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# **Stress, anxiety and depression (SAD) Transcript**

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# **Stress, Anxiety and Depression (SAD)**

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As we move confidently in the developed world into a 21st century where basic survival needs and personal protection are increasingly accepted norms, and we have the potential for significant amounts of time for leisure pursuits, why are we more subject to stress, anxiety and depression than at any time in our history?

The American Medical Association has estimated that around 75% of human illnesses are contributed to by stress and anxiety-related conditions. Suffering and death through depression-related disorders is second only to cardiovascular diseases and if one considers that they actually contribute significantly to the latter it seems likely that depression is probably the major cause of reduced quality of life and longevity for humans living in the developed world. It also contributes significantly to another insidious and seemingly intractable problem in the developed world, namely obesity, which will be the subject of my next lecture on November 11th.

The economic cost of stress, anxiety and depression disorders is not, of course, restricted to healthcare. A survey completed in the UK in November 2000 estimated that 6.7 million working days are lost each year as a result of stress, costing UK businesses around £3.7bn. The size of the problem also appears to be increasing with a survey in 2001/2 reporting that 1 in 5 of all working individuals considered that their jobs were very or extremely stressful and over half a million felt that this stress was making them ill.

In this lecture I will focus on what stress, anxiety and depression are, what they have evolved for, what controls them, what happens when they become uncontrolled, what treatments are used and what simple things we can do to try to reduce problems. I will also point out some of the factors that may be contributing to the prevalence of these conditions. We seem to be facing a stress, anxiety and depression pandemic in the developed world and it is clear we need to adapt in order to better cope with lives in a material world where we are divorced from the simple immediate concerns surrounding reproduction and survival.

## **So what are stress, anxiety and depression and why do we experience them?**

Stress, anxiety and depression are words that the general public and even science and health care professionals often bandy about interchangeably and without having any clear understanding of what they mean. One thing we all seem to be clear about is that they have a negative connotation and represent states that, for the most part, we neither consider pleasurable nor want to stay in for any length of time – although we often seem to claim that we are experiencing them either in order to impress or to evoke sympathy. To a large extent these latter claims are equivalent generally to someone with a normal head-cold exaggerating by saying that they are suffering from a virulent form of influenza. Those individuals experiencing the symptoms of major depression are usually way beyond the stage of wanting to use it as a means of seeking sympathy!

If we are going to try to provide a simplistic explanation of stress, anxiety and depression, it is important to understand from the outset that although they are, to some extent, distinct physiological and psychological processes they represent part of an integrated set of responses that animals have evolved as adaptive mechanisms to promote survival of their species. The broad spectrum of adaptive physiological, behavioural and emotional responses that they represent also includes fear and pain. As we will see, they involve many common hormonal and chemical systems within the body, and drugs which have been developed to control one state will often also be effective in influencing the others too.

“Everybody knows what stress is and nobody knows what it is”

Hans Selye (1973)

What Hans Selye (often regarded as the founder of scientific investigations into stress) means is simply that we all recognise the symptoms of acute stress – feeling alert and muscles becoming tense, dry mouth, cold skin, sweaty palms, increased heart and breathing rate, maybe feeling a little nauseous. Most of us also realise that where stress is prolonged it can affect a wide range of physical and psychological functions:

*Emotional symptoms:* You may find yourself worrying too much about things, trembling, waking up frequently and recalling nightmares, being nervous around other people and generally feel either angry or depressed, having intrusive thoughts that you cannot control, experiencing panic attacks, bursting into tears without apparent good reason etc.

*Behavioural symptoms:* You may feel constantly tired, work less efficiently, experience periods of confusion and have trouble paying attention, become forgetful, lash out at others, lose interest in things and become restless

*Physical symptoms:* You may experience frequent headaches, stomach upsets, chest tightness and pain, breathlessness, palpitations, excessive perspiration, dizzy spells, feeling light headed, and be prone to a high frequency of minor ailments such as colds, skin and gum problems.

However, we often know far less about why this happens, or how, let alone what to do about it. Even today there is no universally accepted definition of what stress is, although clearly the term is borrowed from engineering where it describes a force that exerts a physical strain on a structure. In a biological context stress is primarily a physiological process that, in the immediate short-term, prepares the body for some form of action so that we can either face up to what is disturbing us more effectively or alternatively avoid it with all possible speed. In this respect it is often referred to as the “fight or flight” response. Hans Selye in 1936 made a first attempt at providing a definition by calling it “a syndrome produced by diverse noxious agents”. A more specific recent definition, although still frustratingly general, is that “stress is a condition in which an individual is aroused by an aversive situation”.

By definition the external challenges that provoke stress responses are described as “stressors”. Stressors can either be primarily physical in nature (such as being injured or exposed to extreme temperatures or lack of oxygen etc) or psychological (losing a loved one, social isolation, being subjected to the criticism or anger of others or being expected to complete seemingly impossible tasks). The extent to which an individual “stressor” will evoke a stress response is of course highly variable. This is because the level of stress response exhibited depends on an individual’s perception and emotional response to any given “stressor” at any moment in time. It can also depend on both genetic and experiential factors. In the case of the latter these include social and maternal rearing experience, position in a dominance hierarchy, presence of social bonds and coping style.

### *Anxiety*

Anxiety is an emotional mood state that results from being unable to predict the outcome of, or deal with, existing or imminent stressful situations or thoughts. It is, in essence, a short-term anticipatory reaction that helps us to prepare either for unavoidable events or predicted future ones. In this respect it is very similar to fear, although fear reactions tend to be rapid instinctive responses to potentially dangerous stimuli whereas anxiety is more of a conscious cognitive state where the emotional consequences of different potential outcomes are constantly being considered. An important consequence of this cognitive element is that the state of anxiety provoked can often be completely out of proportion to the size of the threat (phobias for example) and can even be elicited in the absence of any external stimulus.

Since anxiety is a state of enhanced stress and arousal in anticipation of a perceived or imagined threat it is often treated as being analogous to an exaggerated acute stress response with the situation or thought acting as the stressor. Indeed, anxious individuals are often prone to experience greater stress responses to a wide range of potential stressors. However, individuals with specific phobias, sometimes only exhibit anxiety and heightened stress responses to a particular potential stressor (spiders, snakes, confined or open spaces) whereas reactions to other stressors are quite normal. Anxiety can also be triggered in some individuals by stimuli or experiences that are not widely considered to be stressors at all. Alternatively, traumatic experiences can lead to recurring bouts of anxiety with no obvious immediate cause in terms of a defined stressor.

