Capes, Bays and the Double Helix: Why Geography has More to Offer in the Prevention of Chronic Degenerative Diseases than Genetics

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Introduction

Thirteen percent of English geneticists, 50 percent from Eastern and Southern Europe and all of those polled from India and China accepted that "an important goal of genetic counselling is to reduce the number of deleterious genes in the population".[1] While few people would deny that potential parents, carrying genes for major genetic disorders such as Tay Sachs and Huntington's disease, should carefully consider the implications of reproduction, there is a new eugenics which aims to free humanity from genetic aberrations thought to be responsible for a wide range of degenerative diseases.[2] Such beliefs imply that the major causal variables in chronic disorders/diseases, such as esophageal cancer, Alzheimer's disease and multiple sclerosis, are genetic and that the benefits of deleting them from the human gene pool would greatly outweigh any costs. This article will show that both of these assumptions are incorrect, a fact that has significant implications for the prevention and treatment of such diseases.

Why Chronic Degeneration Diseases Cannot be Primarily Genetic

If chronic degenerative diseases develop largely as a result of genetic inheritance, three corollaries follow.[3] Firstly, the genetic aberrations responsible for such common diseases must be widely distributed throughout the human population. If this is the case, each degenerative disease ought to display a relatively uniform but random pattern of age-adjusted mortality. Incidence and prevalence, in contrast, would vary with global differences in age structure and life expectancy. Secondly, genetic diseases are constrained by the slow pace of human reproduction. There can be no rapid changes in their incidence or mortality rates without large scale immigration and emigration and even then, such fluctuations would be due to changes in age structure of the population. There can be no epidemics or pandemics of genetic diseases. Thirdly, if a disease is preeminently caused by a widely dispersed genetic aberration, there can be no significant change in its incidence or mortality because of migration since the dominant risk factor would be internal.

These three corollaries make it possible to examine the widely held belief that major risk factors in chronic degenerative diseases are genetic. This objective can be achieved by comparing the existent spatial and temporal patterns of incidence and mortality with those that ought to occur if a particular disease were of genetic origin. It follows, of course, that the more closely the global pattern of the disease matches that implied by the genetic hypothesis, the greater the likelihood that it is the correct one. Conversely, the reverse holds true. If the actual and implied geographies are very different, it is impossible for the key causal variable of the disease/disorder to be genetic. While available space limits the following discussion to five chronic diseases/disorders, namely osteoporosis, Alzheimer's disease, esophageal cancer, multiple sclerosis and schizophrenia, it would have been a simple matter to apply the same principles, with similar results, to numerous other chronic degenerative illness.

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Osteoporosis

The evidence is very clear that there are strongly developed international, regional and local differences in the spatial distribution of osteoporosis. To illustrate, individuals with osteoporosis frequently suffer hip fractures and the incidence of such broken bones is a strong indicator of the prevalence of osteoporosis. Globally, age-adjusted annual hip fracture rates are highest in the USA where they are 10.16 per 10,000 for females and 5.05 in males.[4,5] Fractures are roughly half as common in Holland and Finland but drop to only 0.53 for women and 0.56 per 10,000 for men in the South African Bantu. Clearly, therefore, there is no relatively uniform, random global spatial pattern for osteoporosis.

The ranchers of Texas are well aware that migration can alter bone strength and density. Cattle raised on the high plains of Deaf Smith County are larger and heavier than those from elsewhere in Texas.[6] Indeed, fully grown 6-year old cattle moved onto pasture in the high plains will gain a minimum of 250 pounds as their bones increase in size and weight. The skeletons of residents of Deaf Smith County are similarly dense and highly mineralized. The elderly there rarely show signs of demineralization and osteomalacia which are so common in other mature Texans. Cortices of their long bones are approximately one-half greater in thickness than those seen in Dallas County. In Deaf Smith County, the bones of residents 80 years or older only break as the result of severe trauma and then heal rapidly without pins or supports. In contrast, bones of the elderly of Dallas County often break as the result of demineralization and then heal only with great difficulty. It is obvious from these observations that, in cattle, migration can greatly affect bone formation and that the environmental factors that promote it also affect humans in the same manner.

