, *op. cit.* p. 348; Severs W. B. and Daniels-Severs A. E. Effects of angiotensin on the central nervous system. *Pharmacol. Rev.* **25**, 415, 1973; Gronan R. M. and York D. H. Effects of chronic intraventricular administration of angiotensin II on drinking behavior and blood pressure. *Soc. Neurosci. Abstr.* **III**, 162, 1977; Malvin R. L., Mouw D. and Vander A. J. Angiotensin: physiological role in water deprivation-induced thirst of rats. *Science* **197**, 171, 1977; Simpson J. B. and Mangiapane M. L. A pharmacological analysis of cholinergic and peptidergic drinking at the subfornical organ. *Soc. Neurosci. Abstr.* **III**, 166, 1977; Epstein A. The neuroendocrinology of thirst and salt appetite. In *Frontiers in Neuroendocrinology* (Edited by Ganong W. F. and Martini L.), Vol. 5, pp. 101–134, 1978; Fitzsimons J. T. *The Physiology of Thirst and Sodium Appetite*. Cambridge Univ. Press, Cambridge, 1979; Guyton

- A. C. *et al.* Salt balance and long term blood pressure control. *Ann. Rev. Med.* **31**, 15, 1980.
27. Cannon W. B. *Bodily Changes in Pain, Hunger, Fear and Rage: An Account of Recent Researches into the Function of Emotional Excitement*, 2nd edn. Appleton, New York, 1929.
 28. Selye H. *The Physiology and Pathology of Exposure to Stress*. Acta. Montreal, 1950; Selye H. *Stress of Life*. McGraw-Hill, New York, 1956.
 29. There is recent evidence, for example, that the mechanism for maintaining the normal rhythm of the heartbeat may require catecholamines (epinephrine, norepinephrine). See Pollack G. H. Cardiac pace-making: an obligatory role of catecholamines. *Science* **196**, 731, 1977.
 30. Mason J. W. Organization of endocrine mechanisms. *Psychosom. Med.* **30**, 565, 1968; Mason J. W. A re-evaluation of the concept of "nonspecificity" in stress theory. *J. Psychiat. Res.* **8**, 323, 1971; Mason J. W. Organization of psychoendocrine mechanisms. In *Handbook of Psychophysiology* (Edited by Greenfield N. S. and Sternbach R. A.). Holt, Rhinehart & Winston, New York, 1972.
 31. Robertson, *op. cit.*, [20].
 32. Aw W. Y. Cortisol stimulation of parathyroid hormone secretion by rat parathyroid glands in organ culture. *Science* **193**, 1015, 1976.
 33. Golde D. W., Bersch N. and Li C. H. Growth hormone: species-specific stimulation of erythropoiesis *in vitro*. *Science* **196**, 1112, 1977. At the same time as erythropoiesis is stimulated, catabolic hormones, such as cortisol, suppress production of white blood cells (Selye, *op. cit.*). There is also a mutual hormonal inhibition between these two kinds of cells in terms of production: hormones, such as erythropoietin, that stimulate red blood cell production, suppress white blood cell production, and vice versa: Van Zant G. and Goldwasser E. Simultaneous effects of erythropoietin and colony-stimulating factor on bone marrow cells. *Science* **198**, 733, 1977.
