CORTISOL
CHAPTER - II

CORTISOL

2.1 INTRODUCTION

Cortisol is involved in the response to stress and increases pressure and blood sugar level and suppresses the immune system. Production of Cortisol and the diseases are also discussed. Cortisol relationship with Temporary Memory loss, the degenerative cascade, brain degeneration, levels of Cortisol during human aging, cognitive changes are also studied. The role of Cortisol in psychosocial contexts, predictors of stress reactivity in early social context, temperament and security of attachment, stress reactivity in peer groups particularly Cortisol levels in these Contexts have also been discussed. The brain responses to acute stress, release of steroid hormones and Cortisol vital roles in marshaling systems throughout the body have also been studied. A comprehensive theory of the general adaptation syndrome was published and the review by Dr. Selye and his summary figure to out -line the acute phase response have also been included to show the stress response.
2.2 CHEMICAL STRUCTURE OF CORTISOL

Fig 2.1 Chemical Structure of Cortisol (hydrocortisone)

<table>
<thead>
<tr>
<th>11,17,21-trihydroxy-(11beta)-pregn-4-ene-3,20-dione</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS number</td>
</tr>
<tr>
<td>50-23-7</td>
</tr>
<tr>
<td>Chemical formula</td>
</tr>
<tr>
<td>Molecular weight</td>
</tr>
<tr>
<td>Pregnancy category</td>
</tr>
<tr>
<td>Delivery</td>
</tr>
</tbody>
</table>

53
Synthesis

Cortisol is separated from progesterone, which is made from the precursor of all Steroid hormones called pregnenolone. The conversion involves hydroxylation of C-11, C-17 and C-21. The synthesis is done in the zona fasciculate of the cortex of the Adrenal Glands. While the Adrenal Cortex also produces aldosterone (in the zona glomerulosa) and some six hormones (in the zona reticulosa), Cortisol is its main secretion [43][51].

The synthesis of Cortisol in the adrenal gland is induced by the anterior lobe of the pituitary gland with Adrenocorticotropic Hormone (ACTH), production of ACTH is in turn stimulated by Corticotrophin Releasing Hormone (CRH), which is released by the hypothalamus.

Physiology

The level of Cortisol will be higher in the early morning [43][51], and lower in the evening, several hours after the onset of sleep. Information about the light/dark cycle is transmitted from the retina to the paired suprachiasmatic nuclei in the hypothalamus. Changed patterns of the serum Cortisol levels have been observed in connection with abnormal ACTH levels, clinical
depression, psychological stress, and such physiological stressors as hypoglycemia, illness, fever, trauma, surgery, fear, pain physical exertion or extremes of temperature. There is also significant individual variation, although a given person tends to have consistent rhythms. Cortisol also prevents the secretion of Corticotrophin Releasing Hormone (CRH), resulting in feedback inhibition of ACTH secretion. Some researchers believe that this normal feedback system may break down when animals re exposed to chronic stress. In normal release, Cortisol has widespread actions, which help restore homeostasis after stress. It acts as a physiological antagonist to insulin by promoting gluconeogenesis, breakdown of lipids, and proteins, and mobilization of extra hepatic amino acids and ketone bodies. This leads to increased blood glucose concentrations, resulting in increased glycogen formation in the liver. It also increases blood pressure. In addition, immune and inflammatory cells have their responses to stress attenuated by Cortisol, and thus the hormone lowers the activity of the immune system. Bone formation is also lowered by Cortisol. These normal endogenous functions are the basis for the physiological consequences of chronic stress prolonged `Cortisol secretion causes muscle wastage, hyperglycemia, and suppresses immune / inflammatory responses. The same consequences arise from long-term use of Glucocorticoids drugs. Also, long term exposure to Cortisol damages the cells in the hippocampus. The damage results in impaired learning. However, short-term exposure of Cortisol helps to create memories; this is the proposed mechanism for storage of flash bulb memories.
Pharmacology

Cortisol is also known as hydrocortisone. It is used as an immunosuppressive drug, given by injection in the treatment of severe allergic reactions such as anaphylaxis and angioedema, in place of prednisolone in patients who need steroid treatment since cannot take oral medication, and perioperatively in patients on long-term steroid treatment to prevent an Addison crisis. It is given by topical application for its anti-inflammatory effect in allergic rashes, eczema and certain other inflammatory conditions. It may also be injected into inflamed joints resulting from diseases such as gout [43][51].

2.3 THE ROLE OF THE CORTISOL IN THE BODY

Cortisol can:

- Help the body to manage stress [128].
- Convert protein into glucose to boost flagging blood sugar levels.
- Work in tandem with the hormone insulin to maintain constant blood sugar levels.
- Inhibit inflammation.
- Contribute to the maintenance of constant blood pressure.
- Contribute to the workings of the immune system.

Conditions Treated with Cortisol-Like Drugs

Some of the conditions treated with Cortisol-like drugs include:

- Skin disorders - such as Psoriasis.
- Inflammatory diseases - such as asthma, ulcerative colitis, lupus and some forms of arthritis.
- Cancer - particularly cancers related to the immune system, such as leukemia and lymphoma.
- Addison's disease - an autoimmune disorder that stops the adrenals from making sufficient hormones, including Cortisol.
- Organ transplants - Cortisol-like drugs are used to inhibit the body's immune response so that a transplanted organ is not rejected.

