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'Of Molecules and Mind: Stress, the Individual and the Social Environment'

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Overview:
This wide ranging lecture explored the relationships between conditions and behaviours of everyday life and the biological and psychological (neuro-endocrine) pathways through which the stresses of everyday life are related to mortality and morbidity. In addition to looking at these from an individual perspective, the lecture also examined the associations which exist between socioeconomic inequality and health.

Key ideas:
- **Allostatic load**: The extent to which the body must change in order to maintain stability under stress.
- **Stressed out**: A feeling of being chronically under stress and overwhelmed by everyday events.
- **Telomere**: The ends of linear chromosomes that are required for replication and stability; the tip (or end) of a chromosome.
- **Allele**: Alternative form of a gene; one of the different forms of a gene that can exist at a single locus.
- **Cytokines**: Any of several regulatory proteins that are released by cells of the immune system and act as intercellular mediators in the generation of an immune response.
- **Dendrites:** The branching process of a neuron that conducts impulses toward the cell. A single nerve may possess many dendrites.
- **Sympathetic:** Part of the autonomic nervous system functioning in opposition to the parasympathetic system, as in stimulating heartbeat, dilating the pupil of the eye, etc.
- **Parasympathetic:** Part of the autonomic nervous system functioning in opposition to the sympathetic system, as in inhibiting heartbeat, contracting the pupil of the eye, etc.

Summary:
Professor McEwen's theses are complex, but reasonably summed up the illustration below which appeared on his first slide. A range of external factors – everyday environmental factors, major life events and traumas – combine with individual differences in nature and nurture and behavioural responses to create a perception of stress in the brain. This generates physiological responses which, in the normal course of events, lead to stress adaptation and recovery. However, where stressors become chronic rather than acute this leads to an increase in allostatic load which in turn has adverse consequences for health and wellbeing. Prof McEwen began by quoting data from the well known Whitehall study which has demonstrated the existence of a positive relationship between socioeconomic status and health for both men and women. Prof McEwen expanded on this work using data which showed a similar relationship between income / education and mental health. He then proceeded to ask how socioeconomic status gets under the skin by posing the question "how do brain and body communicate?".

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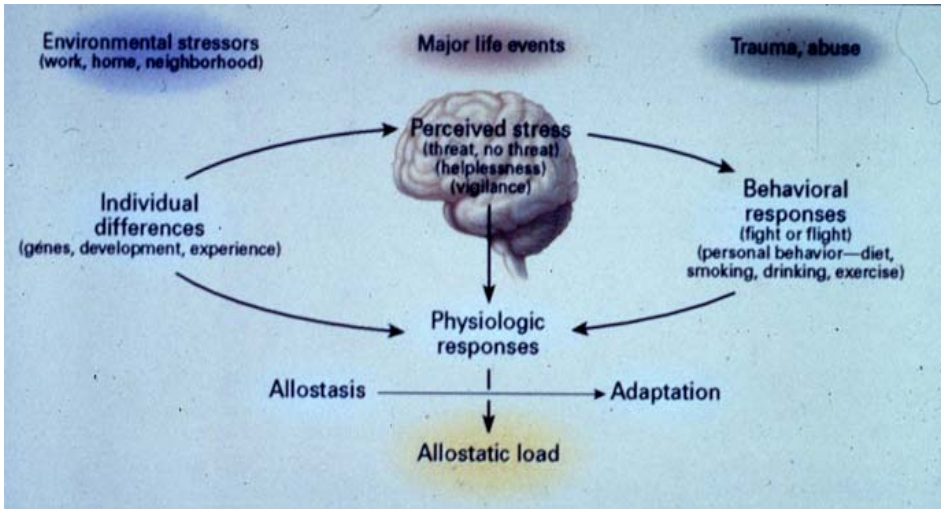

He set out the three main routes of communication as:

1. the autonomic nervous system which has two parts (sympathetic and parasympathetic) and is visceral in nature i.e. the quickening of the heart, the tightening of the stomach;
2. the endocrine system which regulates the hypothalamic response to all major hormones; and
3. the immune system which is dispersed throughout the body and responds to almost all major hormones in the body.

He went on to explain that while we think mostly of adrenalin and cortisol in relation to stress, the network of mediators of stress response is much wider than this. It also involves sympathetic and parasympathetic responses, inflammatory and non-inflammatory cytokines and reactive oxidative stress elements all interacting in a non-linear network, impossible to measure all at once. These responses and the deployment of these stress mediators add up to an allostatic load – the extent to which the body changes in order to maintain systemic stability (homeostasis) through the regulation of heart rate during periods of exertion, for example. He suggested that while this is helpful in acute situations, it creates difficulty during periods of chronic stress, such as those more commonly experience by people living in poverty. The increased allostatic load required to maintain stability in such situations eventually creates disease and disorder through the wear and tear associated with more constant use and frequent deregulation of mediating systems.

Professor McEwen then distinguished stress from being stressed out. He suggested that acute stress responses such as “fight or flight”, which typically include adaptation and recovery, can be healthy. He distinguished this from chronic stress (being “stressed out”) which also involves anxiety and is damaging to health and wellbeing. He summarised this using data from laboratory experiments and models of cortisol cascades produced by stress which indicate that acute stress response enhances immune response, memory and cardiovascular function. Chronic stress on the other hand suppresses immune function, is associated with memory impairment, mineral and bone loss, muscle wasting and metabolic syndrome[1].