 34. Wurtman, *op. cit.*, [20].
 35. This figure is the average pressure of human populations which are relatively little disturbed by modern society. All groups and diets are represented in these populations, so one cannot attribute the low pressures to a particular set of genes or to avoidance of a particular dietary substance. In particular, the black tribes in Africa from which New World slaves originated have markedly lower blood pressure than contemporary American blacks, whether urban or rural. In general, the genetic factor contributes less than 20% of the variance in blood pressure observed in populations for which inheritance has been closely studied. See Eyer J. Hypertension as a disease of modern society. *Int. J. Hlth Serv.* **5**, 539, 1975. High salt consumption (20 grams per day, among Thai Buddhist farmers) is compatible with low blood pressures: Henry J. P. and Cassell J. C. Psychosocial factors in essential hypertension: recent epidemiologic and animal experimental evidence. *Am. J. Epidemiol.* **90**, 171, 1969. E. Marshall Thomas reports that the Kung, who have among the lowest of recorded population blood pressures, also salt their food heavily: *The Harmless People*. Vintage, New York, 1959. This was recently denied by Truswell and Hansen (see "Medical Research Among the Kung" in Lee and Devore (1976) cited in [3]) based not on behavioral observations but on measurements of urinary output of sodium by the Kung. This method ignores the fact that the Kung live in a hot, dry environment and must excrete a major part of their sodium via perspiration. Indeed, it is hard to imagine that survival could be possible in such an environment without a relatively high level of salt intake. The most important social correlate of blood pressure yet identified is the degree of involvement in a money economy. This correlation remains strong and significant even after controlling for salt consumption and, in men, for body weight. Waldron I. A quantitative analysis of cross-cultural variation in blood pressure and serum cholesterol. *Psychosom. Med.* **41**, 582, 1979.
 36. The effect on the thymus, a major organ of the immune system, and on white cell and antibody production, is mediated in part, as Selye showed, by cortisol. There is evidence, however, that the brain, particularly the hypothalamus, has major influences on the immune system via a variety of other mechanisms as well: Stein M., Schiavi R. C. and Camerino M. Influence of brain and behavior on the immune system. *Science* **191**, 435, 1976. The elevation of cortisol, for instance, not only causes a shrinkage of the thymus and a decrease in the production of potentially reactive new T-cells (small lymphocyte precursors), but it also inhibits the inflammatory process, thus preventing the "walling off" of large bacteria or cancer cells by fibroblasts as well as other healing-repair processes. The elevation of epinephrine and norepinephrine inhibits the proliferation of both T and B cell precursors into active immunocytes (small lymphocytes in the cellular system, plasmacytes in the antibody-producing system), the production of antibody and interferon, and the cytotoxic attack of small lymphocytes, as well as the activation of memory cells in secondary immunity: Bourne H. R., Lichtenstein L. M., Melmon K. L., Henney C. S., Weinstein Y. and Shearer G. M. Modulation of inflammation and immunity by cyclic AMP. *Science*, **184**, 19, 1974. The impact of sympathetic arousal on the blood and lymph circulation may also have important effects on immunity.
 37. Melatonin suppresses release of LH-RH and PRH from hypothalamus and LH from the pituitary: Martin J. E. and Klein D. C. Melatonin inhibition of the neonatal pituitary response to the luteinizing hormone releasing factor. *Science* **191**, 301, 1976; Brooks C., Ishikawa T. and Koizumi K. Autonomic system control of the pineal gland and the role of this complex in the integration of body function. *Brain Res.* **87**, 181, 1975.
 38. Felig P. and Wahrer J. Fuel homeostasis in exercise. *N. Engl. J. Med.* **293**, 1078, 1975.
 39. Weiss J. M. Psychological factors in stress and disease. *Scient. Am.* **226**, 104, 1972a. Weiss was, of course, careful to use animals who were littermates and who were reared together; also, the experiments were repeated with a sample large enough to eliminate the possibility that differences were due to individual genetic variation.
 40. Many authors since Selye have used the term "stress". Weiss, for example, speaks of the determinants of "stress" levels. We avoid this term, primarily because it signifies so many different things. "Stress" can refer either to the external environmental demand, or to the internal physiological responses or to the feelings that accompany coping. We prefer to distinguish as clearly as possible between internal and external events, between different levels of organization (physiological, psychological and social), and to focus on the processes by which these are interrelated. It is difficult to maintain clarity while employing a term for which there are many, idiosyncratic meanings.
 41. Selye, *op. cit.*; Weiss, 1972a *op. cit.*; Weiss J. M. Influence of psychological variables on stress-induced pathology. *Physiology, Emotion and Psychosomatic Illness*. Ciba Found. Symp. No. 8, pp. 253-265, 1972; Coover G. D., Ursin H. and Levine S. Plasma cor-

- ticosterone levels during active avoidance learning in rats. *J. comp. Physiol. Psychol.* **82**, 170, 1973; Hanson J. D., Larson M. E. and Snowdon C. T. The effects of control over high intensity noise on plasma cortisol levels in rhesus monkeys. *Behav. Biol.* **16**, 333, 1976.
