INVITED REVIEW

THE PSYCHOLOGY IN PSYCHONEUROENDOCRINOLOGY

Holger Ursin

Department of Biological and Medical Psychology, University of Bergen, Aarstadveien 21, N-5009 Bergen, Norway

(Received 8 July 1998)

SUMMARY

This paper reviews the psychology (P) of psychoneuroendocrinology (PNE). The relationship between the P factors and the endocrine responses (E) is described within cognitive reformulations of stress theory and activation theory. The formulations are valid across species, including man. The emphasis is on acquired expectancies, which are assumed to determine the physiological response, including the E responses. The terms coping, helplessness, and hopelessness are defined, and related to other labels covering the same or similar phenomena. The implications of contemporary P theory for the typical PNE experimental situations are discussed. Finally, the PNE positions outlined in 1968 by Mason is revisited. The 30 years of PNE research that followed confirm and expand his conclusions. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords—Stress; Activation; Coping; Helplessness; Hopelessness.

INTRODUCTION

The technical possibilities of identifying and measuring biologically active molecules increase, almost by the day. There is a corresponding increase in the number of reports that demonstrate that these new molecules are under control of the central nervous system (CNS). They are often measured in animals or man under 'some sort of stress', and then published as new contributions to psychoneuroendocrinology (PNE). The position of this paper is that too many of these reports ignore that there has been an increase in our knowledge and understanding also of psychology. There is more to the psychology (P) bit of PNE than 'some sort of stress'. The aim of the paper is to furnish the 'P novice' with information on the P aspects of PNE, to avoid confusion and distress.

The first part of this paper is to present a cognitive approach to stress theory, and describe a simple model for the relationship between the P factors and the endocrine responses. The second part will examine the typical experimental situations in PNE, and suggest nomenclature for identification of the psychological variables that determine the PNE in the different types of experimental situations. Finally, this paper reviews 30 years of progress in understanding the P part of PNE, by discussing PNE positions outlined by
Mason (1968), one of the PNE pioneers. With this key to 30 years of PNE research, the ‘P novice’ should have possibilities to explain why some stimuli are regarded as negative by some individuals, but positive by others, and why previous experience with the stimulus, or similar stimuli, determines the endocrine response. In short, why do individuals with brains differ from each other? How do we change the ‘noise’ from individual variance to meaningful data and PNE ‘music’?

The relationship between psychological dimensions and physiological concomitants has gone through an enormous development during the more than 60 years since Selye formulated his stress theory. His formulations are historically important and interesting, but do not cover the field today. The developments in cognitive learning theory, as well as in neurophysiology (activation theory), psychophysiology (PP), psychoneuroimmunology (PNI), and PNE have given us a dramatically new understanding of the relationship between psychology and somatic responses. Old positions within psychosomatic medicine must be revised and reformulated.

The PP field is a respectable and well developed part of psychology. Contemporary developments in brain mapping and brain imaging have increased the importance of this contribution. The PNI is still in its infancy as regards the serious contributions to psychological theory. The PNE has not received the interest it deserves. Too few psychologists understand endocrinology (and immunology), too few endocrinologists have any ideas about what psychology is all about.

COGNITIVE MECHANISMS IN PNE

It seems fair to state that one of the areas that has developed most in psychology in recent years is cognitive science, in particular cognitive neuroscience. In PNE research, and in all stress research, the main cognitive factor to be considered is the existence of filters that evaluate or ‘appraise’ the stimuli. In a review of the stress concept, Levine and Ursin (1991) formulated three consensus statements on the relationship between the PP, PNE, and PNI responses to an external challenge or threat, the stress response. The first was that if there was anything common to the stimuli that produced the physiological changes described as ‘stress’, this was not the physical characteristics of the stimuli. The second consensus statement was that psychological, emotional loads were the most frequently reported stress stimuli. The third consensus statement was that all stimuli are evaluated or filtered by the brain. These three factors produce the individual difference, and the P part of PNE is to understand the principles for this variance.

