



Transcript of Professor Andrew Steptoe's lecture:
Tuesday 25 October 2005

HOW STRESS GETS UNDER YOUR SKIN: PSYCHOBIOLOGICAL STUDIES OF SOCIAL STATUS, STRESS AND HEALTH

Dr Harry Burns:

Good evening and welcome to the first event in our second series of lectures hosted by the Glasgow Centre for Population Health. For the few of you who don't know me, I'm Harry Burns. I'm a founder member of the Glasgow Centre for Population Health, now unfortunately working in Edinburgh, but back here at every available moment. It gives me very great pleasure to welcome Professor Andrew Steptoe.

When we first began to think about the Glasgow Centre we really challenged ourselves to try and come up with a different paradigm of thinking about health inequalities and how social and economic status impact on health. Critical in that thinking was the work that Professor Andrew Steptoe and his colleague, Sir Michael Marmot (another name that you will know) have done over the years. Andrew is a graduate of both Oxford and Cambridge and he has worked extensively in London as a lecturer in psychology and more recently researching at University College London the relationship between psychology, social status and health and the papers he has produced have helped us really begin to shape our thinking of how Glasgow's health was formed. So I'm very excited to hear what he has got to say tonight. We are very grateful to him for coming and, without any further ado, I ask him to come and speak to us.

[Applause]

Professor Andrew Steptoe:

Well thank you very much and I am delighted to be here. It's been a few years since I've been in Glasgow, but every time I come it seems to be getting nicer and nicer for a poor southerner like me. I'm going to talk about the work that we are doing in psychobiological research in this whole area and I must say just hearing this afternoon about the Glasgow Centre I'm very impressed by the integrated approach that has been planned and that is taking place here.

I'm from University College in London and that's how it looks on sunnier days *[referring to slide show]*, founded, as some of you will know, in about 1826 under the precepts of the utilitarian philosopher Jeremy Bentham whose principles really led to some of the basic kind of principles behind University College. It's interesting that, in England, it was the first university to admit non-protestants, to admit Catholics, it was the first university to admit Jewish people and the first university to admit people from the Far East and so it was always quite an eclectic place.

Jeremy Bentham, being a utilitarian, wanted to use things to the maximum including using his own body for dissection and he decided before he died that... obviously before he died *[laughter]*... that he would donate his body for dissection because at that time the only people who were dissected - technically anyway, apart from Burke and Hare's kind of activities - were criminals and so this was relatively unusual for a middle class gentleman. Afterwards he also decreed that his body should be reconstituted and put in this box and where it sits outside the library at UCL and indeed it does to this day so this is Jeremy Bentham himself. It's a bit kind of creepy as you go past him everyday *[laughter]*. The head over there on the right hand side is actually a wax one. They did used to have the head in the box as well, but students from other colleges kept stealing it *[laughter]* and, you know, merry jinks of medical students and it ended up in the quad so now it's only brought out on high days and holidays.

In some sense the principles behind Bentham's thinking and this sort of egalitarian nature of the college has persisted and to some extent in the department in which I work now which, as Harry said, is directed by Michael Marmot, which has been involved with a number of studies. These are the current population studies that are run in one sense or another from the department. A number of studies to do with social factors in particular and health outcomes, including, of course, the Whitehall studies which are the studies that I do my work within, but also a number of other types of investigation that we are also involved with. The broad context of what we try to do is really outlined in this rather grandiose slide which Michael generated which starts at social structure on the top left and ends with disease and health at the bottom right. It's really trying to fill in the various aspects, both in terms of population epidemiological studies of the social environment, in particular the work environment, but also some of these other processes down at this end and this is really the part that I'm going to be talking about much more this evening - how these processes, the social factors, actually get under your skin and influence physical disease outcomes and physical health and what we can do to try and integrate those biological studies into a population framework.

What I would like to do this evening is to talk about these four issues here in one way or another, and we will see how we get on in terms of time. I'm going to describe very briefly things which many of you will already know about so I'm not going to dwell long on them which is to do with psychosocial factors in relation to physical health outcomes, then say rather more about what we mean by psychobiological processes and what they are, and then about what sort of methods we can use to investigate them. In particular, how we can link those into population studies in order to try and look at social demographic and other types of environmental exposures. Then lastly to say something about what we know so far about how these responses actually relate to health outcomes.

Let me start off with the issue of psychosocial factors and physical illness. It will be well known to you, coming from Glasgow, because there are large socioeconomic disparities in this part of the world that, in a way, the most basic kind of psychosocial factor or social factor is social position. This is an old slide using the older Registrar General's classification of people by occupation with 'one' being the professional groups and 'five' being the unskilled manual groups, showing the premature mortality rates in men between the ages of 20 and 64. There are three different census cohorts included on this slide showing, if anything, the gradient has got worse. Psychosocial factors, of course, go beyond socioeconomic status, although many of the other social factors / psychosocial factors are socially graded and the ones that we typically look at I would tend to divide out into these three broad categories: one has something to do with various types of chronic life stress exposure, exposure to unpleasant or difficult conditions over long term periods; the second are features of the social environment to do with social connectedness and social support. These sort of factors are by in large protective; then there are a number of more psychological factors which are thought to be important as well which include depression, but also some other aspects of what might broadly be described as negative emotions.