42. See Mason J. W. A review of psychoendocrine research on the sympathetic-adrenal medullary system. *Psychosom. Med.* **30**, 631, 1968; Mason J. W. A review of psychoendocrine research on the pituitary-adrenal cortical system. *Psychosom. Med.* **30**, 576, 1968; Greene W. A., Conron G., Schalch D. S. and Schreiner B. F. Psychologic correlates of growth hormone and adrenal secretory responses in patients undergoing cardiac catheterization. *Psychosom. Med.* **32**, 599, 1970; Brown G. M. and Reichlin S. Psychologic and neural regulation of growth hormone secretion. *Psychosom. Med.* **34**, 45, 1972.
 43. See both articles by Mason and by Brown and Reichlin *op. cit.*, [42]; also Westlake P. T., Wilcox A. A., Haley M. I. and Peterson J. E. Relationship of mental and emotional stress to serum cholesterol levels. *Proc. Soc. exp. Biol. Med.* **97**, 163, 1958; Thomas C. B. and Murphy E. A. Further studies on cholesterol levels in the Johns Hopkins medical students: the effects of stress at examination. *J. chron. Dis.* **8**, 661, 1958; Grundy S. M. and Griffin A. C. Effects of periodic mental stress on serum cholesterol levels. *Circulation* **19**, 496, 1959; Grundy S. M. and Griffin A. C. Relationship of periodic mental stress to serum lipoprotein and cholesterol levels. *J.A.M.A.* **171**, 1794, 1959.
 44. Levi L. *Stress and Distress in Response to Psychosocial Stimuli*. Pergamon Press, New York, 1972. Frankenhauser and Gardell found that urinary epinephrine increased in sawmill workers in direct proportion to the speed and repetitiveness with which they were required to work and in inverse proportion to their subjective reports of "well-being". Urinary norepinephrine increased in direct proportion to restriction of their work posture, lack of control of work pace, and subjective "irritation": Frankenhauser M. and Gardell B. Underload and overload in working life: outline of a multidisciplinary approach. *J. Human Stress* **2**, 35, 1976.
- Robert Karasek has analyzed the data from a large Swedish longitudinal survey of jobs and health, and shown that two factors associated with the job strongly predict not only coronary heart disease and hypertension mortality, but death rates for many other causes as well. Job demand, including both intensity and novelty, is one dimension. The other is degree of decision-making power which the worker exercises over the work process and its demands. Jobs at the opposite extremes of risk on these two factors show a threefold difference in coronary heart disease death rates. See Karasek R. A., Baker D., Marxer F. and Theorell T. Job decision latitude, job demands and coronary heart disease—a cross sectional and prospective study of Swedish men. Mimeo, Columbia University, 1979.
45. Mason J. W. and Brady J. V. The sensitivity of psychoendocrine systems to social and physical environment. In *Psychobiological Approaches to Social Behavior* (Edited by Leiderman P. H. and Shapiro). Stanford Univ. Press, Stanford, 1964; Halberg F., Engeli M. and Hamburger C. The 17-ketosteroid excretion of a healthy man on weekdays and weekends. *Exp. Med. Surg.* **23**, 61, 1965; see also Mason's reviews, *op. cit.* [42].
 46. Kreuz L. E., Rose R. M. and Jennings J. R. Suppression of plasma testosterone levels and psychological stress. *Archs gen. Psychiat.* **26**, 479, 1972. Rose has shown a similar pattern for testosterone in rhesus monkeys: the hormone is elevated when the males are in an easy social situation and falls when they lose control by being decisively defeated by a large group of males: Rose R. M., Gordon T. P. and Bernstein I. S. Plasma testosterone levels in male rhesus: influences of sexual and social stimuli. *Science* **178**, 643, 1972. See also Sassenrath E. N. Increased adrenal responsiveness related to social stress in rhesus monkeys. *Horm. Behav.* **1**, 238, 1970.