Originally most common in industrialized countries, osteoporosis has become pandemic. To illustrate, the incidence of hip fractures in Malmo, Sweden has been studied since 1924.[7] Data from the 1950s to the 1980s showed an almost exponential increase in hip fracture incidence but fortunately this trend stopped in the early 1990s. A similar increase has been recorded in Britain where about 10,000 men with osteoporosis fracture their spines each year and 12,000 break a hip. This is a six-fold increase since the 1950s.[8] Similarly, in Texas, mortality from hip fractures in both genders and in whites and blacks increased through the 1990s.[9] This rise in osteoporosis is not limited to the Developed World, with its incidence rising rapidly, for example, in Pakistan.[10]

It is apparent from this brief summary that osteoporosis does not have a random, relatively uniform spatial pattern, bone size and mineralization can be altered by migration and osteoporosis is generally increasing much faster than the population is aging. That is, it is a chronic disease that is largely controlled by environmental and lifestyle variables not genetic aberrations.

Alzheimer's Disease

Multi-infarct dementia is common in Japan but Alzheimer's disease incidence seems to be much lower than in Europe.[11] This is unlikely to be due to racial variables because, in China, vascular dementia predominates in Beijing and Alzheimer's disease in Shanghai.[12] At the regional scale, spatial variations in the incidence and prevalence of Alzheimer's disease are far greater. Two hospital-based studies[13] involving brain autopsies of every patient dying with dementia in Maracaibo, Venezuela, a city with a population of some 650,000, discovered only one Alzheimer's case in over a decade. In contrast, in the worst affected Norwegian municipalities, during the period 1974-1983, the median annual age-adjusted Alzheimer's disease mortality rates were between 44-55 per 100,000 for males and 87-109 per 100,000

for females.[14] These figures suggest that Alzheimer's disease is at least 1000 times more common in the municipalities along the south and southeastern coasts of Norway than in Maracaibo, Venezuela. Even within Norway itself, Alzheimer's mortality was higher by a factor of 15 in some municipalities than in others, during this period.

Studies of temporal change in dementia incidence are expensive, complex and involve extensive fieldwork. As a result, they are rare. The best probably comes from the Swedish island of Lundy[15] where the entire population was medically examined several times between 1947 and 1972. Interestingly, all levels of dementia were found to have decreased by the end of the period. This seems unusual since more recent studies conducted in the United States,[16] England,[17] Australia,[18]Canada,[19] and Norway[20] all suggest that Alzheimer's disease is becoming increasingly common.

Two recent research projects have demonstrated that migration greatly influences the prevalence rates of dementia. Graves and coworkers[21] established that, in the Japanese Americans of King County, Washington State, dementia was more common than in Japan. In addition, the distribution of subtypes of dementia in Japanese Americans was found to be much more like that of North American and European Caucasians than of Japanese residing in their homeland. As a result, Alzheimer's disease was more common and vascular dementia less prevalent in Japanese Americans than might have been expected. A similar study conducted in Indianapolis and Ibadan, Nigeria by Hendrie and coworkers[22] established that Alzheimer's disease was more than twice as common in African Americans than in Nigerian Yoruba of the same gender and age ranges.

Globally and regionally Alzheimer's disease does not have a random, relatively uniform spatial pattern. It appears to be increasing faster than the population is aging and its incidence and prevalence is greatly affected by migration. In short, it shows none of the expected geographical characteristics of a primarily genetic disease.

Esophageal Cancer

Esophageal cancer is almost invariably more prevalent in males than females. Nevertheless, the differences in the spatial patterns of this disease seen in men repeat themselves, at lower levels of incidence and mortality, in women. Globally, the most striking aspect of the distribution pattern of esophageal cancer is the Central Asian High Incidence Belt.[23] This consists of parts of northern China and regions of extremely elevated mortality in Kazakhstan, Uzbekistan and Turkmenistan. Also included in this belt are northeastern Iran and northern Afghanistan. To illustrate, the world's highest cumulative esophageal cancer rate, 20 percent, occurs in males living in northeastern Iran. This disease is 300 times more common in this region of Iran than it is in Nigeria, which has the planet's lowest incidence rate for esophageal cancer.[24]

As Day[23] has pointed out, esophageal cancer has even more striking patterns of local spatial variation. In some small regions, for example in China, this disease achieves incidence rates unknown for any other form of cancer, yet within a hundred miles, esophageal cancer can be extremely rare.[25] Indeed, Ghadirian and coworkers[26] have estimated that at the regional level there is roughly a 500-fold difference in incidence rates. Such variations in Chinese incidence over short distances suggest the key causal variables are environmental, not lifestyle or genetic.