**Different Forms**

Cortisol-like drugs can be administered in various ways, depending on the condition. Some of the forms Cortisol treatment may include:

- Creams - applied to the affected areas of the skin.
- Tablets - dosage varies, but generally is kept to less than 10mg per day.
- Injections - straight into the affected joint, this prevents many of the side effects that occur when the medication is taken by mouth.

**Side Effects of Cortisol-Like Drugs**

Since Cortisol acts on so many organs and tissues of the body, several unwanted side effects may occur during treatment with Cortisol-like drugs. It will be dangerous to suddenly stop the medication, so continue taking your regular dose and consult your doctor if you are troubled by side effects.
Some common side effects of Cortisol-like drugs are:

- Fluid retention
- Thin skin
- Susceptibility to bruising
- High or increased blood pressure
- Susceptibility to infections
- Build-up of fat around the face, chest and abdomen
- Thinning of the limbs
- Osteoporosis (thinning of the bones)
- Bone fractures, particularly in the spine and ribs.

**Drug-Induced Osteoporosis**

Cortisol-like drugs can cause a loss of bone density, especially amongst postmenopausal women and young men. The bones of the spine and ribs are the most vulnerable to fractures. Cortisol-like drugs interfere with the proper functioning of the bone cells and prevent the intestine from properly absorbing calcium.

Symptoms of osteoporosis can include:

- Severe back pain
- Kyphosis (hunching of the upper back)
- Loss of height
- Bone fractures.
Managing the Side Effects

Some of the suggestions to manage the side effects of Cortisol treatment:

- Reduce the daily dose under strict medical supervision
- Seek immediate treatment for any infection
- Eat a high calcium diet
- Use vitamin D and calcium supplements
- Use other medications to maintain bone strength
- Consideration using hormone replacement therapy (HRT) to prevent Osteoporosis if you are a postmenopausal woman.

High Dose Treatments

High doses of Cortisol-like drugs over a long period of time can disrupt the workings of the pituitary and the adrenal glands and prompt a severe drop in the body's own Cortisol production. Symptoms of Cortisol insufficiency can include:

- Fatigue
- Nausea and vomiting
- Low blood pressure, particularly when standing up from a sitting or lying position (orthostatic hypotension)
- Low blood sugar
- Shock
- Coma.
- Cortisol is a hormone made by the two adrenal glands, located one on each kidney.
• Some disorders can be treated with synthesized Cortisol, called cortisone or corticosteroids.

One of the main side effects of long term treatment is osteoporosis (thinning of the bones).

Cortisol is the most potent glucocorticoid produced by the human adrenal. It is synthesized from cholesterol and its production is stimulated by pituitary Adrenocorticotropic hormone (ACTH) which is regulated by Corticotropin releasing factor (CRF). ACTH and CRF secretions are inhibited by high Cortisol levels in a negative feedback loop. In plasma a majority of Cortisol is bounded with high affinity to corticosteroid binding globulin (CBG or transcotin). Cortisol acts through specific intracellular receptors and affects numerous physiologic systems including immune function, glucose counter regulation, vascular tone, and bone metabolism. Cortisol production has an ACTH-dependent circadian rhythm with peak levels in the early morning and a nadir at night. The factor controlling this rhythm is not completely defined and can be disrupted by a number of physical and psychological conditions. ACTH and Cortisol are secreted independent of circadian rhythm in response to physical and psychological stress.

**Diseases**

Hypercortisolism: Excessive levels of Cortisol in the blood result in Cushing’s syndrome. On the other hand if the adrenal glands do not produce sufficient amounts of Cortisol, Addison’s disease in the consequence [43][51].
2.4 THE ADRENAL GLANDS

The adrenal glands are two small structures situated one atop each kidney. Both in anatomy and in function, they consist of two distinct regions. An outer layer, the adrenal cortex, which surrounds the Adrenal Medulla using cholesterol as the starting material, the cells of the adrenal cortex secrete a variety of steroid hormones.

Fig2.3
Structure of Cortisol location
61
Adrenal gland
Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Medulla
Cortex
Capsular artery
Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Medulla
Capsular artery
Preganglionic sympathetic terminal
Medullary vein

**Fig 2.4 Structure of Adrenal medulla**

Mineralocorticoid (aldosterone)
Glucocorticoids (e.g., cortisol)
Androgens (DHEA and androstenedione)
Epinephrine
These fall into three classifications

Glucocorticoids (Ex. Cortisol)
Mineralocorticoids (Ex, aldosterone)
Androgens (Ex, testosterone)

The secretion of ACTH from the anterior lobe of the pituitary triggers production of all three classifications.

These hormones achieve their effects by:

- Traveling through the body in the blood. Because they are so hydrophobic they must be carried bound to a serum globulin.
- Entering form the blood into all cells
- Binding to their receptor - a protein present in the cytoplasm and/or nucleus of “target” cells

  - The hormone-receptor complex binds to the second to form a dimmer.
  - The dimmer migrates into the nucleus (if it did not form there).
  - The hormone-receptor, dimmer binds to specific hormone response elements in DNA.

  - These are specific DNA sequences in the promoter of genes that will be turned on (sometime off) by the interaction.