 47. Friedman M., Rosenman R. H. and Carroll V. Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress. *Circ.* **17**, 852, 1958. See also Cassel J. The use of medical records: opportunity for epidemiological studies. *J. occup. Med.* **5**, 185, 1963, for an example of rises in serum cholesterol in workers with little opportunity for social interaction. Taggart and Carruthers have provided an additional example of elevated cholesterol and free fatty acids with emotional arousal and shown that it is dependent on increased sympathoadrenal medullary activity: Taggart P. and Carruthers M. Endogenous hyperlipidemia induced by emotional stress of racing driving. *Lancet* **1**, 363, 1971; Taggart P. and Carruthers M., Suppression by oxyprenol of adrenergic response to stress. *Lancet* **2**, 256, 1972. See also Mason, *op. cit.* [42], for reviews of the early literature on this subject.
 48. Kasl S. V. and Cobb S. Blood pressure changes in men undergoing job loss: a preliminary report. *Psychosom. Med.* **32**, 19, 1970.
 49. Brown and Reichlin, *op. cit.* [42].
 50. Greene, *et al.*, *op. cit.* [42].
 51. Funkenstein originally suggested that norepinephrine increases with outwardly directed anger and epinephrine with anger directed inward: Funkenstein D. H. Norepinephrine-like and epinephrine-like substances in relation to human behavior. *J. ment. Dis.* **124**, 58, 1956. Henry and Stephens (*op. cit.* [18]) have reviewed recent work along these lines with some sympathy. In addition, these authors suggest a dichotomy between the sympatho-adrenomedullary system which, they argue, is controlled by the amygdala, part of the brain's limbic system, and the hypothalamo-pituitary-adrenocortical system, which they suppose to be under control of the hippocampus, another part of the limbic system. In this excellent review, Henry and Stephens pay a great deal of attention to the differential responses of these two systems. They argue that the former is for "fight-flight" when those behaviors are possible, and that the latter is for physiological regulation when "control of the territory...when old patterns of responding fail to pay off..." (p. 140). They view the pituitary-adrenal response as a part of a "depressive" response to loss of control and marshal much fascinating evidence in support of their thesis.
- Their review tends to focus on the behavioral dimensions of territoriality, competition and dominance-subordinate behavior and tends to interpret *all* behavior as distributed along these dimensions. As a consequence, they tend to minimize the instances where catecholamines (epinephrine and norepinephrine) are secreted *simultaneously* with cortisol and minimize the well known synergistic effects of cortisol on the action of the catecholamines.
- We explain elsewhere why we think it a mistake to divide the brain, as they have, assigning particular behaviors to particular parts: Sterling P. Principles of central nervous system organization. In *Biological Bases of Psychiatric Disorders* (Edited by Fraser A. and Winokur A.). Spectrum, New York, 1977; Sterling P. Ethics and effectiveness of psychosurgery. In

Controversy in Psychiatry (Edited by Brady J. P. and Brodie H. K.). Saunders, Philadelphia, 1978.

- It is equally a mistake, we think, to assign to particular hormones responsibility for particular emotions or behaviors. Hormones cause particular metabolic and physiological responses which may be associated with a variety of emotions and behaviors, depending on the context. The context is simply too rich and our measurements of the hormonal patterns under different circumstances too impoverished to adopt such a narrow focus. We wish to leave no doubt, however, that we recognize the rich possibilities, some of which have been demonstrated, for differential responsiveness of the catecholamine and pituitary-adrenocortical systems. See also Mason J. W., Maher J. T., Hartley L. H., Mougey E. H., Perlow M. J. and Jones L. G. Selectivity of corticosteroid and catecholamine responses to various natural stimuli. In *Psychopathology of Human Adaptation* (Edited by Serban G.), pp. 147-171. Plenum, New York, 1976.
52. Wadeson R. W., Mason J. W., Hamburg D. A. and Handlon J. H. Plasma and urinary 17-OH-CS responses to motion pictures. *Archs gen. Psychiat.* **9**, 146, 1963; Levi L. The urinary output of adrenalin and noradrenalin during pleasant and unpleasant emotional states. *Psychosom. Med.* **27**, 80, 1965.