The coping ‘filter’ is the best understood and best developed concept in the stress literature, and, also, in many related disciplines (Carpenter, 1992). The concept is found in PNE, PNI, and PP, in animals and in man (Toates, 1995), as well as in clinical psychology (Ursin and Hyttinen, 1992) and developmental psychology (Gunnar, 1989; Levine, 1969, 1983). It is a crucial concept in contemporary formulations of the relationships between environmental factors and health, psychosomatic pathophysiology (Dantzer, 1989; Levine and Ursin, 1991; Murison and Overmier, 1988), and in psychiatric, psychological, and somatic therapy (Carpenter, 1992; Haug et al., 1994; Wilhelmsen et al., 1994). The term, or related terms, are essential in the theories for ‘healthy work’ (Karasek and Theorell, 1990), in sports psychology (Pensgård and Ursin, 1998), and in educational psychology (Skinner, 1996).
In spite of a considerable degree of consensus the terminology is not standardized. Coping is used both for the strategies selected (Folkman and Lazarus, 1985; Lazarus and Folkman 1984), and for the expected results of these strategies (Ursin, 1988). Only in the latter case does the concept attain predictive power for PNE, PNI, and PP, and, therefore, for health issues. Coping refers to states where this outcome expectancy is positive. When the expectancy is that the outcome is negative, the state is referred to as ‘hopelessness’. When the expectancy is that there are no relationships between available responses and results, the condition is referred to as ‘helplessness’ (Levine and Ursin, 1991; Overmier, 1988; Overmier and Seligman, 1967). All these expectancies have a tendency to generalize. This affects mood, and health. The PNE, PNI, and PP consequences of these expectancies or ‘states’ have been studied extensively in man and animals, in acute laboratory stress situations in man (Brosschot et al., 1992; Olff et al., 1995) and in animals (Dantzer, 1989; Murison and Overmier, 1988; Toates, 1995). There is also an extensive literature from field experiments like parachutist jumps (Schedlowski et al., 1993; Ursin et al., 1978) and free fall lifeboats (Endresen et al., 1991), and from longlasting stress situations (expeditions, submarines, space simulations (Ursin et al., 1991; Værnes et al., 1993), hyperbaric environments (Vernes and Darragh, 1982), military stress situations (Sandal et al., 1998), serious life events (Lindstrøm, 1997)).

There are also several related concepts. The ability or possibility to cope with the environment is often referred to as ‘control’ (Heckhausen, 1991; Skinner, 1996). The most important model in the work stress literature is the demands/control model of Karasek and Theorell (1990). In their theory, control is used for the formal aspects of the work situation, which may or may not lead to ‘mastery’, which, again, is determining whether the work situation is healthy or not. The essential aspect seems to be the subjective or perceived feeling of being able to control the situation (Skinner 1996), which develops into what Levine and Ursin refer to as a positive response outcome expectancy. For both terms, the generalization from one situation to all situations is an important aspect (Skinner, 1996). Individuals feeling that they have control over their situation are said to have an internal ‘locus of control’ (Parkes, 1988; Rotter 1975). Other related concepts are toughness (Dientsbier, 1989), hardiness (Kobasa et al., 1982), high self esteem, and affective stability (Zorrilla et al., 1995).

The most consistent finding across species and experimental situations is that whenever a subject has acquired control over a potentially dangerous situation, and is given clear and salient feedback that this is the case, the PNE, PNI, and PP responses are reduced, compared to what happens if the individual has not acquired this type of outcome expectancy. Under these conditions humans report subjective feelings of being able to control or cope with the situation. The cognitive formulations of these expectancies make it possible to draw conclusions across species. It is not acceptable to state anything about the feelings of a rat, but it is acceptable to state what kind of expectancies that are established in the rat brain. The assumed consequences for the endocrine and immune system have been confirmed in many different types of experiments (Dantzer, 1989; Overmier, 1988; Toates, 1995).

Psychological defense is an additional filtering mechanism. Psychological defense is only identified in humans. It covers cognitive mechanisms that distort, deny or explain away threatening stimuli. Therefore, it may be said to be related to the stimulus expectancies (Bolles, 1972), rather than to the response outcome expectancies. Psychological defense reduces the endocrine response to a threatening stimulus, without the individual being aware of this strategy. Defense is operationalized with questionnaires, tachistoscopic
methods, or clinical interviews (Olff et al., 1991). At least in tachistoscopic experiments defense seems to be associated with particular ways of handling new and threatening information (Eriksen et al., 1996).

