Transcript of Professor Bruce McEwen's lecture:
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Dr Harry Burns
Welcome to the latest in the third series of Glasgow Centre for Population Health Seminars. I'm very pleased tonight to introduce Professor Bruce McEwen from Rockefeller University in New York. Every researcher will have the experience of wrestling with a problem and then suddenly encountering a reference or a bunch of references that seem to make the problem clear. You know that feeling of the hair standing up on the back of your neck as suddenly you find someone that has done something that really is significant and I had that experience a few years ago when I came across publications that Bruce had done around central nervous system development and the link between social conditions and physical conditions. So it's a really great pleasure to have him here in Scotland. Bruce started out by graduating in chemistry in the United States and went to work initially in psychology and then went to work in Sweden in neurobiology. He's been at Rockefeller University since 1981, he's a member of the National Academy of Sciences, The Institute of Medicine, The American Academy of Arts and Sciences and a Fellow of the New York Academy of Sciences. He's a very distinguished guest that we have got here. He's a member of the McArthur Foundation Research Network on Socioeconomic Status in Health and having heard what this network is doing it seems to me to have a lot of relevance to Scotland and Glasgow in particular in terms of translating evidence into policy. So it's a really great pleasure to have him here tonight to talk about 'Molecules and Mind: Stress, the Individual and the Social Environment'.

Bruce.

[Applause]

Professor Bruce McEwen
Thank you very much Harry and it's a great pleasure to be here. I have had an opportunity to discover a little bit about my McEwen ancestor who was a covenanter and was deported to New Jersey in about 1685 so it's been fun to sort of reconnect with that history and visit Bothwell Bridge today.

I'm a neuroscientist and an endocrinologist and as Harry indicated I'm also part of the McArthur Foundation Network for Socioeconomic Status in Health and becoming part of this network as a neuroscientist about ten years ago was a life changing experience in the sense that it broadened me out from work in the laboratory, which I still do, to a broader perspective about the impact of experiences that we have, adverse experiences, especially on brain function and on health and so that's what I'm going to talk to you about today.

You will notice among the names here, Sir Michael Marmot who founded the Whitehall Study which really presented to the world the notion that income and education (referred to as socioeconomic status or SES) is related in a very linear fashion to people's morbidity and mortality. From Whitehall 1, both men and women, according to the occupational status of their husbands – more recently according to their own occupational status – show linear gradients of life expectancy in which obviously the people at the highest levels have the best chance of living a long time. The same thing is true for morbidity to a number of diseases and this is, of course, a fascinating puzzle and so as part of our McArthur Foundation Network and, of course, here in Glasgow and many other places, those of us who are interested in this topic are asking the question 'How does SES get under the skin?' and so that's the topic of this evenings talk.

Not only is it true for physical health, but also, in as much as it's been studied for mental health, affective disorders, anxiety disorders and substance use all show gradients according to income and education. Not surprisingly, gradients according to income show the greatest problems at the lowest income levels, perhaps because of the fact that people with these problems are not able to get or maintain jobs, but it's perhaps more interesting and meaningful to see the gradients that you can see with education. We know now that many of these so called psychiatric disorders are accompanied by disorders in physical health and we'll get more into that as the talk goes on. So I'm going to address a series of questions and attempt to provide you answers and start you thinking about some of these areas. Admittedly I'm going to cover a lot. My students and colleagues refer to talks like this as Big Mac attacks and so you are about to get a Big Mac attack.

So the first question: how do brain and body communicate? Well, in the title I used the word 'mind' which the Oxford English dictionary defines as the seed of thought of awareness, volition and feeling. William James said that feelings and emotions were, in part, due to the perceptions of autonomic and visceral reactions – the tightening of the stomach, the palpation of the heart – and clearly our experiences reflect our physical and social environment including times when we have a stomach ache or feel pain or have a cold or the flu. In fact, what we refer to as mind really reflects the whole body and that reflects a two way communication using nerves, immune and the neuroendocrine system which are depicted here *[referring to slideshow]*. The autonomic nervous system has two parts: the sympathetic and parasympathetic branches. The neuroendocrine system involves the hypothalamic brain regulation of all major hormone systems of the body and the immune system is a disperse system throughout the body which is innervated and responds to virtually every hormone in the body.

