

## Upstream and Downstream Approaches to Inequalities in Health

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### INTRODUCTION--

It is a great honor to be invited to present a Karolinska Research Lecture at the Nobel Forum. As I look at the list of other speakers for this Spring series I am struck by the importance of their contributions. Their work represents the frontiers of science in its connections with human biology, physiology and health. Thus, I note reports on nuclear regulatory proteins that control energy and fat metabolism via their actions on genes, the link between early-onset Alzheimer's Disease gene mutations and processes leading to apoptosis, the DNA damage checkpoint and genomic stability, host defense pathways operating through a billion year-old receptor molecule, and studies of the viral genome of the Norwalk virus that are leading to the development of a candidate vaccine.

These are exciting times, and basic discoveries in the molecular sciences driven by rapidly expanding knowledge in genomic sciences (Figure 1 from Varmus, 1999), marked by accomplishments such as the first complete deciphering of all of the genes of a multicellular organism, the intensively studied roundworm (Figure 2, from Varmus 1999) have led to optimistic statements by many. For example, Harold Varmus the Director of the U.S. National Institutes of Health proclaimed to the United States Congress that "...victory over disease and disability has become an understandably popular and realistic goal." (Statement before the House and Senate Appropriations Subcommittees on Labor, Health and Human Services, and Education, February 23-24, 1999)

While such statements must always be understood within the political context in which they are made, I am less optimistic. I fear that important social epidemiologic perspectives on the determinants of the occurrence of disease and disability in populations are being ignored in our belief that it is only ignorance of the downstream, proximal causes of disease that prevents us from eliminating disease and disability.

What is being left out of the picture is as fundamental to the occurrence of disease as are the proximal, molecular determinants. In fact, knowledge of one without knowledge of the other can only lead to incomplete understanding. As Figure 3 illustrates, disease at the individual, and population, level is a consequence of many

levels of influence. Considerable evidence now supports the assertion that the major causes of disease and suffering in the population are firmly rooted in the behavioral, social, and psychological worlds in which people live, which are, in turn, embedded in multiple environmental, geographic, institutional, and economic contexts. If we are to understand patterns of occurrence of disease, and to accomplish major reductions in the burden of illness and infirmity, then these upstream characteristics must be as much a part of our causal understanding of disease and disability in the population as are the downstream molecular events that are more proximal to the occurrence of disease in individuals..

It is to these upstream characteristics that we must turn if we are to understand in any complete sense, for example, the massive loss of life expectancy experienced by some countries of eastern and central Europe during the last decade or so (Figure 4).

### **INEQUALITIES IN HEALTH--**

In order to further illustrate this point, I take today the example of inequalities in health, particularly those related to the economic position of individuals or groups. Socioeconomic position is not the only metric along which health can be arrayed, but it is an important one that relates in many fundamental ways to the overall health, well-being, and productivity of individuals, communities, and nations. Indeed, it may well be the case that variations in socioeconomic position account for a greater proportion of the disease experience in the population than any other cause.

Generally speaking, regardless of what organ system or disease we're speaking, how we measure socioeconomic position, or when and where the study is conducted, there is the inverse relationship between socioeconomic position and health shown in Figure 5. For the much smaller number of disease for which this is not true, survival is generally worse among those who are poorer.

#### ***A Few Historical Observations--***

Of course it has been known for a long time that for most diseases the poor do worse. For example, Daniel Defoe writing in 1722 in his *Journal of the Plague Years* pointed out that the "misery of that time lay upon the poor...."

It is not hard to find other historical examples. Figure 6, kindly reproduced from a paper by George Davey Smith and colleagues, shows gravestones in a 19<sup>th</sup> century graveyard in Glasgow. As you can see the markers vary in height, with socioeconomic position at death being, literally, marked by the height of one's gravestones. As it turns out, if one plots longevity, calculated from the date of birth and death on the gravestone, there is a monotonic relationship with height of the gravestones--the taller the marker the longer the life.