As lifestyles and environments alter, so too do levels of esophageal cancer. Consequently, although on a global scale, the majority of cases still occur amongst the Chinese, rates in China appear to be in decline.[27] However in the United States, esophageal adrenocarcinoma is increasing rapidly, especially amongst

white males.[28] Simultaneously, the US incidence of squamous cell carcinoma of the esophagus is falling.[29]

Esophageal cancer is still very common in some regions of China, but migration from these areas appears to significantly reduce the incidence of this disease amongst overseas Chinese.[27] This is also true of those of Japanese origin. To illustrate, the annual esophageal cancer incidence per million males, for the period 1968-1972, was 150 in Japan and 46 in Japanese living in Hawaii.[24] Conversely, it has been shown that changing the mineral content of the drinking water in areas with elevated esophageal cancer mortality can greatly reduce death rates. In Xingtai county, Hebei province, for example, jiangshi were used to line water wells. Within ten years of the addition of these calcareous concretions to wells, the average annual esophageal cancer mortality in those drinking the water fell from 275.28 per 100,000 to 54.28 per 100,000, more than a five-fold decrease.[30] No similar decline occurred in neighbouring control communities.

Clearly, esophageal cancer does not have a random, relatively uniform, spatial pattern. It can vary rapidly in incidence and mortality over time and is greatly influenced by both migration and environmental change. That is, it displays none of the geographical characteristics one would expect if its causes were predominantly genetic.

Multiple Sclerosis

There are three global zones of multiple sclerosis. It is most common in a belt which includes northern and central Europe into the former USSR, southern Canada and the northern United States. A similar high risk belt occurs in the Southern Hemisphere encompassing New Zealand and south-eastern Australia. In all these areas, prevalence rates are usually 30, or higher, per 100,000 inhabitants.[31] Such regions of elevated prevalence are adjacent to a second more moderate zone with multiple sclerosis rates of 5 to 29 per 100,000. Rates here are typically of the order of 10 to 20 per 100,000. This moderate zone includes the southern United States, south-western Norway and northern Sweden, the entire Mediterranean basin from Spain to Israel and that part of the former USSR that stretches from the Urals into Siberia and the Ukraine. In the Southern Hemisphere, this intermediate risk zone includes the whites in South Africa and perhaps central South America and Australia excluding the south-east. Elsewhere, multiple sclerosis prevalence rates appear to be low, that is under 5 per 100,000 population. Definitely included in this third belt of minimum risk are Japan, Korea, Africa and the Caribbean and Mexico. At the international level, therefore, multiple sclerosis prevalence appears to vary by at least a factor of 10.

In addition to these major global zones, there is strong regional variation. In the Orkney and Shetland Islands of Scotland, prevalence rates are 152 per 100,000, while in Trail, British Columbia, Canada rates as high as 200 per 100,000 have been recorded.[32] Other clusters include that of Key West[33] and the Zoroastrian, largely Parsi communities in the adjacent Indian communities of Bombay and Poona.[34] Such clustering occurs in many other countries, including Norway, Denmark and Switzerland, where there is a six-fold difference in risk between certain areas. These clusters appear fairly permanent because resurveys, a generation apart, display strong positive correlations between early and later multiple sclerosis prevalence rates.[31]

Migration also has an impact on the probability of developing this disorder. The north of the United States lies in the high prevalence zone, while the south is located in the zone of moderate multiple sclerosis prevalence. This disorder appears to be acquired in childhood or adolescence, long before the clinical onset of symptoms. However, migration from north to south, or visa

versa, during childhood or adolescence clearly reduces or increases the probability of the risk of subsequently developing multiple sclerosis, depending on the direction of migration. Similar migratory effects have been established in other countries.[31]

The global multiple sclerosis prevalence zones are not static and there is considerable evidence of ongoing changes. Lai and colleagues,[35] for example, analysed multiple sclerosis mortality statistics from 35 countries for the period 1965 to 1984. They concluded that the disorder had declined steadily in North America and most of Western Europe, as well as in countries with a Western culture, but had remained stable or increased in Eastern and Northern Europe. Incidence has also increased in many Mediterranean countries, with prevalence rising to 69 per 100,000 in Sardinia.[36] The disorder also appears to be becoming increasingly common in Kenya[37] and Saudi Arabia.[38]

As with the other three chronic degenerative diseases previously discussed, multiple sclerosis, therefore, does not have a random, relatively uniform spatial distribution. It can vary temporarily and is greatly influenced by migration. As a result, it is impossible that its major causal variable is genetic.