  - Other transcription factors are recruited to the promoter and thus begin gene transcription.
Glucocorticoids

The Glucocorticoids go their name form their effect of raising the level of blood sugar (glucose). One way they do this by stimulating gluconeogenesis in the liver: the conversion of fat and protein into intermediate metabolites that are ultimately converted into glucose.

The most abundant Glucocorticoids is Cortisol (also called hydrocortisone)

Cortisol and the other Glucocorticoids also have a potent anti-inflammatory effect on the body. They depress the immune response, especially cell-mediated immune responses.

For this reason Glucocorticoids are widely used in therapy:

To reduce the inflammatory destruction of rheumatoid arthritis and other autoimmune diseases;

To prevent the rejection of transplanted organs.

To control asthma.

2.5 STRESS, MEMORY IN CORTISOL

Chronic over-secretion of stress hormones adversely affects brain function, especially memory. Too much Cortisol can prevent the brain from laying down a new memory, or from accessing already existing memories.

The renowned brain researcher as shown that sustained stress can damage the hippocampus the part of the limbic brain, which is central to
learning and memory. The culprits are “Glucocorticoids”. They are more commonly known as corticosteroids or Cortisol.

The Adrenal Glands immediately release adrenalin, during a perceived threat. If the threat is severe or still persists after a couple of minutes, the adrenals then release Cortisol. **Once in the brain Cortisol remains much longer than adrenalin, then it will affect brain cells.**

**Cortisol Affects Memory Formation and Retrieve**

Cortisol also interferes with the function of neurotransmitters, the chemicals that brain cells use to communicate with each other. Excessive Cortisol can make it difficult to think or retrieve long-term memories. That’s why people get befuddled and confused in a severe crisis. Their mind goes blank because “the lines are down” They can’t remember where the fire exit is, for example.

**Why Do We Lose Our Memory**

Stress hormones divert blood glucose to exercise muscles, therefore the amount of glucose that reaches the brain’s hippocampus gets diminished. This creates an energy crisis in the hippocampus that compromises its ability to create new memories. This may be the reason why some people can remember a very traumatic event, and why short-term memory is usually the first casualty of age-related memory loss resulting from a lifetime of stress.
Cortisol and the Degenerative Cascade

Normally, in response to stress, the brain’s hypothalamus secretes a hormone that causes the pituitary gland to secrete another hormone which causes the adrenals to secrete Cortisol, when levels of Cortisol rise to a certain level, several areas of the brain tell the hypothalamus to turn off the Cortisol-producing mechanism. This is the proper feedback response. The hippocampus is the most damaged area by Cortisol. Thus, a Catch-22 “degenerative cascade” begins, which can be very difficult to stop.

Cortisol and Brain Degeneration Study

Some Research, showed that lots of stress or exposure to Cortisol accelerates the degeneration of the aging hippocampus, because the hippocampus is part of the feedback mechanism that signals when to stop Cortisol production, a damaged hippocampus causes Cortisol levels to get out of control- further compromising memory and cognitive function. The cycle of degeneration then continues.

Cortisol Levels during Human Aging Study

The study was titled “Cortisol levels during human aging product hippocampal atrophy and memory deficits”. A third of the 60 volunteers, who were between ages 60 and 85, had chronically high Cortisol levels, a problem that seems to be common in older people.
The size of hippocampus average 14% smaller in one group and showed high and rising Cortisol levels, compared to a group with moderate and decreasing levels. The small hippocampus group also did worse at remembering a path through a human maze and pictures they had seen 24 hours earlier and two tasks that use the hippocampus.

2.6 COGNITIVE CHANGES ASSOCIATED WITH CORTISOL

Glucocorticoids, Cortisol in humans and Corticosterone in rodents, are associated with a host of changes throughout the brain, both short-term and long-term. Cortisol has multiple functions to permit the HPA response, to stimulate or augment a stress response, to suppress an ongoing stress response, or to prepare for a subsequent stressor. In addition to structures in the HPA axis, the primary targets for glucocorticoids are the higher associative brain structures, particularly the prefrontal cortex (PFC), and structures associated with learning a memory, including the hippocampus [58]. Glucocorticoid receptors in the PFC are primarily associated with terminating an ongoing stress response through a negative feedback loop, which returns Cortisol levels to baseline. Consequences of short-term Cortisol secretion include focused attention and increased acquisition and retention of sensory cues, behavioral strategies, and other information related to the context, increased vigilance and decreased sleep, impaired short-term memory performance (in areas unrelated to current context), enhanced immune system functioning.
Many researchers have noted damaging effects associated with Cortisol secretion, primarily associated with failure of the PFC to terminate HPA activity. Long-term overexposure to Cortisol results in reduction in the ability of the hippocampus to effectively form memory-related associations due to atrophy of dendrites of the pyramidal neurons in the CA3 region, and immune suppression. During development, exposure to chronic Cortisol secretion alters the sensitivity and activity of the HPA system and the targeted neural circuits directly involved in learning and memory, the ability to discriminate subtle variation in sensory information, and ultimately leads to degeneration of noradrenergic axons in the cerebral cortex. These effects are thought to be responsible for the link between early stress and the later development of psychopathologies associated with these neural systems, such a depressive and anxiety disorders. However, chronic secretion of Cortisol while it has cost such as neural degeneration and immune suppression, may not be entirely maladaptive. Cortisol released in response to a controllable stressor facilitates and stabilizes existing neural pathways. It is in response to uncontrollable stressors, as are characteristic of many social contexts, that HPA activity persists and have neurodegenerative effects. Long-lasting activation of the HPA axis in response to uncontrollable stressors is entirely maladaptive, however, and then selection pressures would have eliminated genotypes allowing for chronic activation of this system. It is argued that Cortisol functions to reorganize neural structures and increase specialization of the brain. In other words Cortisol appears to fine tune neural circuits to the
nuances of the stress-eliciting cortex persistent activity by the HPA system in response to uncontrollable rather than controllable stressors, and associated disruption of neural suggests that prolonged HPA activity may function to disrupt the use of ineffective cognitive and behavioral strategies, and through this, provide opportunities to construct potentially more effective strategies.