Another historic example comes from the survival statistics for passengers on the Titanic. As you can see in Figure 7, cabin class—strongly related to social class—was related to survival.

### ***Inequalities in Health Continue--***

I could spend the rest of my lecture showing you current examples of this relationship. In recent years there has been an explosion of interest in the topic of socioeconomic inequalities in health, and several hundred publications appear each month with some aspect of socioeconomic position as an important component (Figure 8). We have learned much from these studies and I will touch on only a few main points.

The relationship between socioeconomic position is still very noticeable. Figure 9 shows results from analyses of the mortality experience of a cohort of approximately one million US adults over the age of 25. It plots relative mortality experience as a function of seven levels of household income.

Similar results were seen in a cohort of over 300,000 men that were screened for the Multiple Risk Factor Intervention Trial. In this case the measure of socioeconomic position was based on the median income of the postal code in which they lived. What Figure 10 shows beautifully is the graded nature of the association—the excess risk associated with socioeconomic position is not found only among the poorest, but shows a graded relationship even at higher levels.

The association between socioeconomic position and health is not restricted to a particular age or stage of development. As you can see in Figure 11, rates of stunting in children (below the 5<sup>th</sup> percentile of height for weight) are strongly related to poverty status. Even in a country such as Sweden with exceptionally good birth outcomes, there are relationships between these outcomes and socioeconomic position (Figure 12).

Contrary to oft-stated views that socioeconomic factors are not very important in the elderly, these effects are found among older persons as well in a number of studies including a Canadian study of over one-half million men that examined post retirement survival as a function of pre-retirement income (Figure 13).

The effects of socioeconomic position on health are not restricted to a particular organ system or set of diseases. For example, Figure 14, taken from the recently published National Center for Health Statistics Chartbook on Socioeconomic Status and Health, shows death rates by education level in the United States for deaths from chronic diseases, injuries, and communicable diseases. The strong generic effect of socioeconomic position on many causes of death is shown in greater detail in results published by Davey Smith and colleagues from the MRFIT study (Figure 15). To make the point even further, Figure 16 shows the large number of conditions associated with lower levels of education in the US National Health Interview Study. Finally, Figure 17 shows that the impact of socioeconomic position is even felt using measures of

subclinical disease, in this case the measure being 4-year progression of carotid atherosclerosis.

The evidence also suggests that the association between socioeconomic position and health outcomes is modifiable, that it is not fixed in time or place. There appears to have been a widening mortality gap by social class and Figure 18 shows the results for England and Wales between 1951 and 1981. However, decreasing trends can also be seen in some cases. For example, there was a decreasing association between paternal education and risk of death in 5-14 year-old children in Finland between 1976 and 1990 (Figure 19).

### **UNDERSTANDING HEALTH INEQUALITIES: A MULTI-LEVEL RESEARCH AGENDA**

How should we approach understanding of the causes of inequalities in health and how to reduce them? Recognition of the multi-level determinants of socioeconomic inequalities in health is not without its problems. It would be much simpler if we could believe that only a single factor and a single or few biological pathways were responsible. However, as we are increasingly learning in other areas of science, complexity is the norm.

Still, it is possible to outline a research agenda for the study of inequalities in health that proceeds not down a single linear track, but rather by a set of overlapping approximations that attempt to acknowledge the complex multi-level determinants.

#### ***Biological Pathways--***

Consider first several aspects of our knowledge of the biological pathways that allow socioeconomic inequalities to influence individual health. To illustrate some of the findings I take examples from a study that we and colleagues at the University of Kuopio have been conducting in eastern Finland for over a decade. Here we see the strong relationship between total serum cholesterol and LDL cholesterol and income level, and we see a similar relationship between income and levels of resting systolic blood pressure, fasting serum glucose, and hemostatic pathways, in this case fibrinogen and tissue plasminogen activator (Figures 20-22)

For the most part, we find no single biological pathway that seems most importantly related to socioeconomic position, and this would be in line with the broad impact of socioeconomic position on health and disease. Perhaps there is a "low-socioeconomic position syndrome?" One possible approach to this lies in the concept of "allostatic load" introduced by McEwen & Stellar in 1993. It refers to a complex syndrome of metabolic, neuroendocrine, and immunologic dysfunction stemming from chronic exposure to excess demands in the face of inadequate resources. The concept of a syndrome, of course, implies that the "whole is greater than the sum of its parts," and this notion of new properties emerging from interactions between multiple systems is the hallmark of complexity theory.

