STRESS AND ADAPTATION:
FROM SELYE'S CONCEPT TO
APPLICATION OF MODERN
FORMULATIONS

Summary

This document results from a WHO meeting on Stress and Adaptation: from Selye's Concept to Application of Modern Formulations, held in Montreal, Canada, 21-23 September 1998.

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This document results from a WHO meeting on Stress and Adaptation: From Selye's Concept to Application of Modern Formulations, held at the Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada, 21-23 September 1998. The following experts participated:

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STRESS AND ADAPTATION: FROM SELYE'S CONCEPT TO APPLICATION OF MODERN FORMULATIONS

1. INTRODUCTION

A WHO meeting on Stress and Adaptation: From Selye's Concept to Application of Modern Formulation was held at the Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada on 21-23 September 1998. An opening statement was given by Dr. B. Mansourian on behalf of WHO and the Advisory Committee on Health Research (ACHR).

After recalling the early pioneering work of Hans Selye on stress research, Dr. Mansourian alluded to the modern advances in the area of stress proteins and to the promises they held for future developments. He emphasized that WHO has always valued science and technology and for this reason, the field of neurosciences had to receive special attention. The ACHR had considered that ongoing and future advances in neurosciences had great potential for prevention, control and treatment of nervous system and mental disorders. The ACHR, endorsing the developments related to the decade of the brain, advised that a focused review of recent advances and their applications in neurosciences should be part of the activities of assessing new and emerging areas of science and technology.

The Committee itself was dealing with a difficult problem, the so-called 90/10 imbalance in global health research, implying that 90% of resources were in the North, while most of the disease burden was in the South. In per capita terms the North spends more than 100 times more than the South on science and technology, publishes 50 times more and produces 500 times more patents. Of the US$2 trillion spent globally on health each year, little contributes to major scientific advances, most contributions arising from the science and technology sector. WHO, with a minuscule proportion of the global health research investment, has a catalytic and facilitating role to play, strengthening cooperation with the scientific community and other relevant partners. A general orientation and strategy was needed, and early efforts such as the 'McKeown report' were mentioned.

A more recent initiative was the Research Policy Agenda for science and technology to support Global Health Development which intended to provide scientific backing to the policy formulation process. The agenda pursued three major goals: the first component examined the relationship between health and global trends (an issue referred to as "evolving problems of critical
significance to global health”). The second component, reviewing the major recent and impending scientific advances, constituted a call to harness the potential of science, technology and medicine in favour of global health development. A third component elaborated on research imperatives and opportunities, in terms of substantive domains as well as in terms of methodologies. Finally, in discussing implementation aspects, the Agenda advocated the use of Intelligent Research Networks (“IRENEs”) to link up all prospective partners, including scientists, foundations, governmental sponsors, research councils, and scientific unions and universities, making use of modern communication technologies.

2. **AIMS OF THE MEETING**

The aims of the meeting were defined as follows:

1. To assess recent progress on the role of homoeostatic mechanisms in the response to stressors.

2. To review the state of current research in this field, relating it to Selye's original concept of stress.

3. To propose future work that will enhance our understanding of fundamental mechanisms that underlie the response to stressors and the adaptation to stress.

4. To identify specific promising areas for new research in this field.

5. To discuss possible implications of this area of work to health and disease.

6. To consider new pharmacological approaches based on interventions that would modulate the response to stress.

3. **Stress and adaptation: from Selye's concept to application of modern formulations**

3.1 **Homoeostasis and adaptation**

The word stress was first coined and used in physics meaning the force or pressure applied between bodies, generally expressed as units of weight per unit of surface. The expression “stress and strain” has been used in relation to the theory of elasticity described by Hooke’s law around the
end of 18th century which defines the relationship between the applied force and deformation. The relationship for limited stress and small deformation is linear and reversible. If the applied stress produces large strains the linearity is lost. If the stress continues to grow an irreversible deformation will follow: that is the plastic regime.

This concept of stress applied in physics is theoretically suitable also for biology. Indeed, living matter responds to applied forces by temporary adaptation and then by plastic changes. These plastic changes in response to acute stress are mostly biochemical, fast and reversible, whereas long-lasting stress may induce changes at the level of gene expression.

The concept that in living matter the natural condition is not static is ancient, starting early in Chinese philosophy. This concept was further developed and described by Greek and Roman philosophers. Heraclitus was among the first to suggest that living things undergo constant dynamic changes. Empedocles based his theory on the dynamic opposition-alliance of elements, making equilibrium a necessary condition for survival. Subsequently, Hippocrates defined health as a balance of elements and disease as a disharmony of them, excluding the intervention of supernatural forces. These general concepts of harmony in living matter were later adopted also by Roman philosophers and physicians. Epicures applied the same equilibrium concept to behaviour, recognizing the importance of the mind in maintaining body equilibrium. These concepts have been followed during the centuries, as witnessed by the work of Thomas Sydenham, an English physician, in the 17th century. In the middle of 19th century the great French physiologist Claude Bernard refined these concepts by formulating the theory of milieu interieur, proposing the existence of a dynamic internal physiological equilibrium. This theory was announced and discussed in a series of lectures emphasizing the importance of a constant internal environment, maintained by several compensatory reactions, which protects the body from the external environment.

The milieu interieur theory further led to the development of the cybernetic concept of feedback. William Cannon in the first half of the 20th century developed the theory and coined the term "homoeostasis" as coordinated physiological processes maintaining the steady state of temperature, pH and osmotic pressure of internal fluids. He also introduced the role of the adrenomedullary system in maintaining homoeostasis, participating to the "fight and flight" reaction, underscoring the importance of adaptation.

Independently, Charles Darwin, in his book *The expression of emotions in man and animals* (1872), asserted that emotional expressions and their behavioural correlates can be inherited as are physical characteristics and are important in the expression of the response to stress.
Hans Selye introduced the concept of stress and the relationship between stress and disease within this context. At first he utilized the term stress, derived from physics, to indicate the mutual action of forces that take place through the body. He further defined stress as the nonspecific response of the body to any demand upon it. He also introduced the idea that the level of stress is important and that it may exert both positive and negative influences according to intensity and duration.

Stress has been studied in human beings, animals and plants as well as in unicellular organisms. Stress is transduced at the intracellular level by heat-shock proteins, also known as stress proteins, which were discovered by Ritossa in 1962 when he observed novel puffs in the giant chromosomes from the salivary gland of Drosophila during thermic stress (heat shock). Since Ritossa’s original report the structures of the proteins associated with heat-related chromosomal puffs were identified. Moreover, it has become clear that heat shock or stress proteins are induced not only by thermal, but also by chemical and psychological stressors as well as seizures and trauma.

We now conceptualize heat shock or stress proteins (hsp) as families of stress-related intracellular molecules that are conserved across species (homology of 50% for hsp70 among bacteria, yeast and Drosophila).

Hsps are classified according to molecular size:

\[
\begin{align*}
\text{hsp } 16-30 & = 16-30 \text{ kDa} \\
\text{hsp } 60 & = 60 \text{ kDa} \\
\text{hsp } 70 & = 70 \text{ kDa} \\
\text{hsp } 100 & = 100 \text{ kDa}
\end{align*}
\]

As specific functions are elucidated for each hsp they are named accordingly. For example, hsp 16 is now known as ubiquitin. More recent work in this field has shown that in addition to enabling the cell to respond to various types of stressors, hsp have key functions in homoeostasis. Hsp 90 binds to the glucocorticoid receptor in the cytoplasm, thus regulating cortisol-receptor interaction. Hsp 70 assists in protein folding or aggregation of proteins. Thus, hsp can serve as molecular chaperones for protein folding.

Given the high level of conservation in the structure of hsp across species, existence in all organisms, and key constitutive and stress-related functions, it is now accepted that these molecules
are key elements of cell function. Importantly, hsp are expressed in the central nervous system of various organisms across the evolutionary scale, from *Drosophila* to man, in discrete brain areas such as the hippocampus. The role of hsp in the modulation of basal and stress-related neural transmission remains to be elucidated and constitutes an active area of investigation at present.

It is interesting to see that some of these categories have developed strategic patterns of response in order to better cope with the stimuli. In man and in animals indeed both physical and emotional stressors induce central and peripheral homoeostatic responses. The central response to stress includes arousal, alertness, vigilance, attention and aggression. Peripheral responses are aimed to redirect energy resources to brain, cardiovascular system and target body sites. Hormones and neurotransmitters control the effect of stimuli and mediate responses to stress and indeed play a fundamental role. It has been suggested that the two main components of the general adaptational response are the corticotropin-releasing hormone, mostly at hypothalamic level, and the locus coeruleus-norepinephrine system.

3.2 Stress and adaptation: a psychobiological interpretation of Selye's concepts

In the last two decades research on stress in the fields of neuroscience, psychiatry, and behavioural sciences has produced a large amount of clinical and experimental results related to the hypothesis and clarified many of the underlying mechanisms of the stress response described by Selye.