COGNITIVE REFORMULATIONS OF STRESS THEORY

The relationships between the external world and changes in the organism, be this within PP, PNI or PNE, were covered traditionally by theories of emotion, later by 'stress' theories, with assumptions of somatic mechanisms that in some ill defined way had its own regulating system. Vegetative nerves were ‘autonomic’, the stress response through the pituitary–corticoid axis was without any or beyond the regular brain control of the organism. Later limbic theories and the understanding of hypothalamic regulation of the endocrine processes were important milestones in a more rational approach to these phenomena, although some of this ‘mysticism’ still seems to linger in the field.

The link from cognitive mechanisms treating the information available to the brain to the PNE, PNI, and PP phenomena requires a more sophisticated model than just referring to ‘stress’. The easiest and least controversial model is still the neurophysiological arousal or activation theory (Levine and Ursin, 1980, 1991). General activation theory has developed from the initial neurophysiological observations of Moruzzi and Magoun (1949) to a well developed concept (Hobson and Brazier, 1980; Vanderwolf and Robinson, 1981) still useful in physiology, psychology, sports science, clinical disciplines, and for the understanding of PNE. The theory was integrated with similar concepts from psychophysiology (Duffy, 1962; Malmo, 1966), and later empirical observations from PNE (Levine and Ursin, 1991; Mason, 1968) and PNI (Dantzer, 1989; Murison and Overmier, 1993). The response is characterized by increased wakefulness in the brain, increased metabolism and turnover of transmitters (Anisman, 1978), increased muscle tone, specific behaviors, and vegetative, endocrine, and immunological changes (Levine and Ursin, 1991).

Lately the most important aspects of activation theory have been reformulated in cognitive terms. Briefly, a Cognitive Activation Theory of Stress (CATS) states that the stress response is identical to activation, and should be regarded as a general alarm system operating whenever the organism registers that there is a discrepancy between what is expected (set value) and what really exists (actual value) (Sokolov, 1963; Ursin, 1988). This means that the stress response—or the alarm—occurs when something is missing, and that the organism does not expect to be able to cope with the challenge (Levine and Ursin, 1991). Lack of control or lack of being able to cope with a situation elicits this alarm, and the individual reports ‘stress’. The general, non-specific activation response yields a general, non-specific PNE, PNI and PP response.

SPECIFIC ACTIVATION MODELS

The main remaining controversy is whether it is really true that there is one and only one, general alarm or activation response, or that the response observed is specific to a particular situation, a particular strategy, or a specific emotion. To some extent both positions are possible, for some theories the existence of specific activation patterns is crucial.
Each individual seems to develop a preference or style in their activation pattern (Grinker, 1966; Lacey, 1950). Both classical and instrumental conditioning contribute to this individual specificity. But to what extent is there any general patterns to the specificity?

There is some data to support that individuals that prefer active problem solving strategies have lower levels of activation than others in similar stress situations. This may be explained by higher levels of positive response outcome expectancies (coping) (Olff et al., 1995). Preference of passive strategies over active strategies is often associated with cortisol-responses in animals (Bohus, 1988; Henry and Meehan, 1981). Cortisol reactivity and regulation is related to depression and stress (Anisman and Zacharko, 1982), in particular to long-lasting effects of trauma (post-traumatic stress disorder) (Yehuda et al., 1996a)

There are several reports of an apparent independence of the reactivity within the cortisol axis and the catecholamine-system (Frankenhaeuser et al., 1980; Toates, 1995), even if both systems respond according to general activation theory. Factor analyses of endocrine responses to an extreme situation, for instance parachutist training jumps, confirm this independence, cortisol and catecholamines appear in two different, orthogonal factors (Rose et al., 1967; Ursin et al., 1978). There are also psychological differences, those that respond most within the cortisol axis tend to have higher defense mechanisms than those that respond mostly with the catecholamine system (Ursin et al., 1978). High defense mechanisms seem related to immune responses (Endresen et al., 1991; Olff et al., 1995). The catecholamine responder is related to the Type A personality (Friedman and Rosenman, 1959; Glass, 1977).