[1] Metabolic syndrome is marked by the presence of usually three or more of a group of factors, such as high blood pressure, abdominal obesity, high triglyceride levels, low HDL levels, and insulin resistance, that are linked to increased risk of cardiovascular disease and type 2 diabetes.

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He further illustrated this point by showing that when a person is feeling overwhelmed, out of control, exhausted, anxious, frustrated or angry this tends to risky health behaviours (sleep deprivation, poor eating habits, smoking and drinking more, neglecting exercise, etc) which in turn increase allostatic load, implying that psychosocial stress is a major factor in stress related illness. He also showed that the stress associated with being a care giver can lead to shortened telomere length through oxidative stress which has the effect of premature aging of up to ten years in some subjects.

Professor McEwen then summarised these ideas in a model which suggests that the level of stress in everyday life lead to a response in the body which varies from person to person. If someone is in a difficult social environment or has heightened anxiety, this can lead to health damaging behaviours and create a chronic physiological burden – allostatic overload. When translated through the chronic elevation of stress mediators this leads to a range of serious health impairments such as hypertension, diabetes, obesity, CHD, arthritis, depression and fatigue. By contrast he quoted a further study which suggests that those with a positive outlook on life have more salutary levels of important physiological indicators (e.g. lower cortisol response, lower resting heart rate, etc) and therefore less stress.

Professor McEwen went on to ask how chronic stress affects the brain. He reminded us that he was setting this argument in a context which included the environment, trauma, behaviour, disposition, etc. He suggested that there were three main areas of the brain to consider here:

- The prefrontal cortex – associated with executive function and memory which atrophies[2] under chronic stress.
- The hippocampus – associated with contextual, episodic and spatial memory which also atrophies under chronic stress.
- The amygdala – associated with emotion, fear and anxiety which first of all hypertrophies[3] under chronic stress and later atrophies.

He illustrated these points by reference to laboratory and human studies which indicate that repeated stress leads to adverse behavioural changes and structural remodelling of the brain, which may change again when stress recedes. He highlighted this point by showing that stress suppresses neurogenesis (the creation of new brain cells) while moderate exercise increases neurogenesis. He also showed that chronic depression is associated with hippocampal shrinkage with corresponding loss of function analogous to ageing. Shrinkage is also related to type 2 diabetes and perhaps poor aging. Other hormones also have access to the brain and are associated with stress response. A further study of pubic speaking shows that a small group of people with low self-esteem have consistently elevated levels of cortisol under repeated stress and reduced hippocampal volume, creating a vicious cycle of elevated cortisol, with detrimental effects implied in memory and associated functions. Further studies of chronic stress among students have shown the effects of stress induced hyperactivity on the prefrontal cortex affecting executive function, mental flexibility, fear conditioning, memory and negativity which returns to normal after a month long break from stress. Looking at early life experiences using animal models, prenatal stress has been shown to increase morbidity and mortality; a trend which is reversed when maternal bonding is restored.

[2] Atrophy – a wasting away of the body or of an organ or part, as from defective nutrition or nerve damage.
[3] Hypertrophy – abnormal enlargement of a part or organ; excessive growth.

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In human populations studies have shown that chaotic environments (e.g. associated with overcrowding) when associated with poverty show a relationship between adverse childhood experience and Ischemic Heart Disease later in life, among other effects. Prof McEwen suggested this compromised the resilience of the mind/body to deal with stress which shows up in impaired language and executive function, working through increase in blood pressure and body mass index already discernable by nine years of age.

There is evidence of a genetic component to allostatic overload. A study from New Zealand suggested that those with variants in the gene for monoamine oxidase respond to abusive conditioning as a child by becoming themselves more likely to inflict abuse on their own progeny. This is a tendency rather than an inevitability and represents a powerful yet subtle balance between nature and nurture.

Turning finally to social hierarchy, Prof McEwen suggested that animal studies have shown that subordinate males have low levels of testosterone and high stress hormones and numerous changes in brain chemistry, with some subordinates being more stressed that others. Both dominant and subordinate males show reduced dendrite complexity in the hippocampus with the dominant if anything having smaller dendrites, even though dominants have larger adrenal glands. This suggests that it is a complex array of mediators and endogenous factors in the brain which operate in chronic stress situations and not just cortisol. Additional studies show complex and different changes for males and females in stable and unstable hierarchies.

Returning to human hierarchies, he suggested that a combination of perceived and actual social position and discrimination, educational resources, access to/use of health care, lifestyle and everyday stressors from work, family, neighbourhood and life events combine to explain how stress gets “under the skin”.

Finally Prof McEwen spoke of some interventions which have a salutary impact on stress and allostatic load. The first group of these relate to pharmaceuticals which are effective but largely treat symptoms and often come with unwanted effects. He then spoke about social support initiatives, physical activity and programmes which combine the two. For example, one study suggested that those with more and stronger social ties have lower allostatic load that those with fewer weaker connections. Physical activity studies have suggested that exercise improves cognitive function, is an effective treatment for depression and increases neurogenesis particularly in the prefrontal cortex and the hippocampus.

Prof McEwen’s last example combined both physical activity and social connection. He described a study of a school programme in which elderly people became classroom assistants – “The Experience Corps”. The study followed 128 volunteers aged between 60 and 86 years in elementary schools in Baltimore. At follow up a wide range of positive health indicators had improved compared to a control group. At the same time educational outcomes for children also improved.