When we think of stress we think, I think, most commonly of things like adrenalin and cortisol, but in reality the network that is activated when we are under stress is much broader than that and this is, even in a small subset of all the mediators, but, at least, it includes not only sympathetic, but parasympathetic influence, the so called inflammatory and anti-inflammatory cytokines and inevitably linked to this inflammatory process are the generation of reactive oxygen species and so called oxidative stress. The point is that although we tend to measure only perhaps one or several things at a time, like our heart rate or blood pressure or our cortisol levels, in fact, all the time when we are stressed all of these mediators are being activated and they are regulating each other so we are talking about a network, a non-linear network, rather than a simple linear chain and we have to keep that in mind even though we are not able to measure the whole system at once.

In 1988 Peter Sterling and Joseph Eyer at the University of Pennsylvania introduced a term 'allostasis', which literally means to maintain stability by being different or by changing. They were referring to blood pressure which, of course, increases when we wake up in the morning and get out of bed; increases when we walk up a flight of stairs or are emotionally aroused and it helps us to adapt to situations; it helps us to survive situations. At the same time if our blood pressure doesn't come down, if it stays elevated then adverse consequences result. So, with the late Elliot Stellar we broadened the concept to include all of the mediators involved in stress and all mediators of allostasis and we coined the term 'allostatic load' which refers to the fact that although the system may maintain or achieve stability or homeostasis, under stressful circumstances, the repetition of these stressors and their dis-regulation, a dis-regulation of this network of allostasis can result in a wear and tear on the body and brain which, over time, can lead to diseases and various disorders.

So, the next question then: what do we mean by stress? Stress is a word that occurs in many languages, it's a term that many of us use regularly to refer to things in our daily lives, but it's also an ambiguous term. If we're thinking about a zebra being chased by a lion, as this cover of this wonderful book by Robert Sapolisky, it's the fight or flight response, the acute response that gets the prey out of danger perhaps and then after that then there is the process of replenishing depleted energy stores and repairing wounds and the like, but at the same time, perhaps, the zebra is not worried and goes back to it's grazing and so forth until the next encounter. Human beings have the problem that we worry, we have anxieties. As a result of those anxieties, and other things in our lives, we often engage in health risky behaviours. The experiences that we are talking about here are perhaps better described under the term being 'stressed out' and we will come back to this a little bit later.

Now, the important thing to remember about the mediators of allostasis are that they have acute adaptive effects, but produce chronically and when dis-regulated they can also cause problems and you can see this with cortisol. First, on the left *[referring to slideshow]* is the summary of the idea of a stress cascade, the notion that experiences, neural inputs culminate, focus on the hypothalamus and cause the secretion of two chemicals, CRH and vasopressin which go to the pituitary gland and cause it to release ACTH which travels to the adrenal cortex and causes it to produce cortisol. Meanwhile there are neural impulses that more rapidly have reached the adrenal medulla and have triggered the production of epinephrine or adrenaline. Now acutely cortisol and also adrenaline have the ability to enhance immune function. I'll say more about that in a minute. They enhance certain aspects of memory like memories that will keep us out of trouble the next time danger occurs, specific events of something that might be helpful. They're involved in energy replenishment and making cardiovascular function more efficient. But chronically, we know very well that they suppress inflammation, they suppress immune function and as I'll tell you they also impair aspects of brain function including memory and produced chronically as in Cushing's disease or melancholic depression they can promote bone mineral loss, muscle wasting and they contribute to the metabolic syndrome. To a great extent this is true of all of the mediators of allostasis: in small amounts, properly regulated, they promote an adaptation and yet dis-regulated they contribute to these diseases.