Schizophrenia

Schizophrenia is still quite uncommon in many parts of the Developing World but as industrialization occurs there is often a sharp accompanying increase in the illness.[39] Even so, prevalence rates still display at least an eight-fold difference among industrial nations. The highest such rates occur in Ireland, Scandinavia (especially parts of northern Sweden) and in Eastern Europe (particularly Croatia). In parts of Western Ireland, 4 out of 100 inhabitants will be afflicted during their lifetimes. Intermediate prevalence rates, 1 out of 100, can be found in England, Germany, Japan and the United States. In contrast, in the Developing World, for example Ghana, the prevalence rates are much lower, estimated at 4 per 1000,[39] roughly one-tenth of that found in Ireland. Within countries regional variations also occur. In the United States, for example, schizophrenia is traditionally almost twice as common in states where soils are selenium deficient than in those where this mineral is elevated.[40,41]

The impact of migration on the prevalence of schizophrenia is less obvious, although there is evidence that schizophrenia is more common amongst the Irish in North America than in other ethnic groups.[42] Nevertheless, schizophrenia occurs more often amongst migrants to urban areas[40] and in those eating Western diets.[43]

The incidence and prevalence of schizophrenia has not been static. As Torrey and Miller[42] point out in the Invisible Plague: The Rise of Mental Illness from 1750 to the Present the baseline rate of insanity in human history appears to have been approximately one case for every 2,000 members of society. Since the Industrial Revolution the prevalence of insanity, largely schizophrenia, has been rising rapidly. In England, Ireland, Canada and the United States, schizophrenia as a rate per population, increased by at least sevenfold between the mid-eighteenth and the mid-twentieth centuries. In Ireland the rise was even greater. These authors argue that such dramatic increases in schizophrenia rates are the strongest evidence against the root cause of this disorder being primarily genetic.[42] This viewpoint seems to be supported by the higher rates seen in the industrialized world, especially in cities.

Implications for Prevention and Treatment

The preceding brief discussions of osteoporosis, Alzheimer's disease, esophageal cancer, multiple sclerosis and schizophrenia clearly indicate that none of these diseases/disorders can have a predominantly genetic cause. This is not the result of careful selection on my part. In the last twenty years, I have studied the spatial and tem-

poral patterns of 74 diseases, 90 percent of which were chronic. During this time I have not found one chronic disease that meets the three corollaries that would suggest it to be primarily of genetic origin. It would have been just as easy, for example, to demonstrate that the dominant causal variables in, Parkinson's disease, amyotrophic lateral sclerosis, [44] stroke, cardiovascular disease, diabetes mellitus,[25] and numerous cancers[45] are not primarily genetic.

Bishop and Waldholz[46] in their book Genome, point out that "aberrant genes do not, in and of themselves, cause disease. By and large their impact on an individual's health is minimal until the person is plunged into a harmful environment." What then is a harmful environment? It is clear from the distribution patterns of numerous chronic degenerative diseases that these milieu must vary markedly from illness to illness. Osteoporosis is typically common in acid environments where the water contains high levels of dissolved aluminum.[5] Such environments, especially if they are deficient in calcium, magnesium, fluorides and silica, also appear to promote Alzheimer's disease.[47] In contrast, esophageal cancer seems most common in high sodium, low calcium and selenium regions, especially if the population consumes excessive alcohol, hot fluids and smokes heavily.[25] In contrast, multiple sclerosis prevalence rates, like those of Parkinson's disease and amyotrophic lateral sclerosis appear to be particularly high in recently glaciated areas where iodine levels are low.[44] In summary, the evidence suggests that in certain types of environment, with specific mineral and toxin concentrations in their soils and water supplies, the significance of particular genetic aberrations are either mitigated or exacerbated.

