

D. HEALTH AND MORTALITY IN DEVELOPED COUNTRIES

Shiro Horiuchi provided a general framework for the understanding of the processes leading to significant declines of mortality over the history of humanity. Five epidemiological transitions were identified, three that characterized past experience and two that were still to take place. Each transition was associated with a change in the major causes of death. The first occurred when external injuries gave way to infectious and parasitic diseases as the most important causes of death. Horiuchi indicated that such transition was associated with the sedentarization of the human population which, by increasing population concentration and reducing the dependence on hunting reduced the likelihood of injuries and favoured the transmission of infections. The second transition was more recent, having occurred mostly during the nineteenth and twentieth centuries, and consisted of the decline of infectious and parasitic diseases as causes of death and the increase of degenerative disease. The third transition involved the decline of cardiovascular disease as a cause of death and was the one experienced since the 1970s by developed market-economy countries. The next transitions expected would involve, respectively, the reduction of cancer as a cause of death and the slowing of senescence. The very recent reductions in mortality rates due to cancer recorded in some developed countries (e.g., the United States) seemed to indicate that the fourth transition might be starting.

Horiuchi noted that such a framework did not imply that there had necessarily been a continuous and progressive reduction of mortality through human history. Reversals were possible and had occurred. Thus, the concentration of population in rapidly growing cities caused by the industrial revolution led to higher risks of contracting an infectious disease and, consequently, to higher mortality. More recently, the high prevalence of smoking and excessive alcohol intake combined with a high-calorie, high-fat diet and sedentary lifestyle, especially among the inhabitants of countries with economies in transition, had not only prevented the reduction of mortality due

to cardiovascular disease but had even led to increasing mortality caused by cancer and injuries. Lastly, the emergence of new infectious diseases, such as HIV/AIDS, or the re-emergence of well-known ones also threatened to reverse the transitions already experienced by some populations.

In developed market-economy countries, the number of persons surviving to very advanced ages had risen markedly. Among the oldest-old (persons over age 80 or 85), the proportion of deaths due to cardiovascular disease and cancer declined with age whereas the proportion of deaths due to senescence, that is, to the deterioration of normal bodily functions and especially of the immune system, increased. Thus, whereas middle-aged and older individuals tended to die of cardiovascular disease or cancer, the oldest-old were more likely to succumb to influenza, acute bronchitis, pneumonia, acute digestive disorders or congestive heart failure.

In presenting the paper by Manton, Stallard and Corder, Larry Corder focused on the problem of establishing the limits of longevity. Reviewing the different approaches that had been suggested to establish such limits, Corder noted that the distinction made between endogenous (i.e., genetical) and exogenous (i.e., environmental) factors as determinants of the length of life was not useful to establish the possible limits of longevity because recent biomedical research had shown that the interaction of both types of factors was necessary to prolong life. The study of the mechanisms of cell growth and the preservation of its functions had shown that, because of the time lag in the response of complex systems to environmental stresses, such response usually involved an excess expenditure of energy to counterbalance the anticipated change in the environment during the lag between perception and response. Such augmented response not only increased the probability of survival of the organism but also its ability to meet, over the long run, greater environmental stress. That is, the organism's "fitness" was enhanced. In the case of human populations, such mechanisms might be at the root of the observation that the rate of loss of certain types of biological

functions, such as cardiovascular function or the ability to improve voluntary muscle function through training, was lower in elderly persons with no manifest chronic diseases that previously observed.

Mention was also made of experiments with mice showing that restriction of caloric intake increased life span. The most frequently cited explanation for this finding was considered to be that caloric restriction reduced oxidative stress. However, in human populations, the epidemiological evidence relating caloric intake with life span did not show consistently the expected inverse relationship.

Consideration of two basic mechanisms involved in the maintenance of cellular function when subject to stress, heat shock proteins and drug metabolizing enzymes such as the P450 group, indicated that under certain circumstances exogenous factors could mimic endogenous cell regulators, so that both endogenous and exogenous chemicals could affect the genetic regulation of cell function. It was therefore incorrect to assume that a person's genetic mechanisms were fixed and not alterable by external intervention. Similarly, the immune system could be altered by exposure to external factors and there was growing evidence about the fact that viral or bacterial infections could be the underlying cause of certain chronic diseases.

