Rauffer-Bruyère, N., Chatellier, J., Weiss, E., Van Regenmortel, M. H. V. and Altschuh, D. (1997), 'Cooperative effects of mutations in a recombinant Fab on the kinetics of antigen binding', *Mol. Immunol.*, **34**, 165–173.

Rose, S. (1998), 'What is wrong with reductionist explanations of behaviour?', in G. Bock and J. Goode (Eds), *The Limits of Reductionism in Biology*, Novartis Foundation Symposium, No. 213, Wiley, Chichester, UK, p. 176.

Rosenberg, A. (1994), *Instrumental Biology or the Disunity of Science*, Chicago University Press, Chicago, IL, p. 193.

Russell, R. B., Sasieni, P. D. and Sternberg, M. J. E. (1998), 'Supersites within superfolds. Binding site similarity in the absence of homology', *J. Mol. Biol.*, **282**, 903–918.

Schaffner, K. (1993), *Discovery and Explanation in Biology and Medicine*, Chicago University Press, Chicago, IL.

Tauber, A. I. (1994), *The Immune Self. Theory of Metaphor*, Cambridge University Press, Cambridge, UK, p. 354.

Tobin, M. B., Gustafson, C. and Huisman, G. W. (2000), 'Directional evolution: the "rational" basis for "irrational" design', *Curr. Opinion Struct. Biol.*, **10**, 421–427.

Van Regenmortel, M. H. V. (1996), 'Mapping epitope structure and activity: from one-dimensional prediction to four-dimensional description of antigenic specificity', *Methods: Companion Meth. Enzymol*, **9**, 465–472.

Van Regenmortel, M. H. V. (1998), 'From absolute to exquisite specificity. Reflections on the fuzzy nature of species, specificity and antigenic sites', *J. Immunol. Meth.*, **216**, 37–48.

Van Regenmortel, M. H. V. (1999a), 'Biosensors and the search for structure–activity correlations', *J. Mol. Recogn.*, **12**, 277–278.

Van Regenmortel, M. H. V. (1999b), 'Synthetic peptide vaccines', in M. H. V. Regenmortel and S. Muller (Eds), *Synthetic Peptides as Antigens*, Elsevier, Amsterdam, pp. 281–317.

Van Regenmortel, M. H. V. (1999c), 'Molecular design versus empirical discovery in peptide-based vaccines. Coming to terms with fuzzy recognition sites and ill-defined structure–function relationships in immunology', *Vaccine*, **18**, 216–221.

Van Regenmortel, M. H. V. and Pellequer, J. L. (1994), 'Predicting antigenic determinants in proteins: looking for unidimensional solutions to a three-dimensional problem? *Peptide Res.*, **7**, 224–228.

Chapter 5

Reductionism in Medicine: Social Aspects of Health

Elisabeth A. Lloyd

Department of History and Philosophy of Science, Indiana University, Bloomington, IN, USA

Introduction

I review in this paper a number of empirical findings which show that not all appropriate or powerful medical research is done at the molecular or even clinical level. Socioeconomic factors turn out to be powerful predictors of health outcomes, both for the rich and the poor, and these factors cannot be investigated if all research funds are concentrated at problems conceived at the molecular level. I first review some relevant but surprising facts, and then summarize some current hypotheses concerning how social-level phenomena become embedded in individual organisms. I conclude by reiterating a well-designed research program to explore these phenomena that appear well above the molecular level.

What we know

Socioeconomic gradients and health

There is a socioeconomic gradient in health status. Those with higher income, better education, and jobs with more status, prestige, and decision latitude provide the best ecological niche for adult human beings. Those with less of these things enjoy progressively higher morbidity and mortality.

This in itself is not too surprising. What is much more surprising is that a number of cross-national surveys have shown that the degree of income inequality in a given society is strongly related to the society's level of mortality. The more steep the income gradient (the more severely the poor

Promises and Limits of Reductionism in the Biomedical Sciences
Edited by M.H.V. Van Regenmortel and David L. Hull © 2002 John Wiley & Sons, Ltd

are poorer than the rich), then the worse off everyone is, not just the poor. The health status of each social class within the population seems to be better than the classes below, and worse than the classes above, regardless of the actual level of material wealth. Thus, middle-class people in a very rich society may die sooner than upper-class people from a less rich society, even though they have more material goods.

We would expect absolute levels of income to be related to morbidity and mortality, but there are many new studies showing strong associations between levels of *income inequality* and mortality (after adjustments for absolute income differences) in the 50 states of the US. The results show that *increased mortality at all per capita income levels* is associated with higher income inequality (Kaplan *et al.*, 1996; Lynch *et al.*, 1998; see also Kennedy *et al.*, 1996). That is, the size of the gap between the wealthy and the poor (vs. the absolute standard of living held by the poor) matters in its own right. A higher per capita income was still significantly associated with lower mortality ($r = -0.21$), but this association was *weaker* than the effects of income inequality on mortality. In other words, being in the top 10% of income in a society with a steep income gradient increases your chances of morbidity and mortality, compared to living in a society with a less steep difference between the rich and the poor.