An example of immune function is in the work of the former student, Firdaus Dhabhar for his PhD thesis. If you immunise a rat or a mouse and then several weeks later expose the ear to the chemical antigen, the ear swells and you can measure the swelling with a pair of callipers. And it's not just because water is coming in, it's because immune cells are moving in from the blood to fight the pathogen, if that was what it was, or even to repair a wound. This is the basal response; it's called a delayed type hypersensitivity response. If you stress the animal by restraining it at this point before applying the antigen the ear thickness is enhanced and if you do a more severe stress of immobilising the animal and also shaking it, the response is even greater and you see it lasts for as much as six days. Now that's acute stress. If you do repeated stress for 21 days restraining the animal, the two hours of restraint, at the end of the 21 days the DTH response by the antigen is now markedly suppressed. So somewhere in between the single stress and 21 days of repeated stress you achieve reversal and a profound suppression in which immune cells now do not traffic as readily to the ear. The same repeated stress scheme I'll describe later and show you some of its effects on brain cells.

Ok, being stressed out: when we are feeling overwhelmed, out of control, exhausted, anxious, frustrated and angry, what happens to us? We lose sleep at night, we eat too many of the wrong things, drink too much alcohol or smoke if we are so inclined and, because we are focused perhaps on solving problems (writing that grant, doing something that keeps us in front of the computer and otherwise away from doing things out of doors), we neglect regular moderate exercise. All of these contribute to allostatic load because they help to dis-regulate these mediators of allostasis. An example of what happens with sleep deprivation, even getting say four or five hours of sleep several days in a row, we have increased blood pressure, decreased parasympathetic tone, elevated evening cortisol glucose and insulin, elevated levels of inflammatory cytokines, increased appetite due, in part, to the production from the gut of grelin which is a hormone that actually has effects on the brain as well and these can increase them when we eat more – choleric load helps to increase the first three of these. There may be depressed mood and impaired cognitive function from sleep deprivation. We all, I think, know this from our own personal experience.

If this goes on for long periods of time it accelerates allostatic load and there are many people in our society who, for a variety of reasons, because of work or because of anxieties and so on, suffer from inadequate amounts of sleep. One of the recently reported consequences of panic stress mediated by oxidative stress is the shortening of telomeres and the inhibition of telomerase. Now, telomeres are the ends of chromosomes, they're DNA pieces that… each time a cell divides, they get shorter and the measurements are made, in this case, on samples like blood cells which have the capacity to divide the immune cells when an immune response occurs. In this particular study the care givers of autistic children were studied and as a function of whether they perceived this experience to be stressful (perhaps because of lack of adequate social support and so on; because of the severity of the autism and also as a function of length of time being a care giver) there was up to one decade of accelerated ageing; shortening of telomeres and inhibition of telomerase. Other investigators have reported telomere shortening with ageing (that's well known) and also with disorders like diabetes and cardiovascular disease and also depressive illness. So, this is a new end point. What's not clear is the degree to which the shortening of telomeres in white blood cells is responsible for, for example, impairing wound healing or impairing immune defence responses – that would be logical to assume. So, we don't know the physiologic significance of this as yet.

So this is a scheme where we think about, not so much about the major events, but the stresses of daily life operating on a pre-existing state of brain and body, which we will come back to later, resulting in varying degrees of chaos, conflict, lack of control. This is a very important aspect of all of our lives – feeling out of control or lack of control – leading to anxiety, depression and disturbed sleep; leading to behaviours like over eating, smoking, heavy drinking or lack of physical activity and then causing this increased physiologic stress burden we call allostatic load or overload resulting in chronically elevated cortisol, insulin, inflammatory cytokines; conditions like tachycardia, hypertension, hyperlipidaemia and then, over time, exacerbating diseases (the so called diseases of modern life) – hypertension, diabetes, obesity, coronary artery disease, arthritis, depression and chronic fatigue are all different manifestations of this.

There is a good side. Andrew Steptoe who spoke here in another lecture in this series and his colleagues, Jane Wardle and Michael Marmot, have examined people in terms of their positive or negative attitude towards their lives independently of daily hassles. They published this paper that showed that people who have a generally positive affect have lower levels of cortisol, a lower resting heart rate and they generate less fibrinogen which is one of the acute phase response factors in response to an applied experimental stressor. Of course there is increasing interest in the phenomenon of so called positive help and whether it is simply more than the absence of allostatic load, whether there are chemicals that are particularly related to that aspect.