2.7 THE ROLE OF CORTISOL IN PSYCHOSOCIAL CONTEXTS

The development of human stress response system, particularly the HPA system, is primarily suited to respond to psychosocial rather than physical stressors (e.g., predator avoidance). Humans have constructed our environment in such a way that we are protected from many of the other types of stressors that are encountered by other species (e.g., predators), but this creates a context in which other people are the primary competitors for resource control or are the primary selective pressures from an evolutionary perspective[58]. It follows, then that the release of glucocorticoids (Ex. Cortisol) is delayed following a stressor and thus not immediately useful in predator avoidance, but more useful in response to anticipated social stressors, particularly those involving other humans tends to be more prolonged and ambiguous than other types of stressors, and Cortisol may function in these situations to prepare for a subsequent, similar stressor. The ambiguous nature of the human social context limits the extent to which the stress response system can be channelized early in development, because social dynamics are fluid and never completely predictable. These studies are consistent with the cost-benefit trade-offs
common to evolved systems. Given there are costs (ex. Neurotoxic and immunosuppressive effects), the very presence of Cortisol suggests that it serves a vital adaptive function. It is proposed Cortisol is released under conditions of threats and opportunity, particularly in the social realm. Cortisol is responsive to situations that involve opportunity for loss or gain, particularly of socially salient resources (ex. Social support). This framework is more parsimonious and helps to resolve conflicts in literature that have shown that conditions of adversity fail to produce uniform effects in Cortisol profiles.

In other words, elevations in Cortisol level are not always associated with negative affect, and can result from positive experiences that involve opportunity for gaining social resources or increasing social influence. For example, surgent children have high Cortisol levels upon entering a new social group, not because they are “stressed” per se, but because they see an opportunity for social engagement. This is consistent with assertion that Cortisol functions to adaptively reorganize the brain by destabilizing existing ineffective neural pathways and facilitating the connection and stabilization of new ones. The high Cortisol of surgent children may be part of a sequence in response to the new social context. These changes, in turn, may allow for better later control of social dynamics. Under this framework, Cortisol can function to adaptively pattern behavior to the demands of the ever-changing social environment, and can be, therefore ultimately beneficial. The mechanisms that mediate the relation between this neural and behavioral reorganization and Cortisol include the dynamics of early social context (Ex.
Parent-child interactions), individual traits such as temperament, and later in
development, peer relationships.

Predictors of Stress Reactivity in Early Social Context

The HPA system, like many other neural systems, is exceptionally
plastic during the course of development, presumably reflecting the need in our
species' history to adjust this system to the demands of the unpredictable social
climate. Plasticity will be advantageous when it is necessary to adjust to
changes occurring within an individual's.

Life span and not over generations the largest source of this variation in
many social species is social dynamics, as noted. Consistent with this
perspective, early parent-offspring dynamics appear to calibrate the HPA
system in a number of species, from rats to humans. Infants and children react
to relevant features of their social environment and adjust their cognitive and
behavioral strategies accordingly. One such relevant feature is the predictability
of maternal support.

Studies with both humans and nonhuman animals have shown that the
quality of maternal care in the early postnatal period influences the
development of the stress response system. In rats, high quality maternal care
typically consists of frequent nursing bouts and high-energy maternal behaviors
such as arched-back, or hypnotic, nursing and extensive licking and grooming
of pups. The young ones reared by mothers high on these behaviors show lower
fearfulness in novel contexts in addition to increased glucocorticoid feedback
sensitivity and reduced Corticosterone response to acute stress. In humans, disruptions in maternal responsiveness and positive affect are linked with low quality maternal care and alterations in infant and child HPA reactivity. In mammals with significant postpartum care, disruptions in the mother-infant relationship (e.g., maternal deprivation) often lead to a hyper-responsive (or in some cases hypo-responsive) HPA system, whereas high quality maternal care, on average, is associated with a stress response system that is more selective in its activation. Selective activation, in turn, reduces the costs of Cortisol secretion.

In species with significant postpartum brain development, maternal behavior appears to serve as a cue to the demands of the ecological conditions she is experiencing. In humans, children of depressed mothers have altered HPA responses to stressors, demonstrating that maternal responsiveness results in rapid changes within the child’s HPA system, which may serve to prepare this child for unpredictable and uncontrollable social dynamics.