I'm going just briefly to touch on some of the evidence which relates these to physical health, and I'll do that by illustrating through the area which I work in primarily, which is coronary heart disease, mainly because that is my work interest, a lot of which is sponsored by the British Heart Foundation, but also because this remains one of the major causes of mortality and morbidity in this country and there is a strong social gradient in this, so it's of considerable interest. Coronary heart disease, of course, has a number of well known risk factors such as high blood pressure, high cholesterol levels, diabetes and cigarette smoking. Nonetheless, it's interesting to note that a substantial number of people actually end up having coronary heart disease who don't have high levels of known risk factors. This is illustrated in this slide here which is a compendium really from some 15 prospective randomised controlled trials in the literature. Just looking at the prevalence of conventional risk factors, the four major risk factors which are smoking, high blood pressure, high cholesterol and diabetes, in a group of nearly 90,000 patients with coronary heart disease. What's quite interesting is that most of these patients don't have very many risk factors. Just under 20% have no recognised risk factors and another large chunk, nearly half the people, don't have more than one, so that could be just people who are smoking for example, or people who have high blood pressure without having the other factors. So although these risk factors clearly are important, they're not accounting for all the mortality and morbidity in this area and this is one reason why we look at these kind of psychosocial factors as well.

Well, to take an example first of all from the area of exposure to life stress, a lot of work is done on work stress as many of you here will know, one reason for that being of course that people who are fortunate enough to be in paid employment, do spend a great deal of their time at work and so the exposure is prolonged over years and decades of life and so there could well be influences that influence physical health outcome. This is just one example of the association between work stress and future cardiac mortality. These slides all have the same sort of format, that is the risk factor was studied at baseline and then people were followed up for various numbers of years, in this particular case 25 years. The outcome in this case here is cardiac mortality and what's shown here are the relative risks associated with being low or high on that risk factor after controlling for a number of other things which are also known, of course, to influence CHD and cardiac mortality. In this particular slide what's shown is a particular model of work stress which is the relationship between the amount of effort people put in and the amount of reward that they gain from their work. Those people who seem to have a greater imbalance in this, that is they put in a great deal of effort for little reward, are at higher risk (approximately twice the risk) over this 25-year period. This is a study of men from Finland and what's interesting is that this association is independent of the regular, established cardiovascular risk factors and also of some of the behaviours which are also relevant to cardiovascular disease, such as body mass and physical activity.

An example from the area of social factors and social integrations is provided here, in this particular case. This is incidence of new cases of people with coronary heart disease - so at the beginning they were disease free - followed up over a 15-year period. There are two different classifications here. One is based on a measure of social integration, so these people here are socially isolated and these people have high levels of social connectedness. So the risk goes down where people have higher levels of social connectedness compared with those who are more socially isolated. On the right hand side is a measure of emotional attachment - more supportive aspects of the social environment rather than just the structural aspects of the social environment - again showing that people with greater emotional attachment are at lower risk.

Then the third example is from the domain of psychological experience and in relation to cardiovascular disease, one of the main interests of recent years has been in depression - not just clinical depression, but also sub-clinical depressions and elevated levels of depressive symptomatology. This slide here is showing relative risk over a ten-year period in people who are not depressed at the beginning compared with those who are depressed at the beginning in both men and women with an increase of about 50% in the likelihood of developing new cardiovascular disease, again controlling for risk factors including social factors such as poverty.

Now there are a whole host of studies like this and I'm not going to continue with this kind of litany, but just to point out one or two other effects, not so much to do with the cardiovascular end point, but with another issue which I think is particularly interesting in the area of psychobiology and becoming of increasing interest altogether as far as cardiovascular and other diseases concerned, which is metabolic syndrome. This is a syndrome of a series of risk factors which are essentially to do with adiposity - that's body weight particularly around the waist - together with disturbances in lipids - that's high levels of triglycerides, low levels of HDL cholesterol which is the good cholesterol - disturbances of glucose metabolism and high blood pressure. This constellation or syndrome has been of increasing interest because it relates not only to coronary heart disease, but also to the development of type II diabetes which is of course becoming increasingly important in Great Britain. Here is just one example of a prospective population study looking at the relationship between the metabolic syndrome and another form of what one might call chronic stress, which is to do with marital satisfaction. This is a follow-up, over 11 years, of women only, looking at the likelihood of the development of metabolic syndrome, controlling for obviously their initial disease state and risk factor state, comparing those who said they were 'very satisfied' with their marital situation, those who are 'moderately' and then the 'dissatisfied' ones who are at substantially elevated risk, interestingly again controlling for things for physical activity and alcohol consumption, smoking and also for education, so some kind of control for socioeconomic position.

