Chapter 3
The Link from Stress Arousal to Disease

The notion that one's psychosocial environment, lifestyle, and attitudes are linked to disease is by no means a new idea, as discussed in Chap. 1. In a scholarly meta-analysis, Tower (1984) reviewed 523 published reports investigating the relationship between psychosocial factors and disease. Ultimately selecting 60 of those studies on the basis of design considerations, she then submitted the data to a meta-analysis. The results supported the conclusion that there exists a strong relationship between psychosocial factors and illness. She notes, "Psychological well-being appeared to be most strongly associated with coronary heart disease and infectious processes … although it was significantly associated with all diseases [investigated] except complications of pregnancy" (p. 51). To assess the power of her findings, Tower calculated the number of fugitive studies required to reject the findings of her meta-analysis. The results of this analysis of outcome tolerance revealed that over 28,000 fugitive studies would be required to reject the conclusion that psychosocial factors are related to disease. More recently, researchers have studied the link between psychosocial factors and heart disease (Low, Thurston, & Matthews, 2010), depression (Bonde, 2008) and even musculoskeletal pain (Macfarlane et al., 2009).

In the tradition of Pasteur, however, in order for a stimulus to be recognized as being a credible cause or contributor to disease, the pathophysiological processes that culminate in target-organ disease and dysfunction (sometimes called *mechanisms of mediation*) must be understood. Chapter 2 reviewed a model by which a *stressor* may activate *stress-response mechanisms*. That chapter further detailed potential stress-response effector mechanisms that might undergird such pathogenic relationships as confirmed by Tower (1984). The chapter offered evidence that an aggregation of neural, neuroendocrine, and endocrine response axes, collectively referred to as the *stress response*, were indeed vulnerable to extraordinary activation upon exposure to psychosocial stimuli. This chapter examines the logical extension of stress physiology by reviewing several noteworthy models of target-organ pathogenesis, that is, those proposed factors that link *stress arousal* mechanisms, once they are activated, to *target-organ disease.*

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Although the literature in psychosomatic phenomenology as a global concept is voluminous, relatively few models exist that concern themselves more directly with the link between extraordinary arousal of the stress axes and the ultimate manifestations of stress-related disease. Let us take this opportunity to review several of those models.

Selye's "General Adaptation Syndrome"

In Chap. 2, Selye's General Adaptation Syndrome (GAS) was introduced as a means of integrating the manifestations of the stress response as a sequential series of physiological events. Its triphasic constituency was described at that point: (1) the alarm stage, (2) the stage of resistance (adaptation), and (3) the exhaustion stage. The GAS is mentioned in the present chapter because, not only does it serve to integrate, from a temporal perspective, many of the stress axes described earlier, but it also serves to explain the link from stress arousal to disease. As described by Selye (1956), Stage 1 of the GAS involves a somatic "shock" and initial "alarm reaction" for biological sources within the body following exposure to a stressor. The insult to the bodily tissues during this acute alarm phase could be so great as to deprive the target organ of its ability to compensate. If this happens, as might occur in cases of burns, electrical shock, or acute psychological trauma, the target organ may simply cease to function (e.g., in the case of cardiac fibrillation). Thus, the target organ will have been traumatically exhausted and rendered incapable of further functioning. Serious illness or death may then result.

If, however, the resources of the body are not completely compromised as a result of the "alarm" phase, then the stage of resistance is entered. Here the body's resources are mobilized to reestablish homeostasis. This is what usually occurs in most stress-related conditions. Yet, in order to maintain homeostasis in the face of a persistent stressor, there is a chronic drain of "adaptive energy," that is, physiological resources. Should the stressor persist indefinitely (even in the form of cognitive rumination) or should Stages 1 and 2 recycle themselves too frequently, eventual exhaustion of the target organ is predicted. This is the third and final stage in Selye's schema, the exhaustion phase. Thus, stress-related disease manifestation would occur as a result of a depletion of adaptive physiological resources and the subsequent target-organ exhaustion would be considered a result of excessive "wear and tear" (Selye, 1974). This then is the GAS as it attempts to define the stress-to-disease process. The GAS has been criticized for its global generality and lack of sensitivity for physiological response specificity (Mason, 1971).