Animal studies examining the effects of early experience and deprivation on later development are also of interest. These results are often used, somewhat metaphorically, to help explain some of the increased rates of health and developmental problems in poor children. The results of these studies suggest that early physical and social deprivation, as well as high levels of stress, result in modifications of the hypothalamic-pituitary-adrenal axis. For example, there are data showing that such deprivation results in alterations in the feedback circuits that modulate glucocorticoid and catecholamine responses to stress resulting in over-exposure to these metabolically costly substances, thereby presumably increasing the likelihood of later disease. Similarly, other studies have indicated the importance of early environmental and physical stimulation in the normal development of both sensory capacity and the ability to form emotional ties.

And there are the tragic naturalistic experiments such as the massive institutionalization of large numbers of Romanian infants that in some cases appeared to have resulted in alterations to the hypothalamic-pituitary-adrenal axis as well as developmental delays. These laboratory and unfortunate "natural" experiments establish that serious deprivation, fortunately rare even in families suffering the very worst of economic deprivation, can have an impact on health and development. But surely a complete understanding of the causes of these problems in the case of the Romanian infants, and how they could be prevented, must include an analysis of the political, social, and economic conditions that led to the children first being born and later being institutionalized.

Gene-environment interactions may also have a role in inequalities in health. For example, Figure 23 shows the extent of 4-year progression of carotid atherosclerosis in a population of men in eastern Finland, stratified by level of physical demands at work, and the propensity to respond to stress with a heightened hemodynamic response, a trait that seems to have a reasonably strong genetic loading. As you can see, there is a much faster progression of atherosclerosis in those who are exposed to both the demanding workplace and who are predisposed to heightened vascular responding. Presumably this reflects some heightened effect of vascular reactivity on atherosclerotic progression, possibly through increased potential for endothelial injury or other factors. Now, if we assume that this reactivity genotype is not differentially distributed by socioeconomic position, which is reasonable, but that exposure to physically demanding workplaces is, then we will observe a socioeconomic gradient in atherosclerosis partially reflecting gene-environment interactions. Note, however that what is driving this is the differential exposure to physically demanding jobs among those who are poorer, which in turn is probably a marker for other sources of stress, different community resources, and a range of other exposures that are differentially distributed by socioeconomic level. A multi-level, causal explanation of socioeconomic gradients in atherosclerotic disease will, thus, have to examine the social, community, and political arrangements that are responsible for these differential patterns of exposures.

In short, discovering a simple or complex pattern of biological responses related to higher or lower socioeconomic position cannot be the end of our causal story for we must ask why some individuals or groups of individuals are exposed to more or less of

whatever the toxic ingredients are. Presumably, the answers to such questions will lie in the study of the individual and upstream determinants of this exposure.

### ***Behavioral and Psychosocial Pathways--***

Similar analyses are called for when considering the behavioral and psychosocial pathways that are involved in inequalities in health. There is no question that there are strong links between socioeconomic position and both behavioral and psychosocial measures. For example from our studies in Finland you can see strong association between education level and pack-years of smoking, heavy consumption of alcohol, and being sedentary (Figure 24). Similarly consumption of vegetables, fruits and berries, dietary fat, and sodium are also all related to income level (Figure 25).