How does stress affect the brain? That's where most of our laboratory studies are going and we do collaborate with investigators who do structural and functional imaging of the brain. The big picture again… the notion that the brain, of course, is the organ that perceives and decides if something is threatening, stressful; it regulates the behavioural responses we've talked about, the physiologic responses that lead to adaptation and that also can produce allostatic load. We know that perceptions of stress are highly individualised, they depend on differences in our genetic constitution, or early developmental history and experiences we have in adult life. I'll talk a little bit about the first two as we go on, but again, just to remind you that besides trauma and abuse and the major life events, the daily hassles of daily life, of course, are also (and perhaps more) important in determining ultimate allostatic load.

The three areas of the brain that we are particularly interested in include the hippocampus (which is involved in contextual episodic and spatial memory), the amygdala (which is the seat of emotions and fear, anxiety and aggressiveness) and the prefrontal cortex (which is involved in executive function, decision making, working memory and a number of other things I'll mention later). With disorders like major depressive illness… there are reports that with prolonged depression there is shrinkage of the hippocampus, also some shrinkage of the prefrontal cortex and ultimately shrinkage of the amygdala, but in the initial phases of depression there are some reports that there may be hypertrophy of the amygdala. In any case, mood and anxiety disorders are accompanied by amygdala hyperactivity and I'll say more about this as we go forward.

In laboratory studies of stress we use a restraint stress (the one that we use to study the immune system), a more severe immobilisation stress (which is commonly used in laboratories to enable investigators to sample blood from the tail using both restrainer immobilisation), and then in a more naturalistic setting. The tree shrew which is like a squirrel, but it an insectivore… if you put an intruder into the cage next to a dominant animal that likes it's own privacy the intruder is subjected to harassment and I'll say more about this a little bit later. In all of these conditions, if this goes on for a number of weeks, there are changes in behaviour: impaired spatial learning, increased aggression, increased fear, behavioural depression and learned helplessness and impairment in mental flexibility. Also, as I'll be telling you very shortly, there are changes in the structure and connectivity of nerve cells. There is reduced neurogenesis in the hippocampus, shortening of the dendrites (the processes of nerve cells in the hippocampus and in the prefrontal cortex, or parts of the prefrontal cortex) but there is expansion of dendrites in another part of the prefrontal cortex, called the orbital frontal cortex, and in the basal lateral amygdala which is probably responsible for the increased aggression and increased fear. So it's not damage, it's a remodelling process that changes both the structure of the brain and the behaviour and responses that the animal generates.

In the hippocampus, which we have studied most extensively – this is the circuitry of the hippocampus, it's a cross section through this brain structure – the input from the rest of the brain comes in here to the dentate gyrus and is relayed first by the mossy fibre pathway and then the Shaffer collateral system to this part of the hippocampus and that's the output side. This is the particularly sensitive and vulnerable circuit. The cells of the dentate gyrus are replaced slowly, not all of them, but some of them are replaced during adult life and these cells are particularly vulnerable to seizures for a variety of anatomical and physiologic reasons. They are the first to die when there are seizures and it perhaps then makes sense with repeated stress, which activates this system, these dendrites shorten, shrink and the connectivity is reduced. This may actually be mother natures' attempt to reduce the damage that might result. So this is one of the things that we study in the laboratory. This is what these cells look like, the CA3 neurons. Their atricle dendrites are these wonderful tree like branches, the have basal dendrites, this is the cell body where the cell nucleus is and with repeated stress there isn't any major change in the basal dendrites, but the article dendrites become shorter and less branched. This is a reversible process, it's not permanent damage. In the dentate gyrus, which I showed you earlier, there's the replacement of nerve cells because there are progenitor cells that are derived from the so called glial cells or support cells of the brain and they slowly divide and replace neurons that are dying at a rate of about 9,000 per day and each new neuron lasts for perhaps about 30 days, although the survival of these new neurons can be increased by voluntary exercise and by certain kinds of learning that require the function of the hippocampus. At the same time stress suppresses neurogenesis and interestingly enough antidepressants, including exercise, increase neurogenesis and this is thought to be perhaps one of the biological processes that mediate the effects of antidepressants on depressive illness.

