

REVIEW ARTICLE

Looking ahead: some genetic issues of the future*

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We are nearing the end of the exhilarating week-long intellectual feast presented by the Ninth International Congress of Human Genetics. This is an appropriate time to attempt to look both forward and backward, with respect to some of the developments and issues that have characterized the field of human genetics in the recent past, and old and new issues that may arise in the future.

The First International Congress of Human Genetics was held in Copenhagen in 1956. You will recall that the Watson-Crick hypothesis had been enunciated in 1953, but the genetic code was still unbroken in 1956, and our minds were relatively unsullied by molecular considerations. Some of you younger members of the audience will wonder what we found to talk about. I assure you there was no dearth of topics, largely pertaining to the morphological and biochemical approach to human inheritance. The topic of the genetic risks of ionizing radiation was also front and center.

Although there were sessions on registries of genetic disease and genetic counseling in the 1956 Congress, there was a studious avoidance of the subject of eugenics and – speaking as one who was present – a quiet resolve to avoid the mistakes perpetrated in the past in the name of eugenics. On the other hand – and this is relevant to my later discussion – the Congress did not shrink from taking a stand on topical issues, adopting a resolution to the effect that studies of the genetic effects of radiation on humans should be greatly extended “with a view of safeguarding the well-being of future generations”.

Fear not, I shall not try to lead you through the seven international congresses intervening between that first and this present Congress, nor will I attempt to summarize even the highlights in the emergence of the molecular approach in human genetics now so well reflected in the proceedings of these past congresses, and which so dominates the content of this Congress. Geneticists in general, but especially we human geneticists, have been privileged to participate in one of the most exciting and profound periods in all of human intellectual history. The rapidity of intellectual advance has undoubtedly been fueled by unprecedented governmental support of non-applied research. My own special insight into the rate of intellectual advance is that whereas, at that First Congress, the primary indicator of the genetic effects of radiation on humans was congenital malformations and certain sentinel phenotypes, now, 40 years later, studies at the molecular level are being piloted out (Neel, 1995a).

The over-arching issue for the future: A non-eugenic approach to reconciling the world's population with its resources

With this nod to the past, let us now turn to some of the possible future emphases and developments in human genetics. Admittedly viewing the world through the eyes of a population geneticist, I will argue that the first order of business is the preservation and protection of the human gene pool, in all its poorly-understood diversity.

Many persons, as well as national and international organizations, have discussed the increasing tension between the needs of a rapidly-expanding population and the equally rapidly-dwindling resources to support that population (Goldsmith *et al.*, 1972; Heilbroner, 1974; Lamm, 1985; World Commission on Environment and Development, 1987;

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Potter, 1988; McKibben, 1989; Scientific American, 1989; Turner II *et al.*, 1990; Weiner, 1990; Ehrlich and Ehrlich, 1990, 1991; Thomas, 1992; Wilson, 1992; Gleick, 1993; Hardin, 1993; Bongaarts, 1994; Neel, 1994; Pimentel *et al.*, 1994). In the year of my birth, the world's population was estimated at 1.9 billion. This year it is estimated at 5.8 billion. By the year 2020, with current trends, and barring major breakdowns in local distribution systems or major famines or epidemics, it is projected to be approximately 8 billion. The accelerating loss of agricultural, mineralogical, hydrological, oceanic, and sylvatic resources that has accompanied that population expansion is especially well documented in the annual publications of the Worldwatch Institute, entitled, "State of the World". Furthermore, at this point, the collective evidence (cf. Federation of American Scientists, 1996; Flavin, 1996) strongly suggests that a "greenhouse" effect, created by an excessive consumption of fossil and renewable fuel by too many people plus very large scale animal husbandry, is upon us. The precise consequences of this greenhouse effect and its time table, and how this might be slowed, are difficult to predict, but rising oceans due to the melting of the polar ice caps and shifting rain and temperature patterns at the very least imply profound social disruption as a result of the population movements resulting from efforts to adapt to the situation. The dilemma is that if society waits to initiate full-scale remediation efforts until the evidence for a greenhouse effect satisfies even the most skeptical, then valuable time for intensifying our current somewhat feeble activities will have been lost.