While it is well-recognized that behaviors such as smoking, physical activity and alcohol consumption are importantly associated with the risk of developing many diseases, there is also increasing evidence that psychosocial states are as well. For example, we have found accelerated progression of atherosclerosis associated with high levels of hopelessness and cynical hostility. Figure 26 shows both the association between socioeconomic position and hopelessness and the association between hopelessness and 4-year progression of intima-medial thickening of the carotid arteries.

Again, however, we must see the socioeconomic patterning of behavioral and psychosocial processes, and their role in inequalities in health, within a multi-level context. There is no obligate relationship between exposure to behavioral risk factors and socioeconomic level. As Figure 27 attempts to portray, over the years there has been an alteration of the socioeconomic gradient for smoking. Initially, tobacco was scarce and expensive, its use being more prevalent among the wealthy. With the invention of the cigarette machine, mass production of cigarettes became possible, the price was lowered and via mass marketing, cigarettes became a product of mass consumption. With a focus on the health effects of smoking reaching higher socioeconomic strata first, we see a complete reversal with smoking now more prevalent among those who are poorer in most developed countries. While in developing countries we see the same pattern repeating itself.

But understanding the socioeconomic distribution of smoking requires more than this historical discussion. Nicotine is a powerful psychoactive drug and we cannot ignore the extent to which it represents a form of self-medication for those who feel frustrated with their life chances, find themselves stuck in boring, repetitive, time-paced jobs, or who are overwhelmed by stress and multiple demands. In addition, the targeted marketing of cigarettes to people occupying different socioeconomic strata, differential access to information regarding health effects of smoking, to environments in which smoking is prohibited, and to smoking cessation services must all be considered. Thus, to some extent the socioeconomic distribution of smoking represents the socioeconomic distribution of working conditions and other aspects of people's lives.

Similar considerations apply to the socioeconomic distribution of psychosocial states such as hopelessness, depression, social isolation, or cynical hostility. Evidence suggests that these are not fixed characteristics, but are reactive to the social and economic environments in which people find themselves. For example, using data from a cohort that had been followed for 29 years we found that levels of depression, cynicism, and optimism all reflected economic trajectories over the last 29 years (Figure 28). All three increased in prevalence with the number of bouts of poverty. Similarly, in the same cohort the incidence of social isolation was increased among those who reported a job loss or financial problems (Figure 29). These results suggest that study of the everyday environments and experiences of people may lead to clues to the reasons for the socioeconomic patterning of psychosocial states.

In short, any explanation of socioeconomic inequalities in health that takes refuge in the differential distribution of behavioral or psychosocial states by socioeconomic position must take up the causal issue of why these states are more prevalent among those with lower status. To simply attribute the increased risk of cardiovascular death among the poor to higher rates of smoking or depression, for example, is to mistake an intermediate, mediating factor for a cause. Again, we are forced to develop a research agenda that includes upstream, as well as downstream, determinants.

### ***Communities and Neighborhoods--***

As the research literature on the socioeconomic position has been expanding, so has a related literature indicating that social and economic characteristics of the neighborhoods and communities in which people live are associated with risk of death, morbidity rates, and other outcomes. These two sets of findings fit together nicely because the neighborhoods and communities in which people live are likely to be one of the important contexts in which socioeconomic inequalities in health are generated. An example of these studies is one we completed a number of years ago. Figure 30 shows the 9-year survival experience of community residents who lived in or outside of areas of high levels of poverty and social disadvantage. It is not surprising that those who lived outside of the poverty area were healthier. After all they were richer, better educated, more likely to be employed, had better medical care, and differed in many other ways from those who lived in the poverty area. However when we statistically took all of these differences into account, those who lived in the poverty area still has almost a 50% increased risk of death (Figure 31). A replication of this study at the national level confirmed our findings, even when there was adjustment for total cholesterol, systolic blood pressure, and a number of other factors, and major cause of death were considered separately. There are now 20-30 studies that show these independent effects of area of residence in mortality, morbidity, and chronic disease risk factors; some of them using the most advanced multi-level analytic techniques.