Areas with high income inequality and low average income had an excess mortality of 139.8 deaths per 100 000, compared with areas with low inequality and high income. In 1995, the magnitude of this mortality difference was comparable to the combined loss of life from lung cancer, diabetes, motor crashes, HIV, suicide, and homicide combined (Lynch *et al.*, 1998, p. 1079).

The conclusion is that there is a high mortality burden associated with income inequality. In other words, the greater the gap in income between the rich and the poor in any given society, then the lower the average life expectancy, while the latter is relatively unrelated to average national income. The life expectancy is lowered even for the richest tenth, in societies with steep income gradients. This result has been confirmed in a number of cross-national studies (Kawachi *et al.*, 1997; LeGrand, 1987; Rodgers, 1979; Wilkinson, 1986, 1990, 1992, 1997).

The range of diseases which display this phenomenon is astonishingly broad, and includes the following: accelerated aging, allergies, angina, arrhythmias, asthma, atherosclerosis, cancer, coronary artery disease, epilepsy, essential hypertension, Grave's disease, headaches, herpes, multiple sclerosis, myasthenia gravis, myocardial infarction, peripheral vascular

disease, post-traumatic stress disorder, rheumatoid arthritis, stroke, systemic lupus erythematosus, and type 2 diabetes mellitus (Kelly *et al.*, 1997, p. 438).

The results regarding socioeconomic gradients undermines the hypothesis that the principal social class influence on health is material deprivation. In fact, the social class gradient in health cuts deeply into the affluent middle classes. The implication is that the conditions under which people live can affect human health directly, and not only through material deprivation. 'Early childhood experience, one's place in the social environment, and the experiences of daily life must be powerful determinants of the length and healthfulness of life' (Kelly *et al.*, 1997, p. 438).

If all this is correct, then there must be some process of 'biological embedding' wherein life experiences condition individual biological responses, which lead to systematic differences in resilience and vulnerability to disease across the range of social class experience.

Studies examining the relationship between socioeconomic status and health have also been carried out comparing various US states, e.g. comparing the degree of household income inequality and state-level variation in all-cause and cause-specific mortality. In an independent study, Kaplan *et al.* (1996a) examined the association between income inequality and state-level and household-level variations in total mortality rates. In all cases, increased steepness of inequality was associated with higher death rates overall.

Common myths

Several factors have long been believed, both popularly and in public health, to be decisive contributors to the health gap between the wealthy and the poor. The real questions regarding population health were thought to revolve around identifying which aspect of people's material circumstances were responsible for the social gradient in health, e.g. occupational hazards, differences in diets, housing, and air pollution? Reviews of some recent findings regarding determinants of population health from the 1980s are therefore in order. First, medical services 'were not a major determinant of population health - and certainly not of the substantial social gradient in health found even in countries providing universal access to medical care' (Wilkinson, 1999, p. 48). Another common myth is that well-known behavioral risk factors, such as smoking, obesity, and lack of exercise, explain the social gradient in health; in fact, these well-known risk factors left most of the social gradient in health unexplained. Finally, social selection

(reverse causality, wherein sick people tend to become poor) made only a minor contribution to health inequalities (Wilkinson, 1999, p. 48).

The puzzles

One puzzle that arises from these results is to understand the mechanisms by which *relative* socioeconomic position leads to variations in health. Degree of income inequality is an 'ecologic' variable – it is a property of the population and not of the individual. This is not how we ordinarily think about health, which is conceptualized as a property of an individual body, while socioeconomic level is usually conceptualized as a property of an individual or a family, and is measured by income, education, occupation and social class. Large conceptual changes in our understanding of the biology of disease have been required, in order to account for these new findings. I review below several key theories put forward to explain the challenging findings revealed in these cross-populational correlations between socioeconomic status and morbidity and mortality.

Hypotheses

The biological problem is that the pathways and mechanisms of the association between income inequality and mortality levels are still unknown. These questions are, nevertheless, fundamentally biological, as they must address how social influences can somehow enter into or embed themselves in the functioning body.

Wilkinson

Richard G. Wilkinson's hypothesis is that the key lies in understanding the biology of social anxiety. It is not the absolute standard of living that is important, but the levels of depression, isolation, insecurity and anxiety that are associated with relative poverty, which he describes as *psychosocial characteristics*. During the 1990s, it became established that there were important psychosocial influences on health e.g. 'life events', social support and sense of control were all closely associated with health. The questions for epidemiologists thus became – what ideational states were damaging to health? Wilkinson concluded that anything contributing to chronic anxiety was likely to affect health.