It has been suggested that these psychological and corresponding PNE expressions may be dependent on different limbic structures. According to Henry and Meehan (1981), amygdala may be more related to catecholamine reactivity, while hippocampus may be more related to cortisol reactivity. This does not seem to be supported by later findings. But there is accumulating evidence for the importance of amygdala, particularly its central nucleus, for the reactivity and regulation of at least the cortisol axis (LeDoux, 1993). The possibility of specific neurotoxic effects on the hippocampus by very high levels of cortisol suggested by Sapolsky et al. (1987) does not seem to be related to this issue.

The possibility of specific relations between particular coping strategies and specific personality traits should be investigated further. Recent data point to the possibility of relationships between particular personality traits and characteristics, in particular expressions of sensation seeking behavior, and specific neuroendocrine reactivity (Zuckerman, 1994). But in these experiments the general, non-specific activation must be accounted for. It is also possible that apparent personality differences in endocrine response profiles are due to differences in the time course of the general activation pattern (Eriksen et al., 1998).

**CONSEQUENCES FOR PNE RESEARCH DESIGN AND INTERPRETATIONS**

*Single Events: Short-lasting*

Most experimental situations involve a short-lasting stimulus. The simplest situation is the presentation of a novel, short-lasting stimulus without any significance for the individual. This is referred to as a non-signal stimulus. The first presentation produces an orienting response, characterized by arrest of ongoing activity, general activation, and
orienting behavior’ directed at the source of stimulation. Pavlov referred to this response as a ‘what is it’ response. The PP aspects of the response is well mapped, and is related to a short-lasting arrest also of the heart, evident as an increment in the interbeat interval (Graham, 1979). The stimulus and the response are too short-lasting to have any impressive endocrine effects, but the effects of novelty in itself must be considered in any PNE experiment.

Presentation of a short-lasting stimulus with significance has effects dependent on this significance. The significance is based on previous experience with this stimulus, or, within learning theory, by previous conditioning. In simpler terms, the significance depends on the meaning of the stimulus. The stimulus carries signal value, it signals a positive or negative reward (reinforcement). Presentation of this signal elicits conditioned responses (or expectancies). If the stimulus is presented out of context, i.e. in a different setting, additional effects may be produced by orienting responses.

The reinforcing properties of the stimuli that are ‘signalled’, the events that are expected to follow, depends on the quality of these events. ‘Noxious’ stimuli are often used in stress experiments, varying from air puffs to electric shocks. Why stimuli are reinforcing is not always a simple question, and may depend on previous experience.

Single Events: Long-lasting

**Exploration.** When an animal or a child is placed in a novel environment, the response pattern seems to follow a standard pattern. After an initial stage of fear and inactivity (freezing), the individual starts exploring the new environment. This is a fear-reducing strategy, the exploration yields information about the new environment which reduces the uncertainty, and, therefore, the anxiety or fear (Jellestad et al., 1991). The same mechanisms seem involved in humans faced with uncertainty. The most challenging aspect of this problem area is the relationship between these basic mechanisms and curiosity, creativity, exploration and sensation seeking behavior in humans (Zuckerman, 1994).

**Life Events, Real Life Stressors.** Real life stress situations are often long-lasting and related to important life events (Rahe and Arthur, 1978). One very frequent long-lasting stimulus situation used is (medical) students preparing for an exam (Kiecolt-Glaser et al., 1984). In this case, as in other long-lasting situations, the psychological situation is very complex, with many factors producing individual differentiation. Learning factors change the reinforcing properties of the ‘stimulus’. In addition to the coping, control, defense, and expectancy factors we have described, we must account for motivational factors, achievement motivation, previous results, and other psychological dimensions specific for this particular situation, for this particular individual or group of individuals. In humans most dimensions are covered by standardized questionnaires. Whenever new questionnaires are tried, these must be tested for reliability and validity. In animals long-lasting stress stimuli (immobilization, isolation, crowding, labile social hierarchies, maternal separation) may be very complex, and the dynamics of the learning may often be difficult to account for. However, this should be attempted, to avoid seemingly meaningless attributions to physical properties of the stimulus.