Even in less severe cases, children react to their social environment and adjust the physiology of the HPA system, according to their behavior, and presumably their social cognitions. Cortisol appears to play a key role in this behavioral and HPA adjustment to social context. In particular, the quality of family dynamics and associated stressors appear to influence social cognition (e.g., internal working models of social relationships) and later behavior. Children reared in environments with unstable parental relationships, unpredictable or limited child investment and insecure attachment to caregivers
often show a constellation of traits and behaviors that indicate that these stressors resulted in some modification of behavioral and/or cognitive strategies relative to children who did not experience these stressors. The cognition of these children support less trust in social relationships. These children are more likely to experience early menarche, engage in sexual activity at a younger age, have unstable pair bonds themselves, show limited investment in their own children, and have more children overall. Further, enduring familial stressors change the threshold for HPA activation, resulting in either hyper- or hypo-responsive neural pathways, which, in turn, may be associated with many of the behavioral changes listed above (e.g., unstable pair bonds).

Paternal behaviors and other forms of investment, while much less studied, are an implicit part of the social context in which the child develops and thus, may have an influence on the development of HPA reactivity. Warm father-daughter relationships are associated with delayed menarche and delayed sexual activity, and with a tendency toward monogamy and high investment in children in adulthood. Father absence and associated factors (e.g., maternal stress) along with the presence of a step-father or maternal boyfriend, on the other hand, are associated with earlier menarche and an earlier onset of sexual behavior. Thus, social dynamics in early to middle childhood may lay the groundwork for later behavior and perceptions of social relationships, though some individuals may be more predisposed or genetically sensitive toward a high or low parental investment strategy. As discussed below, experience with
early social dynamics may also alter the nature of later peer relationships and methods coping within these relationships.

As noted, Cortisol has a direct role in forming and modifying associated cognitive structures to prepare better the individual to cope with specific social dynamics. Theoretically, Cortisol will be released, when, on average, this potentially costly destabilization and reorganization of cognitive structures and behavioral strategies might be advantageous. The cost-benefit trade off for false alarms (activating the HPA system when, in fact, there is no opportunity for loss or gain) or misses (failure to detect a threat or opportunity) will vary with predictability in the social context. An increase in the probability of a false alarm will also result in a decrease in the probability of a miss, and this combination will be less costly in a risky and unpredictable social environment because the probability of threat and associated losses are much greater in these contexts. Similarly, the cost of a false alarm will be higher and the loss associated with missed opportunity will be lower in a less risky, relatively predictable context. Further, the stress response system is mediated, in part, by the perception of the situation, which is in turn, influenced by individual characteristics such as temperament. These perceptions (e.g., social stimuli are overwhelming), along with early social adversity, may lead to a HPA system that over-reacts when exposed to subsequent uncontrollable or perceived uncontrollable psychosocial stressors, such as peer interactions, discussed below.
Temperament and Security of Attachment

As noted, the HPA system and its threshold to respond to social stimuli are also influenced by child characteristics, such as temperament, and how those characteristics interact with parental behavior (i.e., attachment security) and early environmental demands (e.g., economic hardship). He discussed the relationships with temperament here, rather than personality, which is more typically measured later in childhood and early adulthood, for several reasons. First, much of the literature on traits that affect HPA system arousal, such basic approach and avoidance tendencies, examine infants, toddlers, and very young children, making temperament rather than personality the most appropriate measure. In order to link the effects of these traits with Cortisol, temperament is the closest measure to previous findings. Second, Rothbart and colleagues have noted considerable consistency between temperamental traits, and traits measured by personality assessments, such as the Big Five Personality Assessment in studies of adults. Although these scales don’t overlap completely the purpose of this research is to uncover underlying individual differences in basic reactivity to the environment, and temperamental traits such as these have been reliably assessed in adults [58].

Early adversity does not produce uniform effects, such as hyperactivation of the HPA system, across all individuals. The calibration and response sensitivity of this system (the phenotype) is heavily dependent on the genotype. Children with extreme temperaments (e.g., behaviorally inhibited or surgent) seem to be biologically more sensitive to social context, and are thus
more likely to be influenced by features of their early rearing environment, they secure and predictable or insecure and chaotic. In rhesus macaques, for example, behaviorally inhibited individuals were disproportionately targeted for attacks under conditions of crowding stress, but had much lower incidents of injuries compared with their peers during low stress periods. In a related species, tufted capuchin monkeys, individuals that were more apprehensive, fearful and submissive showed higher Cortisol reactivity, higher baseline Cortisol level, more solitary play and less social play than more aggressive, confident, curious, and opportunistic individuals. Similarly, in humans, children with more reactive temperaments and insecure attachments are more likely to have negative outcomes such as anxiety disorders later in childhood, and have concurrent difficulty with peer relationships. Further evidence suggests that both Cortisol response and attachment style are partially dependent on temperament, and that each of these factors is related to children’s coping behaviors. Behaviorally inhibited children—children very reluctant to approach novel situations are more likely to have insecure attachments and to use inadequate social coping skills, whereas securely attached children are more likely to use social information as a primary aspect of their coping strategy. For example, when placed in unfamiliar or strange situations, insecurely-attached inhibited children are more likely to use distraction by engaging in solitary play with familiar toys and avoid social contact. Securely attached children, on the other hand, whatever their temperament, are more likely to use social referencing (e.g., looking to a
caretaker for emotional cues) in unfamiliar or novel contexts. Further, behavioral inhibition may be a way of reducing arousal and Cortisol secretion. Children difficult temperaments show greater Cortisol reactivity only when the children are insecurely attached. Thus, caregivers—from rodents to humans—appear to buffer HPA axis activity. Sensitive and responsive care giving allows children to express and experience distress in ways that do not elicit unnecessary Cortisol responses. It is likely that the same traits later in development influence peer interactions and the use of peer relationships as sources of support.