The crucial investigative questions for Wilkinson are as follows. How hierarchical is the social hierarchy? What are the depths of material insecurity and social exclusion tolerated by society? What are the direct and indirect psychosocial effects of social stratification?

He believes that the clinching pieces of evidence where psychosocial pathways may make the largest single contribution to the socioeconomic gradient in health came from the evidence regarding income and health. Specifically, income was found to be related to health within developed countries (and within US states), but not between them. Thus, it seemed likely that the relationship was not one between absolute living standards or material circumstances, 'so much as a relationship with relative standards or with relative income serving as a marker for social status' (Wilkinson, 1999, p. 49). Independent confirmation for this theory came from evidence that, 'although mortality rates in developed countries were not closely related to average income, they were related to income distribution. [Thus], Measures of income inequality can plausibly be interpreted as measure of the burden of relative deprivation on health in each society' (Wilkinson, 1999, p. 49).

Further independent confirmation came from studies of the biological effects of social status among nonhuman primates. R. M. Sapolsky's studies of wild baboons, and C. A. Shively's studies of macaques in captivity showed that a number of physiological risk factors had similar associations with social status among animals as those among human beings. The reason that these animals studies are so compelling for those studying risk in human beings is that the physiological risk factors associated with social status among nonhuman primates and people are pretty much the same. Characteristics reported to be associated with social status among *both* human beings and non-human primates include the following: worse HDL:LDL ratios, central obesity, glucose intolerance, increased atherosclerosis, raised basal cortisol levels, and attenuated cortisol responses to experimental stressors (Wilkinson, 1999, pp. 49–50).

In addressing the basic question, then, of why more egalitarian societies tended to be healthier than less egalitarian ones, Wilkinson believes that the most plausible explanations focus on the way that the social environment is affected by inequality. He emphasized cases in which unusually healthy and egalitarian societies provide circumstantial evidence that more egalitarian countries were more socially cohesive than less egalitarian ones. Data observed from several sources have strongly confirmed this pattern (Wilkinson, 1996; Kawachi and Kennedy, 1997).

For instance, Wilkinson found that people are much more likely to feel trustful towards others in those US states in which income differences were smaller. Similarly, the hostility scores for 10 US cities found by R. B. Williams *et al.* (1995) were related to city mortality rates ($r = -0.9$), which have also been found to be related to the extent of income inequality in those cities. In addition, R. D. Putnam studied the functioning of regional governments in Italy, and notes that his index of 'civic community' (measure of the strength

of people's involvement in community life) was closely correlated with the extent of income inequality (Wilkinson, 1999, p. 51).

There is also evidence from a large number of studies that homicide and violent crime are substantially more common in less egalitarian countries. (A meta analysis carried out by Hsieh and Pugh showing violent crime and homicide rates related to income inequality covers 34 studies (Hsieh and Pugh, 1993).) All of this evidence strongly suggests that as social status differences in a society increase, the quality of social relations deteriorates. The countries studied included the US, UK, Italy, and Japan, plus a number in Eastern Europe.

However, what is it about social status and social integration that makes them so important to health? One proposal is that social status indicates social capital, and that it is a person's social capital which is most important to health. Wilkinson rejects this hypothesis, stating that 'social capital' is an epiphenomenon 'and that we still have to identify the causal factors underlying it' (Wilkinson 1999, p. 52).

According to Wilkinson, 'No one has yet provided a plausible explanation of why either social cohesion/capital or friendship and the quality of social relations are important to health. Good social relations of all kinds - from close 'confiding' relationships, to having more friends, to involvement in community associations - all seem to be beneficial to health' (Wilkinson, 1999, p. 52).

Looking for the direct results of social status is also difficult. 'The fact that a number of the same physiological risk factors are associated with low social status among humans as have been reported among monkeys, means that they are unlikely to be explained by smoking, unemployment, bad housing, and the like. Among monkeys, the physiological risk factors associated with low social status can be confidently attributed to the chronic anxiety that comes from the constant threat of being attacked and bitten by superiors. However, the sources of the chronic anxiety inherent in low social status among people are rather different and usually more subtle' (Wilkinson, 1999, p. 52).

Wilkinson concludes, 'We do not really know why social affiliation matters to health, we do not know why social cohesion is associated with better health, and we have not yet identified what is inherently stressful about low social status' (Wilkinson, 1999, p. 52).