In Selye's original exposition, he states, "It seems to us that more or less pronounced forms of this three-stage reaction represent the usual response of the organism to stimuli such as temperature changes, drugs, muscular exercise, etc., to which habituation or inurement can occur" (1936, p. 32). Yet subsequent researchers

such as Mason (1971) argued that the stress response and subsequent target-organ pathology may indeed be rather specific, rather than generalized, pathogenic processes. This was a point with which Selye would have to contend for the rest of his career.

Given that Selye's important formulations were from the perspective of an endocrinologist more interested in pathogenic mechanisms than target-organ pathology per se, later writers in the emerging field of psychosomatic medicine would greatly elaborate upon the link from stress arousal to stress-related disease. Those mechanisms we consider most important are summarized below.

Lachman's Model

In a "behavioral interpretation" of psychosomatic disease, Lachman (1972) proposes an "autonomic learning theory" that emphasizes:

> … the role of learning in the development of psychosomatic aberrations without minimizing the role of genetic factors or of nongenetic predisposing factors. The essence of the theory proposed is that psychosomatic manifestations result from frequent or prolonged or intense … reactions elicited via stimulation of receptors. (pp. 62–63)

Lachman argues that a major source of frequent, prolonged, or intense emotional and physiological reactions is a *learned* pattern of emotional and autonomic responsiveness. More specifically, he notes with regard to the stress-to-disease phenomenon, "In order for emotional reactions to assume pathological significance such reactions must be intense or chronic or both" (p. 70). He goes on to state that which end-organ structure will be affected pathologically depends on the following:

1. Genetic factors that biologically predispose the organ to harm from psychophysiological arousal.
2. Environmental factors that predispose the organ to harm from psychophysiological arousal, including such things as nutritional influences, infectious disease influences, physical trauma influences, and so on.
3. The specific structures involved in the physiological reactivity.
4. The magnitude of involvement during the physiological response, which he has defined in terms of intensity, frequency, and duration of involvement of the organ.

Lachman (1972) concludes that the determination of which structure is ultimately affected in the psychosomatic reaction depends on "the biological condition of the structure" (whether a function of genetic or environmental influences), "on the initial reactivity threshold of the organ, and on … learning factors" that affect the activation of the organ. He goes on to note that the "magnitude of the psychosomatic phenomenon" appears to be a function of the frequency, intensity, and chronicity of the organ's activation.

Sternbach's Model

In a somewhat more psychophysiologically oriented model, Sternbach (1966) provides another perspective on the stress-to-disease issue, which is considered a variation on the diathesis–stress model of Levi and Andersson (1975).

The first step in Sternbach's model is *response stereotypy*. This term generally refers to the tendency of an individual to exhibit characteristically similar patterns of psychophysiological reactivity to a variety of stressful stimuli. Sternbach views it as a "predisposed response set." That such a response stereotypy phenomenon does indeed exist has been clearly demonstrated in patient and normal populations (Lacey & Lacey, 1958, 1962; Malmo & Shagass, 1949; Moos & Engel, 1962; Schnore, 1959).

Response stereotypy may be generally thought of as a form of the "weak-link" or "weak-organ" theory of psychosomatic disease. Whether the weak organ is genetically determined, a function of conditioning, or acquired through disease or physical trauma is unclear.

The second step in the Sternbach model entails the frequent activation of the psychophysiological stress response within the stereotypical organ. The mere existence of response stereotypy is not enough to cause disease. It is obvious that the organ must be involved in frequent activation in order to be adversely affected.

Finally, Sternbach's model includes the requirement that homeostatic mechanisms fail; that is, once the stereotypical organ has undergone psychophysiological arousal, that stress-responsive organ must now evidence slow return to baseline level of activity. Such homeostatic failure has been implicated in the onset of disease since the work of Freeman (1939). Freeman advanced the theory that autonomic excitation that is slow to deactivate from an organ system does increase the strain on that system. Malmo, Shagass, and Davis (1950) empirically demonstrated that such a phenomenon exists. Lader's (1969) review on this issue implicates it as a potential precursor to disease.

Sternbach (1966) has then put forward these conditions as prerequisites for the development of a stress-related disorder. The reader is referred to the work of Stoyva for further commentary on the Sternbach model, as well as other theories of psychosomatic illness (Stoyva, 1976, Stoyva & Budzynski, 1974).