The time factor is also an important factor for the type of response to be observed. There is a gradual change from the initial stages influenced by novelty and the orienting response, to acquisition of the signal value of the situation, and the appreciation of what coping and defense mechanisms can do to the situation, and what would happen if nothing is done to the situation.
Long-lasting stress situations are valid experiments in animals, and valid situations for humans, for the understanding of the development of psychosomatic consequences of 'stress'. Due to the many psychological and physiological mechanisms that act to dampen the response, this is often a complex situation to disentangle. If the attempt of the experiment is to illustrate any pathophysiological contribution or effect, the experimenter should account for this mechanism. It is also important to discuss whether there is any epidemiological reason to believe that this possible pathophysiological mechanism has any real impact on the condition.

Repeated Events: Response Decrement

Habituation. Repeating a stimulus with no signal value with inter trial intervals of seconds or minutes leads to a decrement in the orienting response after ten to 30 trials. This gradual decrement in response is referred to as habituation (Thompson and Spencer, 1966). The term is also used for response decrements in simpler circuits (Rayport and Kandel, 1986), but still habituation should be identified as a process distinctly different from adaptation and fatigue. When the pattern or the setting is changed, the response reappears. If the brain shows habituation to a sequence of tones, it is sufficient to reverse the order of the same tones to reestablish the response. The response also reappears if activation is produced by a new, different stimulus, the next presentation of the first stimulus now again produces the orienting response (dishabitation). Repeated presentations produce habituation, this time more rapidly (rehabituation) (Kimmel et al., 1979).

Adaptation. This is the most treacherous term. Used in the broadest sense, any observed phenomenon in nature may be said to be 'adaptive', otherwise it would not exist. In general physiology, it is used for changes that are due to exposure to a particular environment, for instance low or high atmospheric pressure, bed rest, or cold. It takes time to be established, it lasts for some time after the exposure. However, to refer to learning phenomena as adaptation is too imprecise for meaningful communication. In the neurosciences, the term is sometimes used for receptor up- or down-regulation, again, there are better terms, up- or down-regulation is understood by us all. In neurophysiology, a clear, non-controversial and consistent use is to reserve the term for processes in the sensory organs themselves.

Fatigue. Fatigue is most often used for processes that are tied to the effector organ itself, in particular for muscles. Fatigue is the gradual decrement in contraction power in muscles due to repeated contractions. It should be kept separated from exhaustion (Vøllestad and Sejersted, 1988).

Learning. The most important, and most interesting, reason for response decrement is that the individual learns something about the situation. Uncertainty is reduced, outcome expectancies are established, the individual learns to cope, to control, to master the situation. Even if there is no consensus on terminology, there is enough consistency in this literature at the present time to plead for more consistency. There is no excuse for adding to the confusion by neglecting the literature and inventing new terms, or use vague or extremely general terms for phenomena that have been described and categorized.

Repeated exposures to novelty, or fear-inducing stimuli, may lead to extinction of the fear responses. This happens under, for instance, handling of experimental animals.
(Dobrakovova et al., 1993) or extinction of fear responses. Fear reduction may also be due to learning to avoid the fear source, and developing ‘coping’ (Coover et al., 1973).

Repeated Events: Increased Responses

Sensitization. Repeating stimuli may lead to an increased response. A classical finding is an increase in the orienting response during the first couple of stimulus presentations, before habituation appears. The dual process theory of Groves and Thompson (1970) ascribed this phenomenon to two opposing processes, an initially dominating sensitization, i.e. an increase in response, which is then gradually taken over by habituation, i.e. a response decrement.