So how does Wilkinson propose to fill these gaps in our biological knowledge? He is sure that, once we have identified the main sources of chronic anxiety, there are a variety of plausible biological pathways from there to physiological illness and death. He also believes that, when the 'stress reaction' (fight or flight) is activated for brief emergencies, little harm

is done. 'But when the anxiety and worry lasts for months and years, and the body is frequently in a high state of arousal, there is likely to be a variety of health costs' (Wilkinson, 1999, p. 53). This is because, among other things, when the body is mobilizing resources for muscular activity, other system-maintenance and repair processes (such as growth, tissues repair, immunity, digestion, reproductive functions, etc.) are put on hold (Sapolsky, 1998). Risk of blood clots is also increased, and therefore risk of heart attacks. If the energy resources that are mobilized are not used, they increase accumulation of cholesterol in blood vessels. All of this means that the variety of physiological processes affected by chronic anxiety mean that its health effects are analogous to more rapid aging. 'Our aim then is to understand the central sources of chronic anxiety related to the main risk factors for population health in the developed world' (Wilkinson, 1999, p. 53).

One of the primary sources of anxiety considered by Wilkinson is violence. He notes the association between income inequality and homicide. Among the 50 US states, it accounts for half of the very large variations in homicide rates between states. The higher violence was not between rich and poor. 'The violence associated with greater inequality occurs largely among the most deprived' (Wilkinson, 1999, p. 54). This makes sense, according to Wilkinson: 'Where more people are denied access to the conventional sources of respect and status in terms of jobs and money . . . people become increasingly vulnerable to signs of disrespect, that they are being treated or regarded as inferior, insignificant, and worthless' (Wilkinson, 1999, p. 54). Wilkinson sees all this as very significant, because it shows how much social status matters to people, and can perhaps start to show how low social status may be a direct source of anxiety.

Wilkinson also notes the importance of emotional development in early life: poor attachment and emotional trauma in early childhood affects health. As he notes, there are observed associations between health and social status, between health and friendship, and between health and early emotional development. All three of these must be considered prime candidates for sources of social anxiety.

One mistake which Wilkinson urges us to avoid is to picture human characteristics as having evolved in relation only to a physical environment; one of the primary hostile forces has always been other human beings. The importance of social interactions should not be underestimated. One example that he gives is that blood pressure tends to rise when people are interviewed by a higher- rather by than an equal- or lower-status interviewer. This is fundamentally a response of the sympathetic nervous system to the social anxiety induced by interacting with someone who is of higher social status.

In sum, Wilkinson focuses his explanatory hypothesis on social anxiety. He links social anxiety to shame, depression and violence, and emphasizes that social anxiety has its roots in perceptions of inferiority, unattractiveness, failure or rejection. This helps explain why health is so closely related to lack of friends, low social status, violence and poor early emotional attachment, all of which are associated with similar patterns of raised basal cortisol levels and attenuated responses to experimental stressors. He concludes, therefore, that social anxiety is a very plausible central source of the chronic anxiety that depresses health standards and feeds into the socioeconomic gradient in health. As he puts it, 'the most important psychosocial determinant of population health is the levels of the various forms of social anxiety in the population, and these in turn are determined by income distribution, early childhood and social networks' (Wilkinson, 1999, p. 60). Thus, social anxiety is suggested as an explanation for the links between health and friendship, health and early emotional development, health and the direct psychosocial effects of low social status, the patterning of violence and health in relation to inequality, and health and social cohesion (Wilkinson, 1999, p. 61).

While Wilkinson's approach is perhaps the best known, I will review several other hypotheses in the remainder of this section.

Kaplan

George Kaplan has shown that US states with greater inequality have higher rates of violence, more disability, more people without health insurance, less investment in education and literacy, and poorer educational outcomes, all of which he calls 'structural' characteristics. Moreover, the socioenvironmental characters of population areas are importantly related to the mortality rates, *independent* of the characters of individuals. In addition, personal and socioeconomic risk factors cluster together in areas of low income and high mortality. In a thorough local study of Alameda County, California, Kaplan examined parts of the pathways linking social class and mortality. His basic claim is that health inequality is correlated to social instability, which is in turn correlated to the lack of investment in 'structural' characteristics, such as education, proximity of healthful food outlets, pharmacies, accessibility of transportation, etc.

Kaplan criticizes the usual approaches to uncovering the biological and physiological pathways that allow social class to 'get under the skin', claiming that they fail to examine the larger social contexts. (For example, more smoking is correlated with higher fibrinogen, although the researchers don't explain why.) The most fundamental flaw that he observes with

conventional approaches is that they see socioeconomic status (SES) as an individual-level trait. Approaching SES this way ignores 'patterned sets of exposures, opportunities and resources that differ by social class level,' all of which can make a difference to health outcome (Kaplan, 1996, p. 508). In his studies, Kaplan includes ecological as well as individual variables, for example, in his Alameda County study, 'residence in a poverty area' turned out to be a key determinant of health (Kaplan, 1996, p. 509).