 53. Wolfe C. T., Friedman S. B., Hofer M. A. and Mason J. W. Relationship between psychological defenses and mean urinary 17-hydroxycorticosteroid excretion rates. I. A predictive study of parents of fatally ill children. II. Methodologic and theoretical considerations. *Psychosom. Med.* **26**, 592, 1964.
 54. Hofer M. A., Wolfe C. T., Friedman S. B. and Mason J. W. A psychoendocrine study of bereavement. Part I. 17-hydroxycorticosteroid excretion rates of parents following death of their children from leukemia. *Psychosom. Med.* **34**, 481, 1972a; Hofer M. A., Wolfe C. T., Friedman S. B. and Mason J. W. A psychoendocrine study of bereavement. Part II. Observations on the process of mourning in relation to adrenocortical function. *Psychosom. Med.* **34**, 492, 1972b.
 55. Depression, which Freud described as an essential part of grieving, may be accompanied by extremely high levels of cortisol. Thus, although the behavioral manifestations of depression differ markedly from the "fight/flight" type of arousal, the endocrinological manifestations may be similar. Wyatt R., Portnoy B., Kupfer D., Snyder F. and Engelmann K. Resting plasma catecholamine concentration in patients with depression and anxiety. *Archs gen. Psychiat.* **24**, 65, 1971.
 56. Friedman M. *Pathogenesis of Coronary Artery Disease*, p. 86. McGraw-Hill, New York, 1969.
 57. Rosenman R., Friedman M., Straus R., Jenkins C., Zyzanski S. and Wurm M. Coronary heart disease in the Western Collaborative Group Study: a follow-up experience of 4½ years. *J. chron. Dis.* **23**, 173, 1970.
 58. Eyer J. and Sterling P., *op. cit.* [9]; see also Braverman H. *Labor and Monopoly Capital. The Degradation of Work in the Twentieth Century*. Monthly Review Press, New York, 1974.
 59. McClelland D. *The Achieving Society*. Van Nostrand, New York, 1961.
 60. Waldron I. Why do women live longer than men? *Soc. Sci. Med.* **10**, 349, 1976.
 61. United States Department of Health, Education and Welfare, Public Health Service, National Center for Health Statistics. *Vital Statistics of the United States 1970*, Vol. II. Mortality part A. Tables 1-8. U.S. Government Printing Office, Washington, D.C. 1974.
 62. Kannel W. Some lessons in cardiovascular epidemiology from Framingham. *Am. J. Cardiol.* **37**, 269, 1976.
 63. Kannel W. B. and Sorlie P. Hypertension in Framingham. In *Epidemiology and Control of Hypertension* (Edited by Paul O.), pp. 553-592. Symposia Specialists, Miami, 1975.
 64. Stamler J. *The Hypertension Handbook*. Merck, Sharpe & Dohme, West Point, 1974. *Info memo*, prepared by NHBPEP (NHLBI), May 1978 (No. 13).
 65. Pickering G. Hypertension. Definitions, natural histories and consequences. *Am. J. Med.* **52**, 570, 1972.
 66. Blumenthal S. *et al.* Report of the task force on blood pressure control in children. *Pediatrics* **59**, Suppl. 797, 1977.
 67. Guyton A. C. *et al.*, *op. cit.* [26]. These authors state: "hypertension caused by any factor that does not cause a simultaneous change in kidney function will be self correcting. This logic implies that the kidney must become a salt-retaining organ; otherwise the state of long-term salt-loading hypertension cannot occur". In searching for the reason why the kidney becomes a salt-retaining organ, the authors ignore the massive evidence the task is accomplished by the rich, arousal-sensitive neuro-endocrine mechanisms we have cited (cf. [26]).