The neurophysiological mechanisms for habituation and sensitization on the synaptic level have been mapped in great detail (Rayport and Kandel, 1986). Sensitization processes have also been suggested as being relevant for memory, as for instance in the long term potentiation studies of the hippocampus (Bliss and Lømo, 1973). However, simple sensitization is the most frequent source of error in conditioning experiment since this really is ‘pseudo’ conditioning rather than true associative conditioning. If you repeat a stimulus and the response changes due to the repeating of the one and same stimulus, this is pseudoconditioning, or sensitization. Conditioning means that one stimulus given in combination with another stimulus changes the response to the first stimulus, as in classical conditioning. If Pavlovs dog had started salivating just because the bell had been presented many times, this would not be conditioning, it would be sensitization or pseudoconditioning. The hot issue in learning research is whether the sensitization produced by a single stimulus is a condition for conditioning to occur. The long term potentiation may be related to learning if the sensitization given by the unconditioned stimulus is enough to change the total reactivity of neurons, thereby changing the reactivity also to the first, originally neutral stimulus. This remains a hypothetical substrate for learning.

Sensitization may be an interesting phenomenon from a psychosomatic point of view. Sensitization occurs in pain pathways, in this case it is not a non-stimulus. However, repeating pain producing stimuli leads to an increased sensitivity, tenderness, and increased responses. This may be an important mechanism for increased sensitivity to pain, and to subjective health complaint states, i.e. muscle pain, fibromyalgia, and low back pain (Ursin, 1997). The same substrate has been suggested for multiple chemical sensitivity (Bell, 1994) and for sensitivity to noise (Nivison and Endresen, 1993).

Learning. When the increase in response strength is due to the association with other events, learning has occurred. The new course of events is determined by the relationship between stimuli, or the relationship between stimuli and available responses. These relationships are described within learning theory. This is the best—some say the only true—theory in psychology. There is no way to ignore this theoretical foundation, even if it requires work to penetrate a field with its own nomenclature. Many of us have found it easier, and more convenient, to stick to the simpler formulations in cognitive reformulations of learning theory (Bolles, 1972; Dickinson, 1980). Within the cognitive reformulations of stress theory, it is the expectancy to the situation which is the overall determining factor. When one stimulus is presented, what does the individual now expect? What does this stimulus signal? Which responses are available, and what is the result to be expected?
THE 30 YEARS ANNIVERSARY OF THE MASON PRINCIPLE

Psychoendocrine studies prior to 1955 had produced indirect and non-specific information indicating that the adrenal cortical activity could be influenced by psychological factors. At that time, the relationship was mapped with the help of biochemical measurement of 17-hydroxy corticosteroids (17-OHCS). In his very influential review in 1968, based on about 200 studies, Mason concluded with what is later referred to as the ‘Mason principle’: “Psychological stimuli are capable of influencing the level of pituitary–adrenal cortical activity”. He saw no longer any room for any reasonable doubt on this basic conclusion, and emphasized that the burden of proof rested on those that did not realize this. If they wanted to prove that any observed change was not due to psychological factors, they would have to eliminate or minimize extraneous environmental and psychological stimuli to obtain the necessary control. Thirty years of research has proven him right on most or all counts.

Mason formulated eight different conclusions. They will be reviewed in the following, all seem to be confirmed by the research since 1968. The psychological principles he outlined have been established and systematized in contemporary psychology, and are in consensus with general theories and knowledge in psychology today.

Mason’s Principle no. 1

“Psychological influences are among the most potent natural stimuli known to affect the pituitary–adrenal cortical activity”.

This conclusion has been substantiated in a long series of empirical work, in animals and in humans, and across a variety of situations. It should be admitted that there is still some resistance in the acknowledgment of this basic fact, as pointed out by Mason in 1968. However, these factors must be taken into account in any measurement of cortisol, or any other physiological process in an intact animal or human with an awake brain.

Mason Principle no. 2

“The central nervous system (CNS) exerts a constant ‘tonic’ influence on this axis, much in the same way as had been demonstrated for the autonomic and skeletal muscular effector systems”.

Mason referred to the psychological influence as tonic meaning that the influence was not restricted to sudden and unusual events. Later research has confirmed that the influence includes everyday events. Mason did not refer to general activation theory or any brain system maintaining wakefulness and level of activation. However, within this theory the influence is simply a function of the activation level of the brain. This influence rides on top of the circadian rhythm, and may completely override the circadian rhythm under particularly stressful circumstances.