It seems likely that these effects of place are important in understanding socioeconomic inequalities in health. But, we know little about the ways in which where one lives influences one's health and there is an important need for research in this area. For example, are the influences through differences in material standards of living and

institutional resources, differences in exposure to successful or unsuccessful role models, differences in levels of environmental contaminants, stress, or any of many other possibilities--or all of them?

From a multilevel perspective, it makes little sense not to look upstream. The levels of resources and strains within a community often represent factors operating outside of that community. For example, closure of a major source of jobs within a community will send economic and social ripples throughout the community, and the resultant social and economic characteristics of that community, and of those who live in it, must be seen as a consequence of those decisions. Again, we see that an understanding of community factors that generate inequalities in health needs to be grounded in an appreciation of the upstream factors that create the community conditions.

### *Social and Economic Policy--*

On the one hand, there can be little doubt that social and economic policies through their impact on material conditions and resources at the individual and community level, access to basic necessities, availability of supportive institutional resources, and many other ways, must have a substantial impact on inequalities in health. On the other hand, we have precious little evidence of this impact. This is largely because health and inequalities in health have generally not been part of the evaluation agenda for these programs. Yet, changes in economic and social policies may have substantial consequences. There is a major need for multi-level research on the impact of such policies on health and health inequalities.

We do have some indirect evidence. In the United States, between 1980 and 1990 there were increases in income inequality in all states except one. That is, the gaps between the rich and poor got larger. Of course, mortality rates improved in all states during that period, but the rate of improvement varied between states. When we considered reductions in mortality rates over that period, the smallest reductions were in those states that had the largest increases in the income gap between the rich and the poor.

Some experimental evidence suggests that change in material circumstances of the poor may have substantial and far-reaching effects. For example, the Gautreaux study in Chicago randomly allocated, from a waiting list, poor families living in areas of concentrated poverty to better housing in suburban areas (Figure 32). There were substantial effects on the mothers and their children. We do not know if these educational, economic, and social effects translated into better health, but it seems likely that they did.

While there is a tremendous need to better evaluate the impact of social and economic policies on health and inequalities in health, there are also numerous methodological problems. My own view is that cross-national studies are not likely to be useful and that we should rely more on observational and quasi-experimental studies within individual countries.



But even if we are able to accomplish such goals, there will still be a need to investigate in detail the mechanisms at the community, family, and individual level that provide the links between policy and the body.

You see, the imperative to carry out multi-level investigations of the genesis of inequalities in health applies to those studying upstream determinants as well it does to those studying the downstream side.

### **WHAT CAN WE DO TO REDUCE INEQUALITIES IN HEALTH?**

I have presented a research agenda that will seem to some critically important and to others overly ambitious and, perhaps, foolish. I believe the truth lies somewhere in between.

My basic task has been to convince you that inequalities in health are an important object of study, that they are best studied from a multi-level and multi-disciplinary perspective, and we should resist overly simplistic attempts at reductionism. Complex problems often require complex approaches.

But, for a topic of such fundamental importance, I would be remiss if I did not suggest some ways in which we might be able to reduce inequalities in health. I believe there is reason to support the following five steps:

#### ***Use what we know--***

The recent report of the British Independent Inquiry into Inequalities in Health Committee, chaired by Sir Donald Acheson, recommended a sweeping set of steps be taken in order to reduce inequalities in health. Some of the recommendations followed a very simple model—if there is a disease determinant that is differentially distributed by social class, and if there is an intervention that can change this, we should do it. Thus, for example, they recommended increasing school food programs, fluoridating water, and providing inexpensive nicotine patches as a way of leveling inequalities in health.

There can be no arguing with the logic of these recommendations. The reduction of inequalities in exposure to potentially health damaging substances or provision of health enhancing substances ought to reduce inequalities in health. Thus we should use the knowledge we already have at hand. The only limitation of this approach is that there may be many as yet untested interventions that we may still need to move forward on.