2.8 STRESS REACTIVITY IN PEER GROUPS

Differential activation of the HPA system is, not surprisingly, seen in the context of peer groups as well as adult-child interactions, though much less research has been done in this area. Most of the research in this area has focused on children’s peer relationships, and there is very little research on adolescents and young adults, a time when peer groups are not only highly salient, but significant sources of both psychosocial stress and support [58]. The rise in Cortisol levels over the course of the day in daycare settings coincides with the age that peer relationships become salient, that is, during the preschool years.

The rise in Cortisol over the school year is largest for less socially competent children, suggesting that they may perceive the social dynamics that occur in these contexts as uncontrollable for them. On the other hand, surgent
children, who are exceptionally high on approach and low on fear, are more likely to show an initial rise in Cortisol levels upon entering a new social group, and then show decrease and leveling off as the school year progresses. The pattern suggests two things: first, surgent children may see a new social group as an opportunity for gain and may be adaptively adjusting their behavioral strategies and presumably their cognitive structures to best take advantage of this opportunity. Second, these findings suggest that peer groups are salient social stressors, as indicated by the rise in Cortisol levels in these contexts. Cortisol levels of surgent children decline because these children have adjusted to the new social group. The Cortisol levels of inhibited children remain relatively high because they have not behaviorally or cognitively integrated into the group.

**Peers and Coping - Salience of Peers**

The literature on peer relationships in late adolescence and early adulthood is so limited, the focus here on the research that is available, that is, peer research in children and adolescents [58]. He will attempt to extrapolate to older adolescents and young adults where literature in the area is lacking, as many of the underlying dynamics are similar. Whereas the family climate appears to be the most salient factor in early childhood (see sections above), peers become increasingly important sources of social support and conflict as children move into middle childhood and adolescence. This is true for other primate species as well. Family relationships often serve as social references,
but they often do not have completely overlapping interests in the realms of mate selection and social network development two imperative aspects of the social context that increase in importance with development, reaching their peek importance in late adolescence and early adulthood. Thus, age mates may be better sources of support for developmentally contingent concerns, while at the same time providing the social arena itself. In other words, peers can be supporters and/or adversaries and set the tone for the social context in which the child or adolescent is situated. The importance of peers is reflected in general adjustment and group acceptance in middle childhood and adolescence. Children who are not well accepted by peers often report feelings of loneliness and social dissatisfaction, but the effects of loneliness are significantly reduced if a child has just one good friendship. Further, rejected children (e.g., few if any friends) who are temperamentally more inhibited have higher Cortisol levels than their more accepted peers over the course of the school year. This suggests that these children may perceive the social context as potentially threatening. However, these children may never devise an effective coping strategy (in the absence of direct instruction) to perceived threats in these situations, resulting in chronic Cortisol secretion.

The Brain's Response to Acute Stress

In response to seeing the bear, a part of the brain called the hypothalamic-pituitary-adrenal system is activated.
2.9 SELYE’S CONCEPTS OF GENERAL ADAPTATION SYNDROME

Selye published a review in 1946, where he already gives a comprehensive theory of the general adaptation syndrome, which is supported by experimental facts [101]. He also talks about the possibility that diseases of adaptation do exist. He states that, after exposure to stress, initially there is shock, which is followed by a counter shock phase, and this gradually goes into a stage of resistance. If however, he states that, after exposure to stress, initially there is shock, which is followed by a counter shock phase, and this gradually goes into a stage of resistance. If the stressor persists, resistance may go into exhaustion and death may ensue. He points out that specific and nonspecific resistance follow the same course but this latter “cross resistance” will fall much sooner and stays below normal during the period of resistance.

He also presents data of Blood sugar and chlorine changes and points out that white blood cell counts rise invariably during stress, regardless of the stressor used. The changes in the adrenal cortex and of thymus involution are also illustrated histologically. The adrenal cortex becomes wider with loss of lipid granules and the border between the zone fasciculate and reticular is no longer distinct. The thymus shows a depletion of cortical thymocytes. Nuclear debris is evident and pyknotic thymocyte nuclei are abundant. He notes that this “accidental involution” becomes most pronounced during the counter shock phase when the adrenal cortex reaches its maximum development. Large macrophages engulf the dead thymus cells and carry them away through the
lymphatics. At the same time he noted that thymic reticulum reverts to its original epithelial type and the cells become roundish or polygonal and rich in cytoplasm. When involution is most acute the entire organ is distended with jelly-like edema. He points out that lymph nodes, the spleen and other lymphatic organs are almost as markedly affected as the thymus, although they do not involute quite as rapidly and their involution cannot be completely prevented by adrenalectomy. His summary figure is a fairly accurate outline of the acute phase response as we recognize it today.