Kelly, Hertzman and Daniels

On Clyde Hertzman's theory, the socioeconomic gradient in health status discussed in the previous section cuts across a wide range of disease processes and is capable of replicating itself on new disease processes as they emerge in society. In order to understand the gradient, we need to understand what makes human organisms become generally vulnerable or resilient to disease over time. According to Hertzman, 'The hypothesis that best fits current evidence is that the gradient is an "emergent property" of the interaction between the developmental status of people and the material and psychosocial conditions they encounter over their life course' (Hertzman, 1999, p. 85).

Hertzman focuses mainly on child development: socioeconomic differences in the quality of early life experiences contribute to subsequent gradients in health status through socioeconomic differences in brain sculpting and the conditioning of host defense systems that depend on communication with the developing brain. The contribution to the gradient in health is theorized to occur through a combination of latent effects, pathway effects and cumulative disadvantage.

In work carried out with Shona Kelly and Mark Daniels, Hertzman's approach to explaining the correlations between socioeconomic variables and health is to treat life as a cumulative process. According to their view, life experiences, especially early childhood brain development, condition individual biological responses, especially resilience and vulnerability to disease. According to Kelly, Hertzman and their co-workers, the most plausible biological connection is the central nervous system, which 'talks to' the immune, hormone and clotting systems, all of which can be involved in disease processes (Kelly *et al.*, 1997, p. 438). In addition, chronic stress leads to subtle, long-term changes in endocrine, hemostatic, and immune system function. These authors are able to draw on the extensive knowledge regarding socioeconomic gradients in health status, the biology of stress, and the connections between consciousness and host defense mechanisms.

However, they note, there is no scientific consensus 'that the conditions of life actually do embed themselves in human biology over the lifecycle,' or, even if they do, that this is a 'significant determinant of health in the populations of high-income countries' (Kelly *et al.*, 1997, p. 438). In fact, this has never been subjected to rigorous empirical scrutiny, for a good reason. It would require lifelong longitudinal studies of large representative population samples, involving both extensive questionnaire responses and biological sampling at frequent intervals (however, see the following section).

Lynch

In addressing the question of how income inequality is linked to population health, Muntaner and Lynch (1999) identified two strands of causation, thus combining the approaches of Kaplan and Wilkinson. First, they claim that income inequality is associated with a set of social processes and economic policies that systematically under-invest in physical and social infrastructure (e.g. education). Secondly, large disparities in income distribution may have direct consequences on people's perceptions of their relative place in the social environment, which leads to behavioral and cognitive states that influence health.

Kawachi

Ichiro Kawachi and co-workers have pursued a hypothesis that centers on social cohesion and trust. They claim that the growing gap between the rich and the poor has led to declining levels of social cohesion and trust, or disinvestment in 'social capital,' i.e. features of social organization such as civic participation, norms of reciprocity, and trust in others. Social capital is understood as civic engagement and levels of mutual trust among community members, and civic engagement is the extent to which citizens involve themselves in their communities, as most often measured by either membership in groups and associations. Social capital is thus a 'community level' ('ecologic') variable whose counterpart at the individual level is measured by a person's social networks. There is a large literature linking social networks to health outcomes at the individual level, but studies of social capital have so far only focused on performance of civic institutions, which does not really get at the flavor of Kawachi's variable.

In a 1997 study, Kawachi and co-workers (Kawachi *et al.*, 1997, p. 1492) reported on a test of three linked hypotheses as follows:

(1) 'That state variations in income inequality predict the extent of investment in social capital'.

(2) 'That the degree of investment in social capital predicts state variations in total and cause-specific mortality'.

(3) 'That there is little residual direct association between state income inequality and mortality after investment in social capital has been controlled'.

The results were that income inequality was strongly associated with lack of social trust, and that states with high levels of social mistrust had higher age-adjusted rates of total mortality (level of social trust explained 18% of variance in total mortality, under their regression). Lower levels of social trust were associated with higher rates of most major causes of death, including coronary heart disease, malignant neoplasms, cerebrovascular disease, unintentional injury, and infant mortality.

On the other hand, per capita group membership was strongly inversely correlated with all-cause mortality. Level of group membership was also a predictor of coronary heart disease, malignant neoplasms, and infant mortality.

When Kawachi and co-workers carried out a path analysis, it indicated that the primary effect of income inequality on mortality is mediated by social capital (as measured by level of perceived fairness). Income inequality exerts a large indirect effect on overall mortality through the social capital variable. As income inequality increases, so does the level of social mistrust, which is in turn associated with increased mortality rates.