Pathological forms of anxiety have been classified into six disorders:

- *generalised anxiety disorder* - unrealistic, excessive and long-lasting worry, tension and rigidity of movement, restlessness, irritability, difficulty sleeping, hypervigilance.
- *social phobia* - aversion, fear and autonomic arousal (increased heart-rate etc) in unfamiliar social settings
- *specific phobia* - aversion, fear and autonomic arousal (increased heart-rate etc) in specific situations (spiders, snakes, blood etc)
- *panic disorder* - brief recurrent, unexpected episodes of terror which usually reach a peak within 10 minutes and trigger a generalised stress response, shortness of breath, fear of dying and losing control and de-realization
- *post-traumatic stress disorder* - following an extremely stressful event involving actual or threatened injury recurrent episodes of fear are often triggered by reminders of the trauma and individuals show autonomic arousal (increased heart-rate etc).
- *obsessive-compulsive disorder* - recurrent obsessions and compulsions: these are persistent intrusive or inappropriate thoughts that cause anxiety that lead to the individual performing repetitive acts to alleviate the anxiety.

At least one of these disorders is likely to be experienced by 1 in 5 individuals at some time during their lives in countries in the developed world. In the USA, for example, the economic cost is estimated to be a staggering \$44 billion per annum.

### *Depression*

Depression is also an emotional mood state. It tends to follow from experience of a pattern of stress and anxiety evoked by social situations, or other personal achievement or materialistic ambitions, where the final outcome falls significantly below our expectations.

Our failure to achieve specific expectations may lead us to adopt a protective pattern of behaviour where we deliberately de-motivate ourselves to engage in similar future activities that might cause us stress and anxiety through repeated failure. During this period we may become obsessed with our own shortcomings and consider that the problems we are encountering are self-generated. However, the adaptive function of this behaviour is to better prepare us for developing a new course of action that is more likely to result in future success. To help us achieve this our withdrawn and submissive aspect are likely to provoke sympathetic and supportive reactions from other members of our social group while temporarily reducing any chance of further aggression towards us from individuals that may have been responsible for causing our unexpected failures in the first place.

The idea therefore is that experiencing a depressive state infrequently and for a brief period of time can actually improve our subsequent ability to cope with specific life challenges and may even help to re-affirm social bonds. The main problem that occurs is that, just as with stress and anxiety, when episodes of depression become frequent and prolonged the individual becomes part of a vicious downward spiral where persistent feelings of isolation, apathy, fatigue, low self esteem, social withdrawal etc can lead to suicide. Indeed, depression is usually seen as a form of continuum with different levels of severity being assigned different classifications (see Persaud, 2001 and Thase and Lang, 2004 for more detailed descriptions).

At its most severe level a classification of "major depression" is assigned where mood is suddenly and severely depressed for at least two weeks and where the majority (at least five and including one of the first two) of the symptoms below are experienced:

- Persistent sad, anxious, or "empty" mood nearly every day (observation made by others = tearful), hopelessness, pessimism etc
- Rarely feel pleasure or joy during activities that were once enjoyed, including sex
- Feelings of guilt, worthlessness, helplessness
- Decreased energy, fatigue, being "slowed down"
- Difficulty concentrating, remembering, making decisions
- Insomnia, early-morning awakening, or oversleeping (hypersomnia)
- Appetite and/or weight loss or overeating and weight gain
- Thoughts of death or suicide; suicide attempts
- Restlessness, irritability

- Persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain

Where “mild depression” symptoms occur then several of the above are experienced, again with a rapid onset, but they do not persist for more than two weeks. If “mild depression” symptoms persist for long periods (generally for 2 years or more) then this is classified as “dysthymia”. To make matters more complex it is possible to have “dysthymia” and to experience an episode of major depression and this is termed double depression. Not surprisingly the different levels of depression can be experienced progressively if no effective remedy is achieved. Depression and anxiety states are also often experienced together.

A rarer form of serious depression disorder which is somewhat different from the other forms is manic depression (often referred to as bipolar disorder). As the descriptions of this disorder suggest it is characterised by opposing mood swings between depression and mania. Depression symptoms are already described above and those of mania are described below:

- Abnormal or excessive elation
- Unusual irritability
- Decreased need for sleep
- Grandiose notions
- Increased talking
- Racing thoughts
- Increased sexual desire
- Markedly increased energy
- Poor judgment
- Inappropriate social behaviour

Raj Persaud in his book “Staying Sane” provides some worrying statistics about the incidence of depression in the UK and trends indicate that the scale of the problem is increasing:

- Two thirds of suicides are under 35
- Young men are at particular risk of suicide with dramatic increases in the last few decades (33% increase from 1980-1990 and 85% increase in 15-24 year olds).
- Average age for onset of clinical depression is 30 with highest rates in young married women with children.
- One in five people will experience clinical depression at some stage of their lives
- At least 40% of GP consultations involve mental health problems (most of which are in relation to depression).
- In any one week one in ten adults are significantly depressed.
- After puberty the incidence of depression is twice as high in women than in men.
- In the UK there are 5000 deaths a year from suicide and more than 100,000 suicide attempts (suicide is one of the top ten causes of death).

### *Summary of why we have evolved stress, anxiety and depression responses*

It is easy to see that stress, anxiety and depression should, in the short term, promote enhanced ability to deal with current or future challenging situations and allow us to live to fight another day. If we are faced with challenges both our body and our mind need to be in peak readiness for appropriate action and the physiological changes promoted by the release of stress hormones do just this by priming out muscles for action and enhancing levels of arousal, attention and even cognitive skills. Anxiety can similarly be a positive force for promoting appropriate action by pumping up our level of arousal in anticipation of challenges, but also calling into question whether we have the necessary strength or skills to overcome whatever problem is anticipated to occur in the near future. This is potentially a very important stage in helping us make decisions as to whether to tackle a particular problem or to avoid it. Depression is primarily a protective mechanism where we adopt a submissive and withdrawn state when events fail to conform to our expectations; we see no immediate solution to the situation and anticipate that it is likely to be repeated because we do not have what it requires to alter the likely negative outcome.