The tree shrew I introduced to you before *[referring to slideshow]*. If this intruder is experiencing stress for 28 days living next to the hostile dominant, the intruder shows a reduction in body weight compared to a caged control, an increase in cortisol in its urine, an increase in catecholamines, adrenaline in its urine and sustained over this period of time. They also show the de-branching of dendrites and the reduction in neurogenesis in the dentate gyrus and they show, as a result of this stress, depressive-like symptoms that can be prevented along with these morphologic changes also prevented by certain kinds of antidepressant drugs. This, I should add, is the work of Eberhard Fuchs who's at the German Primate Centre and we have collaborated with him on some of this, but a lot of this is work that he's done quite independently. With prolonged depressive illness (the work of Yvette Schollen in St Louis) there is a reduction in hippocampal volume. This is what a part of the hippocampus looks like when you image the brain from one angle, the other part when you do a cross section, the hippocampus is there and you can measure it and estimate it's volume and the longer the depression goes on, ten years or more, you begin to see reductions in hippocampal volume.

The same thing is true for mild cognitive impairment in ageing. This is a condition of memory loss that is not at the level of what occurs in dementia. MCI is accompanied by a reduced volume of the hippocampus; there is work from Mony de Leon group in New York, at NYU. Alzheimer's disease results in a much more severe disconnection in shrinkage of the hippocampus. MCI is interesting because it is a risk factor for dementia later on and one of de Leon's colleagues, Antonio Convit, has shown the severity of MCI is related to poor glucose tolerance, not at the level of type II diabetes. The worse the glucose tolerance the smaller the hippocampus and the worse the memory performance and Convit now has a study showing that with type II diabetes there is much more severe hippocampal shrinkage. Now, the hippocampus has glucose transporters, like many of the peripheral organs, which are insulin sensitive and insulin does get into the brain and this is something that is very important to keep in mind because type II diabetes is a risk factor for Alzheimer's just as MCI is and so part of the whole of unsuccessful ageing process may very well be linked as much to impaired glucose utilisation as also elevated cortisol and indeed cortisol is elevated in MCI.

Now I just wanted to point out very briefly that a number of hormones – insulin, IGF1 and the hormone that stimulates appetite, that hormone ghrelin and also leptin, which is a fat hormone that is associated with appetite suppression – all of these get into the brain, get in to the hippocampus, are actively transported in and they have some very interesting effects. I've mentioned the effects of insulin, glucose transport, but also neuro protection. IGF1 is the mediator of exercise induced neurogenesis; it's actively taken up during voluntary exercise. Leptin has effects to enhance excitability into improved memory and possibly to act as an antidepressant, but I just saw a paper recently that in anorexia nervosa there is in fact elevated leptin and this may possibly contribute to some of the symptoms of anorexia in terms of arousal and hyper-excitability. Ghrelin, although it stimulates ingestion of comfort foods and sleep deprivation also gets into the brain and enhances memory and promotes the formation of new connections between hippocampal neurons. So it's not just cortisol, but other hormones that seem to have access to the brain and affect many of the same processes we are talking about.

A very interesting sideline that goes back to a study of cortisol secretion *[referring to slideshow]…* This is a public speaking challenge, a study that was done in Germany by Clemens Kirschbaum and Dirk Hellhammer at Trier looking at people's cortisol response to standing up, as I'm doing now, before an audience and giving a talk only in this case the person is actually asked to give a talk about some very personal experience and is obviously somewhat aroused and stressed by it. Most people, the first time they do this, they have elevated cortisol and the second, third, fourth or fifth time they do this their cortisol response is minimal, but there was a sub group of people that produced higher levels of cortisol and every time they produced high levels of cortisol response. These people turned out to have low self esteem and, of course, the notion that cortisol contributes, perhaps, to the shrinkage of the hippocampus in ageing and in some of these other conditions as well as, perhaps, the hippocampus we know controls the shut off of cortisol so it's kind of a vicious cycle, as part of the slide says. Well, a man named Jens Pruessner who is at McGill, who went from the Trier group to McGill, has published a paper not so long ago showing that both a set of young subjects and a set of older subjects that have low self esteem had, in fact, a small hippocampus. So, one of the intriguing new leads in this area is the linkage between this trait that individuals have and, of course, the question is, if you improve somebody's self esteem could you actually make the hippocampus get larger? In Cushing's disease we know there is a smaller hippocampus and if you treat the Cushing's there is some evidence that the hippocampus will get larger again. So again this may not be permanent damage, but some kind of a remodelling process.