 68. Louis W. J., Doyle A. E. and Anavekar S. Plasma norepinephrine levels in essential hypertension. *N. Engl. J. Med.* **288**, 599, 1973; Engelman K., Portnoy B. and Sjoerdsma A. Plasma catecholamine concentrations in patients with hypertension. *Circ. Res.* **27**, Suppl. I, 1-141, 1970; De Quattro V. and Chan S. Raised plasma catecholamines in some patients with primary hypertension. *Lancet* **1**, 806, 1972; Geffen L. B., Rush R. A. and Louis W. J. Plasma dopamine β -hydroxylase and noradrenaline amounts in essential hypertension. *Clin. Sci.* **44**, 617, 1973; De Quattro V., Miura Y. and Lurvey A. Increased plasma catecholamine concentrations and vas deferens norepinephrine biosynthesis in men with elevated blood pressure. *Circ. Res.* **36**, 118, 1975; De Champlain J., Farley L. and Cousineau D. *et al.* Circulating catecholamine levels in human and experimental hypertension. *Circ. Res.* **38**, 109, 1976.
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Similarly, an enlarged thymus in children was baselessly considered pathological by many doctors since the beginning of the 20th century. At first this condition was treated by surgical removal of the thymus, and from the 1930's through the 1950's, millions of infants and children were treated by X-irradiation for this condition. A high rate of thyroid cancers has now been identified in persons previously irradiated for this condition. Favus M., Schneider A. and Stachura M. *et al.* Thyroid cancer occurring as a late consequence of head and neck irradiation. *N. Engl. J. Med.* **294**, 1019, 1976. In the light of present knowledge on the essential role of the thymus in cell mediated immunity (see [112]), it could be anticipated that these children should also develop higher rates of cancer and other diseases regulated by the immune system in later life.

By now it should seem quite predictable that interfering in any significant way with a complex biological system will produce, sooner or later, untoward and often unanticipated effects.

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151. In addition to its antihypertensive use, propranolol has come into very wide use as an antianginal agent in combination with the nitrates. Many in the medical community now believe that propranolol in this use goes beyond symptomatic relief to reduce the incidence of subsequent myocardial infarction. As no double-blind placebo-controlled trials have yet been reported (though several are underway), it is impossible to fully evaluate the evidence usually adduced to support this belief. For example, the studies by the Goteborg group in Sweden comparing treated and untreated individuals are interpreted as showing that medical care, including hypotensive treatment with propranolol, can postpone C.H.D. in patients with mild to moderate hypertension. See Svardsudd K., Berglund G. and Tibblin G. Morbidity and mortality in untreated and treated hypertension: results from the Goteborg 50-year-old men study. *Drugs* **11**, Suppl. 1, 34, 1976. A more recent report of ongoing experience in a large treatment versus nontreatment trial by the same group notes "the lack of a placebo-treated control group makes interpretation of the findings hazardous. Although we have tried to take into account as many influencing factors as possible, this cannot entirely make up for the fact that the trial was not primarily designed to answer the question at which we have directed our analysis; yet these results suggest that antihypertensive treatment might have a substantial impact on the incidence of coronary heart diseases". Berglund G., Sannersfedt R., Andersson O., Wedel H., Wilhelmson L., Hansson L., Silvertsson R. and Wikstrand J. Coronary heart disease after treatment of hypertension. *Lancet* **1**, 1, 1978.
- The absence of a placebo control is not the only difficulty with these studies. For example, the authors of the second study mentioned above focus on the large difference in fatal and nonfatal C.H.D. found between a group (D) with initially high blood pressure on screening who were subsequently left untreated, and a second group (C) which was brought under antihypertensive drug treatment as a result of detection in this screening. However, there is a third group (E) of people already under treatment for hypertension, whose average blood pressure was lower at initial screening, reflecting control by the drugs. This group had higher heart disease mortality rates than the nontreated control (cf. Table 3 and Fig. 1). It is certainly debatable whether the group only recently brought under drug treatment, or the group which has been treated for a long time, represent better the prospects for the impact of propranolol and other antihypertensives on C.H.D.