Among the most important and novel contributions to the stress concept are those derived by research on psychopathology. The relationship between adaptation promoted by stressful experiences and liability to pathology has been always a difficult point to clarify in stress theories. The traditional view relates pathological risk to the intensity and duration of stressful conditions. According to Selye's interpretation, persistence of a stressful condition leads to exhaustion of defence mechanisms, thus promoting pathological outcomes. An important new advance in the conceptualization of the role of stress in psychopathogenesis is the diathesis-stress hypothesis proposed for the etiology of schizophrenia. The diathesis-stress hypothesis, by stating that liability to stress effects depends on genetic fragility, suggests a major role for individual characteristics as determinants for the intensity of the stress response.

A second, important aspect revealed by the diathesis-stress theory is the role of genetic factors in determining the type of pathological outcome of a stressful experience. An increasing
number of evidence points to alterations of dopamine (DA) receptors in different types of psychopathology. Nevertheless, linkage studies do not support a role of genes encoding for the different types of DA receptor in such pathologies. These discrepancies suggest that specific alterations of brain DA receptors may arise from the impact of stress on a specific genetic susceptibility. Such a possibility has been tested recently in laboratory animals, showing that the density of mesoaccumbens DA autoreceptors is a polygenic trait controlled by a major genotype versus stress interaction. This possibility is relevant to clinical research since it supports the view that different pathological profiles may derive from genotype-dependent adaptation of brain systems to environmental pressure. In line with the diathesis-stress theory, these results suggest that brain adaptation under conditions of stress may be highly specific. This specificity is not limited to brain adaptation.

A number of preclinical studies have shown that the degrees of novelty of a given stimulus as well as the degrees of predictability of an aversive stimulus determine the extent of pituitary-adrenal activation in animals. Moreover, elevation of plasma corticosterone, the primary stress response by the hypothalamus-pituitary-adrenal (HPA) axis in rodents, is consistently observed under many experimental conditions where reinforcement contingencies are altered. Finally, animals allowed to fight with conspecifics during shock delivery, will present a dramatically reduced number of gastric ulcerations in comparison with animals receiving the same amount of shock but prevented from fighting.

These observations related liability to a prototypical stress disease with controllability. Studies on the behavioural responses observable during and following exposure to experimental stressors in animals indicate that controllable and uncontrollable stressful experiences promote opposite responses. Moreover, opposite responses by the immune system were observed depending on the levels of controllability of stressful stimuli and only uncontrollable/unpredictable stress was observed to promote activation of endogenous opioid systems.

A body of evidence has pointed out the main role of several brain structures in regulating HPA system functioning, thus indicating that a "first mediator" should be envisaged in the central nervous system and in its complex and integrated functions. Moreover, it is well known that receptors for steroid hormones are located in different brain areas (those of the mesocorticolimbic systems) involved in the integration of cognitive information as well as in emotion and motivation. The activation of glucocorticoid receptors in the hippocampus or in the prefrontal cortex appears necessary to control HPA hormone response to stress, through feedback mechanisms that inhibit hormone release when it reaches high functional levels. This means that there is a strong cross-talk
between brain and HPA axis during the stress response, thus suggesting that cognitive and emotional integration of the experience is extremely important in the stress response. Finally, it has been shown that there are two main circuits leading to activation of the HPA axis, processive (originating in the associative areas of the brain) and systemic (originating in the brain stem). Involvement of one or both circuits depends on the type of stressor that activates the HPA axis.

Neurochemical changes in selected brain areas are also different depending on the degree of controllability of the stressor. The most striking differences in response to controllable and uncontrollable stressors have been observed for changes in DA release within the nucleus accumbens (NAS), the principal area of projection of ventral tegmental area (VTA) DA neurons. In mammals, mesencephalic DA neurons participate in a number of important cognitive and physiological functions including motivational processes, reward processing, working memory and conditioned behaviour. One interesting point is that activation of midbrain DA neurons hardly occurs after non-noxious aversive stimuli. On the other hand, it was observed that when aversive stimuli appear in close proximity with physically very similar appetitive stimuli, the discrimination between aversive and appetitive stimuli by DA neurons loses its all or none character and is expressed by a quantitative preference for appetitive stimuli. This observation supports the idea that conflict-eliciting, hence stressful, stimuli are different from simply aversive stimuli and may be identified by their ability to generalize cell activation in dopaminergic nuclei. This generalized activation of mesencephalic DA cells and the neurochemical events that it promotes may thus represent the first response to stressors, possibly involved in arousal-related processes. Consequently, the first step in stress response is cognitive appraisal of internal and external indexes within the context of innate or acquired experiences.

The next step in the stress response will be attempts to cope with discrepant/conflicting information. Behavioural responses that are part of the species-specific repertoire and individual history represent the fundamental tool for coping. Classical, physiological stress responses may help the organism to sustain homoeostatic balance in the presence of the increasing demands required by these strategies. Enhanced mesoaccumbens DA release increases the rate of behavioral responses, thus increasing the effectiveness of defensive strategies. Instead, if no coping is possible due to external (environmental) or internal (genetic or historical background) constraints, the organism will cease any attempt at behavioural coping and undergo a different type of adaptation. Thus, uncontrollable stressors promote passivity towards both aversive and rewarding stimuli and active inhibition of mesoaccumbens DA release.

In conclusion, the whole of the stress response, including the stressful quality of stimuli and
experiences, is determined by organism-environment interactions. This view has important implications for stress management. In fact, new developments in psychological techniques and in psychopharmacology provide unique tools to affect the environment, the organism, and the interaction between them.

3.3 **Homoeostatic processes in neuroendocrinology**

Survival, adaptation, and homoeostasis depend on the successful integration of stimuli that originate from the environment, the genome, and from metabolic processes. Neuroendocrinology is the discipline that studies the central regulation of homoeostatic endocrine function, related central nervous system circuitries and behaviours. There are two key events in neuroendocrinology: neuroendocrine transduction and neuroendocrine regulation. Neuroendocrine transduction is the transformation of neural information mediated by action potentials into informational molecules that can either diffuse from the cell of origin or be secreted, circulating into the blood and acting at distant sites where they regulate the functioning of various systems. Neuroendocrine integration consists of a complex network of hormones that regulate both the short- and long-term functioning of all organs and systems. The neuroendocrine control of homoeostasis has multiple time domains:

- minutes (short pulses of PTH)
- hours (insulin response to meals)
- day (circadian rhythm of HPA function)
- weeks (menstrual function)
- months (hormonal regulation of pregnancy)
- years (neuroendocrine regulation of development, including puberty and aging).

A key question in contemporary neuroendocrinology is the following: what regulatory pathways and mechanisms enable the neuroendocrine system to simultaneously control homoeostatic changes that occur over various times scales encompassing intervals that last minutes, hours, days, weeks, months, and decades, and that integrate signals originating from the environment, from the genome, and from metabolic processes?

Several neuroendocrine-regulated systems contribute to homeostasis:
One area that has received considerable attention in recent years is the role that peripherally secreted factors, such as the adipocyte hormone leptin, may have in the regulation of endocrine function. Recent studies have shown that peripherally secreted pulses of leptin may contribute to regulate key aspects of neuroendocrine function and homoeostasis. The systems that are regulated by leptin include the hypothalamic-pituitary-adrenal axis, the hypothalamic-pituitary-gonadal axis, the hypothalamic-pituitary-thyroid axis, and more recently it has been demonstrated that leptin contributes to regulate functions as diverse as immunity and angiogenesis. Thus, the decades-old assumption that homoeostasis and neuroendocrine regulation are exclusive functions of the brain has to be re-examined in the light of the neuroendocrine and homoeostatic effects that peripherally-secreted substances such as leptin have. The metabolic importance of leptin is further substantiated by the profound disturbances in homoeostasis, body weight, and neuroendocrine function in individuals with genetic mutations resulting in deficiency of leptin action.

Recent research data indicate that leptin modulates hypothalamic-pituitary-adrenal (HPA) function. As the HPA axis is essential to life and represents a crucial element in the stress response, it has been proposed that leptin might be a stress hormone with a role in systemic illness. In addition to regulating endogenous levels of cortisol, leptin enhances cytokine production and the phagocytic activity of macrophages. In patients critically ill with acute sepsis, a recent study showed that leptin's circadian rhythm was disrupted, with no nocturnal rise in plasma levels and a loss of relationship between plasma leptin and plasma cortisol. Mean leptin levels were three times higher in the patients who survived the septic episode (25.5±6.2 ng/mL, n=10) than in those who did not (8.0±3.7, n=6, P<0.01). Future studies should test the hypothesis that leptin may be a stress-related hormone whose
secretion is important in the pathophysiology of critical illness.

Future directions in neuroendocrinology include the following: (1) Identification of molecular mechanisms for hormone action. (2) Identification of a complex cascade of informational substances that exist both peripherally and centrally, within widespread but discrete circuitries, and that integrate metabolic homoeostasis. (3) Identification of new genes that are relevant to neuroendocrine regulation. (4) Development of increasingly sophisticated analytical methods that are applicable to clinical studies in neuroendocrinology. (5) Development of non-peptide neurohormone antagonists for the clinical treatment of neuroendocrine dysfunction. It is hoped that progress in all five of these areas will permit a continuing expansion of the frontiers of existing knowledge in neuroendocrinology, resulting in work that is conceptually novel and medically relevant.