Now the thing about all these factors which is relevant, especially to the psychobiological argument, is that these are what I would call chronic challenges. They're not acute stresses in peoples' lives. These are things which go on month in, month out, year in, year out, often over decades and so they may be influences on the long term development of disease rather than on some single acute manifestation. So we may be looking at relatively small but persistent differences in mechanisms (which are what psychobiological responses are) but could be contributing to this increasing risk. Not, you know, very exaggerated and grand and easily to observe kind of responses, but quite small differences that we should be looking for. The other thing to point out of course is that when we talk about these factors we are not talking about them as the cause of these kind of physical illnesses, but as contributory risks along with all the other factors that we know are important. So the question comes of what are the mechanisms.

Now, when we talk about mechanism, of course, that can be understood at many different levels: at social levels, at structural levels, at economic levels; but also, in one way or another, whatever happens in the outside environment or in your brain, it's got to influence the physical disease processes in the end. It's got to get down inside to alter things in the blood, it will alter things in terms of cardiovascular activity or gastrointestinal activity or something like that. And it's at that sort of level, right down at the level of how things kind of get installed within the biology which I'm going to discuss.

When we think about that, there are really two broad sets of mechanisms that we typically think of. One is that, in one way or another, these sorts of psychosocial adversities may influence people's habits. So it may be associated with less healthy habits in terms of things like smoking or food choices leading to high levels of fat intake, sedentary behaviour and so forth, so that people, for example, under work stress or people who are socially isolated may have a less prudent lifestyles, which could then contribute to disease outcomes. Now, to some extent that is of course true. The literature is actually quite a complicated one relating those lifestyle behavioural processes with psychosocial practice, but there is certainly some evidence for these things. The most striking case, of course, would be smoking in relation to socioeconomic position, which has a very strong gradient in this country. However, most of the slides that I have been showing you, if you have been having a look at the bottom left corner you will see we were trying to control for many of these sorts of behavioural risk factors and so the effects I showed you were, as it were, independent of these kind of lifestyle processes, suggesting that something else more fundamental or more biological might be going on. That's what the psychobiological approach is to do with. It's to do essentially with mechanisms, more direct mechanisms, from the psychosocial environment into the biology through neuroendocrine pathways, cardiovascular pathways, immunological pathways and other physiological responses. So I'm going to go on in the next section to say a little bit about what these processes are. I know that many people here are not so familiar with biology so I will try to keep this fairly broad, but it is important that I try and explain what the processes are.

Essentially what we are talking about are the links between the brain, the neocortex (the bit that does our thinking, decision making, planning, memory and so forth), and the biological systems, the physiology. Essentially this is driven through the rather more primitive areas of the brain, in particular, areas known as the limbic system, which is phylogenetically a rather primitive area including such things as the hippocampus, the amygdala and so forth, and also this area of the hypothalamus all of which are right inside as it were near the top of the brain stem which is coming up inside here [*referring to slide*]. And these areas are important in the regulation of various biological functions that we look at in terms of physiology. What sort of responses are we talking about? We are actually talking about quite a wide range of responses, which can be manifest in many different systems. This rather daunting list is just some of the processes that are looked at in this kind of work. I won't be talking about all of them, but just to give you an idea that we are talking about quite broad integrated patterns of biological response which are related to people's behaviour and experience. A lot of this is integrated through neuroendocrine pathways, which I'm going to describe a little bit more in a moment. There are clearly quite a number of direct cardiovascular processes which are important and increasingly important are these, what I've called inflammatory processes. These are markers to do with relatively low levels of inflammation. Obviously if you get some external kind of injury or pathogen you may get an acute inflammation, a large inflammation, but what we are talking about here is more low level kind of chronic inflammation which is marked by such variables as C-reactive protein and interleukin (IL) 6. Then there are a number of changes in metabolic processes to do with cholesterol levels and lipid levels in the blood and the way in which glucose is metabolised. Some things to do with haemostatic (that's blood clotting) processes and then other areas of immune function.

Now this is quite a lot of responses, but it's relatively easy to understand because these things are integrated at the higher levels of the way in which the brain influences the response processes, and critical in that are these neuroendocrine and autonomic processes and I'll just describe a couple of those. A key one is cortisol. Cortisol is a hormone which circulates through the blood and it's synthesised in the adrenal gland and it's been known for 50 years or so that its control is regulated from the brain, in particular from this area, the hypothalamus, which leads to a cascade of processes to the release of ACTH corticotrophin as it's shown in this slide here, which circulates until it gets down to the adrenal gland, which is down near the kidneys, which then leads to the release of cortisol. There is a very sophisticated feedback system so the more cortisol you generate you get inhibition going back up to the brain. There are two important features of this which I wanted to point out. One is that the function of this system, which is often regarded as a kind of self-regulated system, is influenced also by higher centres, in particular by emotional stimuli coming from the limbic system which in turn relates to the neocortex. The other thing is that cortisol itself has a whole series of effects on various tissues (the cardiovascular system, the liver, the adipose tissue / fat tissue) and also the immune system which is the way in which it may influence disease outcomes. Now, cortisol is released, of course, naturally and it has a number of effects which are to do with the regulation of a whole series of different biological responses many of which are to do with the preparation of the body for vigorous activity, for example, the release of fatty acids from fat stores, stimulation of glucose production in the liver and other processes such as immune regulation and so forth.