In short, stress prepares us for action; anxiety warns us that we might not be quite up to dealing with the action required to solve a situation - but to be pumped up and ready to give it a go; depression tells us that we do indeed lack the necessary

skills to deal with something, to avoid circumstances where we will inevitably fail again and to take stock of what caused us to fail to deal with the situation in the first place.

An obvious example of this which can be applied to any animal species is the quest for social dominance. Being at the top of the social hierarchy has many advantages for all social species. These range from preferred access to food, sex, companionship and increased personal protection. When you encounter another individual in the social group who intends to threaten your position this initially promotes stress and anxiety to help deal with an immediate agonistic threat. If the situation is not fully resolved this could be followed by a further period of anxiety to help you maintain a state of heightened arousal and help anticipate a future encounter and whether you are equipped to meet the challenge. Depression may result if you either realise that you are ill equipped to win an aggressive encounter, and must back off, or if you engage in a fight with a rival and lose.

Another context might be a man who finds social contact difficult but is looking to form a relationship with a woman and sees one he knows and is attracted to smiling in his direction across the room. This may evoke both stress (the woman is perceived as a "stressor") and anxiety (that she might not respond appropriately to any advances made) responses. Depression could easily result from her rejection of any advances made. However, the whole process viewed in a positive sense should allow him to keep the motivation to try again and help provide him with an alternative strategy that might result in better success on a future occasion.

### **So what are the physiological changes responsible for causing stress, anxiety or depression and what happens when we can no longer control them?**

We certainly understand far more about mechanisms of stress in other animals than in humans and many other species exhibit the physiological and behavioural signs of mood states such as anxiety and depression.

### **The physiology of an acute stress response**

Experience of a given "stressor" can produce a variety of changes in the activity of the brain and peripheral nervous systems and a host of hormonal and biochemical changes with the potential to alter the functions of virtually every organ and tissue in our bodies. It is not my intention to describe all of these in great detail but rather to give a flavour of the general principles that appear to operate in humans and other animal species.

When we perceive some kind of "stressor" this is first identified and interpreted by sensory, cognitive and emotion control centres in the brain. These, in turn, alter activity in parts of the brain that control our level of arousal and peripheral nervous systems (via the brainstem) and then activate centres in the base of the brain (hypothalamus) that regulate release of chemicals from the pituitary gland which then influence hormonal release from our peripheral endocrine organs (particularly the adrenal gland). These hormonal changes act to shut down all immediately non-essential bodily functions (digestion, metabolism, immune responses etc) and are expressly designed for preparing our bodies for some kind of immediate and potentially strenuous action. This is done by maximising production of nutrients that provide energy (glucose), increasing the amount and speed of delivery of these nutrients and oxygen to the muscles (by adrenaline release causing increased blood pressure and flow) and also by diverting these key resources away from non-essential organs and tissues.

The changes in our bodies promoted by an initial stress response feedback to the brain to promote heightened mental alertness and increased production of its own natural source of analgesia (opioid peptides, such as  $\beta$ -endorphin, which are the brain's equivalent to morphine) to help reduce sensitivity to pain. In this way we can all turn temporarily into the "Incredible Hulk" or "Superman" and will sometimes carry out amazing feats of physical strength and endurance even in the face of significant injury. Superior performance by an athlete can also be achieved through the controlled activation of this stress system. Indeed, the use of an effective psychological "pumping up" process prior to competition will often make the difference between winning and losing.

Switching on the stress supercharger is designed to help us deal with short-term avoidable problems but keeping the system permanently engaged is effectively a great way of inducing a physical burn out scenario whereby the body progressively stops working properly and destroys itself. For this reason just as the brain has very efficient mechanisms for triggering the

body's stress response it also has active mechanisms for shutting it down. Both cognition and emotional control centres in the brain play essential roles in regulating the activity of arousal and hormonal control centres and one of the ways this is achieved is that they themselves contain special receptors for stress hormones (such as the adrenal hormone corticosterone). In this way a complex set of feedback loops serve to promote, maintain and shut down the body's stress response.

## **The physiology of the chronic stress response**

It should have been quite easy to work out from my description of what happens during an acute stress response why maintaining it chronically should spell bad news for the health of any animal species. The catalogue of prospective damage that can result from being in this state too long is extensive and I will just confine myself to considering just a few of the major entries in it.

### *Stress and the cardiovascular system*

Current estimates suggest that individuals experiencing chronic stress are around 2.5 times more likely to experience serious cardiovascular problems. The reasons for this are not fully understood. On the one hand the long-term effect of increased pressure on the heart by having to work harder during conditions of stress may well cause it to malfunction at an earlier age. One of the other likely contributory factors is that stress causes fat stores to be converted into fatty acids and glycerol which enter the blood to help with meeting increased energy requirements. However, the down side to this is that this process may actually increase the amount of fat circulating in the vascular system and cause progressive blocking of the arteries to the heart. Of course additional strains will be placed on cardiovascular function by the effects of reduced immunocompetence which I will describe in a moment, as well as compensatory behaviours such as smoking, drinking, drug-taking and overeating which are often adopted in an attempt to reduce stress.

### *Stress and diabetes*

While stress may not cause diabetes *per se* it might well hasten its onset and once an individual has become diabetic then stress can certainly cause significant problems. This is because one of the major effects of stress is to increase blood glucose levels and reduce insulin production. Uncontrolled, this scenario can spell bad news for an existing diabetic and hasten the onset of the condition by placing excessive strains on insulin-secretion and response mechanisms.

### *Stress and the immune system*

The immune system has two functional divisions, an innate non-specific system and an adaptive specific one. The innate system is the first line of defence against infectious agents (viruses, bacteria, fungi and parasites) and endeavours to prevent them from establishing an overt infection. The adaptive immune system produces a specific reaction to each pathogen (antigen) which will eradicate it. This latter system forms a recognition memory, with the aid of B and T memory cells, which both maintains this reaction and enhances it each time the specific antigen is encountered. Both divisions of the immune system consist of a number of humoral (molecules) and cellular (leucocytes) factors which are distributed throughout the whole body and act in a co-ordinated way to counter infectious agents.