3.4 Homoeostasis of cerebral circulation in relation to neuroprotection

Stress not only initiates profound activation of neuroendocrine mechanisms but invariably co-activates autonomic pathways. Much of the autonomic activation acts largely to initiate circulatory adjustments to protect the brain from ischaemia and, more importantly, hypoxia. The need for such protection relates to the fact that the brain is an incessantly active metabolic machine demanding a continuous supply of oxygen and glucose to maintain function and cell survival. In evidence are the facts that interruption of blood flow to brain results, within 10 seconds, in unconsciousness and, within 10 minutes, neuronal death.

There are in nature, however, two states in which cerebral oxygenation or cerebral blood flow may be reduced to nearly toxic levels during specific behaviours. These are the marked hypoxaemia sustained during submersion in diving vertebrates or the profound reductions in regional cerebral blood flow (rCBF) accompanying hibernation. These suggest the presence in the brain of mechanisms which may protect the organ from injury, probably by engaging circuits linked to autonomic regulation. Recent evidence suggests the presence of two distinct yet interrelated homoeostatic mechanisms organized in brain: reflex neurogenic neuroprotection and conditioned neurogenic neuroprotection

**Reflex neurogenic neuroprotection**

The prototype of reflex neuroprotection is the oxygen-conserving reflex of which the diving
reflex is a special case. The response is characterized by expiratory apnoea, bradycardia and intense peripheral vasoconstriction which functions to redirect blood from the periphery to the brain and thereby to replenish a dwindling oxygen supply. The autonomic reflex appears to result from activation of a small group of neurons in the rostral ventrolateral reticular nucleus (RVL) which are a group of phenotypically adrenergic medullar neurons. The RVL neurons, the only neurons in the area excited by hypoxia, are the tonic vasomotor neurons which function to maintain resting arterial pressure (AP) and to mediate the changes in AP elicited by stress.

Excitation of RVL neurons by hypoxia or NaCN also elevates rCBF without changing cerebral metabolism and synchronizes the EEG. The cerebral effects, however, are mediated by a caudal subdivision of RVL (RVLc) which is not hypoxia-sensitive. Lesions of RVLc block most of the cerebral vasodilation elicited by hypoxiaemia but not hypercarbia, indicating specificity and suggesting that hypoxic cerebral vasodilation is primarily reflex. The pathways by which RVL elicit cerebral vasodilation are still unknown but it appears that such information is relayed through a small region of subthalamus including portions of the zona incerta\lateral hypothalamus. In the cortex vasodilation depends upon the integrity of local neurons, including a small subset whose activity results in vasodilation.

**Conditioned neurogenic neuroprotection**

Another system for neuroprotection is represented in the cerebellar fastigual nucleus (FN). Excitation electrically increases rCBF by activating RVLc. However, excitation of intrinsic neurons simulate hibernation by lowering cerebral metabolism and hence rCBF. Stimulation of the FN for 1 hour can reduce by 50-80% the volume/neuronal loss elicited by focal cerebral ischaemia, global ischaemic loss of hippocampal neurons, or excitotoxic damage. This protection persists for about 2 weeks and is reversible. The mechanism of protection is unrelated to changes in rCBF or metabolism. It entails, in part, a reduction in cortical excitability but, most prominently, a widespread down-regulation in the response of cerebral vessels to proinflammatory stimuli (impairing expression of iNOS and ICAM, possibly mediated by up-regulation of the IFN subunit of the NFkB complex). Neuroprotection, unlike changes in rCBF, arises from intrinsic FN neurons. These findings therefore indicate that the brain contains systems dedicated to regulating rCBF independently of metabolism. Such systems may serve to protect the brain by selectively increasing rCBF or by initiating complex molecular events resisting apoptotic neuronal loss. These systems are presumably coactivated by stress and act to maintain the integrity of the brain in the face of real or threatening impairment of blood flow and/or oxygen flow to that tissue. Impairment of that system may facilitate neuronal loss in stress.
3.5 Neurotransmitters regulate energy metabolism in astrocytes: implications for functional brain imaging

Astrocytes are ideally positioned to couple neuronal activity with energy metabolism. Thus, particular astrocytic profiles, the end-feet, surround intraparenchymal capillaries, implying that they form the first cellular barrier that energy substrates entering the brain parenchyma, in particular glucose, encounter. In addition, astrocytes possess receptors and reuptake sites for neurotransmitters, and astrocytic processes ensheath synaptic contacts; these features imply that astrocytes are ideally positioned to sense increases in synaptic activity and to couple them with energy metabolism. Three metabolic processes regulated by neurotransmitters in primary astrocyte cultures prepared from neonatal mouse cerebral cortex have been characterized: glycogenolysis, glycogen resynthesis and glycolysis (for a review, see Cerebral Cortex, 1996, 6: 50-61). Glycogen is the largest energy reserve of the brain, localized almost exclusively in astrocytes containing vasoactive intestinal peptide. Vasoactive intestinal peptide (VIP) and noradrenaline (NA) promote glycogenolysis via protein kinase A (PKA) (VIP and α receptors) and PKC (α1-receptors) at a rate of 5-10 nmol/mg prot/min, which is a rate of the same order as that of glucose utilization by the grey matter. PACAP and ATP exert a similar effect. Following this rapid (within 1-5 min) glycogenolysis, VIP and NA induce a massive glycogen resynthesis maximally expressed after 8 hours, which brings glycogen to levels tenfold higher than before VIP or NA application. This glycogen resynthesis is mediated by cAMP-dependent induction of gene expression. Both early and late genes have been found to be related to energy metabolism. Thus, VIP and NA induce C/EBP § and γ, which are members of an immediate-early gene family acting as transcription factors for genes involved in energy metabolism regulation in liver and adipose tissue. In addition, transfection of cultured astrocytes with cDNA encoding for C/EBP § amplifies the resynthesis of glycogen evoked by NA. Northern blot analysis has shown that the mRNA encoding for glycogen synthase is massively induced within 4 to 6 hours by VIP and NA. These results strongly suggest that VIP and NA can regulate the expression of early and late genes that encode for gene-products involved in their metabolic effects.

Another neurotransmitter-regulated metabolic process has been described in astrocytes. Thus, the excitatory neurotransmitter glutamate, in addition to its receptor-mediated effects on neuronal excitability, stimulates glycolysis, i.e. glucose uptake and lactate production, in astrocytes. This effect is mediated by the Na-dependent uptake of glutamate into astrocytes which triggers a cascade of molecular events involving the Na⁺/K⁺-ATPase, leading to the glycolytic processing of glucose and to the release of lactate by astrocytes. The stoichiometry of this process is such that for one glutamate taken up with three Na⁺, one glucose enters astrocytes, two ATPs are produced through
glycolysis and two lactate are released. Within the astrocyte, one ATP fuels one "turn of the pump" while the other provides the energy needed to convert glutamate to glutamine by glutamine synthase. Since glutamate release occurs following the modality-specific activation of a brain region, these data are consistent with the view that during activation, glutamate uptake into astrocytes leads to increased glucose utilization and lactate production, which can be subsequently used by neurons to meet their energy needs. Further support for this notion of an "astrocyte-neuron lactate shuttle" in the brain has been provided by the recent identification of two lactate transporters, MCT-1 and MCT-2, and two isoforms of lactate dehydrogenase, LDH-1 and LDH-5, selectively expressed in astrocytes (MCT-1, LDH-5) or neurons (MCT-2, LDH-1). In vivo $^{13}$C MRS studies support this model. Thus, the simultaneous measurements over a range of synaptic activity of the tricarboxylic acid cycle and the cycling of glutamate to glutamine (a process which occurs exclusively in astrocytes) using $^{13}$C MRS has revealed a striking stoichiometric relationship of 1:1 between glutamate cycling (a reflection of synaptic activity) and glucose utilization. These data suggest a prominent role of astrocytes in the generation of the $^{18}$FDG-PET signal.

3.6 Circadian rhythms and sleep in homeostasis and its relevance to stress

The two-process model of sleep regulation

Human sleep is regulated by at least two processes. (a) The first one is related to previous waking. The sleep debt which increased during prolonged vigil is only to a small part compensated by an increase in duration of recovery sleep. It has been proven, however, that sleep loss can be compensated by an enhancement of "sleep intensity." Sleep intensity is measured in the sleep EEG by integrating the power of delta sleep (low frequency - 0.5-4 Hz). It is now proposed that during wake a factor S increases and then exponentially decreases during sleep. (b) The second process is sleep-independent and concerns the circadian clock. This factor can be studied by registering subjects in total isolation from external time clues. The recording of central temperature is a precise index of the timing of the circadian clock. Thus, sleep propensity is highest at the time of the circadian minimum temperature and lowest at the time of the maximum one.