Kraus and Raab's "Hypokinetic Disease" Model

In their treatise on exercise and health, Kraus and Raab (1961) argue that many stress-related diseases are induced not so much by the direct physiology of the stress response, but by the lack of subsequent somatomotor expression of that physiology. They argue that a little over 100 years ago, vigorous physical labor was a way of life that actually served as a protective mechanism against diseases commonly referred to today as "diseases of civilization." These authors suggest that modern sedentary

lifestyles have put that protective mechanism "all but out of commission." Kraus and Raab (1961) conclude:

> The system that has been put all but out of commission, the striated musculature … has an important role which exceeds the mere function of locomotion. Action of the striated muscle influences directly and indirectly circulation, metabolism, and endocrine balance. … Last but not least the striated muscle serves as an outlet for our emotions and nervous responses .... Obliteration of [this] important safety valve … might well upset the original balance to which the bodies of primitive man have been adapted. (p. 4)

Therefore, Kraus and Raab coined the term "hypokinetic disease" (*hypo* = under; *kinetic* = motion/exercise) to refer to a wide array of diseases that as a result of the lack of healthful expression/utilization of the physiological mechanisms of the stress response. The notion of the lack of physical activity serving as a risk factor for disease and dysfunction has been supported by the World Health Organization (Chavat et al., 1964), which concludes that suppression of somatomotor activity in response to stress arousal is likely to lead to increased cardiovascular strain.

Schwartz's "Disregulation" Model

Gary Schwartz, working at Yale University (1977, 1979), devised a general systems model of stress-related pathogenesis that revolves around homeostatic disregulation as its pathogenic core (see Fig. 3.1). He notes, "It follows directly from cybernetic and systems theory that a normally self-regulatory system can become disordered when communication … between specific parts of the system is … disrupted" (1979, p. 563).

> Schwartz (1977) describes his model:When the environment (Stage 1) places demands on a person, the brain (Stage 2) performs the regulatory functions necessary to meet the specific demands. Depending on the nature of the environmental demand on stress, certain bodily systems (Stage 3) will be activated, while others may be simultaneously inhibited. However,

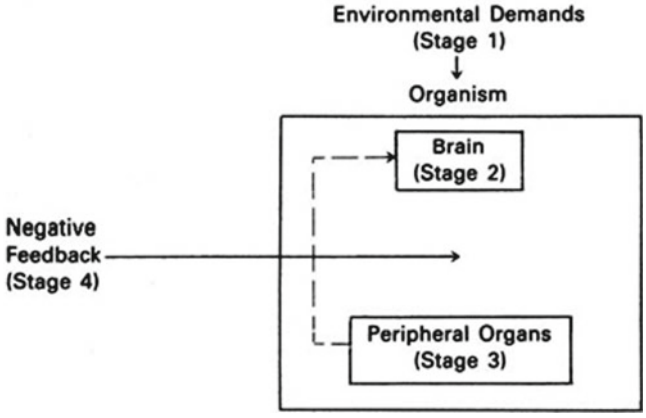

Fig. 3.1 Schwartz's model

> if this process is sustained to the point where the tissue suffers deterioration or injury, the negative feedback loops (Stage 4) of the homeostatic mechanism will normally come into play, forcing the brain to modify its directives to aid the afflicted organ. (p. 76)

Thus, the negative feedback loops described by Schwartz dominate the normal physiological milieu and are necessary to effective, adaptive functioning. Yet Schwartz argues that it is a *disregulation* in Stage 4 homeostatic mechanisms that may lead to a host of stress-related diseases through target-organ overstimulation. Overstimulation may occur by the creation of positive, self-sustaining feedback mechanisms or the blockage of natural inhibitory processes. Schwartz argues that disconnection of any feedback mechanism, from a systems view, is capable of leading to disregulation and thus to disease.

Congruent with the aforementioned model, therapeutic interventions would entail reestablishing homeostasis (homeostatic regulation). Consistent with this is Greengard's (1978) perspective based on the observation of physiological systems: "It seems probable that derangements of homeostatic processes are responsible for many disease states. Conversely, it seems likely that the effects of many therapeutic … agents are exerted on such homeostatic systems" (p. 146). Therefore, as one might expect, Schwartz sees biofeedback and other auto-regulatory therapies as useful agents for the treatment of stress-related disorders.