There have been a large number of studies carried out which have attempted to quantify acute and chronic effects of psychological stress on the immune system and I do not intend to discuss them here in any detail. A recent review of 300 studies conducted over the last 30 years (Segerstrom & Miller, 2004) has produced the following conclusions:

Acute stressors (lasting minutes) tend to boost natural immunity while suppressing some aspects of specific immunity. For example, brief naturalistic stressors (such as taking an exam) tend to suppress cellular immunity while preserving humoral immunity.

Chronic stressors broadly suppress both cellular and humoral immunity although interestingly subjective reports of stress do not associate well with these immune changes.

### *So how can stress influence the immune system?*

In essence there are at least three different ways this can happen:

- Sympathetic nerve fibres descend from the brain into both primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid tissues. These fibres can release a wide variety of substances which influence immune responses by binding to receptors on white blood cells. Some immune cells are more sensitive than others. For example natural killer cells have the greatest response to adrenaline because they have both high density and high sensitivity  $\beta$ -2 adrenergic receptors. By contrast, B cells have high density but low sensitivity and T-cells have low density.
- The hypothalamic - pituitary - adrenocortical axis, the sympathetic nervous system - adrenomedullary axis and the hypothalamic - pituitary - ovarian axis promote secretion of the adrenal hormones adrenaline and noradrenaline and cortisol and corticosterone; the pituitary hormones prolactin and growth hormone and the brain peptides melatonin,  $\beta$ -endorphin and enkephalin. These can all bind to specific receptors on white blood cells and alter their function.
- Lastly, as with other areas where stress can have a negative impact, immunocompetence can also be influenced indirectly as a result of inappropriate stress-management regimes such as alcohol abuse and altered sleeping patterns

### *Stress and ulcers*

One of the most well known effects of the stress response is to increase levels of hydrochloric acid, and therefore acidity, in the stomach. For many years stress was thought to be the psychosomatic cause of stomach ulcers until 1982 when it was discovered that they were actually caused by a virulent bacterium known as *Helicobacter pylori* which could be treated effectively with antibiotic combinations such as ampicillin and metronidazole. While this seems to kick stress into touch as being an important factor it has now become clear that only two out of ten individuals with this bacterium actually develop stomach ulcers and recent research has found that where individuals report experiencing significant levels of stress this proportion doubles to four out of ten. So stress may still be a significant factor.

### *Stress, neurodegeneration and memory*

In previous talks I have given on memory and emotion I have discussed how memories are made very long-lasting if events are experienced in a strong emotional context. However while memories for emotional and stressful events and experiences are long-lasting and influential on our behaviour, the aftermath of stress can reduce our subsequent learning and memory skills and increase our susceptibility to age-related cognitive decline (see Kim and Diamond, 2002).

One of the main reasons for the negative impact of stress on memory function is that many cells in a key structure in the brain for learning and memory, the hippocampus, contain receptors for adrenal stress hormones, notably corticosterone and cortisol. When these receptors become activated by these stress hormones they adversely affect the metabolic functions of the brain cells concerned thereby interfering with their structure and function and ultimately survival. In humans, for example, patients with post-traumatic stress disorder have significant hippocampal atrophy and problems with memory recall. Giving normal healthy humans cortisol artificially also impairs aspects of memory associated with hippocampal function.

### *Stress, sexual behaviour and fertility*

One of the best established effects of stress is that it reduces production of gonadal hormones in both males and females by suppressing the production of gonadotrophins from the pituitary gland. The most immediate effects of this are to interfere with, or even stop, ovarian or menstrual cycles and to reduce sperm production. In both instances this obviously compromises fertility. Reduced gonadal hormone levels can also lower sex-drive. A consequence of prenatal stress in animals is feminisation of male behaviour, presumably as a result of decreased ability of hormones to produce a fully differentiated male brain!

To make matters worse recent studies on rats have shown that anti-inflammatory drugs such as aspirin taken during gestation can also produce feminized male offspring by inhibiting sex steroid induced sexual differentiation of the brain (Amateau and McCarthy, 2004). So both the experience of stress and taking some of medications that help relieve the symptoms of stress (headaches) can have an impact on masculine behaviours! This should be a cause for concern for the future of human males in societies with increasing levels of stress and anxiety!

Experience of prenatal stress has been found to correlate with a higher incidence of homosexuality in offspring. One study has reported that two-thirds of mothers whose children were male homosexuals reported experiencing significant stressful



episodes during pregnancy (death of close relative, divorce, separation, traumatic financial or sexual experiences, feelings of severe anxiety (Dorner, Schenk et al, 1983). For mothers of bisexuals only one-third reported such stresses during pregnancy and for mothers of heterosexuals only 10%.

### *Stress and population control*

It is remarkable that population growth in mammals usually stabilises itself below environmental capacity. There are some exceptions to this in rodent species in Arctic areas, but one hypothesis that has been suggested by John Christian in 1950 is that this is achieved by a form of population self regulation whereby the stress of overcrowding has an impact on the brain-pituitary-gonadal axis to reduce fertility (as described above). Stress effects on the immune and cardiovascular systems would also increase mortality. Overcrowding is one of the severest forms of social stress (which I will discuss in more detail in a moment).

This is an attractive hypothesis which has received some experimental support in laboratory maintained animal populations, although not so much in the wild. Whether this might apply ultimately to the control of a human population explosion remains to be seen. However, it may well turn out that environmental contamination from synthetic oestrogens in plastics and other sources entering our food supply is more important than stress in this respect.

### *Social stress*

Overcrowding in most animal species leads to elevated stress hormone levels, suppression of fertility and usually heightened incidence of disease and premature death. As already mentioned most species, with the potential exception of humans, regulate population numbers quite efficiently so the results of the effects of overcrowding can only be produced experimentally under laboratory conditions.

There is little doubt that for any social species, social relationships represent not only a potent source of happiness, protection and relief from stress, but when they are absent or go wrong, can cause abject misery and considerable stress.

The numbers one and two ranked psychological stressors for humans are death of a partner or child and breakdown of relationships with them and resultant separation. A further major cause of social stress has been identified as bullying in the workplace with as many as one in four workers reporting this experience in the UK and elsewhere (see [www.bullyonline.org/workbully/costs.htm](http://www.bullyonline.org/workbully/costs.htm)).