The second major pathway that is particularly relevant in psychobiological research is the sympathetic nervous system, which is one of the branches of the automatic or autonomic nervous system, which is again regulated from the hypothalamus down through the brain stem and has a number of effects on different systems such as increasing the production of the stress hormones adrenaline and noradrenaline from the adrenals, alterations in cardiovascular function and breathing rate and such things as blood clotting, which, for some reason, is depicted here by someone's eye, I don't quite understand why that might be. *[Laughter]* And again this has a whole host of different kinds of biological effects.

Well these responses are elicited under natural conditions and are sometimes known as 'fight and flight' responses which are adapted to vigorous activity into the mobilisation of the body in to doing something in conditions of danger and hazard. So one can ask 'why are these responses hazardous?' and there are really two major reasons for this. One is that these responses are actually repeatedly elicited in conditions of everyday life so although they may have evolved to help us escape from tigers and mammoths and things like that, they are actually also elicited when we are stuck in traffic jams and our aeroplanes are late leaving for Glasgow *[laughter]* and those sorts of conditions where vigorous physical activity is not really an appropriate response. So that's one thing: that these things are elicited at the wrong time, in the wrong place and repeatedly in everyday life and the second thing is that there are large individual differences in how people respond and some people share heightened reactions or what is proving increasingly important, a failure of post-stress adaptation, so following some challenge in life for some people, the system remains in a more elevated state for minutes, or possibly hours, after that stimulus. Under those conditions these may contribute to the wear and tear which will ultimately increase disease risk.

One can look again... I'm not going to go through a catalogue of these things, but there are potentially damaging effects of all these regulatory processes and I'll just illustrate for cortisol. These are some potentially damaging effects which have been established both in experimental studies, but also clinically in studies of people who are unfortunate enough to have naturally high levels of cortisol, but also many of these are actually side effects of high levels of cortisol administered in medications, including increased levels of low density lipoprotein cholesterol (that's the more damaging cholesterol in the blood), chronic suppression of the immune function, alterations of bone function, increases in abdominal adiposity, and so forth. So one can see a whole range of responses which might emerge if this psychobiological activation is prolonged or repeated under inappropriate conditions.

So that's really the kind of rationale for trying to understand and study these psychobiological responses. The question is how one can go about establishing that and demonstrating that and I'm going to show you two general approaches to doing this and some of the results which we and other people have found in this area to try and explain how this sort of thing works.

It, of course, involves measurement of biological function along with measurement of psychological function and social processes as well. There are two basic ways in which we try and study these things. One is to take an experimental approach and the other is to do some sort of naturalistic kind of monitoring in people's every day lives. Both these methods have strengths and both have limitations. The experimental approach is basically to stress people; to give people unpleasant things to do and to see how they respond biologically. So a typical set up would be something as illustrated here showing a time line of the sorts of experiments we do, and what happens to people during this. I don't know why this person has got a hat, but they come in with a hat on *[laughter]* and they have various physical measures taken - body weight, anthropometry and fat mass. We then put a cannula in their vein, usually in their forearm or on the back of their hand, and that is itself, of course, quite stressful so we then leave people quite a long time to settle down after that's been done and so there is quite a long adaptation period here. We measure other things, for example, blood pressure that I've just illustrated here *[referring to slide]* and so at the end of that we will take some baseline measures and then take a baseline blood sample. What we then do in a typical experiment is to give people difficult things to do over a certain length of time (here, 20 minutes) and then we take measures during that of the things we can and then we take a further blood sample afterwards. Of course, they already have a needle in their arm so they are not being interrupted by further venepunctures and so we hope that what we see in the blood here is really just the response to the conditions we apply rather than further blood taking. Then we have people settling back, (relaxing I like to call it, but whether they really are relaxed is difficult to know) during an extended kind of post-stress recovery period with further measurements done over that time.

What sort of things do we do during this period? Well there are a number of different things we do. One type of stimulus that is used quite often is kind of what I'm doing now - public speaking. We give people simulated public speaking tasks to do which some people find quite stressful. An example would be, people are given a kind of scenario and then they have to give a short speech, a fairly unprepared short speech, and then we measure these biological responses. For example, people are told that they are... imagine you are just leaving a department store (Selfridges in Oxford Street in London would be an example) and just as you're leaving, the store detective puts his hand on your shoulder and arrests you for stealing some knickers and you have to then go to the manager's office and you've got five minutes to vindicate yourself, to show this was a terrible mistake, you hadn't stolen the knickers at all, it's just a state of mistaken identity and that you're perfectly innocent. So that person has a couple of minutes to prepare their speech and then they give a speech for a short time and that's videoed and they're told that this speech will be rated for competence and fluency and how convincing it is. So people find that quite difficult to do.