Conflict Theory of Psychosomatic Disease

Spawned in the formulative years of psychosomatic medicine, Alexander (1950) postulated that specific types of conflicts lead to specific types of physical illnesses. More specifically, specific psychical conflicts engendered specific mechanisms of physiological pathogenesis. The result was a specific target-organ illness. Several specific conflict–illness relationships were suggested:

Guilt → vomiting
Alienation → constipation
Repressed hostility → migraine headaches
Dependence → asthma

More recently, Harris (1991), using a specially designed psychometric instrument, the Life Events and Difficulties Schedule (LEDS), empirically investigated the relation between life events and illness. The following relations emerged:

Long-term threat and loss → depression
Danger → anxiety
Goal frustration → gastrointestinal disorders and Coronary artery disease
Major challenge → amenorrhea or dysmenorrhea

With the possible exception of Rosenman and Friedman's (1974) Type A behavior pattern and its predictive relationship with premature coronary artery disease, the specific conflict approach to psychosomatic illness has not proven very predictive of any specific physical or psychological disorder.

Everly and Benson's "Disorders of Arousal" Model

The "disorders of arousal" model of pathogenesis (Everly & Benson, 1989) is a direct result of an integration of efforts from Harvard University to understand the mechanisms of pathogenesis in psychosomatic disorders (Everly, 1986) and the mechanisms active in the amelioration of such psychosomatic disorders (Benson, 1975, 1987, 1996).

It has been observed for over five decades that various technologies that could be used to induce a hypoarousal relaxation response were able to ameliorate, or at least diminish, the severity of a wide and diverse variety of diseases. Despite data supporting specific clinical and experimental effects for various stress-management methods (Lehrer, Carr, Sargunaraj, & Woolfolk, 1994; Lehrer, Woolfolk, & Sime, 2007), it also seems that the initiation of what Herbert Benson (1975) has called the "relaxation response" has virtually a generic applicability across a wide spectrum of stress-related, psychosomatic diseases. That observation led to an investigation of the source of the broad-spectrum therapeutic effect of the relaxation response as a way of understanding the disorders it was useful in treating. The investigation culminated in an analysis of common phenomenological mechanisms, that is, common denominators (latent), occurring across anxiety and stress-related diseases that would serve to homogenize such disorders.

Based upon an integration of the work of Goddard on "kindling" (Goddard & Douglas, 1976), Post on "sensitization" (Post & Ballenger, 1981), Gellhorn on "ergotropic tuning" (1967), and Gray (1982) on the limbic system, it has been proposed by Everly that the phenomenology of many chronic anxiety- and stress-related diseases is undergirded by the existence of a latent, yet common denominator, existing in the form of a neurological hypersensitivity for excitation (or arousal) residing within the subcortical limbic circuitry (Everly, 1985b). This limbic hypersensitivity phenomenon (LHP) may be understood as an unusually high propensity for neurological arousal/excitation with the potential to lead to, or exist as, a pathognomonic state of excessive arousal within the limbic system. "Hyperstartle reaction," "autonomic hyperfunction," and "autonomic lability" are diagnostic terms commonly used to capture such a notion. The LHP is believed to develop as a result of either acutely traumatic or repeated extraordinary limbic excitation and is credited with the potential to ignite a cascade of extraordinary arousal of numerous and varied neurological, neuroendocrine, and endocrine efferent mechanisms (as discussed in Chap. 2) and, therefore, the potential to give rise to a host of varied psychiatric and somatic disorders. The subsequent disorders are then referred to as "disorders of arousal." This concept is captured in Fig. 3.2.

Figure 3.2 depicts the notion that, responsive to a host of widely disparate etiological factors (stressors) including environmental events, cognitive–affective dynamics, personologic predispositions, and the like, there exists a subtle, latent mechanism of pathogenesis: a neurological hypersensitivity for pathogenic arousal located within the limbic circuitry. Such arousal is believed to be capable of triggering a subsequent variety of physiological effector mechanisms (stress-response axes)