While we regard ourselves as the most social species on the planet, the impact of social stress on other species can be far more severe than for us. A classic example of this is the tree shrew which is a small diurnal mammal that lives primarily in Southeast Asia. In the wild these animals live in pairs and defend their territories vigorously against intruders of the same sex. Under laboratory conditions where two same-sexed individuals are introduced to one another they fight vigorously. In the aftermath of the battle the defeated animal sits in a corner and the victor seems to primarily ignore it. Even though during the next week after the fight there are few, if any, further aggressive encounters the defeated animal almost invariably dies. This is mainly as a result of being constantly in the presence of the victor and occurs even when a see-through barrier screen is constantly in place between the victor and the vanquished to prevent any physical interactions. It does not occur however if the screen between the two animals is opaque (see Von Holst 2001).

In the defeated animals, levels of adrenal corticosterone are elevated 6-times above normal and their immune systems severely compromised. For those animals dying within 8 days, urea nitrogen (and creatinine) levels are raised over 10-fold, causing a fatal uremia as a result of kidney failure. Similar kinds of findings have been reported in hares and field voles.

In primates position in the social hierarchy also has an impact on the levels of stress experienced. In both baboons, rhesus and talapoin monkeys dominant male monkeys in small stable social groups consistently have lower heart rates and cortisol levels than subordinate ones although in unstable social hierarchies the opposite may occur with dominant males being stressed through having to try to maintain their position. However, the stress outcome may be different in the two different situations. Studies in talapoin monkeys have shown that effective drug treatments for dominant animals stressed by an unstable hierarchy are those used for anxiety in humans. On the other hand those which are effective for subordinate animals are more suitable for the treatment of depression.

### *Treatment of chronic stress*

Traditionally drug treatments for chronic stress are those which boost the brain's inhibitory systems such as benzodiazepines (librium, valium etc) or produce anaesthetic effects such as alcohol, opiates and barbiturates. The main advantages of these drugs are that they relieve symptoms very fast (usually within minutes) although their greatest drawback is that they are addictive. There are however other ways of tackling the problem that may not require you to resort to drugs and I will consider these in a minute.

## **Anxiety**

### **The physiology and treatment of anxiety**

Anxiety is caused mainly by excessive excitatory neurotransmission in the brain and that is why, in the same way as for chronic stress, the most effective pharmacological treatments are with drugs that have anaesthetic or inhibitory neurotransmission properties such as alcohol, barbiturates, opiates, beta-blockers and benzodiazepines.

Brain imaging studies in humans have shown that anxiety disorders are associated with increased baseline activation in the cingulate cortex and parahippocampal gyrus and evoked activity in response to anxiety-provoking stimuli in the amygdala, parahippocampal gyrus and frontal cortex (these are all brain regions that are important for control and expression of emotions). Removal of the cingulate gyrus can be an effective treatment for individuals with obsessive compulsive disorder that does not respond to other therapies. Animal studies have also shown that anxiety-reducing actions of benzodiazepines are mediated via GABA receptor effects (the main inhibitory neurotransmitter in the brain) in these regions.

In recent years the drug treatment of choice for anxiety disorders has been the selective serotonin re-uptake inhibitors (SSRIs) such as Prozac, Zoloft, Celexa and Paxil which act primarily to boost the amount of the neurotransmitter, serotonin, available for influencing neural activity by preventing it from being taken away from its site of release, metabolised and rendered inactive. Brain imaging studies have shown that these drugs also reduce the levels of excitation in areas associated with anxiety symptoms. Their advantage is that they are non-addictive; although the bad side is that they only act slowly – generally 2-4 weeks – since their therapeutic actions seem to require some structural alterations within the brain.

### *Genetic and experiential factors that contribute to high stress and anxiety disorders*

There are marked individual differences in responses to stress and it is clear that some individuals are more susceptible than others, just as they are for anxiety and depression. To a large extent however, individual differences are most easily explained by the propensity with which specific stressors gain access to the stress response mechanisms. This places the problem well and truly in the cognitive and emotional domain and suggests a strong influence of experience.

Studies on monozygotic and dizygotic twins suggest around a 30-40% genetic contribution which is only moderate and somewhat less for heritable mental disorders such as schizophrenia and Huntington's disease. Bipolar disorder (manic depression) also has a high level of heredity. One might therefore predict to find significant gene-environment interactions as predictors of anxiety pre-disposition. This is exactly what has been found.

As far as genetic factors are concerned then there is a small significant predisposition for anxiety in individuals that carry a specific variant of the serotonin transporter gene (5-HTT). Approximately 32% of Caucasian populations carry two shorter alleles in the promoter of this gene and have less 5-HTT and a higher score for neuroticism (and a lower score for agreeableness) (Lesch et al., 1996). Even as babies, individuals carrying this form of the gene show increased anxiety scores. Brain imaging studies on individuals carrying this form of the gene show potentiated activation to fearful faces in the amygdala. It seems strange that inhibiting 5-HTT in adulthood is anxiolytic whereas doing the same throughout life is anxiogenic. However, work in mice lacking expression of the 5-HTT gene has confirmed such anxiogenic effects and pharmacological blockade of the transporter in the first two weeks of life produces the same effect. So we are left with the conclusion that this transporter has differential importance for an anxiety phenotype in early life as opposed to adulthood. Differences in this 5-HTT gene also relate to susceptibility to depression.

Another interesting twist is that the majority of chemical systems in the brain that are important for promoting the formation of social bonds (notably oxytocin, vasopressin and opioids) can also act as anxiogenics. Mice lacking the genes for producing these substances show significantly reduced anxiety compared with normal animals and similar findings have been reported

in sheep and monkeys using pharmacological treatments. It would seem therefore that our anxiety system is also used to encourage us to be social. The pleasure we derive from social interactions may therefore be both from anxiety relief as well as through direct activation of parts of the brain that make us feel pleasure (dopamine reward systems).

In theory this should make relatively asocial individuals less prone to anxiety and in general this does seem to be the case, although being unable to respond to social rewards would also make individuals more susceptible to depression. It is relevant to point out in this context that drugs which effectively reduce feelings of social reward (like opioid antagonists) can be used to treat human social disorders, such as autism, through stimulating an increased need for social contact.