The two-process model provides a link between the circadian rest-activity rhythm, a ubiquitous feature of living organisms, and sleep, a process that has been specified only in vertebrates. It is proposed that mammalian sleep is the combined result of a circadian and a sleep-dependent process. The circadian component of sleep appears to be related to the circadian rhythms of metabolic and endocrine processes. Circadian rhythms may have been of adaptative significance.
on an evolutionary scale. "Need-fulfilment" can be advanced as an explanatory construct to account for the sleep-dependent component of sleep regulation. Nevertheless, the specification of the "need" in terms of physiological and neurochemical processes remains an open problem and continues to constitute a major challenge in sleep research.

**Stress due to acute phase shift: the jet lag model effect of age**

A constellation of symptoms known as jet lag frequently afflicts people who travel rapidly across time zones. It includes insomnia, fatigue, weakness, sleepiness, gastrointestinal complaints, irritability and malaise. Travel across time zones has also been associated with impaired cognitive performance, recurrence of depression, diabetic ketoacidosis, sleep paralysis and decreased athletic ability.

In exploring the mechanisms by which jet lag symptoms are produced, and the reasons why they are worse in middle-aged persons, three alternative hypotheses could be considered. The first, and perhaps simplest, is that jet lag symptoms are produced when one begins to live on the new time zone, and the myriad biological rhythms controlled by the circadian timing system have not yet fully adjusted to the sudden shift in schedule. It is possible that symptoms remit when the discrepancy between the social schedule and the circadian timing system falls below a certain threshold that may be dependent upon age. The second hypothesis is that the stress of sleep deprivation produces many of the symptoms of jet lag, and the severity of symptoms depends on the ability to obtain recovery sleep and thereby recover from the effects of sleep deprivation. Middle-aged persons may not respond as fully to sleep deprivation as young persons. The third hypothesis, which is the most likely, is a combination of the above two. It would require the presence of both a circadian timing system that has not fully adjusted to a change in schedule and of sleep deprivation which directly produces some of the symptoms of jet lag.

**Stress due to chronic disruption of the circadian system: shiftwork**

Of more concern are the potential effects of chronic, repeated disruption. At risk is the large and increasing segment of the population in industrialized societies called upon to work evening, night, and rotating shifts. A number of studies have been conducted since the first observations of increased medical complaints in shiftworkers in the armaments industry during the First World War. However, epidemiological studies of shiftworkers are hampered by methodological difficulties. In particular, the incidence of pathology in shiftworkers tends to be seriously underestimated because of a number of characteristics of the population. Complaints related to sleep and wakefulness are the
The most predictable consequences of shift-work.

The problem of workers falling asleep on the job is a serious issue for those who must staff continuous operations. In a series of confidential surveys of industrial plants, between one-third and two-thirds of shift-workers report that they fall asleep at least once a week on the job, and this occurs because of the chronic circadian phase disruption, not only during the night shift but also during day and evening shifts. With the increasing technological complexity of the jobs that shift-workers are called upon to perform, and the consequences for the health of others - whether it be flying aircraft or operating the control rooms of chemical, manufacturing, and nuclear plants - this problem is becoming one of serious dimensions.

The disrupted sleep of the shiftworkers is presumably one of the causes of the higher incidence of accidents among them, especially during off-duty hours. In addition, workers required to perform at the nadir of their performance rhythms are at considerably higher risk of accidents. With further research it may be possible to define a "shift maladaptation syndrome" sufficiently rigorously to exclude the larger number of individuals who would prefer to obtain daytime jobs rather than rotate shifts. Every shiftworker is fatigued and/or has problems sleeping at certain phases of his or her schedule, but these complaints typically resolve with a long weekend break during which the worker can catch up on sleep. Those with more serious complaints typically have a more fragmented sleep-wake cycle that is not corrected by two or three days of rest. Similarly, transient dyspepsia related to an ill-advised meal should be distinguished from more serious and prolonged gastrointestinal pathology.

Risk could potentially be reduced by the prospective identification of a subgroup of workers who seem particularly prone to the adverse effects of shift-work. It is possible that intolerance to shift-work may be associated with a low-amplitude body temperature rhythm, which may be an indication of a lack of robustness of the endogenous circadian system, or it may be a result of chronic desynchronization of the body temperature rhythm from the work-rest schedule. This conclusion lends support to the notion that the pathophysiology of shift maladaptation syndrome relates to a loss of internal coherence in the multioscillator circadian timing system.

3.7 The amygdala and stress

Considerable progress has been made in elucidating the brain pathways involved in detecting and responding to threatening stimuli, and learning about novel threats. Much of this progress has come from studies of fear conditioning, in which a relatively neutral stimulus, like a tone, acquires
aversive properties after being paired with a noxious event. Conditioned stimuli of this type, like other threatening stimuli, activate the HPA axis, making fear conditioning a useful model for approaching the question of how psychologically meaningful events trigger stress responses. The pathways of fear conditioning involve transmission of information from sensory processing areas in the thalamus and cortex to the amygdala. The lateral nucleus of the amygdala receives and integrates sensory information and sends the outcomes of its processing to the central nucleus. The central nucleus, in turn, is the interface with motor systems controlling automatic or reflexive fear responses of various types (behavioural, autonomic, HPA and other endocrine responses). Sites of plasticity within these circuits, and some cellular mechanisms involved, have also been identified. The earliest synapses within the amygdala are plastic during conditioning, as are several subsequent links, including the central nucleus, suggesting that fear learning is best understood as a property of the system involved rather than of a particular site.

In addition to developing fear responses to the specific stimulus that is paired with the noxious event, fear also conditions to the general context in which the noxious stimulus occurs. So-called context conditioning requires the hippocampus and inputs to the basal nucleus of the amygdala, which in turn projects to the central nucleus. An important issue is how we get rid of fear. It seems that the medial frontal cortex and its connections to the amygdala are involved. Thus, lesions of the medial cortex lead to an intensification of fear and an increased resistance to extinction. Given that stress can adversely affect the hippocampus and medial cortex, and that patients with psychiatric conditions suffer from stress, it is possible that stress-induced changes in these areas contribute to the intense, therapeutically resistant, contextually free fear that psychiatric patients often have. We are thus beginning to uncover the neural mechanisms, from systems to cellular levels, underlying emotional processing, including emotional learning and memory, at least within the fear system. And these findings are beginning to elucidate mechanisms that may be relevant to understanding emotional disorders.

3.8 The human amygdala and stress

Selye defined the general adaptation syndrome and the diseases of adaptation, as, "the sum of all nonspecific systemic reactions of the body which ensue with long continued exposure to stress." The phases include at first signs of damage or shock, then the alarm reaction, followed by a stage of resistance, ending in a state of exhaustion. He assigned the adrenocortical hormones a substantial role in adaptation to stress.

In animals, the role of the amygdala in the physiological and behavioural expression of fear
has been summarized recently in the reviews by Aggleton (1992) and Gloor (1997). Stimulation studies and fear-conditioning models have identified the amygdala and especially its central nucleus as essential components in stress reactions. The connectivity of the amygdala to subcortical and brainstem structures on the one hand, and to widespread cortical areas on the other hand, bring into play autonomic and brainstem functions with cortical sensory modalities. Stimulation of the amygdala in humans and cats provokes an "arousal" electrical response that is an associated feature for fear conditioning.

In humans, the response to stress can be correlated with the emotional expression of fear. Fear appears as an aura in over half the patients with temporal lobe seizures and can be evoked from the anterior insular cortex and most consistently (for a summary, see Gloor, 1997). Stimulation producing déjà vu and hallucinations also indicates that the amygdala can be considered to play an intimate role in emotional memory.

Two lines of evidence from imaging confirm the importance of the amygdala in the expression of fear. First, damage to the amygdala as displayed on magnetic resonance imaging measurements is more frequent in patients who have ictal fear as an aura of their temporal lobe seizures. On the other hand, damage to the region of the amygdala either from encephalitis or after unilateral temporal lobectomy is associated with impaired recognition of a fearful stimulus. Recent studies by positron emission tomography and functional magnetic resonance imaging have both demonstrated that fearful stimuli activate the amygdala. Thus, the amygdaloid complex with its widespread reciprocal connections to subcortical, brainstem and cortical areas has been shown in experimental as well as human studies to play a prime role in the emotional expression of fear and in physiological and behavioural phenomena related to adaptation to stress.

3.9 Stress and the hippocampus

There is considerable evidence in animals to indicate that repeated episodes of stress are associated with damage to hippocampal neurons. Work in animal systems has demonstrated that repeated episodes of stress or elevated glucocorticoid levels, also characteristic of depression, can produce neurotoxic damage to hippocampal pyramidal cells. As little as 21 days of restraint stress in rats resulted in atrophy of apical dendrites of CA3 pyramidal neurons. Similarly, restraint stress or chronic multiple stressors, for example shaking in addition to restraint, produced dendritic atrophy of CA3 neurons. Additionally, social stress or long-term glucocorticoid treatment produced hippocampal neuronal damage in primates. Furthermore, the CA3 subfield of the hippocampus was found to be damaged, and follow-up studies indicated that this damage was due to hippocampal
exposure to glucocorticoids.