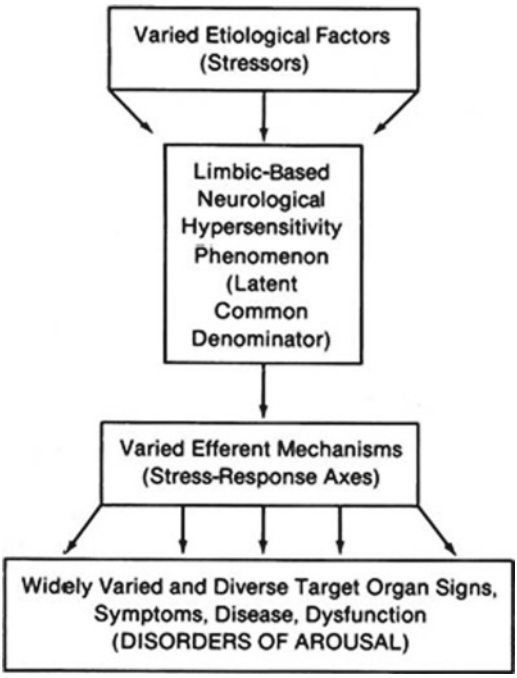

Fig. 3.2 Limbic hypersensitivity phenomenon: the latent taxon in stress-related "disorders of arousal"

within existing patterns of response predisposition (response stereotypy), so as to ultimately give rise to a wide and diverse spectrum of target-organ disorders (disorders of arousal). Included in the disorders of arousal taxonomy would be most anxiety and adjustment disorders, including some forms of depression, as well as virtually any and all stress-related physical disorders. The disorders of arousal will be enumerated in greater detail later in this volume. The reader may also refer to Everly and Benson (1989), Doane (1986), and Post (1986).

The natural corollary of the disorders of arousal model of pathogenesis is the notion that effective treatment of such disorders is highly related to reducing the subcortical hypersensitivity through the use of some "antiarousal" therapy. In addition to various pharmacological interventions, Benson's concept of the relaxation response represents a natural antiarousal phenomenon that appears antithetical to the mechanisms that undergird the disorders of arousal. Thus, it may well be that a major source of the broad-spectrum therapeutic effect exhibited by the relaxation response resides in the homeostasis-seeking, antiarousal phenomenology of the relaxation response, which serves to inhibit the mechanism of limbic hypersensitivity believed to exist as a common denominator among the various disorders of arousal.

In summary, the disorders of arousal model of stress-induced pathology recognizes the influences of environmental factors, cognitive–affective dynamics, patterns of previous learning, and patterns of preferential psychophysiological excitation as described in previous models and summarized elsewhere (Everly, 1986). Yet it

focuses upon the limbic system proper, its efferent influences on cognitive processes, and its effector mechanisms through the hypothalamus. More specifically, it focuses upon a proposed LHP, developed as a result of extraordinary limbic excitation, as key constituents in linking the stress response to stress-related disease formation, especially chronic manifestations of such diseases.

Several different theories have been enumerated here to explain how psychophysiological arousal can be channeled to affect target organs adversely. Despite the disparity between the theories mentioned, there does appear to be one element, either directly stated or implied, that is common to all. That commonality pertains to how the target organs ultimately become dysfunctional or pathological—simply stated, if any given target organ is subjected to psychophysiological overload (overstimulation) for a long enough period, that organ will eventually manifest symptoms of dysfunction or pathology due to excessive "wear and tear," be it biochemically induced trauma or toxicity, or actual visceromotor fatigue or exhaustion. According to Stoyva (1976) in his review of stress-related disorders, "A number of investigators have hypothesized that if the stress response is evoked too often, or sustained for too long, then disorders are likely to develop" (p. 370). In a "behavioristic interpretation" of psychosomatic disorders, Lachman (1972) states, "The longer a given structure is involved in an ongoing emotional reaction pattern, the greater is the likelihood of it being involved in a psychosomatic disorder" (pp. 69–70). Lachman concludes, "Theoretically, any bodily structure or function can become the end focus of psychosomatic phenomena—but especially those directly innervated and regulated by the autonomic nervous system" (p. 71).

Perhaps of greater interest to the clinician than the theory concerning what causes a target-organ symptom to be overloaded is the widely accepted conclusion that target-organ stress-related diseases result from excessively frequent, intense, and/or prolonged activation, that is, overstimulation (see Everly, 1986; Everly & Benson, 1989; Kraus & Raab, 1961; Lachman, 1972; Sternbach, 1966; Stoyva, 1976; Stoyva & Budzynski, 1974). See Table 3.1.