The best known effort to model the general shape of the future is the simulation-based scenario developed by the Meadows and their colleagues (1972, 1974, 1992; Meadows and Meadows, 1973). Time does not permit a detailed analysis of how the model works, nor how it responds to variations in the input parameters. Based upon what the Meadows group considers the most obvious and reasonable assumptions, the future unfolds approximately as shown in Figure 1. Note that the left half of Figure 1 corresponds to the historical facts; the right half, a projection for the next 100 years. We are very close to the time when – with the soil and water depletion that is

upon us – food per capita begins to decline. New technologies may delay the onset of those predictions for some years (cf. Hodges, 1995), but that within the next 50 years we must take very significant steps to reconcile population with resources seems beyond doubt.

The decline in population predicted by the Meadows model, when not self-driven, a response to deteriorating social conditions, will primarily result from periodic outright famines and epidemics involving old and new infectious agents, flourishing in malnourished populations, plus the impact of increasing environmental pollutants. The current AIDS epidemic is an example of what can happen. To the politician and his advisors, mostly economists with little insight into the momentum inherent in these biological developments, 25 to 50 years is a comfortable time frame. We, by contrast, are geneticists, presumably trained to consider the needs of future generations, and these developments are only one or two generations away.

The doleful events predicted by this model will have a patchy onset, overtaking the most vulnerable areas first. Indeed, there may already be areas slipping into this disaster. Consider the present Russian Republic. Although its demographic decline began in the mid-1980s, well before the dissolution of the Soviet Union in 1991, in recent years certain trends have been accelerating (Nelson, 1996). Total live births in Russia have dropped from a peak of 2.5 million in 1987 to 1.4 million in 1994, while total deaths have climbed from 1.5 million to 2.3 million over the same period. Between 1987 and 1994, life expectancy for men dropped from 65 to 57 years, and for women, from 75 to 71 years. Infant

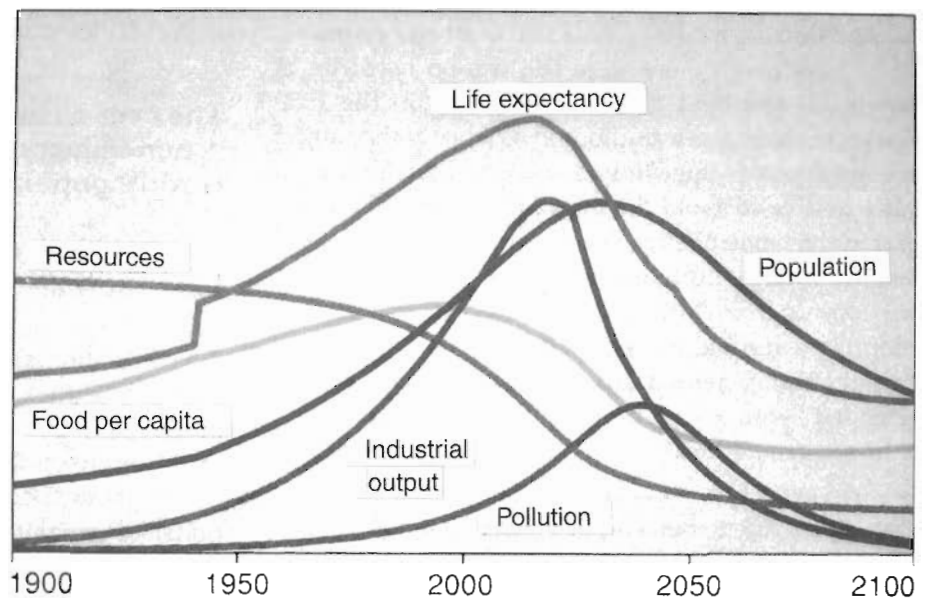


Figure 1 - The most probable population/resource scenario for the next 100 years for the industrialized nations, as predicted by the "Meadows model", after Hayes (1993). Reproduced by permission of Dr. Brian Hayes and *The American Scientist*.

mortality has climbed to at least 20 deaths per 1000 live births, with some experts suggesting the figure could be as high as 30 per 1000, this some three times higher than in the United States and Western Europe. The death rate during childbirth is 50 per 100,000 births – more than six times the rate in the United States and Western Europe.