Research on rodents has revealed effects of early experience of different styles of maternal care on the development of a high stress/anxiety type of phenotype. Strains where mothers pay their offspring less attention in terms of licking and grooming them produce offspring that show high levels of stress and anxiety and also become low licking and grooming mothers themselves. They also seem to be poorer at learning. This is mainly an effect of experience since fostering pups from low licking and grooming mothers onto high licking and grooming ones prevents this. It seems that part of the effects responsible for this are reducing activity of the brain's inhibitory systems (i.e. allowing the excitatory systems to more easily promote anxiety).

Shortening the normal period of maternal care in rodents also results in animals showing higher levels of stress and aggression than normal. Research on both monkeys and humans experiencing a lack of appropriate maternal care has indicated that this produces higher stress and anxiety phenotypes and predispositions towards addiction to alcohol or drugs (see my lecture "Is having a good parent more important than having good genes?" 5 th December 2002 ).

## **Depression**

### **The physiology and treatment of depression**

We still have a great deal to learn about precisely how changes in the brain can cause depression. It has been considered for some time that deficiencies in monoamine transmitters (serotonin, noradrenaline and dopamine) are responsible and almost all current drug treatments try to increase their activity. A recent brain imaging study carried out at the National Institutes of Mental Health in the USA has found evidence for overactivity in key brain regions dealing with the control of emotions (orbitofrontal and cingulate cortices, ventral striatum and medial thalamus) in individuals prone to depression (and in whom depression symptoms can be triggered by depleting serotonin in the brain through reducing levels of its precursor, tryptophan). This change in brain activity is independent of whether depression symptoms are being experienced and cannot be induced in individuals with no history of depression.

The above findings have been interpreted as showing that once an individual has experienced major depression symptoms they are likely to have permanent changes in the organisation of their brain which make it likely they will have them again unless they stay on permanent medication. It also seems likely that repeated experience of major depression actual causes degeneration in the brain which further increases the chances of further episodes.

Whichever way you look at it, this scenario seems to spell the chance for major profits associated with sales of anti-depressant drugs developed by the Pharmaceutical industry.

#### *Drug treatments*

There is a wide range of anti-depressant drugs and it is important to state at the outset that the first one that you may be prescribed has only about a 50:50 chance of working. However, with persistence and changing and combining medications success rate with major depression and dysthymia can be as high as 80%. These drugs do not alter your perceptions or make you feel good *per se*, what they do is push aside the stifling cloak of depressive symptoms and restore your normal abilities to think and feel.

More comprehensive descriptions of the drugs in current use and their actions and potential side effects can be found in Thase and Lang 2004, Nemeroff and Owen, 2002 and Wong and Licinio, 2004).

As with anxiety, the major class of drugs used for treatment of depression are the SSRIs. The idea once again is to increase the availability of serotonin. Some recent drugs, like Venlafaxine, minocipran and trianeptine increase availability of both

serotonin and noradrenaline and are called SNARIs (serotonin and noradrenaline re-uptake inhibitors). A total of 28 million people in the USA take anti-depressants and in the UK so many people are taking drugs like Prozac that it can even be detected in our drinking water!

The side effects associated with taking SSRI's are relatively minor and it does seem possible to contemplate taking them for very long periods to help prevent recurrence of depression. However, recent investigations of the SSRI, Seroxat, have called into question its use (and presumably other SSRIs) in young people – under 18s – where an alarming incidence of suicides has been reported. As with anxiety this may also reflect the differential functional importance of serotonin transporters in children and adults.

Older forms of drug treatment for depression, which are still quite effective and widely used, include tricyclic compounds such as imipramine and monoamine oxidase inhibitors like Tranylcypromine. These also act by increasing availability of brain monoamines.

Future drug development targets for treatment of depression are investigating the efficacy of altering brain sensitivity to hormones that trigger stress responses (such as corticotrophin releasing factor). One advantage of doing this is that they might be effective treatments for stress, anxiety and depression – i.e. one drug might cover everything!

Herbal remedies have also long been used in the fight against depression, the most commonly used being St John's Wort. The important active ingredient in this is thought to be hypericin and this should be at a level of between 900 and 1200 mg/day. At least one study has claimed approximately equivalent success in treatment of mild to moderate depression with St John's Wort compared with antidepressant medicines. However it should be emphasised that it can have side effects and can cause problems if taken with other medications (see Thase and Lang, 2004).

Treatment of manic depression is more difficult although medications which include lithium and anticonvulsant agents such as valproic acid can be reasonably effective.

Trans-cranial magnetic stimulation (TMS)

A relatively new approach to treating depression is to stimulate activity in the frontal cortex on the left side of the brain using a non-invasive technique. It seems that happy thoughts, feelings and expressions are controlled by the left brain hemisphere, whereas negative ones are more likely to involve the right side. The idea is therefore to selectively stimulate brain regions to counter depression by making you feel happy. As far as we know this treatment has no side effects and may be helpful in situations where individuals do not respond well to anti-depressant drug treatments.

Why are women more prone to depression than men?

This is a complex issue since there can be all kinds of contributory factors which can be as simple as men being less likely to seek help for coping with depression. In general, explanations for this sex difference are either in terms of different gender roles (females more involved in child care and domestic chores), expectations (expectations of lower achievement and lower self-esteem), likelihood of experiencing trauma (females are more likely to experience or worry about traumatic personal events – being physically abused, battered, raped etc) and reactions to stress (females tend to deal with problems by mulling over them repeatedly while men tend to try to engage in some form of action – not necessarily for solving the problem). However, hormonal differences are also considered to be major contributors.

In support of this, sex differences in depression do not occur until the time of puberty and it is well established that women experience pre-menstrual syndrome, post-partum depression and menopausal-associated depression. All of these reflect fluctuations in levels of ovarian hormones, particularly oestrogen, and oestrogen treatment has sometimes been found to be as effective in reducing depression symptoms as SSRIs. Indeed, one of the actions of oestrogen is to cause increased activity in brain serotonin and noradrenaline systems which are also the primary targets for most anti-depressant treatments. Women are also more prone than men to experience reduced thyroid gland activity and thyroid hormones act to boost brain serotonin and noradrenaline systems. Finally sex differences tend to even out in old age when sex hormone levels are significantly reduced in both males and females.