Summary

Chapter 2 described a mechanism by which psychosocial factors could serve to ignite extraordinary arousal of the physiological stress-response axes through cognitive–affective integrations and limbic–hypothalamic neurological mechanisms. This chapter pursued the logical extension of stress–axis arousal by reviewing the pathogenic mechanisms that are postulated to link the stress response to subsequent target-organ disease. Let us review the main points covered in this review.

1. All major theories agree that target-organ pathology ultimately results when the specific target organ is overstimulated. Overstimulation may occur as a result of excessively frequent, chronic, or intense stimulation. Pathological states emerge from excessive "wear and tear" on the target organ and can be caused by

Table 3.1 From stress to disease: theories of psychosomatic pathogenesis

Theory	Pathogenic mechanisms	Result
Selye's "General Adaptation Syndrome"	Triphasic fluctuation of neuroendocrine and endocrine mechanisms, especially ACTH. The chronic maintenance of the stage of resistance yields a depletion of adaptive energy	Depletion of adaptive physiological energy → exhaustion → disease, due to excessive wear and tear
Lachman's "behavioral" model	Biological and learned factors interact to establish predisposing patterns of target-organ arousal and disease from excessively frequent stress arousal. Emotional and autonomic learning play a major role in repeated target-organ excitation	Excessively intense or excessively chronic activation of target organs → stress-related disease (excessive wear and tear)
Sternbach's model	Response stereotypy. Frequent stress arousal. Homeostatic recovery failure	Frequent target-organ activation → organ fatigue and pathology
Kraus and Raab's "hypokinetic disease" model	Suppression of somatomotor behavior. Failure to ventilate and utilize the stress response once activated. Increased pathogenic risk	Target-organ overload and pathology
Schwartz's "disregulation" model	Failure in homeostatic feedback mechanisms following stressor exposure	Target-organ overload and pathology
Conflict theory	Specific psychic conflicts lead to specific physical illnesses	Target-organ overload and pathology
Everly and Benson's "disorders of arousal" model	Limbic hypersensitivity phenomenon causing extraordinary arousal of stress response axes	Excessively intense and/or excessively frequent or chronic activation of stress response axes → target-organ overstimulation and pathology

biochemical toxicity or trauma (e.g., necrosis) as well as structural alteration and visceromotor fatigue or exhaustion.

2. The GAS of Selye presents a triphasic model by which acute "shock" or chronic excitation could ultimately deplete the physiological constituents that normally allow target organs to continue to function in the face of stress arousals. The results would be target-organ exhaustion and perhaps even death.
3. Lachman's behavioral model emphasizes the point that emotional and autonomic responses could be learned. Interacting with other biological factors that are not learned, emotional and autonomic learning can cause repeated target-organ excitation. Excessively prolonged, frequent, or intense target-organ stimulation may then lead to disease.
4. Sternbach's psychophysiological model cites response stereotypy, frequent arousal of stress-response axes, and homeostatic recovery delay as factors that

serve to exhaust target organs and lead to disease. Once again, the theme of overutilization emerges as the key pathogenic constituent.
5. Kraus and Raab's model emphasizes the role of suppressed somatomotor expression in the etiology of stress-related pathology. Such suppression leads to target-organ overstimulation, exhaustion, and ultimately disease.
6. Schwartz's "disregulation" model also accepts the overload/overstimulation concept, but emphasizes the role of faulty negative feedback mechanisms in the pathological etiology.
7. The conflict theory postulates that specific psychological conflicts lead to specific physical and/or psychological disorders. This is clearly the weakest of the major psychosomatic theories.
8. Finally, Everly and Benson propose a model that serves to unite stress-related illnesses on the basis of a LHP, that is, a sensitization (increased propensity for activation) of cognitive, affective, and stress-response efferents in the formulation of stress-related disease. It is proposed that excessively frequent, chronic, or intense activation of target organs based upon the limbic hypersensitivity could ultimately exhaust the target organ and lead to a stress-related disease.
9. Thus, we see that all theories of pathogenesis, while emphasizing different phenomenological aspects as to why target-organ overstimulation occurs, agree that, indeed, overstimulation and excessive wear of target organs lead to stress-related dysfunction and disease. Chapter 4 will review specific stress-related diseases commonly encountered in clinical practice.

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