Schematized drawing indicating that non-specific damage causes clinical shock, loss of body weight and nitrogen, gastro-intestinal ulcers, temporary rise in plasma potassium with fall in plasma c1, through unknown pathways but manifestly not through the stimulation of the hypophyseoadrenal mechanism. This is proven by the fact that the above manifestations are not prevented either by hypophysectomy or by adrenalectomy, they even end to be more severe in the absence of either or both of these glands.
Fig 2.5

Functional interrelations during general adaptation syndrome.
Non-specific damage, again through unknown pathways, also acts upon the hypophysis and causes it to increase corticotropic hormone production at the expense of a decreased gonadotropic, lactogenic and growth hormones. The resulting corticotropic hormone excess causes enlargement of the adrenal cortex with signs of increased corticoid hormone production. These corticoids in turn cause changes in the carbohydrates (sugar active corticoids), and electrolyte metabolism (self-active corticoids) as well as atrophy of the thymus and the other lymphatic organs. It is probable that the cardiovascular, renal, blood pressure and arthritic changes are secondary to the disturbances in electrolyte metabolism since their production and prevention are largely dependent upon the salt intake. The changes in g-globulin, on the other hand, appear to be secondary to the effect of corticoids upon the thymicrolymphatic apparatus.

We do not know as yet, whether the hypertension is secondary to the nephrosclerosis or whether it is a direct result of the disturbance in electrolyte metabolism caused by corticoids. Similarly, it is not quite clear, as yet, whether corticoids destroy the circulating lymphocytes directly, or whether they influence the lymphocyte count merely by diminishing lymphocyte formation in the lymphatic organs. Probably both these mechanisms are operative.

Today we know that a variety of insults, including trauma and infection stimulate the release of chemotactic, proinflammatory cytokines, and a whole
host of other mediators from a variety of cells in the damaged area that include mast cells, endothelial cells, platelets. The released mediators attract blood borne leucocytes, such as neutrophilic granulocytes, monocytes/macrophages, lumphocytes, eosinophils and basophiles that release additional mediators, and thus contribute to the inflammatory response. In some cases certain cytokines, such as interleukin-1, tumor necrosis factor-and an interleukin-6, become detectable in the blood and function as acute phase hormones. They act on the brain causing fever and other functional modifications, release certain pituitary hormones and inhibit others, promote general catabolism stimulate the production of new serum proteins known as acute phase reactants in the liver and also elevate the production of leucocytes in the bone marrow, the mechanism of which is not fully elucidated. Thus, with the recent discovery of cytokines and our increasing recognition of their functions, we have begun to fill in the gaps in Dr. Selye’s adaptation syndrome outlined nearly half a century ago[102].

In 1949, Selye discovered that an inflammatory reaction, which can be induced in the rat by the parenteral administration of egg white, is inhibited by cortisone or by purified ACTH on the other hand, desoxytocicosterone acetate, a mineral corticoid compound, tends to aggravate the reaction. These experiments initiated his interest in inflammation which became the most lasting topic in his research and led to the proposition later that diseases, like rheumatoid arthritis, anaphylaxis, etc. are in fact diseases of adaptation as stated in numerous publications. In his review article in Science, entitled
“Stress and disease”, he shows a diagram of the stress response with inflammation clearly in mind.

ANTI-INFLAMMATORY EFFECTS OF CORTICOIDS

The same antiphlogistic corticoids (cortisone and Cortisol) that were shown to inhibit various types of experimental inflammations in laboratory animals exert similar effects in a human being afflicted by inflammatory diseases (for example, rheumatoid arthritis, rheumatic fever, and allergic inflammations). Sensitivity to infection after treatment with antiphlogistic corticoids. In experimental animals, the suppression of inflammation by antiphlogistic hormones is frequently accompanied by an increased sensitivity to infection, presumably because the encapsulation of microbial foci is less effective and perhaps partly also because serologic defense is diminished.

SELYE CONCLUDES AS FOLLOWS

If Selye may venture a prediction, Selye would like to reiterate my opinion that research on stress will be most fruitful if it is guided by the principle that we must learn to imitate - and if necessary to correct and complement - the body's own autopharmacologic efforts to combat the stress factor in disease."

The prediction by Selye that the pituitary gland has the capacity to both stimulate and inhibit inflammatory reactions is the subject of recent investigations and is proven correct [102]. The notion of prophlogistic steroids
has not been studied to a great extent to date, but the anti-inflammatory effect of glucocorticoids is firmly established and it is clear today that the adrenal gland plays an important physiological role in the regulation of immune and inflammatory responses. The disproportion of hormones and other mediators, altered responsiveness in tissues and the significance of metabolic derangements during acute phase reactions related to sepsis, severe trauma and shock are the subject of current investigations and deemed to be highly relevant to prognosis. The involvement of the central nervous system, the liver and of other organs, such as the kidney, is also substantiated. That "conditioning" may also play a role in host defence is also gaining ground. Some hard evidence is forthcoming regarding the corticoid requirements during infection and other forms of stress. The anti-inflammatory effect of cortisone and Cortisol are well recognized and are widely applied in medicine today. That corticosteroids increase the sensitivity to infection is of common knowledge. The phenomenon of stress related anesthesia is well recognized, but opioid peptides rather than steroid hormones are considered to be the mediators.