**How can we manage our stress, anxiety and depression levels more effectively without drugs?**

I must emphasise before embarking on this section that for those individuals suffering from severe clinical symptoms of stress, anxiety and depression it is often necessary to use drugs just to get these under sufficient control to embark on other courses of action. Since all of these conditions tend to be progressive however the idea is to try to take some positive non-drug associated approaches before symptoms reach a level of severity where drug treatments may be the only option.

For humans, the first step on the road to dealing with significant levels of stress, anxiety and depression is to identify what it is that is contributing to them. Often a large amount of counselling time can be spent just getting to the root of the problem. No matter what kind of treatment is given it will not be fully effective unless the real problem is identified and some kind of solution found. In many cases individuals simply try and shut out the problem they are unable to deal with and adopt a range of relatively inefficient coping strategies to avoid trying to find some kind of active solution.

For humans the most popular neutral remedies for coping with stress are watching TV or listening to the radio or music, socialising, reading and exercising. On the other hand equally popular remedies are often potentially damaging to health and include smoking, drinking and eating and indulging in recreational drugs. In reality the most effective ways of coping with stress are simple and involve identifying the problem and avoiding it or finding a way to overcome it. While it may not always be easy to do this the most important take home message is that you must take the initiative and mount some form of active response to the situation. If the symptoms of stress and anxiety are too severe for rational thought to address then the first strategy may be to reduce stress levels by relaxation or exercise.

Sitting down in front of the TV may seem like a universal panacea for coping with stress-related problems but on average the majority of TV programmes we watch leave us mildly depressed and so can actually increase the problem. Listening to music can be more effective although if you only listen to sombre music when you are depressed this can also make things worse. However, if you try using any lighter, happier music that you enjoy this does seem to be more therapeutic. Of course it goes without saying that smoking, drinking and eating as a means of coping can turn out to have a nasty sting in the tail by creating additional health, weight or psychosocial problems that can also potentially worsen depression.

#### *Active and passive coping strategies*

In general coping strategies fall into the categories of either active or passive. Animal studies show clearly that where individuals react to social stress by becoming passive and inactive then death is the most likely imminent outcome. If, on the other hand, they remain active by either avoiding the stressor, or by continuing to engage in normal activities, then death is unlikely. In general it seems that the number one rule for dealing with stress, anxiety and depression in any species, including humans, is to try to cope with some form of active response. Unfortunately many of the things we do to try to deal with them are passive and are, at best, short term fixes.

#### *Seeing the glass half-full rather than half-empty*

The way we perceive challenges in life is also a major focus for helping us cope with stress, anxiety and depression. The books by Raj Persaud "Staying Sane" and Thase and Lang "Beating the Blues" consider different aspects of self-help strategies in considerable detail and are well worth a read. All I really need to say here is the simple message that trying to see even the most serious problems you may be exposed to in a positive light rather than a negative one is a highly effective defence against succumbing to anxiety and depression.

#### *Social buffering effects*

Animal studies provide strong support for the concept that social interaction with another calm individual is a potent way to alleviate stress and anxiety. We have even been able to show in my own laboratory recently that sheep made anxious and fearful by social isolation are immediately calmed just by being able to see face-pictures of familiar sheep (da Costa *et al.*, 2004). This could help explain why so many of us (around 47% in a poll on 9000 people conducted by CNN as a result of our findings in sheep!) carry around pictures of loved ones with us. It even raises a serious proposal that one way to help treat separation anxiety in both pets (particularly dogs) and children may be to give them pictures of their owners/parents that they can see during periods of separation.

On the other hand social interactions with individuals who are stressed are not very effective. Positive social interactions are widely recognised as a way of reducing stress and it is not surprising that solitary individuals seem more prone to stress, anxiety and depression than those with stable partners or a strong social environment.

One slight caveat to the general idea that seeking out good, calm friends can help you deal with stress is that this strategy seems to work better for men than women.

It is probably worth pointing out that social buffering attempts can easily make situations worse if all another individual does is tell you there is nothing to worry about, that you are being silly and to snap out of it. This might be OK for mild cases of feeling anxious or down but is decidedly unhelpful for individuals suffering from more severe symptoms. One has to remember that it is very much a matter of individual perception, what may seem a minor problem to you can be a major one to someone else and it is them, not yourself, who you are trying to help. Help is very much about listening and being positive, not about being critical and giving instructions.

### *Exercise*

Taking regular exercise is widely recognised as being as effective in alleviating symptoms of stress, anxiety and depression as specialised drug treatment. We are not talking about running regular marathons here but any form of regular (perhaps 5 x 30 min sessions a week), relatively vigorous activity. My own experience and that of many others I have spoken to is that taking exercise is an amazingly effective way of beating off the blues and de-stressing. It has to be vigorous enough however so that you don't spend the whole exercise period thinking about whatever it is that is causing you problems!

Why does exercise tend to put you in a better mood and help work off stress? There are a number of answers to this:

- It promotes release of endorphins, adrenaline, serotonin and dopamine in the brain which promote a sense of well-being (i.e. both pleasure and anti-depressant/anxiety mechanisms are being activated).
- Physical health can also be promoted – weight reduction, improved flexibility and muscle tone, reduced risk of heart disease, cancer, high blood pressure, osteoporosis diabetes etc
- Relieves tension, frustration, stress and anxiety by changing heart rate, oxygen intake and stimulating biochemical changes.
- May also increase social interactions – going to leisure centers etc.
- Boosts sense of achievement and heightens self-esteem – you feel a sense of accomplishment after your work-out
- Distracts you from mulling over problems.
- Improves sleep quality – by stimulating muscles, lungs, heart rate, oxygen intake and biochemical changes (but don't exercise just prior to going to bed since it will increase your alertness and body temperature and stop you falling asleep!)

### *Relaxation techniques and meditation*

There are a large number of mind/body meditation and relaxation techniques that can be utilised very effectively to reduce stress and anxiety. These include Yoga, Tai-Chi, some forms of Pilates and Meditation and breathing control techniques. Many of these also include a social element in that they can be group based activities. They act primarily to distract attention from problems and to reduce physiological symptoms of stress such as high heart rate and blood pressure and muscle tension. If you are highly stressed then these are normally the first choice approaches since going out for an energetic run may under these circumstances add to your stress levels since vigorous exercise is in itself a physical stress.