The mechanisms whereby chronic glucocorticoid exposure leads to hippocampal cell death are not fully delineated, but enhanced vulnerability to excitotoxicity may be a primary factor. Glucocorticoids appear to act indirectly by disrupting cellular metabolism and enhancing hippocampal neuronal vulnerability to a wide variety of insults. Glucocorticoid or psychosocial stress-induced atrophy of hippocampal pyramidal neurons is attenuated by NMDA receptor blockers and by phenytoin, a sodium and T-type calcium channel blocker. Collectively, these results support a hypothesis that an interaction between glucocorticoids and glutamate are involved in stress-induced neuronal atrophy.

The relevance to depression of these studies showing that chronically elevated glucocorticoid damage hippocampal neurons depends on the assumption that depression is associated with dysregulation of the glucocorticoid system. There have been many studies indicating that depression is accompanied by dysregulation of the HPA axis, resulting in elevated cortisol levels. In summary, the hypercortisolaemia of depression thus involves hypersecretion of corticotropin-releasing factor (CRF), a compensatory decrease in sensitivity of the pituitary and increased sensitivity to ACTH by the adrenal.

Recent evidence indicates that the hippocampus is sensitive to damage, and studies have found hippocampal atrophy in Cushing's syndrome, recurrent major depression, and post-traumatic stress disorder, all illnesses in which there can be repetitive elevation of glucocorticoid. Based on the preclinical studies discussed above, imaging studies have been conducted to determine whether patients with recurrent major depression have altered hippocampal structure. In an initial investigation women who had a history of recurrent major depression but who were not currently depressed were found, as measured on MRI scan, to have smaller hippocampal volumes on average than controls case-matched for education and age. In addition, the study found that lifetime cumulative duration of major depression correlated with loss of hippocampal volume. Subsequent studies have confirmed this finding and have extended it to include volume loss in the amygdala as well.

The assumption that these hippocampal atrophic changes are due to elevated cortisol levels produced by psychological trauma and stress is supported by a recent study in normal subjects, which showed that in normal elderly subjects baseline elevations in cortisol predicted longitudinal hippocampal atrophy over five years. Furthermore, hippocampal volume showed a significant relationship to delayed memory, and this relationship was not present for other temporal brain
regions, including the parahippocampal and fusiform gyri. The results of studies of other patient populations also suggest a relationship between elevated cortisol levels and hippocampal volumes including Cushing's syndrome and dementia of the Alzheimer type.

The depression-related volume loss does appear to be cumulative, with the implication that early recognition and treatment of depressive episodes is important in preventing cumulative damage from repeated depressive episodes.

3.10 Interaction of stress systems in the adrenal: basic and clinical aspects

The maintenance of life depends on the capacity of the body to sustain an internal homoeostasis. Furthermore, the organism relies on its ability to react and adapt to a constant change of external stimuli. To perform this task, all living beings have developed an efficient but complex signalling system allowing the integration of the necessary defence mechanisms directed against all environmental changes and aggressions to which the organism is subjected, the so-called stress systems. Therefore, a normal stress response is a prerequisite for life. The two major stress systems that have been well characterized are the HPA axis and the sympathetic nervous systems (SNS). The central components of these stress systems are located in the hypothalamus and the brainstem. The regulation and central interaction of the HPA-axis and the sympathetic nervous system and the immune system have been extensively studied. The cross-talk of the two systems in the periphery where the adrenal as the end organ of the two systems unites the cortisol-producing cortex and the catecholamine-producing medulla under a common capsule has now been recently characterized. In this cross-talk, adrenocortical steroids influence the differentiation of adrenomedullary cells. On the other hand, the sympatho-adrenomedullary system influences adrenocortical functions. Neuroendocrine regulation of this type may depend on neurotransmitters released from nerve endings in the adrenal cortex or from adrenomedullary chromaffin cells. These cells secrete different neurotransmitters and a whole series of neuropeptides following splanchnic stimulation that influence adrenocortical steroid production in many species. The effect of adrenomedullary neuropeptides on steroidogenesis varies from stimulation to inhibition. Under basal conditions, secretory products released from chromaffin cells are potent stimulators of adrenocortical steroidogenesis as shown by co-cultivation of the two cell types.

The cells of the adrenal medulla and the adrenal cortex are significantly interwoven in many mammals. This intimate intermingling of the two cell types allows extensive contact zones, which are the prerequisite for the above-mentioned paracrine interactions. In addition to the direct effect of chromaffin cells on adrenocortical cells, adrenocortical innervation and adrenomedullary secretory
products may be involved in the regulation of adrenal blood flow and thus influence the
adrenocortical cells in an indirect manner.

The importance of these interactions is seen in an additional, ACTH-independent regulation
of adrenocortical steroidogenesis. There is indeed compelling evidence that non-ACTH factors play
a significant role in adrenal responses to homeostatic challenges, i.e. in the postnatal period. In
human adrenals, adrenomedullary and adrenocortical tissue are extensively intermingled. This
provides the basis for a close cell-to-cell interaction allowing for a close coordination of the two
stress systems. These interactions are furthermore important in several clinical situations. Adrenal
nodules and adenoma seem to originate frequently from cortical islets in the medulla and
overexpression or ectopic expression of neuroendocrine and cytokine receptors may be involved in
adrenal tumorigenesis. In many clinical situations, including sepsis, surgical stress, depression and
diabetes, there is a dissociation between plasma ACTH concentrations and cortisol secretion.

Under physiological conditions in adult life, the extrapituitary-adrenocortical response does
not seem to be an exclusive but rather an additional pathway of stress regulation. Extrapituitary
regulation of adrenocortical function may be responsible for maintaining a basic reserve of cortisol
production observed in patients with hypophysectomy. Based on a substantial body of data, the non­
ACTH-dependent mechanisms are important in maintaining the normal circadian rhythm, adrenal
zonation, fine tuning of the gland and adrenal growth.

Integration of the molecular and physiological data of the isolated cell systems in the stress
axis has shown that there is a close link and important interaction between all major components of
the stress system including the endocrine, nervous and immune systems. An adrenocortical cell
deprived of its tissue integrity, of its impulses from the nervous system, of its cellular
communication with chromaffin, endothelial and immune cells and of its intercellular connections
such as gap junction loses at each level more of its normal capacity to produce glucocorticoids and to
adequately respond to the homeostatic challenges of stress. The adrenal medulla appears to exert
important regulatory effects on the adrenal cortex. It is thus possible that the cortico-chromaffin cell
interaction is crucial in the response of the adrenal gland to stress and the overall adaptive
mechanisms as well as the pathophysiological development of stress-related diseases.

3.11 Immune response and brain gene expression in relation to stress

The mechanisms mediating the action of immune-related molecules on the endocrine
hypothalamus have recently been the subject of much controversy and debate. This can be explained
by the wide variety of players participating in the neuroendocrine-immune interplay as well as the models of infection/inflammation. Systemic injection of the endotoxin lipopolysaccharide (LPS) is a good tool to increase the release of proinflammatory cytokines by systemic myeloid cells, a treatment associated with wide neuronal activation and a complex series of mechanisms taking place within the central nervous system (CNS). However, LPS has by itself the ability to stimulate cytokine production within the CNS and that activation of phagocytic cells and cytokine release of systemic origin is a distinct and independent response. Bacterial endotoxin causes a profound transcriptional activation of its cell surface receptor CD14 in both parenchymal and non-parenchymal elements of the brain, which may subserve a direct binding ability of LPS to modulate different brain functions, including activation of PVN (paraventricular nucleus of the hypothalamus) neurons. In contrast, the mechanisms mediating the effects of systemic localized inflammation to trigger neuroendocrine CRF neurons are dependent on cytokines of systemic origin. COX-2 and NFκB mRNAs were detected along blood vessels of the entire brain microvasculature following intramuscular turpentine injection, and the signal of these transcripts paralleled the swelling of the left hind limb. Vascular-associated cells are therefore responsible for the central production of prostaglandins (PGs) during systemic inflammation, and circulating IL-1β is a potent mediator of this response. PGE₂ synthesis through NFκB/COX-2 signals may transfer the information, at the level of the BBB, from circulating cytokines to parenchymal elements. These events are likely to occur locally within the PVN, because EP₄ PGE₂ receptors are strongly expressed within CRF neurons during immune challenge. This indicates that PGE₂ synthesized by the endothelium of hypothalamic capillaries has the ability to target its receptor of EP₄ subtype on to neuronal elements of the PVN, a phenomenon that may be directly responsible for triggering the release of CRF and then the corticotroph axis during systemic inflammatory processes.