Now, in both the prefrontal cortex and in the amygdala there is remodelling of neurons. In the medial frontal cortex it shrinks like the hippocampus; in the amygdala it grows. I've already mentioned this, but just to remind you again I've also said that in mood and anxiety disorders the amygdala and also the prefrontal cortex are hyperactive; even though the prefrontal cortex is smaller it's more active. Successful treatment with antidepressants reduces this activity, but in general the amygdala hyperactivity remains even after successful treatment, but we know that the prefrontal cortex exerts downstream inhibitory effects and it may be that that is what is keeping the amygdala somewhat in check and helping to maintain more or less normal mood and levels of anxiety. In fact, the medial prefrontal cortex communicates with the amygdala in a reciprocal way and, as I said earlier, studies of the medial prefrontal cortex which we have done in collaboration with John Morrison's laboratory (he's at Mount Cyanide Medical Centre in New York) have shown the shrinkage of dendrites and also the reduction of the spines, these are sites of excitatory synaptic connections, so repeated stress results in de-branching of dendrites and also a reduction in the input from other cells with the result that there is impaired mental flexibility and yet this is a reversible process. When you cease stress this mental flexibility returns and this has been very nicely demonstrated in a PhD thesis that is not published, but I'm only just going to describe it, but a study on medical students who are studying for their medical licensing exam and the way that stress is assessed is using this ten item perceived stress scale developed by Sheldon Cohen at Carnegie Mellon University. If you notice some of the items on it, it asks questions that really have to do with whether you're stressed out or not. How often have you been upset because something happened that's unexpected? How often were you unable to control the important things in your life? How often have you felt nervous and stressed or stressed out? On the other hand it asks other kind of questions. How often have you felt confident about your ability to handle things? How often have you felt that things are going your way? And so on and so forth. You fill out this questionnaire and it's scored in a way that reflects the degree of the negative side of things and it turned out in this study on medical students that was done by Connor Listen that in fact the medical students who were the most stressed

out were impaired on a test of mental flexibility that's very similar to what we used in rats. He also developed some evidence using functional MRI imaging that supported deficits, reversible ones, in the circuitry that's very analogous to the circuitry in the rat brain. Giving these medical students, after their exam, a month off resulted in a return to normal both in their perceived stress test and also in their performance and in the brain imaging. So again reinforcing the idea that these effects of stress can be reversible.

Now one of the things about the prefrontal cortex is that it is extraordinarily important only for decision making, executive function, for mental flexibility, for extinction of fear conditioning (which is learning of new things to tell us that, well, it wasn't so dangerous after all), working memory, ability to suppress negative thoughts, so it's implicated in mood disorders and also dysfunction of the prefrontal cortex is implicated in and results in learned helpless behaviour, but is also important in downstream and regulation of the parasympathetic system in that there is dysfunction in the medial prefrontal cortex, there is very poor parasympathetic control to counter balance the sympathetic response and the prefrontal cortex also participates along with the hippocampus in shutting off the cortisol response.