In view of the above it was concluded that, in order to adapt successfully to the external environment, exposure to small stresses early in life was necessary to ensure that appropriate cellular defenses developed. Because of the complexity of the systems involved, the risk of death from environmental challenges would have to act over various dimensions and, since the effects of past exposure to different risks would be embedded in the individual, that individual's state at time t would depend on his state at time $t-1$. These considerations led to a model of human aging expressed in terms of a J -dimensional auto-regressive stochastic process. Such a model reflected the conclusion that, because of the complexity of the human body, the limits of longevity could not be established deterministically but were rather the result of stochastic processes. As more

persons survived to more advanced ages, the likelihood that an individual would live more than anyone else before increased stochastically.

Tapani Valkonen spoke next about the widening mortality differentials by socio-economic status in developed countries. He reviewed the various methodological problems faced in measuring those differentials adequately, particularly because the variables used to determine socio-economic status might change over time and be correlated to health status (e.g., persons who were ill or disabled were more likely to have lower incomes or to be out of the labour force than persons who were fit) and because the traditional data sources for deaths by cause only recorded a few indicators of socio-economic status. Furthermore, there was often a lack of consistency in the recording of socio-economic status between the vital registration system used to obtain the numerators of mortality rates and the census used to obtain the denominators. In the Nordic countries the last problem was avoided by linking the death registration system to the population register and thus ensuring the consistency of both.

Focusing on mortality differentials by occupation, which had the disadvantage of leaving out those who did not work, Valkonen reviewed their trends for a number of developed countries. In Denmark, England and Wales, Finland, Norway and Sweden the mortality differentials between manual and non-manual male workers tended to increase between the late 1960s or early 1970s and the 1980s, mainly because mortality due to cardiovascular disease declined faster among non-manual workers than among manual workers. In Finland, a reduction of those differentials was recorded between the late 1980s and the early 1990s, as manual workers experienced a more rapid reduction of mortality due to cardiovascular disease than non-manual workers. In some countries, changes in the relative impact of other causes of death, such as those related to alcohol abuse (Finland) or cigarette smoking (Norway), were also responsible for the trends in the observed differentials, with men in the lower-status occupational groups showing higher mortality

caused by the adoption of such high-risk behaviours.

Reasonably reliable data on trends in mortality differentials by socio-economic status for groups other than working-age men were said to be limited. In the cases of England and Wales and Finland, mortality differentials by socio-economic status had increased significantly since the 1970s for both men and women and it seemed quite plausible that diverging trends in mortality due to cardiovascular disease between the higher and lower socio-economic groups were at the root of such increases for both sexes and at all adult ages. Since WHO had established as an important goal the reduction of socio-economic differentials in mortality, it seemed pertinent to underscore the need to understand better the factors and processes leading to a widening of the differentials so that adequate policy interventions could be devised.

Douglas Ewbank considered the effects of the genetic make-up of populations on mortality by cause of death by focusing specifically on the fact that certain commonly occurring alleles of the APOE gene had been associated with a higher incidence of ischaemic heart disease (IHD) and Alzheimer's disease. Using information on the relative frequency of the different alleles of APOE in different populations, Ewbank proposed a method for estimating the "excess" mortality due to ischaemic heart disease because of the frequency of the high-risk alleles of APOE in one population relative to that of a standard population. Such estimates showed that substantial proportions of the difference in mortality due to ischaemic heart disease in different populations could be explained by differences in the frequencies of the $\epsilon 4/3$ and $\epsilon 4/4$ alleles of the APOE gene between the two populations.

The estimates of excess mortality were made only for developed countries, where populations with high frequencies of the key alleles were concentrated in Northern Europe (Denmark, Finland and Sweden) and in the United States (among blacks) and where high-fat diets that were known to increase the risk of ischaemic heart disease were common. In

developing countries, the frequency of $\epsilon 3/4$ and $\epsilon 4/4$ was known to be particularly high in Africa (e.g., Nigeria) and in Papua New Guinea, where mortality due to ischaemic heart disease and Alzheimer's disease was low. A possible explanation for this outcome was that low-fat diets helped prevent the detrimental effects of the $\epsilon 4/3$ and $\epsilon 4/4$ alleles. In that case, adoption of a high-fat diet by the populations of Africa and Papua New Guinea would likely result in high mortality due to ischaemic heart disease. In contrast, Chinese populations, which were characterized by low frequencies of $\epsilon 4/3$ and $\epsilon 4/4$ alleles, might adopt a high-fat diet with few detrimental effects in terms of increased incidence of ischaemic heart disease or Alzheimer's disease. An important implication of these observations was that, in studying the relation between diet and morbidity or mortality across populations, it was necessary to control for variations in their genetic make-up, otherwise misleading associations might result.