Another example is a more straightforward kind of task and this is just an illustration. You can see that there is a word in the middle (that's meant to be the middle of the screen) the word blue, which is printed in yellow, and the task here is to press a button which corresponds to the name of the colour in which the word is printed in the middle. And you have that going along quite quickly depending on how good your performance is. You can see it's a complicated sort of task and if people get good at it then we make it harder. *[Laughter]* So these sorts of tasks are the kind of thing we do in the laboratory to try and produce a kind of acute stress response. I mean, you know, you think they're moderately stressful, they're not staggeringly stressful compared with what many people confront in their everyday lives.

Well what can we do with this? The first thing we can do is to ask about this issue of individual differences. So do responses in these biological processes vary with people's psychosocial risk profile? People who have more or less of these different types of psychosocial risk factor, do they respond differently? I'll just illustrate that with one example of a recent study looking at this substance called C-reactive protein, which is something which many people are interested in at the moment because it's an inflammatory marker, which may be a risk marker for cardiovascular disease. Well it definitely is a risk marker for coronary disease. What's not quite so clear is what its functional significance is and whether it's just a marker or whether it's functionally more significant, but it seems to be related to low-grade inflammation. If someone is actually affected acutely, C-reactive protein levels are high, but that's a different process. What we are talking about here are variations at the much lower level and its so-called 'acute phase protein', which is synthesised in the liver.

Well we did a study recently looking at how this might relate to work stress. So we challenged everyone with the same challenges but then we looked at variations in work stress. So this particular study, as you can see, was carried out with just over 100 non-smoking men and we were looking at this measure of effort-reward imbalance. So this measure here is to do with how much you invest in your work, how hard you work. You know, 'people say that I devote myself too much to my work', 'when you wake up in the morning the first thing you think about is work'... those sorts of people – sad people like me – and then reward which, fortunately being a professor I get more of, which is to do with how much material reward you get, or how much reward you get in terms of status and prestige. And you can work out an imbalance between effort and rewards and that's thought to be a factor which is related to coronary heart disease. So in this particular study we used two standard tasks. One is that kind of public speaking task and another task I won't describe now, and then we take blood samples. The issue is, are people who have a higher level of effort-reward imbalance more responsive as far as C-reactive protein is concerned? And the answer is yes, they are. What is plotted here are the increases in the levels of C-reactive protein measured in blood samples taken before the challenge, after the baseline and then after the challenge. So these are stress responses basically, these are change scores. What I've done here is plot these increases, which occur on average in everybody, in relation to effort-reward imbalance. So these are the people with the highest level of effort-reward imbalance and these people are the lowest and what you can see is that those people who have higher levels of effort-reward imbalance have bigger responses in this marker suggesting that there is at least an association between how people respond to challenges in their lives and this kind of inflammatory process which might be related to health outcomes.

Now a lot of our interest in our work has been in socioeconomic position and in socioeconomic inequalities and in asking this question about whether socioeconomic inequalities stimulate the biological processes which are relevant to cardiovascular risk. We have done quite a bit of this work in this area in collaboration with my colleague Michael Marmot and I'm only just going to give you a couple of examples of the sort of thing we have done. One thing we have done is to try and look at these responses in a population cohort, which is a difficult thing to do because these types of laboratory study actually take a great deal of work. Each person is seen individually and they may be seen for up to half a day and so the sample sizes we use are relatively small. But what we can do is to sample systematically from a population in relation to the processes that we are interested in and in particular, because we have been interested in socioeconomic position, we have been looking at members of the Whitehall II cohort which many of you will know is a prospective cohort of British men with originally London based civil servants who have been followed up know since 1985. So the people, when we saw them, were aged in their early 50's on average and what we did was to sample people who were still in this Whitehall study from the different grades of employment and this is just showing you the breakdown of grades of employment. These are the higher status civil servants, those who are in the administrative grades, people running departments and making decisions and so forth, and down to the lower grades who are mostly office workers, they are white collar workers, but they're in fairly low status jobs. And we looked at various types of biological response and tasks in the laboratory.

Well this is a typical result that we've found in these studies and I'm showing it to you because it actually illustrates quite an interesting point about these biological responses which is to do with whether one's looking at the magnitude of responses or the duration of responses. What's plotted here is blood pressure, systolic blood pressure (the top one in the two blood pressures that are usually measured) and these are average levels of baseline. Average levels taken during the challenging tasks and then 15 to 20 minutes post tasks and then at 40 to 45 minutes post task, so they do these challenging tasks and then they just sit quietly, they either read or they watch nature films. The people working in my lab get completely fed up with David Attenborough I can tell you *[laughter]* because they see it again and again. So they are just watching those sorts of things, but resting quietly. And what you can see in this experiment is that these tasks did induce quite a brisk response, an increase of about 25 millimetres of mercury pressure, which is quite a big response on that baseline, but that there was no difference by social position in the magnitude of these responses. You can see these lines really overlap very consistently. What did emerge, however, was this difference in the recovery periods, so if we measure peoples blood pressure maybe 20 minutes later or three quarters of an hour later, the higher grade people have recovered more rapidly so that their blood pressure is down here at a lower level than these ones here. In other words, these people are showing a kind of persistent lower level kind of activation of biological systems, which is present long after the challenges are done and we have told them there is nothing else going on, we are just carrying on measuring you over this time.