IL-6 also plays a role in mediating the neuronal response during systemic immunogenic processes. Although IL-6 was shown to trigger the release of CRF from hypothalamic explants in vitro, this cytokine seems unable, in contrast to IL-1β and TNF-α, to induce neuronal activation and CRF gene transcription in the PVN. This lack of effect might be explained by the fact that IL-6 receptor (IL-6) is not present in this nucleus under basal conditions; systemic immunogenic stimuli cause a profound transcriptional activation of the gene encoding IL-6R in the endothelium of brain capillaries and within the parenchymal cells of the rat PVN. It has therefore been proposed that induction of IL-6R synthesis may be an essential step taking place early during inflammation to allow IL-6, when it becomes available in the circulation, to trigger neuronal activity. Quite interestingly, our recent observations suggest that IL-6 signalling is enhanced during endotoxaemia and IL-6 modulates PVN functions only after pre-induction of its receptor in immune-challenged animals. Using a dual labelling technique, it was also found that some CRF neurons express IL-6R,
suggesting that IL-6 may directly target these cells to trigger neuronal activation and CRF secretion. In this regard, systemic LPS insult causes a profound transcriptional activation of the gene encoding IL-6 in the sensorial circumventricular organs (CVO) and the choroid plexus, which provides solid evidence that the cytokine is also produced in the brain and may act on neurons or other parenchymal elements of the CNS. In addition, our latest data obtained from experiments performed in wild-type and IL-6-deficient mice support the concept that IL-6, although not involved during the initial phases of endotoxaemia, is necessary during the later phases for maintaining the stimulation of CRF neurons controlling the HPA axis and for prolonging the activation of neural cells throughout the brain. This phenomenon may be of great importance in protecting the brain and in restoring homoeostasis during bacterial septic shock. Disturbances in these sophisticated endogenous pathways may contribute to the onset and progression of various pathological states characterized by an exaggerated immune and stress response.

3.12 Stress and brain-gut motor alterations

"...should this man receive bad news, or should sad and baneful passions suddenly arise in his soul, his stomach and intestine will immediately cease to act on the foods contained in them. The very juices in which the foods are already almost entirely dissolved will remain as though struck by a moral stupor." Pierre Cabanis statement in 1802 is among the first prescientific recognitions that the brain impacts upon gut function. In 1833, William Beaumont reported clinical observations that emotional states linked with fear or anger disturbed gastric function. Pioneer experimental reports of brain-gut interactions came from Pavlov and Cannon, who demonstrated that psychological stimuli such as sham feeding and fear influence gastric secretory and motor function in dogs and cats, and Hall, who established in rodents that defecation scores are a means of measuring the fearfulness response to unfamiliar surroundings or arousing situations. Selye, while working at McGill University, fathered the unifying concept of stress, initially reported in 1936 as a "syndrome produced by divers nocuous agents" and later defined as the "nonspecific response of the body to any demand". The activation of the pituitary-adrenal axis induced by exposure to various stressors stimulated research on the biochemical coding of the hypothalamic factors triggering the endocrine response. In the 1950s Guillemin’s team (a former Ph.D. student of Selye) and Schally observed independently the presence of a "corticotropin releasing factor" (CRF) in hypothalamic extracts that could stimulate adrenocorticotrophic hormone (ACTH) release from anterior pituitary cells. However, CRF eluded characterization until 1981, when Vale and co-workers (former Ph.D students of Guillemin) reported the isolation of the 41 amino acid peptides involved in the pituitary stimulation of ACTH release. Recently a new CRF-related mammalian peptide, urocortin was identified by the same group in rats and humans and the 40 amino acid peptide share 45% homology
Since the discoveries of CRF and the development of specific CRF receptor antagonists by Rivier et al., the understanding of the neurobiological basis of the stress response has become a near-reality. The following is brief background information on CRF distribution in the brain, CRF receptor characterization and new advances in the development of selective CRF antagonists, providing experimental evidence supporting a role of brain CRF in mediating the gastric and colonic motor alterations induced by stress and its possible pathophysiological relevance to irritable bowel syndrome.

**Brain CRF and CRF receptor distribution and biological actions of central CRF**

CRF is widely distributed in the brain, with the highest abundance in the PVN. A subset of CRF-containing neurons projects to the portal capillary zone of the median eminence to stimulate the secretion of ACTH from the anterior pituitary. The subsequent ACTH-induced release of adrenal glucocorticoid is part of the peripheral limb of the hypothalamic-pituitary axis (HPA) response to stress. In addition to its neuroendocrine role, central injection of CRF elicits a wide spectrum of behavioural, autonomic and visceral responses including anxiogenic behavior and decreases in food intake, increases in sympathetic outflow and decreases in vagal activity and cardiovascular changes as well as immunological alterations which mimic the bodily alterations induced by various stressors.

CRF mediates its action through interaction with specific, high-affinity membrane-bound receptors that are coupled to a guanine nucleotide stimulatory factor (G) signalling protein, resulting in increased intracellular cAMP levels. To date, two different CRF receptors, CRF$_1$ and CRF$_2$ subtypes, have been cloned and characterized in rats as well as in humans. These receptors show an overall 71% identity and differential pharmacological and anatomical profiles, indicative of distinct functional roles. Binding constants in transfected cells indicate that rat/human CRF (r/h CRF) exhibits a higher affinity for the CRF$_1$ receptor compared with the CRF$_2$ subtype. By contrast, CRF-related peptides, sharing a 40-50% structure homology with CRF, namely, sauvagine, a 40-amino acid peptide isolated from the *Phyllomedusa sauvagi* amphibian’s skin, and urotensin-I, a 41-residue peptide isolated from teleost fish, as well as mammalian urocortin display a higher affinity at the CRF$_2$ receptor than CRF while having a similar affinity to that of CRF$_1$ receptor. The CRF$_1$ subtype is the predominant form localized in the pituitary, olfactory bulb and cerebral cortex, while the CRF$_2$ subtype is found in the lateral septum, hypothalamus, amygdala and brain stem.
CRF receptor antagonists

Rivier et al. developed three generations of CRF analogs with competitive antagonistic activity at both the CRF₁ and CRF₂ receptor subtype. Alpha-helical CRF, developed in 1982, and the constrained D-Phe CRF analog (D-Phe, Nle, CaLeu) h/CRF have been extensively used in vivo to assess the physiological role of CRF in endocrine, autonomic, immune, behavioural and gastrointestinal responses to various stressors as well as stress-related changes in gastrointestinal motor functions. However, these antagonists have some limitations because of their poor solubility, persistence of intrinsic activity, and weak potency at the hypophyseal site of action. In addition, alpha-helical CRF has high affinity for the CRF binding protein. Further search in achieving conformational stability of CRF antagonists resulted in the development of astressin, cyclo(30-33) (D-Phe, Nle, Glu, Lys) h/CRF. Astressin's main characteristics are its low intrinsic activity, high solubility in aqueous solutions, increased metabolic stability and high affinity to both CRF₁ and CRF₂ receptor subtypes while lacking an affinity to the CRF binding protein. Recent reports indicate that astressin displays about 32% and 100% higher potency than D-Phe CRF and alpha-helical CRF respectively, to inhibit ACTH secretion from pituitary cells in culture. Moreover, after peripheral administration in rats, astressin is 10 times more potent than any other CRF antagonists reported to date to inhibit stress-induced increases in ACTH plasma levels.

Role of activation of brain CRF receptors in stress-related alterations of gastrointestinal motor function

Consistent reports clearly established that central administration of CRF acts in the brain to inhibit gastric emptying while stimulating colonic motor function through modulation of the vagal and sacral parasympathetic outflow in rodents. Endogenous CRF in the brain plays a role in mediating various types of stressor-induced gastric stasis including postoperative gastric ileus as well as activation of colonic transit and fecal excretion elicited by psychological aversive or fearful stimuli. Brain CRF is also involved in the cross-talk between the immune and gastrointestinal systems as systemic or central interleukin-1B delayed gastric emptying while stimulating colonic motor activity through activation of CRF release in the brain. The PVN and dorsal vagal complex are important neuronal circuitry for the central action of CRF to inhibit gastric motor functions while the PVN and locus coeruleus complex are sites of action for CRF to stimulate colonic motor function.

The inhibition of gastric and stimulation of colonic motor function induced by central CRF action on the autonomic nervous system is mediated by CRF₂ receptors while the anxiogenic and
colonic motor responses involve CRF$_1$.

3.13 Psychological reactions to stress

The rapid social and economic development occurring in China has led to increased exposure to stressors. Therefore, in the last decade Chinese scientists have studied the biological and psychological effects of stress in a wide variety of circumstances such as coronary heart disease, and catastrophes, such as fire and earthquake, as well as following psychological stress. Following coronary artery disease (CAD) in 80 patients in Beijing, the presence of symptoms of anxiety was observed in 93.5% of patients and of depression in 32.5%. At two weeks follow-up, it was found that symptoms of anxiety were present in 71.5% and depression in 13.45%. These rates of depression are lower than those described in Western populations. This is of clinical relevance as the co-occurrence of both CAD and depression increases the mortality of CAD fourfold. Patients with CAD also had increases in cortisol and decreases in IL-2 levels. Following natural disasters such as major fires and earthquakes, it was documented that there were increases in anxiety, depression and posttraumatic stress disorder (PTSD). Students at Beijing Medical University were studied before and after final exams to test the hypothesis that psychological stress could adversely affect health. We found that students facing final exams had increased physical illness, associated with alterations in markers of endocrine and immune function. Our studies have shown that in China a variety of stressors including medical illness, psychological stress and natural disasters have clinical and biochemical correlates which are the topic of active investigation at the present time.