The discussion noted that, given the major advances made in reducing mortality in developed market-economy countries, it was pertinent to ask what were the limits of human life span and whether they could be realized at the population level. Current biomedical research certainly raised interesting prospects about the possibility of increasing longevity, but the papers presented did not offer clear guidelines for action. For instance, it was not clear whether genetic factors played a greater role in survival up to age 65 or beyond. The model proposed by Manton, Stallard and Corder seemed to say little about what the limits of a population's average life expectancy could actually be and the relative risks of dying because of specific causes that were derived from the model did not seem to have immediate relevance for the formulation of health interventions. Besides, it was not clear whether the model was meant to be descriptive or predictive. Estimation of the parameters it required seemed less than straightforward given the current state of mortality and health statistics.

There was considerable discussion about the framework proposed by Horiuchi to analyse the various epidemiological transitions. His

attempt to relate the different transitions to a specific type of society was judged to be too simplistic and possibly misleading. It was noted that the factors determining the transition from one set of causes of death to another varied from country to country, and that the transition from high to lower mortality often occurred in different groups of society at different times and depended on various factors that were subject to greater or lesser control by the individual. It was suggested that a more complex type of framework was necessary, one that allowed for feedback mechanisms, advances and reversals. Any type of framework should recognize the separate relevance of factors such as: control over the environment and sanitation; availability of health services and access to them; the type of political and social organization; the impact of nutrition. Several participants underscored the importance of the latter in understanding why certain transitions had happened. It was mentioned, for instance, that measles killed very few children in developed countries while it was a major cause of death in developing countries, mainly because of the malnourished status of children in the latter. The reduction of mortality caused by infectious diseases in today's developed countries began when the food supply could be assured and the prevalence of malnutrition declined. Despite these observations, it was considered that Horiuchi's framework provided a useful "cognitive map" that put in stark focus the major turning points for humanity in terms of health and mortality and that highlighted the fact that significant improvements were occurring at an ever faster pace.

Noting the generally optimistic tone of the papers regarding the expectation that mortality would continue to decline in the future, a number of participants mentioned possible causes of concern, including the re-emergence of certain infectious diseases that were either resistant to available treatments or that could only be controlled by a concerted public health effort that had been dismantled and might not be undertaken rapidly enough; the emergence of new infectious diseases; the rise of mortality due to violence, outright conflict or war; the potentially negative effects of

rising pollution on health; and reversals in the decline of high-risk behaviours, such as smoking, drug addiction or excessive alcohol consumption.

Considerable attention was focused on the discussion of social inequality and its implications for health and mortality. Although it was recognized that striving to eliminate such inequality was laudable, concerns were expressed about its feasibility, especially in today's developed market-economy countries where individualism was highly valued. Because of the stress on individualism, an increasing inter-personal variation in life choices and lifestyles was to be expected, some of which might involve adherence to high-risk behaviours having detrimental impacts on health. Furthermore, it was likely that such variability would result in the persistence of differences according to status. It was noted, however, that status did not necessarily depend on income. In the former USSR, for instance, those with lower educational attainment had higher mortality than those with higher educational attainment although the incomes of both groups were very similar. Access to health services also seemed not to be the major determinant of mortality differentials by socio-economic status in developed countries, since the evidence suggested that persons with lower socio-economic status made more use of health services than those with higher status. Furthermore, in most of the market-economy countries of Europe, socialized medicine provided similar access to health care to all groups. The likely causes of socio-economic differentials in mortality appeared to lie instead on behavioural and social factors. The adoption of healthier lifestyles and diets or the maintenance of more stable primary relations among those having higher socio-economic status probably made a significant contribution to lowering their risks of dying. Being single, widowed or divorced, for instance, was associated with higher mortality rates among both men and women, but especially among men. Access to social resources was likely to be a major determinant of a healthy life.

Lastly, with regard to the importance of genetic factors, the discussion emphasized the

many questions that still remained regarding their relevance. Furthermore, it was underscored that the genetic composition of populations was inferred from the study of relatively small groups that were not necessarily representative of whole populations. Thus, the assertion that certain alleles of the APOE gene were more common among African populations than among those of Chinese origin was based on a number of studies of small populations that might not appropriately reflect the full variability within either of those groups. Nevertheless, the evidence suggested that significant differences existed between population groups and that they should not be ignored when doing epidemiological analyses regarding the possible factors leading to the high prevalence of certain diseases.