This is just another illustration of that same phenomenon and it's just to illustrate in a slightly different way. What this is showing is the likelihood, as it were, that people will show effective recovery in their blood pressure, so their blood pressure will come right down three quarters of an hour after they have finished the stressful tasks. For example, if you look at diastolic blood pressure here, the likelihood of blood pressure failing to come down is greatly increased in people with lower socioeconomic position and moderately increased in people of intermediate socioeconomic position, as defined by grade of employment.

So we think that something like socioeconomic position, which is quite a difficult thing to get a handle on in the laboratory, may be associated, not so much with differences in responses in this kind of variable, but differences in how quickly and how slowly adaptation takes place. Another example (I'll give you one more example of this sort of laboratory work) is using the cytokine interleukin-6. Interleukin-6 is a substance which circulates in the blood and it's produced by immune cells. It's also produced by fat cells and various other cells in the body and basically it's a signalling molecule, higher levels of which have been associated with not only coronary heart disease, but also with a number of other health outcomes, including type II diabetes, depression and disability.

The research in this area is still at a relatively early stage, but here, for example, is a recent finding showing relationships between high levels of depression (as defined by one of the standard questionnaires) and levels of interleukin-6 (IL-6) in a large population cohort in the US showing that people who are more depressed have high levels of IL-6. We were interested in whether people who varied in socioeconomic position also vary in their stress responses in IL-6 and this slide here shows the results. It's a rather different pattern from one I've been showing you and the reason is that IL-6 takes quite a time to respond; it's not something which just goes up acutely during tasks. This is a longer time frame I'm showing you here - up to two hours - and this is where the tasks take place and this is where the blood pressure goes up but comes down fairly rapidly. IL-6 in the blood takes a much longer time to increase and it's only at these latest stages that we see differences between people of higher and lower socioeconomic position in the magnitude of IL-6 response. This is a 'no stress control' where the IL-6 levels just remain lower throughout.

Well so much for those experimental studies, I'll say something about how those relate to disease a little bit later on, but the disadvantage of that is, of course, you are bringing people into a very artificial environment, you're giving them artificial things to do, you're taking blood from them and you're doing all sorts of horrid things to them which are not typical of their everyday life. And so the alternative approach is to do what we would typically call naturalistic monitoring, which is to try and measure things as people go about their everyday lives. Now these approaches have improved greatly over the last ten to fifteen years and that's really been due to technological advances in the way in which we can measure different sorts of biological function. What we can do by naturalistic monitoring is to look at responses in everyday life, dynamic responses to things that happen in people's lives and we can look at the co-variation between biology and events and experiences. The two methods which have been used most prominently are blood pressure monitoring with so-called 'ambulatory blood pressure measurement devices' and looking at the stress hormone cortisol in people's saliva. The blood pressure monitoring is fairly straightforward. What you have is essentially something very similar to the blood pressure cuff which is used in the doctor's office except it's an automated version so the cuff is put on the person's arm underneath their clothing, there's a box which is kept at the waist and at pre-programmed intervals the box stimulates an inflation of the cuff and then there is a microphone in the cuff which works out the blood pressure levels. So people are going about their everyday life and then suddenly this cuff goes off and they have to obviously stop what they are doing, if they are doing something difficult, for that blood pressure measurement to take place.

What sort of findings do we have with that? Well, this *[referring to slide]* is a typical kind of finding one might see in relation, in this case, to job stress. One important element of work stress is the amount of control people have over their work so people may have quite high levels of demand, but so long as they have sufficient control over their work they may be protected. By 'control over work' I mean people have a choice about how they can carry out the tasks, what order they can carry out the tasks, whether they can delegate responsibility, whether they can take breaks during their work time and so forth. And this slide here is showing measurements of blood pressure, which we took over a working day in people who reported high levels of job control and people who reported low levels of job control. I've averaged the data into four time periods here, but in fact the blood pressure was taken three or four times an hour throughout the whole day and evening and these are aggregated values. What you can see is that, after a control factor such as body mass and gender and concurrent physical activity, people with high levels of job control have slightly lower blood pressure throughout the day; it just carries on at lower levels. Now these are not large differences, but as I was saying earlier, when we are looking at these chronic influences we are not really expecting very large dramatic influences; we are expecting quite small variations in activation, which if they continued over months or years might lead to future risk. The other measure I mentioned was salivary cortisol, this is a measure we can get from saliva which we either get people to spit as they go about their everyday lives at different times or we ask people to put dental rolls in their mouths and this *[referring to slide]* is a typical profile that we get with cortisol. Basically what we usually do, in fact, is we tell the person when we want the measures taken, so in this particular study we gave people 30 minute time windows in order to take the measurements and they put the cotton roll in their mouth for two minutes and then they put it back into a test tube. The cortisol in saliva is fairly stable for quite a time so it can be actually returned through the post. This shows a typical profile *[referring to slide]*. There's a waking response at the beginning of the day and then cortisol goes down progressively over the day. And so one can again look at that in relation to psychosocial factors, for example, job control and here's an example from the same study looking at job control - high levels of job control and low levels of job control. From the cortisol profile over the day what you can see is that the people with high levels of job control have just slightly lower levels of cortisol throughout the day, throughout the morning and evening.