The most difficult aspect of this position is whether there are long-term, tonic changes in the hormonal regulation. Ursin (1980) postulated that ‘psychosomatic’ pathology would result as a response to ‘sustained activation’. This has been difficult to demonstrate, in most experiments any such change is drowned in diurnal and episodic influences, and by homeostatic self-regulatory principles. There are also problems with the model since coping, defined as high self esteem, hardiness, and affective stability, is associated with high—rather than low—basal levels of cortisol (Zorrilla et al., 1995). There are other recent data on what seems to be permanent changes in some of the regulatory mechanisms (Yehuda et al., 1996a).
**Mason Principle no. 3**

“The pituitary–adrenal cortical activity is not related to any specific affective state, but reflects a relatively undifferentiated state of emotional arousal, involvement, anticipation of activity, and coping”.

This is the strongest Mason statement in support of general activation theory, even if he avoided using this term. The statement is also preceding the cognitive reformulations of activation theory, in the emphasis on the importance of coping, involvement, and anticipation of activity. Finally, the statement is also compatible with the essential elements in stress theory, another term Mason avoided. Selye also underlined the non-specificity of his stress response. Cortisol elevations are produced even by amusement (Hubert et al., 1993).

**Mason Principle no. 4**

“Particularly potent influences on the system are novelty, uncertainty, and unpredictability”.

Later research has confirmed this principle. It is, in many ways, the reciprocal formulation of the previous principle. Contemporary psychological theory holds that ‘stress’ and unhealthy work is related to uncertainty and unpredictability. Coping, or perceived control, and restructuring the work situation, aim at establishing predictability and certainty.

**Mason Principle no. 5**

“Intense and disorganising emotional reactions with behavior breakdown are associated with unusually marked 17-OHCS elevations”.

This position is true for pituitary–adrenal activity under special circumstances. Present research interest has moved to questions on whether the CNS regulation of this axis is altered during prolonged exposures to stressors the individual is unable to cope with. The states of helplessness and hopelessness are accompanied by CNS changes, but these go beyond any specific regulation system, and are—perhaps—best understood within non-specific activation theory (Anisman and Sklar, 1979; Coover et al., 1984).

However, there has been a long lasting research interest for the specific CNS regulation of the pituitary–adrenal axis, particularly for depression, lately, also for other chronic ‘stress’ conditions. It is possible that the amygdala nuclei are involved, in particular the central nucleus of amygdala, an important area for emotional activation, arousal, and exploration (Jellestad et al., 1991). The neurons in the central nucleus produce corticotrophin-releasing hormone (CRH), but respond with increased production to increased levels of glucocorticoids, rather than the expected decrease (Schulkin et al., 1994). Similar alterations in this axis have been reported for patients with chronic pain and posttraumatic stress disorders (Yehuda et al., 1996a,b).

**Mason Principle no. 6**

“Psychological factors may either raise or lower the HPA activity”.

The apparent inconsistencies in PNE results are probably due to lack of control and insights in the psychological factors involved. Mason pointed out that the quality of the emotional response might be important, as well as the style and effectiveness of defense. He also pointed out that it was important whether the threat was chronic or acute. He was
right on all accounts, but today these statements should be made more specific, and with the proper operationalizations of the assumed psychological dimensions involved.

**Mason Principle no. 7**

“There are marked individual differences in the response to any particular situation, dependent on multiple psychological and other determinants. The response depends on how that individual interprets this particular situation, what are his goals, and what are his expectancies and defense mechanisms”.

This is a very early formulation of what later has been referred to as ‘interactive’ stress models, the appraisal dimensions of Lazarus and Folkman (1984), and the third Levine and Ursin (1991) consensus statement express the same. All challenging and threatening stimuli are filtered by coping and defense mechanisms, acting on stimulus and response outcome expectations.

**Mason Principle no. 8**

“The measurement of pituitary–adrenal activity offers a particularly interesting, sensitive, and objective index of the psychological or emotional state of the individual. This makes it possible to measure the factors both in man and in animal that prevent, minimise or increase arousal and distress”.