I'll say a little bit about early life experiences because remember in that diagram of the brain as the centre of our ability to handle stress referred to both genetics and early life experience. In animal models prenatally stressing a mother results in increased rates of brain ageing and shorter life span, perhaps in part, because of an increased reactivity and increased levels of cortisol and probably these other mediators I have been talking about. If you separate pups from mothers for a brief period of time after birth then when you put them back with the mother, the mother licks and grooms them and provides exceptional maternal care. This can in fact wipe out the effects of prenatal stress and produces animals that have decreased rates of brain ageing and a somewhat longer lifespan. So this is the animal model going back to the work of Seymour Levine, Victor Denenberg, Robert Ader and more recently Michael Meaney at McGill and Paul Plotsky of Emory University – very important work that gets us thinking about the human condition. Work by Gary Evans at Cornell looking in world poverty, looking at the home environment both in terms of crowding and chaos within the family have shown that chaos in poverty, and I'm sure in other situations, leads to helplessness, leads to poor self regulatory behaviours and an increased level of psychological distress. We know from work of Kim Noble, Martha Farah and colleagues at Penn in collaboration with people in New York that studies of inner city kids in New York and Philadelphia show again in relation to the kind of chaos and the setting that Gary Evans talks about, impaired language ability and also impaired executive function and Evans and others have documented that in this poverty situation the level of adversity is related to increases in blood pressure and body mass already at nine years of age. In the studies of child abuse and neglect by Robert Anda and Vincent Felitti and colleagues they have zeroed in on not only problems with mental health, impulsive behaviour, substance abuse and so on, but increased levels of ischaemic heart disease and they emphasise the importance of the behavioural factors as powerful risk factors for development later in life of ischaemic heart disease. So, this comes back to this diagram you've seen before and we can add in traumatic stress or chaos or neglect in helping to determine a pre-existing state of the brain and body that makes the effects of these daily life stresses and experience that people have even more powerful in terms of their effects on later disease.

Lets not forget about genes and I'm sure most of you are aware of the ground breaking work of Avshalom Caspi and his team based upon studies in Dunedin in New Zealand. In several different papers in Science they showed that normally present alleles of monoamine oxidase A, if you had a certain allele it increased the likelihood that when a child is abused that this child will then as an adult with antisocial behaviour and other things transmit this trait onto his or her own child. In another study looking at normally present alleles of the serotonin transporters which are a big, big deal in biological psychiatry that if you had a certain allele it increased the likelihood that stress in adult life would contribute to major depressive illness. You had to have the experience in order for this allele to make a difference so it's a very nice illustration of the subtle balance between genes and environment or the nature / nurture interaction.

Finally just a brief word about social hierarchies because the implications, of course, of things like socioeconomic status brings to mind social hierarchies in animals. Indeed studies that we have been part of using the visible burrow system in which you put six males and two females together, the males establish a dominance hierarchy – the dominant male is the one with the fewest scars on his body because he is going around biting the other guys. You have an open burrow and several tunnels and then some places chambers where these animals can hide and all of this is videotaped from above. The subordinates have low levels of testosterone, high levels of stress hormones and a lot of changes in brain chemistry that I don't have time to describe and some subordinates are more stressed than others, in fact, some will die within the two week framework in which this is carried out and the dominant, interestingly enough, has smaller adrenals than the subordinates, but larger adrenals than if it was living in a standard cage environment. What's interesting about the hippocampus is that both the dominant and the subordinate show reductions in dendrite complexity in this area of the hippocampus I've already talked about, but, if anything, the dominant has smaller dendrites than compared to the subordinate even though it's the subordinate that has the larger adrenals. Now what this told us is that it is not just cortisol and we know now that excitatory amino acid transmitters and other endogenous factors in the brain help to determine the degree of shrinkage of the dendrites. We also know from studies done at Bowman Gray University on cardiovascular function that in an unstable dominance hierarchy male cynomolgus monkeys, the dominant shows increased atherosclerotic plaque formation. In the stable dominance hierarchy there isn't any difference. For females, this is for males, for females subordinate social status whether it's in a stable or unstable hierarchy increases the rate of arthrosclerosis. There is a lot of other evidence; I just mention these two in passing.

So, we come back to the SES and health links and, of course, recognise that it's an extraordinarily complicated process. I've emphasised things about lifestyle, stressors of daily life, life events. We also have to recognise that perception of social position is a major factor, that perceived or actual discrimination is a factor and that education, resources – not only money and intellect, but also having the life skills to deal with ones daily life – are also very important as well as access to and use of health care. So it's a monumental test on practise and understanding.