I have been talking so far about factors which are kind of bad things, bad things which happen to people. I want to just digress for five minutes, if I might, onto something which is possibly better for people and ask whether we can use these same processes for looking at more protective factors and it's relevant because of the interest that there's been which I know some people in this audience share in the ideas about positive psychology and happiness and wellbeing. There has been a whole spate of literature about these types of process being possibly protective as far as mental health is concerned, but also as far as physical health is concerned as well. And I'll just show you one analysis that we've been conducting looking at whether happiness or positive wellbeing is also associated with a favourable biological profile. What we did in this study - I won't go into the details of this, but essentially we measured people's affective state, so mood state, repeatedly over the day by using simple ratings. So we had people every twenty minutes, in fact, to rate happiness on a five-point scale about how they were feeling at that particular moment in time from 'very low' to 'very high'. And by doing that, we then divided people out into the proportion of time that people felt happy over the day. These data here *[referring to slide]* are from a working day. And we can then divide people up and this is a simple division of people divided out into twenty per cents or quintiles. So this is the top twenty per cent of people who essentially report being happy all the

time. So throughout the working day and evening, they say they're happy. But these glum people here [*laughter*] - twenty per cent of the people essentially weren't happy ever. So all the way through the day and evening they said they weren't happy. Then obviously we have some people here in the middle and so it's a graded structure. I've defined it as being graded as I divided people up according to their happiness. So the question is, how does this relate to people's biology? Well it actually relates in an interesting way, which is, as it were opposite to the more kind of stress related or adversity related effects that I described earlier. This here [*referring to slide*] shows the salivary cortisol levels; again, on a working day and this time I haven't divided out the times of day so these levels here are averaged across the whole day in terms of how happy these people were. So these are the happiest people and these were the least happy people and what you can see is that there is a gradient of cortisol over these variations in states of subjective wellbeing. So those people who did say that they were happy most of the time actually had quite substantially lower cortisol, something about thirty to forty per cent lower on average, than the people at this other level. What was interesting to us is that this was independent of many sorts of factors including things like social status, smoking, but it was actually also independent of distress. This is a measure called the General Health Questionnaire which is a measure of psychological distress, so that in some sense being... having a kind of effect on positive wellbeing was almost independent of the negative effects of feeling bad, of being in psychological distress, and so was quite an interesting finding. That's been published. What hasn't been published are these results here showing a three-year follow up of these same individuals and what I've done here is from about 200 people initially seen, we've followed up about 150 of these individuals and divided them out according to their original levels of happiness. So these are the people who originally, in that area of the graph, said they were happy and these originally are the people who said they were unhappy, but these levels are actually what they rated on a day three years later. And what's remarkable is how consistent it is. So these people here who said they were happy three years before are also still, on average, much happier than these ones down here who remain glum throughout this whole time and three years later they still are unhappy, unfortunately for them. Not much difference interestingly between men and women in this pattern. These were ratings taken on the working day. What was also interesting to us is that the cortisol profiles which we saw before were by and large replicated, so these are again the original happiness quintiles, so this is the people who originally said they were happy and originally said they were unhappy, but their cortisols were measured three years later, but once again there are high levels of cortisol in these groups here and lower levels in the happier individuals. In addition, we saw a relationship with blood pressure as well so that the people who had lower levels of happiness had slightly higher levels of blood pressure too. So I explain that really as an illustration of the way in which these sorts of biological responses can be looked at, not only for studying more adverse effects, but potentially for looking at some of the more protective phenomenon as well and I won't show you this afternoon, but we have also done analysis, for example, of social support and things of that sort.

There are problems with the interpretation of these data and I think in the interests of time I won't go into these in any detail, but one of the problems of looking at cortisol is that, as you can see from the figures I showed you, there is a very wide variation over the day and this means that if you just take a single measure it's really rather difficult to interpret that unless you have it tagged in time and so it is of greater interest to look at particular aspects of the day and one particular aspect that there is a lot of interest in at the moment is the first bit of cortisol: what happens after people wake up in the morning? These unfortunate people, they have to take a cortisol sample as soon as they wake up in the morning and then they take another one thirty minutes later and they're not even allowed a cup of coffee in that time which is really desperate *[laughter]* but they take that and the cortisol does increase under those circumstances. Well what we also can find out is that the response varies with social position and the response also varies with day of the week. What's shown here *[referring to slide]* are the average levels of cortisol when people wake up and then thirty minutes later on a working day and on a weekend day in people who are high in socioeconomic position and lower in social status. There are a number of interesting things which emerge here. First of all there is this increase in cortisol as people wake up. Some people describe this as the 'oh god' kind of response, you know you think 'what I have I got to do today?' sort of thing and you start thinking about it and then your cortisol shoots up, which is bigger on a working day than it is on the weekend days. So when people are less challenged by having to get ready for work and getting other people in the family ready for work then their cortisol responses are smaller. There is also this relationship with social position as well so that the people of lower social status have bigger responses both on the working day and on the weekend day and there is a gender difference which I haven't shown here which is that women have a bigger response on working days than men, but not a bigger response on weekend days. And we think this is probably due to the fact that many women have to do more than just get themselves ready for work when they get up in the morning: they have to get other people such as their partners ready for work *[laughter]* and, not to mention, children.