They concluded that income inequality was directly and strongly related to the postulated causal factor (disinvestment in social capital), but when the causal factor was controlled, there was little residual direct association between the instrumental variable and the outcome (Kawachi *et al.*, 1997, p. 1496).

Wilkinson indicates that he considers social cohesiveness to be an epiphenomenon. The evidence shows that where income differences are greater, violence tends to be more common, people are less likely to trust each other, and social relations are less cohesive. However, the impression that social cohesion is beneficial to health may be less a result of its direct effects, and more of 'a marker for the underlying psychological pain of low social status'. He believes that the biological causal pathways are 'Likely to center on the influence that the quality of social relations has on neuroendocrine pathways' (Wilkinson, 1999, p. 48).

Prospects for research

We are left with many questions still unanswered. What is it about social status and social integration that makes them so important to health? What are the main sources of chronic anxiety, and what are their effects on health? (This is an especially promising question, since we already have a good idea about why stress affects health (Sapolsky, 1998).) What is the association between income inequality and homicide? (Homicide can account for half the variation in mortality rates between states.) How does inequality affect emotional development in early life?

Here is one primary challenge. If the biological embedding hypothesis is correct, and somehow the socioeconomic system is being read into the biology of the body, then it should be possible to show that differences in socioeconomic status and living conditions *precede* the emergence of systematic social class differences in biological variables. Kelly *et al.* (1997), as well as some of the others, have made a testable prediction - the results should show that central nervous system-mediated host defense pathways function differently in people who have more income, better beginnings, better jobs, more social supports, etc. Plus, the temporal relations between socioeconomic, living conditions, and measures of host defense must make sense.

In order to test this, Kelly *et al.* (1997) point out that we need a set of biological markers thought to be sensitive to long-term systematic differences in socioeconomic status and living conditions, and these markers must be feasible to measure in large population surveys, so their role in the biological embedding process can be evaluated on a population-based, person-specific basis.

As mentioned above, such investigations might require a vast longitudinal study. We have birth cohort studies from the UK (1958) and the US, which can already be overlapped with longitudinal studies from working age and old age to simulate the entire life cycle. (These are not complete, but can be pieced together.)

Such longitudinal studies could show how social class factors influence health throughout the life cycle, and motivate investigations into the *biological pathways* linking class and health, e.g. the National Population Health Survey in Canada, begun in 1994.

However, biological measures are needed, and relevant ones. Hertzman and his colleagues have suggested a small group of biologically relevant tests. The idea is to obtain information about the processes by which socioeconomic and psychosocial factors embed themselves in human health. These include biological measures of the status of the psychoneuroimmunology/psychoneuroendrocrinology pathways. In their review article of 1997,

Hertzman and co-workers set out criteria to evaluate potential physiological markers of chronic stress. Recognizing that population health surveys involved a massive number of samples, with some care towards timing and delivery of such samples, they recommend studying the following: glycosylated proteins, especially glycosylated hemoglobin and advanced glycosylation end-products, immune function, particularly antibody response to vaccines (they rule out any test requiring fresh, large volumes of blood), hemostasis, especially coagulation and fibrinolysis systems, and fibrinogen. They also mention peripheral benzodiazepine receptors and waist-hip ratio as possible measures (Kelly *et al.*, 1997, pp. 441-454).

Conclusion

There is already enough evidence available to conclude that phenomena above the level of the individual organism can have a serious and lasting impact upon health. Research programs that focus exclusively on molecular-level understandings of the workings of the human body will be unable to contribute to improving these aspects of population health.

References

Hertzman, C. (1999), 'The biological embedding of early experience and its effects on health in adulthood', *Annals of the New York Academy of Sciences*, **896**, 85-95.

Hseih, C. C. and Pugh, M. D. (1993), 'Poverty, income inequality, and violent crime: a meta-analysis of recent aggregate data studies', *Criminal Justice Review*, **18**, 182-202.

Kaplan, G. A. (1996), 'People and places: Contrasting perspectives on the association between social class and health,' *International Journal of Health Services*, **26**, 507-519.

Kaplan, G. A., Pamuk, E. R., Lynch, J. W., Cohen, R. D. and Balfour, J. L. (1996), 'Inequality in income and mortality in the Unites States: analysis of mortality and potential pathways', *British Medical Journal*, **312**, 999-1003.

Kawachi, I. and Kennedy B. P. (1997), 'Socioeconomic determinants of health: Health and social cohesion: why care about income inequality?', *British Medical Journal*, **314**, 1037-1040.

Kawachi, I., Kennedy, B. P., Lochner, K. and Prothrow-Stith, D. (1997), 'Social capital, income inequality, and mortality', *American Journal of Public Health*, **87**, 1491-1498.