3.14 Identifying biological and health correlates of stress

The biological correlates of stress in two stressor situations, and the general implications that can be drawn for health have been examined. The first investigates the appearance of explicit physiological stress effects due to a known physiological cause. The second analyses the nature of physiological responses to an explicit, external source of stress. The third issue focuses on when and how such responses might be linked to possible health consequences of high levels of sustained stress. Finally, it is suggested that knowledge-based technology could facilitate the assessment of the health significance of stress, at the community level.

The example of acute physiological stress is the effect of anoxia leading to acidaemia in the fetus, especially during delivery. Replacing earlier attention to fetal heart rate (FHR) or its reciprocal, RR interval, recent work has focused on the morphology of the fetal electrocardiogram (fECG). This can be quantified in a rudimentary way by measuring intervals or segmental
magnitudes within the fECG; PR intervals and ST segments have been used. Both exhibit considerable beat-to-beat variation and in any event, there is a relation between PR and RR; consequently the relation between PR and RR has been proposed as an indicator of developing acidosis. The substantial variability of this measure has led to the study of the PR/RR differences between the acidotic and non-acidotic fetus. It has been shown that the result of this particular physiological stressor – anoxia – can be described, in effect, as opening a different neurophysiological “pathway” between PR and RR and that in acidosis this pathway dominates.

In the context of identifying the physiological mechanisms underlying responses to workload stress, examples of heart rate variability measurements in airline pilots are considered. These data are analysed in the light of recent work which showed that the totality of heart rate variability (HRV) results in all circumstances from a variety of influences, certain of which can be attributed to specific physiological mechanisms. Utilizing this information, the nature of the pattern variability can show how appreciable workload stress apparently affects the relevant physiological dynamic control systems. First, there is a reduction or suppression of the 10-second Traube-Hering quasi-oscillation that is thought to originate in short-term non-linear control of blood pressure. Second, the transient and longer period fluctuations that have been attributed to first and second stage thermoregulation also disappear. Similar findings come from other information-handling work-load situations. There is also some evidence of closely reproducible behaviour of the HRV response to broadly similar stress situations.

These and other related observations raise several speculative ideas for discussion, particularly in relation to the linkage between short-term responses to stressors and the long-term responses to stress. There are several distinct threads. In the cases examined here, of acute physiological stress and of short-term workload stress, the stress reaction appears to modify the behaviour of chemically-mediated dynamic control systems in the body. Furthermore, it is believed that at least one body control system (thermoregulatory), which has several increasingly powerful modes of action, changes its control strategy with increased workload. It is suggested that perhaps other control systems do also. There is some evidence that breathing patterns may also change strategy with informational workload stress.

In the severe stress “overload” situation, the control system may be unable to make the controlled system operate optimally. Sub-optimal behaviour means that while more action (physical cost) is demanded, the result is less effective.
It is suggested that, under sustained overloading which leads to sub-optimal performance of a control system, the modified control behaviour can be learned, therefore becoming "habitual" - with generalized stress consequences, particularly through the cardio-respiratory system.

The population-wide impact of generalized stress effects, it is suggested that "Knowledge-based" health indicators Turning to consider may have some value. The essence of this approach is to use expert observations, insights and judgements about selected individual households in a community, collected as extensively as possible. Knowledge of this type can rarely be expressed other than in verbalized statements. However, using such knowledge, it may be possible to construct a knowledge map that shows how these various observations, and the inferences to which they lead as a result of logical analysis, combine to generate a composite picture of specific aspects of community health, such as stress. The approach depends on the application of computational logic.

A more general issue about health has been raised by WHO's ACHR in its Research Policy Agenda for Science and Technology to support WHO's activities in developing global health. This Policy Agenda draws attention to the many severe existing and emerging problems of critical significance for global health. The ACHR has issued a call to harness the efforts of the world scientific community to help solve these problems.

The implementations proposed by the ACHR to achieve this collaborative effort will make extensive use of telecommunication and information technology to establish and operate IRENEs: Intelligent Research Networks. These IRENEs, each on a specific research problem, will make it possible for cooperating researchers to join forces to plan all aspects of the research, to agree on the distribution of work, to monitor progress, to stimulate new workers to join the project regardless of physical location, and to support the work of young researchers and those with less experience, particularly in developing countries.

The IRENE approach would be an ideal means for studying the synergistic effects of stress on health at the community, national and global levels. Many varieties of stressor affect communities around the world and the resulting impact on health is believed to constitute a significant and growing problem that calls for sustained research support from a variety of scientific and technological disciplines.

4. DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

4.1 Discussion
4.1.1 Homoeostasis and adaptation

The historical evolution of the concept of stress was discussed, from antiquity to the present time. The philogenetic characteristics of the response to stress were presented, illustrating how different organisms cope with stress. Stress was identified as a key element in adaptation and evolution. The stress response is now being characterized at the levels of population, individuals, organism, systems and cells. Heat shock proteins and early genes have been identified as elements contributing to the stress response at the intracellular level and further research on their roles in the regulation of homoeostasis and in disease is needed.

4.1.2 Stress and adaptation: a psychobiological interpretation of Selye's concepts

It is essential to study individual differences in the response to stress. Understanding phenotypic features and related genetic factors that lead to susceptibility to stress will provide useful tools to predict the risk for stress-induced pathology.

4.1.3 Homoeostatic processes in neuroendocrinology

Neuroendocrine transduction and neuroendocrine integration are key processes for homoeostasis. Neuroendocrine regulation of homoeostasis involves several time domains ranging from minutes to decades. The response to stressors involves specific changes in a variety of neuroendocrine systems consisting of widespread but discrete circuitries and pathways. Recent work has shown that a peripherally secreted hormone, leptin, contributes to homoeostasis by modulating neuroendocrine transduction and participating in neuroendocrine integration. Future work in the neuroendocrine control of homoeostasis should identify new molecules, mechanisms and pathways that transduce the response to stressors and facilitate adaptation to stress. Diseases of adaptation involve dysregulation of the neuroendocrine response to stress. The cloning of neuropeptide receptors has permitted the development of non-peptide neuropeptide receptor agonists and antagonists as new therapeutic strategies for diseases whose pathophysiology involves dysregulation of the stress response and homoeostasis.

4.1.4 Cerebral blood flow and relation to neuroprotection

Co-activation of the sympathetic nervous system is an early and essential component of
responses to stress. One major function of the response is to protect the brain, the most metabolically active organ, from deprivation of oxygen and/or glucose. Two types of central neural mechanisms contribute to the neuroprotection. One results from activation of oxygen-sensitive neurons in the rostral ventrolateral medulla (RVC) to initiate an oxygen-conserving (driving) reflex which, increases sympathetic activity and redistributes blood flow in the brain. The second, represented in the cerebellar fastigual nucleus (FN), can, after one hour of stimulation, elicit long-lasting (weeks) of protection from focal and global ischaemia and excitotoxicity by mechanisms which in part result from down-regulation of immune responsivity of cerebral vessels. Intrinsic mechanisms in brain-regulating autonomic function, cerebral blood flow and immune response are interconnected and probably are important elements in the response to stress.

4.1.5 Neurotransmitters regulate energy metabolism in astrocytes: implications for functional brain imaging

The brain being the central organ for homoeostatic control, stress and adaptation mechanisms are widely expressed in neural cells. Astrocytes, which make up half of the brain volume, play a central role in coupling synaptic activity to energy metabolism. These cells also show adaptive responses to neurotransmitter stimulation. Thus, genes involved in the control of glycogen metabolism are modulated by noradrenaline and VIP. These two transmitters are released under different modalities: "priming" of the cerebral cortex for noradrenaline, and modality-specific local activation for VIP.

4.1.6 Circadian rhythm and sleep in homoeostasis and its relevance to stress

More attention should be given to the extraordinary impairment of vigilance which is almost always the result of shiftwork or continuous workload. If possible, women should be given fieldwork shifts during the daytime only. If this is not possible, they should have fixed work at night. The health consequences of frequent exposure to jet lag should be examined and prevented.

4.1.7 The amygdala and stress

Two important issues were raised. First, given that fear conditioning occurs similarly in invertebrates and vertebrates, and only vertebrates have an amygdala, how was the earlier function conserved and converted into an amygdala-mediated process? Obviously, no one can turn back the pages of evolution and answer such a question. Nevertheless, it is enormously interesting. At the same time, it is not so different from the question of how locomotion or digestion is conserved across...
life forms that are vastly different. The only thing we can say is that fear conditioning probably proved to be such a good solution to the problem of how to learn about new dangers that the function was maintained in ways, surely transitional steps, that are opaque to us now. Second, what is the role of the amygdala in controlling stress, given that many kinds of stressors are still effective in triggering HPA responses in amygdala-lesioned animals? The amygdala will only be involved in triggering HPA responses to stimuli that the amygdala processes. Psychologically meaningful threats, such as those modelled by fear conditioning, trigger HPA responses through the amygdala because the amygdala is required to process such stimuli, whereas painful and other physically stressful events can activate the HPA axis through other channels and involvement of the amygdala is not expected.