So, what can be done about it? Well, I'm just going to suggest some things or show some evidence of some things that are worth discussion. First we have medicines and we have medicines of various kinds: beta blockers, Prazosin for PTSD anxiolytics, antidepressants, glucocorticoid receptor and CRF antagonists that are experimental, anti-diabetic medications, I should have added statins, anti-craving drugs (the endocannabinoid antagonists) and anti-inflammatory medications. All of these are extraordinarily useful, but they also will each of them have side effects of their own and they are not available to everybody, particularly not in the United States where we have big problems with how the health insurance works, many people uninsured. There is another side which is equally as important as medicines and works in the direction of prevention and these are, not surprisingly, social support, physical activity and programmes that combine both and I'll just briefly mention from the MacArthur studies I've been part of, work that examines social support – whether people have three or more social ties or only a couple of them makes a big difference for both men and women with their allostatic load score; the more social ties you have the lower the score. Physical activity… and we're now not talking about becoming a marathon running, but people who were sedentary who were, over a six year period, encouraged and able to do 30 minutes of walking a day showed an almost sixty per cent reduction in their incidence of type II diabetes. There was another group where activity was not controlled, but they were given metformin which enhances insulin actions and they were also helped. What we know from other studies in animals and people is that exercise improves aspects of cognitive function and also is an effective antidepressant, if you can get people to do this. This *[referring to slideshow]* is just showing some pictures of newly formed cells in the hippocampus, the dentate gyrus. We know that voluntary exercise mediated by IGF-1 uptake enhances neurogenesis, the brain chemicals called neurotrophins are increased by voluntary exercise, and exercise is an antidepressant treatment and chemical antidepressants also increase neuronal proliferation. Studies on people, sedentary people encouraged to exercise like in the diabetes prevention trial for only a six month period, at the end of the time, show enhanced activation of brain areas that are involved in attention and executive function and showing that regular activity benefits the brain as well as the metabolic system. A programme based in Baltimore, but increasingly used in other parts of the United States called the Experience Corp, combines both of these, physical activity and social connectedness. It's called the Experience Corp and involves the training of elderly volunteers to become teaching assistants in elementary schools. They receive some money, the training and obviously the educational processes of the kids works much better because the teacher has someone to help them and somebody with a grandmotherly or grandfatherly personality, but what's also documented here is that the health of the elderly volunteers improves because, as the slide says, they have increased physical activity, increased social interaction and you can say they probably, many of them, found a meaning and purpose in life. This is a programme that may well be adopted state wide in Maryland because the mayor of Baltimore who has become a supporter of this was just elected governor and we will see if this will spread and be a useful type of intervention.

So, as I've said, I've given you a Big Mac attack, covered a lot of territory. There are a huge number of people that I should acknowledge. The remaining question is, how do I manage my allostatic load? All the ways are shown here: having a dog who gives you perspective on life and a total sense of the ridiculous sometimes is a wonderful counterbalance for what we have to go through on a daily basis. I'll leave this acknowledgement slide up for a little while.

Thank you for your attention.

[Applause]

Harry Burns:
Thanks very much Bruce. Like most Big Macs that was very pleasurable and enjoyable! *[Laughter]* This has been a tour de force that filled in for me a lot of stuff that I've not taken in in reading many of these publications over the years.

Well, there has been a huge amount in that. I know that, looking at a lot of the people in the audience, I know that you are going to go away and look into this in a lot more detail. I think it's thrown us a lot of challenges. It's particularly exciting I think in Scotland, you know, given our size, given the nearness that we all have to policy making capacity and so on for us to be thinking about how we turn this kind of research, how we translate it into policy. I think there is a lot here that tells us how we can make Scotland's health better in the future and Glasgow's health, reminding ourselves that this is a Glasgow Centre for Population Health lecture.

Final thank you to Bruce for a terrific lecture and we're grateful to him for taking time out of his busy schedule to come over to Scotland to see us.

[Applause]