Well let me just touch in the last five minutes or so on this last point which is to do with how these things are actually related to health. What I've tried to explain is that they could in principle be related to health, but we haven't actually been showing health outcomes from this research and partly this is because this type of research is at a fairly early stage. Ideally what you want to do, of course, is to measure these responses to track people over time and to see, in an observational study, which people might develop disease. Or else you want to do an intervention and see whether that will alter your disease end-point. The fact is that these studies haven't really been going along long enough to look at many of these kind of disease end-points, but I'll show you a couple of examples to try and illustrate how we think this might be working.

The real issue when trying to look at these things is: do people who are more responsive show a more rapid progression of disease, independently of the original risk profile? Do they get worse more quickly? And so we look at the variation either in the laboratory responses or in what happens in people's everyday life. The simplest way of doing this is first of all to do the kind of assessment of psychobiological responses of the sort I've described and to look at the person's disease risk, and then to repeat that assessment of risk at some point later. So far we have only managed to do this over a three-year period. Even in that period we can see some associations of the sort that we would predict, mainly that people who may be more responsive in the initial assessment are showing more rapid progression of disease risk in the future. This *[referring to slide]* is an example of a recent analysis we have done where we were looking at cholesterol responses.

Cholesterol levels in the blood are obviously related to a whole lot of factors, but among other things they do increase, on average, in response to acute challenges in the laboratory. This slide here shows increases in cholesterol in men and women from a baseline blood sample and then a blood sample taken after stress and, even though we control the various factors that might be related to cholesterol, there is on average a response, but it's quite a variable response - some people show a big cholesterol response; some people show a smaller cholesterol response. So the question is, are those people who are more, as it were, stress responsive in cholesterol, are they at higher risk? And the answer is there is some evidence that they are. What is shown in this slide here is the change in fasting cholesterol levels over a three-year period. So these are levels of total cholesterol, but they are not the ones that you will be familiar with because these are just changes from the baseline. So if someone was starting off at 5.2 for example, this would be a change up to 5.4. So these are different scores and I've plotted these against the magnitude of the cholesterol stress responses so these people over here [referring to slide] are more responsive to this initial challenge. These people are much less responsive to the initial challenge. You can see that there is a relationship so that those people who were more stress responsive are indeed more likely to show an elevation of cholesterol level. So what we think is going on here is that the... what we see in the laboratory in this case is, as it were, a kind of snapshot of the way in which a person might be responding to everyday life experiences. They're showing an increase in cholesterol which will be a short term increase. It may be a larger one or it may be a smaller one, but if those sorts of responses repeatedly occur over this time period (in this case over the three-year period) then gradually that individual who is more responsive may end up being at higher risk. It's a bit like, you know, none of these responses are important in pathological terms in themselves, but may, as it were, contribute to risk in the longer term. Just as a single cigarette has an acute biological effect that doesn't have a disease effect, but a single cigarette taken every half an hour, every day, every week, every month, every year for decades does have an effect because it's the accumulation of the small hits. It's the same sort of thing that we think may be going on here. One further example of this is in relation to the metabolic syndrome (this is the same set of measures of metabolic syndrome). We can also see an association between the, as it were, the failure of blood pressure to recover effectively and progression in the metabolic syndrome as well over this kind of time period.

So I've tried to explain how we might use these responses. I'm afraid I've skated rather quickly about how these responses relate to health outcomes. Let me just close with showing you the general kind of model in which we try to carry out this sort of work. We're assuming that socioeconomic position as defined by these different ways in terms of a person's occupation, income, early life experience, and so forth, has associated with it a variety of psychosocial factors, some of which are protective and some of which are adverse. So the adverse factors may include such things as work stress, neighbourhood strain, financial problems, and so forth. These may be offset to some extent by various protective factors including social networks and possibly psychological coping responses and also some more enduring psychological factors such as self esteem. These same factors may influence a whole series of mediators before they get to the disease outcome; they may have direct effects on psychological wellbeing, which I haven't really spoken about today; they may have effects on health compromising behaviours such as lifestyle factors, smoking, patterns of eating and so forth, and also on the psychobiological responses as well. These things themselves are interrelated. I explained to you this afternoon how psychological wellbeing and the psychobiological processes may themselves be interrelated, but we think this may be part of the pathway and the critical issue at the moment is how to really show all this going on at once. I have shown you bits and

pieces, but neither we nor anyone else has yet been able to put this completely together in order to show every stage of this process. And that's something that we're hoping to do over the next few years and it's something which I think the Glasgow Centre is also well positioned to find out much more about. And just in conclusion I would like to acknowledge various colleagues who are responsible for different aspects of this work.

Thank you very much.