- In addition, the "untreated control" group (C) had an excess over the recently treated group (D) not only in cardiovascular disease, but even more so in cancer and other causes of death on which it is very unlikely that propranolol or other antihypertensives have any impact. This raises the serious possibility that the "untreated control" group (C) is weighted with high risk individuals, a possibility the authors mention in their text at one point and gloss over at another by comparing only age, blood pressure, serum cholesterol, and smoking habits between the various groups. In light of these difficulties it is impossible to credit the objectivity of the studies.
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163. The PHS authors report the size of the whole group initially passing the screen (1600 with $90 < \text{dbp} < 115 \text{ mmHg}$), the number of those excluded for other reasons prior to the placebo pretrial period (505), the number whose blood pressure fell below 90 mmHg (d) over several days after the initial screening but before tablet placebo pretrial (352), and the number whose blood pressure fell below 90 mmHg(d) when placed on tablet placebo (282) for three months. They also report the mode (140-49/90-95) and other details of the distribution (79.1% fall within the range 90-105 mmHg diastolic) of blood pressure of the group (422) finally admitted to the trial. With this information and the fact that 39 individuals experienced a pressure rise above 115 mmHg diastolic during the pretrial period, it is possible to graphically reconstruct the approximate behavior of the whole blood pressure distribution during the postscreening pretrial period. See United States Public Health Service Hospitals Cooperative Study Group, Morbidity and mortality in mild essential hypertension. *Circ. Res.* 30 and 31, Suppl. II, II-110 to II-124, 1972, especially Table 2 and pages 111, 112, and 114.
- This reconstruction has two parts. First, there is a reconstructed distribution for the tablet placebo pretrial period, consisting of the finally admitted group (422), those whose blood pressure rose above 115 mmHg (d) (39), and those whose pressures fell below 90 mmHg (d) during the 3 month placebo period (282). If the latter are drawn as a smooth continuation of the lower end of the (skewed) distribution of the finally admitted group, if most individuals falling below 90 mmHg (d) end up between 85 and 90 mm, and all between 75 and 90 mm, and if the initial preexclusion group's blood pressure distribution is the same *shape* as the final distribution reconstructed as above, but falling within the initial screening blood pressure limits [90-115 mmHg (d)], then the average blood pressure for the total group (743) undergoing pretrial placebo treatment is about 6.4 mmHg. These are conservative assumptions; the actual decline may have been larger.
- The tablet placebo treatment is not the only placebo effect recorded in these pretrial data, however. 352 additional individuals showed a decline below 90 mmHg (d) in the first few days after screening, when they were presumably aware that they were potential recipients of special care for their condition. Of this group the PHS authors say "we have followed this group to see how many of them subsequently would qualify or develop the need for therapy and it has been a very insignificant, low number." See p. 481 in Smith W. M. *et al.* Intervention trial in mild hypertension. U.S. Public Health Service Hospitals Cooperative Study Group. In *Epidemiology and Control of Hypertension* (Edited by Paul P.), p. 461. Symposia Specialists, Miami, 1975. This group may be understood in at least two ways. They might be people who experienced an extraordinary elevation of blood pressure on being screened for possible admission to the trial but subsequently returned to their usual pressure range. Or they might be a group of exceptionally placebo-responsive subjects who respond to brief medical attention and long term follow-up with a significant decline in blood pressure. If we adopt the latter interpretation, these individuals add to the whole group of placebo responders, now numbering 634, out of a larger total of 1095. Using the graphic reconstruction outlined above, the average decline in blood pressure for this larger total group treated with a medical placebo in some way is 9.6 mmHg.
164. The published information on the second series of VA studies [144] only notes that the eliminated placebo responder group was "large". In the reports on the first series of VA studies conducted in the mid-1950's, however, additional information is given on pretrial exclusions. Of those hypertensive on admission, roughly 35% were excluded from the subsequent trial because their diastolic pressure fell below 90 mmHg in the first few days. The corresponding figure for the PHS study [145] was 352/1095 or 32%. It would therefore not be surprising if the proportion of tablet placebo responders subsequently excluded in the VA pretrial was similar to that in the PHS study. See p. 82 in Veterans Administration Cooperative Study on Antihypertensive Agents. A double-blind control study of antihypertensive agents. *Archs intern. Med.* 106, 81, 1960.
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