Kelly, S., Hertzman, C. and Daniels, M. (1997), 'Searching for the biological pathways between stress and health', *Annual Reviews of Public Health*, **18**, 437-462.

Kennedy, B. P., Kawachi, I. and Prothrow-Stith, D. (1996), 'Income distribution and mortality: cross-sectional ecological study of the Robin Hood index in the United States', *British Medical Journal*, **312**, 1004-1007.

LeGrand, J. (1987), 'Inequalities in health. Some international comparisons', *European Economic Review*, **31**, 182-191.

Lynch, J. W., Kaplan, G. A., Pamuk, E. R., Cohen, R. D., Heck, K. E., Balfour, J. L. and Yen, I. H. (1998), 'Income inequality and mortality in metropolitan areas of the United States', *American Journal of Public Health*, **88**, 1074-1080.

Muntaner, C. and Lynch, J. (1999), 'Income inequality, social cohesion, and class relations: A critique of Wilkinson's new-Durkheimian research program', *International Journal of Health Services*, **29**(1), 59-81.

Rodgers, G. B. (1979), 'Income inequality as determinant of mortality: an international cross-section analysis', *Population Studies*, **33**, 343–351.
Sapolsky, R. M. (1998), *Why Zebras don't get Ulcers: A Guide to Stress, Stress-Related Disease, and Coping*, 2nd Edn, W. H. Freeman, New York.
Wilkinson, R. G. (1986), 'Income and mortality', in *Class and Health: Research and Longitudinal Data*, R. G. Wilkinson (Ed), Tavistock Press, London.
Wilkinson, R. G. (1990), 'Income distribution and mortality: a 'natural' experiment', *Social Health Illness*, **12**, 391–412.
Wilkinson, R. G. (1992), 'Income distribution and life expectancy', *British Journal of Medicine*, **304**, 165–168.
Wilkinson, R. G. (1996), *Unhealthy Societies: The Afflictions of Inequality*, Routledge, London.
Wilkinson, R. G. (1997), 'Socioeconomic determinants of health: Health inequalities: relative or absolute material standards', *British Medical Journal*, **314**, 591–595.
Wilkinson, R. G. (1999), 'Health, hierarchy, and social anxiety', in N. E. Adler, M. Marmot, B. S. McEwen and J. Stewart (Eds), *Socioeconomic Status and Health in Industrial Nations: Social, Psychological and Biological Pathways*, Vol. 896, New York Academy of Sciences, New York, 48–63.

QUESTIONS AND DISCUSSION

Alex Rosenberg: There must be some obvious defect in this explanation, so let me try it out on you. The first component is that inequality is the result of an incentive structure that makes some people work much harder than other people. The second is that harder work *ceteris paribus* produces higher mortality and morbidity, and the third is that higher morbidity at lower socioeconomic status plus contagion leads to higher morbidity and mortality at higher socioeconomic status – end of story.

Elizabeth Lloyd: No, these are all non-contagion related medial situations. I mean, these are all countries in which contagion is not a significant medical factor.

Alex Rosenberg: All right, but now the first two would, by themselves, explain the character both of the relationships between the gradients and the steepness of the morbidity and mortality histograms.

Elizabeth Lloyd: Oh, a common cause. Well, I'd be more inclined to accept something that had a certain economic structure at its center except that these same results have been shown across 159 different countries and several countries in the former USSR.

Alex Rosenberg: But there are still incentive effects in those countries. It is just the pay-offs that are different. You have to work hard to climb the ladder in the Communist Party, as opposed to working hard in climbing the corporate ladder.

Elizabeth Lloyd: Maybe I misunderstood, but the claim that these guys are making is precisely that it is the reflection of differential socioeconomic status that creates the stress in the society that makes people sick. Is that not the explanation you just gave?

Alex Rosenberg: No, the explanation I just gave is that the harder you work, the more likely you are to show morbidity and mortality. And a society which has a stronger incentive structure, for example, a capitalist society as opposed to a highly egalitarian society, is likely therefore to result in individuals working harder and showing greater . . .'

Elizabeth Lloyd: Well it is not a good incentive if it is going to kill you, is it?

Alex Rosenberg: We'll have time in the round table to continue this discussion. John, do you want to talk?