4.1.8. The human amygdala and stress

Fear is an emotion that expresses many of the anatomical and physiological features of the response to stress. It thus can be utilized as a paradigm for examining the effects of stress on the nervous system, as, for example, in fear-conditioning models combined with functional brain imaging. Fear occurs as an aura of the epileptic attack in over half of the patients with temporal lobe seizures which have been shown to originate in the amygdala-hippocampal system. Further investigation of the neural substrate for fear should lead to improved clinical recognition of temporal lobe seizures for which medical and surgical treatment offers highly cost-effective treatment. Patients with epilepsy constitute up to one-third of those attending neurology outpatient clinics, a proportion that justifies public health measures directed towards epilepsy.

4.1.9 Stress and the hippocampus

The biological consequence of depression-associated stress can have a deleterious effect on the hippocampus. Operating most likely through glucocorticoid-mediated neurotoxicity repeated episodes of depression have been shown to produce a loss of hippocampal volume in patients suffering from major depression. The volume loss was cumulative: longer duration of lifetime depression correlated with greater loss in hippocampal volume compared with control subjects. In addition, the core nuclei of the amygdala were found to have volume loss, which was correlated with hippocampal volume loss, suggesting a common mechanism.
4.1.10 Interaction of stress systems in the adrenal: basic and clinical aspects

The hypothalamic-pituitary-adrenal axis and the sympathetic nervous system interact at various levels in the brain and at the level of the adrenal gland. This ensures the plasticity of stress systems, which is both an evolutionary drive and crucial for survival. Local production of cytokines, neuropeptides and growth factors and aberrant expression of receptors are involved in adrenal hyperplasia, cell proliferation and hormone production. Defining the ACTH-independent mechanisms of adrenal regulation will help define a new classification of the endocrine stress systems and help to define more specific therapeutic strategies.

4.1.11 Immune response and brain gene expression in relation to stress

Systemic inflammatory insult causes activation of the corticotroph axis, which is reflected by an increase in circulating glucocorticoids. Such increase is essential to restore homoeostasis through activation of transcription factors involved in immunosuppression. Activation of COX-2 within cells of the blood brain barrier to trigger PGE₂ production may be a crucial mechanism for informing the parenchymal elements of the brain, and expression of specific EP receptors may explain the selectivity of the response, such as activation of neuroendocrine CRF cells. Glucocorticoids in return may suppress COX-2 in stimulating I-KBα in a direct genomic effect within the endothelium of brain capillaries. Obviously, such a mechanism may not be attributable to all models of systemic inflammatory challenges, but is a clear link through which circulating pro-inflammatory molecules inform the brain and the neuroendocrine system. The effect of bacterial endotoxin on transcription of its membrane form CD14 receptor first within the sensorial CVOs and then across the brain parenchyma may be a central event to up-regulate pro-inflammatory cytokines of central origin. Whether these molecules play a role in the control of the PVN cells still remains an open question, although their involvement in protecting neuronal material should be considered. Taken together, the molecular mechanisms participating in the neural-immune interaction are complex and depend on the severity, duration and model of infection/inflammation but are crucial in restoring homoeostasis during a profound stress response.

4.1.12 Stress and brain-gut motor alterations

The neuropharmacological approach has pinpointed specific brain nuclei involved in the action of CRF to induce alterations of gastric and colonic motor functions, which overlap with those mediating the endocrine and anxiogenic responses. Strategies used to dissect receptor subtypes
involved in different actions of CRF include selective central CRF antagonists, pre-treatment with oligonucleotide antisense, or CRF antagonists with selective affinity for each CRF receptor subtype.

4.1.13 Psychological reactions to stress

The recent rapid social and economic development occurring in China has exposed a large population to new stressors. At Beijing Medical University Chinese scientists have studied biological and psychological reactions to medical illness, natural disasters, and psychological stress. It has now been documented that in China stress results in psychiatric disorders such as anxiety, stress, and post-traumatic stress disorder, as well as in physical illness, with biochemical substrates as evidenced by abnormalities in neuroendocrine function, catecholamines and immunity. Further research will continue to elucidate biological and psychological reactions to stress in China.

4.1.14 Identifying biological and health correlates of stress

Bearing in mind the widespread and growing impact of stress on health, which affects the family, society and the economy in many countries of the world, it is recommended that research on the public-health effects of stress be encouraged, particularly using the IRENE approach, which is well suited to such research.

4.2 Conclusions and recommendations

All participants agreed to define stress as mechanisms of acute and chronic adaptation necessary for evolution and survival. The integrated stress response is part of the homoeostatic balance, and dysfunction of such response may contribute to disease. Largely unknown to the general health community alterations of the endocrine, neural and immune responses to stress are involved both in the etiology and the pathophysiology of the most common health problems in modern society.

Therefore, the participants of this WHO meeting strongly recommend further research on stress in the basic sciences, clinical medicine and public health.

4.2.1 Need for Further Research

- Explore the mechanisms of gene regulation controlled by neurotransmitters in the brain, which are undoubtedly involved in adaptive processes in the brain. Brain plasticity is also
likely to contribute to adaptive processes.

- Explore further interactions between glial cells and neurons. Evidence is accumulating that proper synaptic function, neuronal survival and possibly the expression of neuronal plasticity are dependent upon a well-coordinated exchange of information between glia and neurons.

- Further studies are needed on the mechanisms of biochemical coding and neuroanatomical substrates of stress-related alteration of gastrointestinal motor dysfunction and visceral pain.

- Further multidisciplinary research is needed on the role of neuropeptide-mediated stress-related gastrointestinal dysfunction in animal models and in human diseases such as postoperative ileus, colitis, and visceral pain.

- The mechanisms by which stress contributes to neuronal death should be elucidated.

- The homoeostatic mechanisms protecting the brain from deleterious effects of stress should be further studied.

- The role of the blood brain barrier in homeostasis should be further studied, with particular attention paid to the concept that the blood brain barrier can be a site through which circulating peripheral immune mediators send secondary signals into the CNS that modulate neuronal function. The molecular mechanisms by which immune-brain interactions occur should be the topic of further investigation, as it is of key importance to neuroscience and to pathophysiology.

- Further research should be conducted on pharmacological interventions which may reverse neurotoxic effects of stress.

- Intrinsic alterations of the endocrine, neural and immune systems are involved in the pathogenesis of major health problems such as diabetes, cardiovascular disease, autoimmune disorders, chronic infectious diseases, gastrointestinal disorders, and mental health problems. An interdisciplinary approach of neuroscientists, endocrinologists, immunologists and clinicians is required to approach the task of elucidating and unravelling the complex cellular and molecular mechanisms of stress in disease. Only if this is done will more specific and promising therapeutic strategies become available.
In order to better understand the response to stress at the cellular level it is suggested that a future WHO meeting be convened on heat-shock proteins (hsp) and other markers of cellular activations such as early oncogenes. Such a meeting should cover the role of hsp in general physiological stress, health, medicine, and clinical applications.

4.2.2 Implications for public health

The relevance of the stress response can be interpreted at different systemic levels: biological, environmental, socioeconomic. For example, biochemical coding relates to several clinical specialties and has implications for diagnosis, intervention and control of diseases. The same considerations would apply in understanding the mechanisms of neuronal death or in designing pharmacological approaches for neuroprotection from stress overload. Acute and chronic exposures to noxious environmental agents are a well-recognized public health issue. Lifestyle-related problems such as violence, malnutrition and smoking can also be interpreted in the light of a stress response.

At the socioeconomic level, demographic phenomena such as migration (including flows of refugees) and urban growth have an impact, whereas more specific stressors can be identified in the field of occupational health. More generally, efforts are needed in the education sphere and in multidisciplinary research and cooperation. Furthermore, increased capacity for epidemiological surveillance is required, for example, in recognizing that the fear reaction occurs as an aura of the epileptic attack in many patients. Epilepsy is indeed a well-documented public health problem.

The importance of work cycles was discussed. It was agreed that the health consequences of shiftwork and jet lag should be further studied. Individual ability to undertake night work can be investigated by means of sleep latency tests. Females may be more susceptible than males to changes in circadian patterns and this should also be the topic of further study.

It is suggested that a future WHO meeting be convened on the implications of stress for public health.
5. **FURTHER READING**


Lacroix S, Feinstein D, Rivest S. The bacterial endotoxin lipopolysaccharide has the ability to target the brain in upregulating its membrane CD14 receptor within specific cellular populations. Brain Pathol, 1998 (in press - October issue).


Magistretti PJ, Pellerin L. Cellular bases of brain energy metabolism and their relevance to


Taylor HO. *Greek Biology and Medicine*. Boston, MA, Oxford University Press, 1941.