Dr. Lorand Bertok, upon his return to Budapest from Selye's Institute, brought the news that the study of mast cells was in the focus of interest and he also brought a copy of the book written by Dr. Selye: "The mast cells". As it turned out, the inflammation Dr. Selye induced years earlier in rats by the injection of egg white was due to the discharge of mast cells. Because of my intentions to go to Dr. Selye's laboratory, and studied this book and was struck by the importance of mast cells in various pathological phenomena. At that
time the role of mast cells in immune mechanisms had not been firmly established. However, a related cell type, the basophilic leucocytes role in immune mechanisms was known already. Selye was interested in mast cells mainly because they play a major role in inflammation and he was puzzled by the powerful effects of mediators released by mast cells which could play a role in various pathological processes, such as inflammation, necrosis, calcification or thrombohemorrhagic phenomena.

**RELEASE OF STEROID HORMONES**

The HPA systems trigger the production and release of steroid hormones (glucocorticoids), including the primary stress hormone Cortisol. Cortisol plays a vital role in marshaling systems throughout the body (including the heart, lungs, circulation, metabolism, immune systems, and skin) to deal quickly with the bear response by the Heart, Lungs and Circulation to Acute Stress. As the bear comes closer, the heart rate and blood pressure increase instantaneously.

Breathing becomes rapid and the lungs take in more oxygen.

Blood flow may actually increase 300% to 400%, priming the muscles, lungs, and brain for added demands.

The spleen discharges red and white blood cells, allowing the blood to transport more oxygen.
2.10 CORTISOL VICTIM

- The stress hormone Cortisol has been found to cause weight gain in some susceptible individuals.

- Losing weight for such people involves a strategic combination of exercise modalities and lifestyle.

- Food plays a major role in the weight gain, as Emotional Eating is a common coping strategy while some food items can aid in stress relief.

- Exercise is a stress buster but can be counterproductive in some people. The key lies in planning the right amalgamation of routines for such susceptible individuals.

Have you been working out, “dieting” and still not losing any weight, or worse still, steadily gaining in girth? Are you anxious, annoyed and frustrated with your apparently pointless weight loss efforts? Well, you may very well be one of those people suffering from an overload of stress hormone Cortisol. It has been found that in certain people, Cortisol overload leads to weight gain, particularly around the abdomen [110].

I am often faced with clients who believe they are near starving themselves, working out like dogs and yet not losing any weight. Aside from the irony that most dogs rarely work, it is with some trepidation that I approach this situation. It has been found that on questioning, most individuals underestimate how much they exercise.
What is Stress

If, however, it is established that you honestly are unable to lose weight despite following the necessary precautions, it may be time to evaluate the rest of your stress levels as one of the causes for weight gain or failure to lose weight.

Emotional stress is defined as a person’s reaction to any situation that places special physical or psychological demands on the person so as to unbalance his/her equilibrium. Everyone from the corporate executive, housewife or student is under stress. How one’s body responds to stress may vary. Although the biochemical reaction to stress is similar for every human being, some individuals lose their appetite and weight during stressful times, while others gain steadily.

The Stress Response

According to Dr. Selye the pioneer of Emotional stress, when the human body is faced with a stressor (or what it perceives as a stressor), the sympathetic and endocrine system of the body set in motion physiological responses that include the release of hormones Cortisol and Epinephrine from the adrenal glands. Once the stressful event has passed, the body reverts to its ‘normal homeostasis’. Most times however, when the stress is ongoing or the individual has a personality type that responds to most situations like they are disasters waiting to happen, the body remains in a ‘high alert’ situation with the continuous outpouring of stress hormones. These situations cause certain
bodily changes that include weight gain! Research findings suggest that Cortisol is the offender.

In today’s fast paced society there is hardly an opportunity for the body to revert to normal homeostasis after a stressful event. Consider, deadlines at work, traffic jams, financial crisis, sick children, an unpleasant mother-in-law, school admissions, the list is endless. The stage is set for a body that is constantly on an over dose of Cortisol and other stress hormones.

The Food Connection

To make matters worse, food as we all know is not used solely to alleviate hunger. It is also seen as a form of psychological fulfillment. Periods of stress in your life whether a bereavement, loss of job, divorcee, exams or even change of home can be times when you reach for food as comfort leading to weight gain. This is called Emotional Eating and is a common coping strategy to soothe disturbed feelings. The weight gain and dieting itself can be a source of stress especially in today’s world where the pressure to look slim is foisted on most people (particularly women), by the media depiction of super slim models. This often-unrealistic image can lead to a self perpetuating cycle for a lot of women.
Stress-Related Weight Gain

Besides the regular exercise/healthy diet combination, “lifestyle” changes and a holistic approach fitness has to be observed if stress is to be effectively combated.

Exercise by itself is a great stress reliever. Conversely, it may serve as a source of stress for some people who approach it competitively or generate their own stress by setting unrealistic goals.

Mind-Body Fitness disciplines like Yoga, Tai Chi and Pilates, which are introspective and focus on the breath, can be used for stress management. They are an ideal support system to a regular cardio and iron pumping routine.

Strategies

The importance lies in the strategic combination of exercise modalities for each individual depending on his requirements. Some may need emotional assessment and counseling while others may require longer slower cardio sessions interspersed with high intensity weight training and/or Yoga. It is complete foolishness for instance for an obese individual to rely solely on a ‘stress relieving’, breathing and Yoga routine paying no attention to his food or cardio in the hope of losing weight. He would also need to burn adequate calories to make a difference to his fat percentage.

Certain foods and herbs like ginseng, ashwagands, amla are believed to be useful in combating stress and are called ‘adaptogens’. Inclusion of these foods may be beneficial for some individuals.