John Dupré: Yes, I suppose, partly my reaction is a little similar to Alex's in the sense that the first thing that surprised me more than anything else was your surprise at these results. And I guess the reason I'm surprised is that in the course of your talk, about 10 different hypotheses occurred to me, most of which you discussed. As far as the pathogens are concerned, surely we don't know which major diseases have some pathogenic component in them, and that could be more important you suggest. It seemed to me that as you went through, you mentioned a whole lot of things and you said of them that ethos doesn't explain a whole lot of the difference. Another thing that Alex suggested was that it is very difficult to get causal direction; a lot of the things, particularly social cohesion, might well be a cause of these inegalitarian societies, as well as mentioned, half of these hypotheses reflecting my general intuition that these are generally more dysfunctional societies with less social cohesion, a lot more violent. And of course the murder rate – the violence causes stress. One knows, in fact, rich people aren't usually victims of violence but we all know lots of rich people whose lives are made miserable by the stress that the fear of violence causes to them, and so on, and so on. It just seems the likely explanation is dozens of explanations, dozens of things that are dysfunctional in these societies that all contribute at least a little bit to a higher mortality rate.

Elizabeth Lloyd: One thing that was very difficult for me in sorting through this literature was deciding why these people thought they disagreed with each other so much, about what the explanatory hypotheses were. Now it is true that they did have different explanatory emphases in their theories. One of them, one that kills me the most, quite frankly, is the guys who go out and measure and get a response, because that is what I want to see (laugh)! Then I have some numbers that I can look at and I can see and compare with other numbers. And the thing is they do have lots of numbers already – it is just that with psychoneuroimmunology having progressed so much just in the last 5 years, the kind of information would provide genuinely new data.

John Dupré: It doesn't sound that anything you said goes strongly against the hypotheses that they are all right . . .

Elizabeth Lloyd: I would say nothing I said goes against the hypothesis that they are all right.

John Dupré: You add them all together, and there is not so much of a problem.

Elizabeth Lloyd: Right.

Robert Williams: Can I make two points? One – nobody has ever suggested that the population of England works harder than any other population. Everybody always says exactly the opposite. Certainly academics all through Europe. I don't think working hard can be put opposite the British problem. The second is, when you draw straight lines, this is more serious, as you have to look at the asymptotes as well as at the gradients. Now the question is, can you then show us anything about asymptotes, so let's just see what actually happened in a population. In Finland, they've undergone a very considerable experiment on these lines. They've increased the life expectation quite considerably in a very simple way. And so I'd love to know where Finland lies in these studies before, let's say, about 15 years ago and today, because I think what has happened is the whole line has been just lifted up and I don't believe that the socioeconomic status, the slope of it, I can hardly believe that this is changed much, although it has become a much more successful society.

Elizabeth Lloyd: According to the theory, what matters to these guys, the phenomena that these guys are looking at, is not the gross national product, but what the gradient is.

Robert Williams: Yes, but where does the line intersect the axes? Where is the intercept, because if you plot intercepts, do you get any result at all about mortality? It would be very strange if you didn't.

Elizabeth Lloyd: Well, Finland has gone up in expected age, and the Russians have gone down. Some of the studies that I was reading in preparation for this talk were on the former Czech Republic and on other areas behind the Iron Curtain, where the mortality rate has skyrocketed since 1989 through all sources of death, all causes of death, and that is very interesting. In these cases, the line went from being very flat with a little flip-up at the end to being extremely steep, and you had a dramatic fall of life expectancy. That is actually a beautiful confirmation of what these guys had been predicting was actually the case. So I don't know about the Finland case, but for the other cases it's clear.

Chapter 6

'Who's Afraid of Reductionism?' 'I Am!'

Stanley Shostak

Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA, USA

Introduction

For more than thirty-five years, I've been studying evolution – originally the evolution of cancer (Shostak and Tammariello, 1969; Shostak, 1981), and more recently, the evolution of tissues (Shostak, 1993; Shostak and Kolluri, 1995). During this time, I have encountered reductionism, sometimes as a prod and frequently as an obstacle. I have learned, thereby, to appreciate the difficulties that reductionism presents for studying evolution. Thus, when Daniel Dennett, the philosopher of evolution and consciousness, asks in his perennially popular, *Darwin's Dangerous Idea*, 'Who's Afraid of Reductionism?' (Dennett, 1995, p. 80) I'm compelled to answer 'I am!' and explain why.

Of course, one could hardly have lived through the second half of the Twentieth century without marveling at the accomplishments of reductionism – there would be no biotech industry or Human Genome Project without it. Nevertheless, a considerable part of what interests biologists – between the beginning and end of evolution – is not necessarily congenial to reductionist approaches. Reductionism prescribes that we take what we know and apply it to the past as long as the evidence produces no contradictions, and we use what we have learned about events and processes on a small scale to understand events and processes on a large scale unless overwhelmed by incongruities. Thus, instead, of acknowledging that what we know of the present cannot be applied *ipso facto* to the remote past, to the Prephanerozoic or Archean, reductionists extrapolate from data for extant species to unknown ancestors. In addition, instead

Promises and Limits of Reductionism in the Biomedical Sciences
Edited by M.H.V. Van Regenmortel and David L. Hull © 2002 John Wiley & Sons, Ltd