Such relationships are complicated by lifestyle choices which, in themselves, through dietary and/or other cultural, religious or personal decisions, can affect both the significance of the local environment and individual genetic traits. To illustrate, it is well known that anyone with two copies of the APO E4 allele has a 15 times greater risk of developing Alzheimer's disease than someone without this form of the gene.[48] If such an individual lives in one of the high risk areas of Norway, drinks acidic water which contains high levels of dissolved aluminum and eats a diet that is low in calcium and magnesium, he or she will almost certainly develop Alzheimer's disease. Conversely, if the same individual decides to live in Maracaibo, Venezuela, drinks the local tap water and eats a diet rich in calcium and magnesium they will not. Exactly how aluminum magnifies the significance of the APO E4 allele is unclear but geneticists appear to accept that one of the initiating events for Alzheimer's disease is an abnormality in the processing of beta-amyloid precursor protein and beta-amyloid peptide.[49,50] Interestingly, Campbell and coworkers[51] have demonstrated that aluminum promotes the formation of both beta-amyloid and ubiquitin in neurons. There is a good possibility that the APO E4 allele encourages the negative impact of aluminum because it is known that Alzheimer's patients absorb, probably for genetic reasons, much higher levels of aluminum than is normal.[52] It seems very likely that there are similar genetic-environmental-lifestyle-biochemical links for all common chronic degenerative diseases and one of the best ways to identify them is to compare and contrast environments and lifestyles in regions of abnormally high or very low incidence and mortality for individual diseases.[25]

Given all the evolutionary disadvantages of the genetic aberrations that predispose to chronic diseases, one might have expected that they would have disappeared long ago from the human gene pool. Clearly, they have not. This appears to be because they represent balanced morphisms, like that seen in the sickle cell anaemia trait. In heterozygotes, this characteristic increases the chance of surviving malaria,

while homozygotes develop sickle cell anaemia.[53] This author has argued elsewhere that there are four genetic traits that predispose those who carry them to schizophrenia.[54] Nevertheless, one or more of these traits appears to increase intelligence, since a recent Scandinavian study has established that children of university graduates are almost twice as likely to develop schizophrenia as those of non-graduates.[55] Similarly, Karlsson[56] has shown that Icelandic males, with psychotic family members but in good mental health themselves, have more skills and are higher achievers in a wide variety of fields than are those from families without this illness. There is also good evidence that one or more of the genetic traits, linked to a predisposition to schizophrenia, provides significantly increased protection against lung cancer.[57] It would seem likely, therefore, that there has been a Darwinian balancing of the benefits and costs associated with schizophrenia and probably with other chronic degenerative diseases. As a consequence, any new eugenic attempt to remove specific traits from the gene pool is likely to carry with it significant costs.

It is a relatively simple matter to greatly alter, for better or for worse, the incidence of mortality from disease by environmental or social change. This cannot be said to be true of gene-therapy which has so far usually proved more dangerous than the illnesses it has sought to cure.[58,59] It seems likely that gene-therapy will, for the foreseeable future, be expensive, dangerous and be conducted at the individual level only. In contrast, the addition of iodine to salt[60] has already prevented millions of cases of goitre and cretinism. Selenium supplemented fertilizers similarly have prevented thousands of cases of hepatitis,[61] Keshan and Kasch-Beck diseases.[62] Jiangshi can greatly reduce mortality from esophageal cancer,[30] as can a higher dietary intake of selenium.[63] The latter trace element also reduces the incidence of prostate cancer[64] and its addition to tobacco fertilizers would significantly lower the death rate from lung cancer.[65] Indeed, large improvements in health can be achieved by the stroke of a pen. Clancy and coworkers,[66] for example, have compared the directly-standardised non-trauma, respiratory and cardiovascular death rates in Dublin in the 72 months before and after a ban on coal sales. The resulting improvement in air quality was found to have resulted in about 116 fewer respiratory deaths and 243 less cardiovascular deaths each year since the ban, representing mortality declines of 15.5% and 10.3% respectively. In short, the quickest and most effective road to better health leads through environmental change, not genetic manipulation, because the former plays a much more significant role in the etiology of chronic degenerative disease than the latter and can be changed much more easily.

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