#### ***Help the Most Vulnerable--***

There appears to be an almost world-wide epidemic of reductions in social benefits, brought on more by the tidal wave of globalization than by some global change

in compassion. We see an increasing rhetoric that the poor somehow have themselves to blame, are free-loaders who are unwilling to work, and represent both a culture in poverty as well as a culture of poverty. As an example of how this is playing out in the United States, Figure 33 shows the increasing gap between the minimum income necessary for a poor family in the State of Illinois and the actual welfare payments.

There can be no underestimating the pervasive and long-acting effects of systemic poverty on health and development. In addition to increasing health burdens, such poverty creates a drain of talent and intellect on a society as well as the potential for social problems that effect all. Thus, health professionals need to help develop assessment techniques that will allow us to assay the health effects of policies that impoverish many, and to serve as lobbyists for the disenfranchised—a role that lies at the foundations of public health.

### ***Invest in Children--***

Poor children are beset with a variety of material, environment, and social burdens (Figure 34). I believe that this amounts to a policy of what can be called “compound disinterest (Figure 35).” Thus, the provision of the basic necessities for healthy human growth and development, in addition to being a basic human right, lays the foundation for the reduction of inequalities in health. We must invest in our future, for the child is no less the father (or mother) of the man (or woman) than in Shakespeare’s day (Figure 36).

### ***Build Communities--***

In many areas of the world we see increasing geographic stratification, with larger and larger gaps between wealthy and poor residential areas. At its worst we find areas of concentrated poverty that are bereft of human and social resources, areas where there are multiple generations of family members who have not worked, and who live in areas that have no jobs. As the literature grows documenting the health effects of such living conditions we need to take seriously public health interventions that are more oriented toward community development than they are to screening or health education. We need to train public health scientists who are able to both assess the health of a community as well as to see the links between a community’s health and development, zoning, social services, and other public activities.

### ***Decrease Income Inequality--***

World wide, the last two decades have generally seen an increase in the extent of income inequality. There is an increasing consensus that the extent of income inequality, the gap between the rich and the poor in communities, has an impact on the physical, social, and mental health of its residents as well as the health of the community as a whole. For example, in one study we showed that the age-adjusted mortality rates of states in the US was strongly related to the extent of income inequality within each state, here measured by the proportion of total state household income received by the least

well-off 50% of the population (Figure 37). This effect was independent of the average level of income in each state. What's more, increased income inequality was associated with a general pattern of less investment in human and social capital.

The health effects of low income and high income inequality can be enormous. (Figure 38). In our analyses of US metropolitan areas, this effect was equivalent in size to the combined mortality burden from lung cancer, diabetes, motor vehicle crashes, HIV disease, suicide, and homicide in 1995.

From a policy perspective we do not know the best way to reduce income inequality, nor do we know if such reduction will improve health—although the evidence suggests that it will. Some preliminary results shown in Figure 39 present an interesting perspective on the issue. Shown are rates of infant mortality in US states and Canadian provinces as a function of the same measure of income inequality. Canada and the US share many common features, however there are major differences in taxation, entitlement and benefit programs that result in substantially lower levels of income inequality in Canada. This in turn seems to be associated with substantial reductions in infant mortality.

## CONCLUSIONS

Social inequalities in health are pervasive, and they represent a major drain on the health and productivity of most societies. They are the proper object of scientific enquiry and present many methodologic and conceptual challenges. The evidence suggests that a broad, multi-level perspective is required in order to understand the mechanisms by which inequalities in health are generated and how they can be reduced.

Furthermore, considerable evidence points to the need to consider the upstream determinants of social inequalities if we are to reduce them. We cannot hope to significantly reduce the burden of disease in societies unless we grapple with these determinants. Should this be seen as outside the boundaries of the public and health sciences I would simply point out this insight lies at the very foundations of the science and practice of Public Health, and that little evidence has accumulated in the last century and a half to suggest otherwise.