Again, Mason was indeed right, and the HPA axis has remained one of the favoured psychoendocrine indicators of the central state and the psychological state, in spite of the increased laboratory possibilities to measure almost any physiological consequence of activation. One reason for this is the relatively slow response, which makes it possible to evaluate the situation before the biological sample was obtained. The molecule is also very stable, and this makes it useful under field conditions. The sensitivity has been impressive, there are, for instance, examples of the HPA axis reacting to the change from a fixed ratio to a variable ratio of reinforcement (Coover et al., 1984).

In humans, the possibility to supply standard questionnaires by simply asking what happened is often ignored. It is permissible, and recommendable, to ask the subjects. The human advantage is that they talk. But it should be remembered that interview data are particularly sensitive to expectancy bias, from the experimenter, and from the subject. Interviews are also a validation of the research questionnaires. Far too many researchers rely on the label of their questionnaire. This ‘label’ research should be avoided, and may be a main source of inconsistency in this literature.

**CONCLUSIONS**

To all of us that have been involved in this type of research the Mason principles are amazingly representative of what I believe to be consensus. The most important addition is what he predicted in his conclusion. He suggested that the evolution of psychoendocrine research on the pituitary adrenal cortical system provided a valuable guide to the lines to similar research on other endocrine systems which should follow. He suggested that similar conclusions would be reached also for other endocrine systems when evidence was collected along these lines. As he pointed out in his principal number no. 2, there is now overwhelming evidence supporting that the endocrine system responds in much the same fashion as autonomic and skeletal effector systems, and the last twenty years of psychoim-
mune research has included also this system in a generalised type of response to psychological stimuli and psychological states.

One of the most fascinating aspects of PNE is that the data and principles derive partly from animal experiments, partly from humans. Laboratory experiments, often in the animal laboratory, have contributed to the development of general theories in psychology. On the other hand, the development in general psychology has contributed to the understanding of PNE. The relationship between results and concepts from animal research and research on human individuals is sometimes so close as to warrant caution against too simple generalisations. There are some differences left, particularly those related to the variance and individual differences found in humans. This is not noise, this is psychology. It should also be noticed that there is more consensus, conventions, and clarity in the terminology used in animal research, particularly in experiments related to learning theory. The terms are operationalized and tied to well defined and standardised experimental situations. In ethology, the terminology is looser and more difficult to standardise. In the human literature the operationalizations are most often tied to particular instruments. The P novice should exert caution in accepting the names on the dimensions measured. Instruments claiming to measure ‘defense’, for instance, do not necessarily measure the same phenomenon (Olff et al., 1990, 1991).

It has taken some time to accept the existence of the networks within the brain, and the feedback loops between the brain and peripheral somatic processes. It has taken almost 100 years to get rid of the dichotomy between the James Lange position and the Cannon Bard position for the physiology of emotions. Psychology students through the ages have been taught that these were two different theoretical positions, and they have even been taught that one is wrong, and one is right. Cannon Bard held that emotions were primarily a brain event with physiological concomitants: James Lange pointed out that an essential part of emotions was the feedback from the peripheral physiological activation. Within an activation and psychobiological concept, realizing the importance of feedback circuits for activation and emotional arousal, these two positions are just describing two legs of a feedback circle. Cannon Bard describes the efferent link, James Lange describes the afferent link.

However, the stumbling block for the P in PNE has, in my opinion, very often proven to be the traditional dualistic way of thinking about body and soul. This position is deeply rooted in religious, philosophical and even political points of view. For the psychobiological scientist this position is untenable. Private beliefs must be adjusted to the basic findings on the reciprocal relationship between brain and body.

PNE is, or should be, an interdisciplinary field. This is what makes it interesting, and this is the condition for meaningful new contributions. It is also the foundation for our contributions to science in general, and to our understanding of man. We live in exciting times, and have the privilege of being able to reveal secrets of how man functions. Finding a new molecule and a new gene location is great. However, to be able to explain the relationship between our mind and our body is even greater, and this gives us a unique role in the history of mankind. It is close to sacrilegious to spoil this opportunity by ignoring the literature, and playing it safe by sticking to our favorite molecule, favorite stimulus contingency, or favorite questionnaire. We simply have to try a little harder, all of us.
REFERENCES