### *Diet and Nutrition*

This is a complex and somewhat controversial area. There is little doubt that maintaining a good diet will help counter effects of stress, anxiety and depression. This consists of plenty of fresh vegetables, fresh fruits, whole grain breads and cereals, fibre, B-complex vitamins, iron, proteins and recommended daily intake of other vitamins and minerals.

**Caffeine and sugar** – these are two-edged swords by giving you an initial high for perhaps an hour or so but can then contribute to low mood or even mood swings. It is all too easy to end up resorting to combined caffeine/sugar fixes every few hours but this will end up exaggerating mood swings, causing problems with sleep and eating a proper balanced diet.

Excessive intake of these substances is also both damaging to health and addictive

**Comfort eating and drinking** – Eating and drinking alcohol are also short-term fixes for stress and anxiety with a decided sting in the tail if indulged in to excess. They are pleasurable experiences and can make you feel better but probably best combined with some form of positive social interaction (i.e. don't do it alone) and involving healthier food options and low alcohol beverages

**Vitamin supplements** – This is a minefield to discuss since research is not extensive or consistent enough to provide any clear recommendations. Some studies have reported that depression can be associated with low levels of B vitamins (B6, B12 and folic acid). Several studies have indicated that on average 35% of depressed people – rising to 90% of depressed elderly people – are folate deficient. Taking folate (400-800 mg a day) has also been claimed to enhance the efficacy of SSRI treatment. The amino acid, tryptophan, has also been claimed to be beneficial since it boosts serotonin production. However, it is best to take this by eating foods high in tryptophan (high carbohydrate, high protein foods such as soy products, seafood, meat, whole grains, beans and rice) rather than as a supplement. Omega-3 fatty acids found in cold water fish (tuna or salmon), fish oil and flaxseed have also been reported to be beneficial and researchers point out that consumption of these kinds of foods is declining in many countries. These fatty acids are important for maintaining healthy cells in the brain.

#### *Light therapy*

I have dealt with seasonal affective disorder in one of my previous lectures (“Biological clocks: Human and animal concepts of time” – 26 th February 2004 ). This is also a form of depression resulting from chemical imbalances in response to reduced amount of daylight when day lengths become shorter. The most effective treatment for this is to sit in front of a high intensity (10,000 lux) lightbox for an hour or so a day. Interestingly, even for those people who suffer from depression, but where it is not directly related to short days, some benefit of similar exposure to light can also often be seen.

#### *Early life experiences and quality of parental care*

It is well recognised that traumatic early life experiences in humans can have long-term consequences for levels of stress, anxiety and depression. It seems likely that the most influential negative experiences in this respect are psychosocial ones such as result from psychological or physical abuse by socially important individuals.

Animal studies have consistently emphasised a significant contribution of both the quantity and quality of parental care received on the development of stress and anxiety responses in their offspring. Some evidence for this has also been reported in humans in terms of whether parental care is present or not.

As many human societies move progressively towards conditions where the amount of time spent by parents with their children is reduced due to economic and lifestyle pressures, one is forced to at least pose the question as to whether this is contributing significantly towards the increased incidence of stress, anxiety and depression. It is abundantly clear that social buffering is a key factor in coping with stress and the influence of parents in this respect is likely both to encourage use of this strategy in their children and to reinforce its therapeutic qualities. If parents simply aren't around when children need this social buffering support then they are likely to use and value it less as a stress/anxiety reducing strategy.

Whether the impact of large amounts of positive physical contact between parents and their children is important in the same way as it appears for rats is also a matter for speculation. Physical contact in terms of touching, hugging, caressing, kissing can be very comforting and can also promote release of substances within the brain that promote pleasure and the formation of social bonds.

High achieving parents are more likely to produce children with stress, anxiety and depression related problems. There is also an increased likelihood that if your parents are constantly anxious and depressed then so will you be. While there may be a genetic contribution to this, animal studies show that influence of parental behaviour is very strong even when foster parents are involved.

It is important to emphasise that the issue is not about parents being overprotective and preventing their children from experiencing any distressing life events, it is about them being available and providing positive social support when they do!

#### *Having a sense of purpose*

I think we all appreciate the fact that even the most difficult challenges in life are easier to cope with if we feel that by surmounting them we have achieved something of great value. Having a strong sense of purpose is a very important buffer against pretty much anything life can throw at you. However, it is equally true to say that for many of us our sense of the importance of our lives and what we do is not very strong and can easily be undermined. In this sense it is interesting that in those individuals who have strong religious convictions the incidence of serious anxiety and depression is lower than for those who do not. Alternatively for those individuals suffering from depression having a strong religious belief seems to improve the speed of recovery. As such it is easy to make the speculation that the decline of religious belief in an increasingly material world may be a major contributor to our rising levels of anxiety and depression. One might even risk taking this further and speculate that in cultures which embrace Islamic Fundamentalism in a widespread manner, population levels of anxiety and depression are likely to be low even under circumstances of severe economic stress and higher threats to individual survival and health.

I should point out however that having a strong religious belief is not the only answer to achieving a strong sense of purpose to help protect you from anxiety and depression. It has also been claimed that convinced atheists are similarly protected – presumably because they have derived an alternative but equally strong *raison d'être*. It seems that problems are more likely to occur when religious relief is weak or you are agnostic!

### **General conclusions:**

- The negative impact of uncontrolled stress, anxiety and depression is growing
- We cannot simply get rid of them since they have important survival value
- Chronic stress damages most bodily and mental functions
- Constant anxiety and depression also damage bodily and mental functions
- There are some genetic contributions to these disorders but...
- Early life experiences may have the major impact on susceptibility
- There are many effective drug treatments for serious anxiety and depression
- They do have potential side effects and may have to be taken for life
- Since conditions are progressive it is important to deal with them early
- Use active coping strategies – maintain positive attitudes – friends who are positive and listen – regular exercise – relaxation/meditation – good diet
- Try not to get stressed out during pregnancy
- Parents try to be there more for your children
- Develop a strong sense of purpose

### **Final comment**

While we may have a greater variety of problems to deal with in modern life than our ancestors did, there is no reason to conclude from this that our lives are inherently more stressful than theirs. The problem is more to do with our modern lifestyles and values progressively eroding our capacity to cope with all the challenges we have to face. These are things we can do something about without simply sitting back and waiting for Prozac to be added to our drinking water or the next generation of anti-depressant drugs to be developed.



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