The causes of this decline are complex, and certainly are diverse, including the effects of pollution, poor diet, deterioration of medical and social services, and lack of confidence in the future. Some of Russia is within the area subjected to fallout from the Chernobyl disaster, and, while the radiation exposures are so low that these statistics cannot be a direct result of those exposures, they may reflect the psychology created by the exposure. It is presumed this is a temporary situation, but only the future will validate the truth of this presumption. This scenario, repeated a hundred times over, would do much to bring the world's people back into some semblance of balance with resources – but what a failure of our high-tech civilization and at what cost in human diversity? True enough, localized decimations and even extinctions of human groups have been common in the past, and some remnants of the primitive thinking that regards this as an acceptable way to bring the world into “balance” persist down to the present, but haven't our various civilizations demonstrated a collective intellectual bankruptcy if, having out-reproduced our resources, we leave the necessary demographic transition to the traditional Four Horsemen of the Apocalypse?

It will take the efforts of many kinds of people to blunt – not completely avoid, but at least to blunt – the catastrophe that is taking shape. A very integral part of that effort must be attempts to decrease the rather reckless consumption of energy and resources that characterizes some segments of society, and even some nations. Chief among the latter is surely the country I represent. Numerous national and international groups have already weighed in on the issues involved (Royal Society of London and U.S. National Academy of Sciences, 1992; Union of Concerned Scientists, 1992; World's Scientific Academies, 1993). The preferred and ideal way to reduce the birth rate to a level consistent with the sustainable use of the world's resources would be to advance the health, socioeconomic, and educational levels of the world's economically disadvantaged, so that a large number of surviving children would not be seen as the best insurance against an impoverished old age, and birth rates would fall to those of Western Europe.

Unfortunately, this economic transition is simply not going to happen in the foreseeable future.

The alternative approach is to couple efforts toward more equitable resource distribution with voluntary limitations of family size. Already, as a consequence of the activities of various organizations and governments, there has been substantial progress in reducing birth rates and population growth in various parts of the world in a much more humane manner than implied by the recent developments in Russia mentioned above. Unfortunately, as noted earlier, human numbers are still increasing at an alarming rate.

For some 25 years now I have been urging a return to the ethic of our tribal ancestors, who over much of the world were in the various crude ways consistent with their technology, generally holding population increases to a rate suitable to the exigencies of their culture (Neel, 1970). In this, they displayed a sophistication that we, their descendants, have long since abandoned. The core of this program would be a worldwide quota system, wherein the goal for each couple, regardless of ethnicity, social status, or personal attributes, would be the same number of children (Neel, 1970), that I now would set at two (Neel, 1991, 1994). This is a completely egalitarian approach to population control. It is not a eugenic measure, not a dysgenic measure, but, rather, an isogenic approach to the human gene pool. It can be estimated that with this policy, for various reasons, the realized average number of children per couple would be about 1.8. Unfortunately, even if this approach were initiated immediately, because of the present age structure of the world's population, the total world population would continue to increase for some three or four decades, peaking in the neighborhood of 6.7 billion in the year 2030. Thereafter, it should slowly decline. Such a policy would simply freeze the human gene pool in all its poorly understood diversity, aside from the effects of genetic drift, whatever genetic selection is taking place, and whatever systematic genetic pressures result from developments in the therapy of genetic diseases. It is as non-eugenic a policy as can be formulated, a policy that I hope in due time will be endorsed by the various genetic societies of the world.

I published a little note in the *American Journal of Human Genetics* (Neel, 1995b) concerning the need to regulate population growth. In writing that note, I assumed all geneticists would understand why geneticists should have a particular interest in this problem and was truly amazed when one of my reviewers suggested I should clearly state why this was an issue of particular interest to geneticists. Why, indeed, should geneticists be concerned to implement such a program? What other group in society should have a greater interest in the genotypic and phenotypic

well-being of future generations? And, given how poorly we still understand the significance of the genetic variation in populations, who has a more vested interest in ensuring the continuing representation of all subdivisions of the world's gene pool in future generations? Surely geneticists, in their involvement with the major effort to establish cell lines from indigenous genetic isolates, commonly termed the Human Genome Diversity Project, have a strong moral obligation to align themselves with all the groups attempting to better the lot of these populations and ensure their survival. There is also a strong element of genetic self interest in population control: there is no way the next generation will have the resources to exploit either the implications or the applications of the new genetics, if current population trends continue.

The most resolute recent effort to blunt the growth of a national population is that of the People's Republic of China, with the well-known One-Child Family Policy it initiated in 1978, and reaffirmed recently. There has been considerable criticism of the element of coercion many perceive in the implementation of this policy. I suggest that these critics are not fully aware of the urgency of the situation that confronted that nation, once it had embarked on the policy of industrialization that every nation sees as its birthright, the way to raise, ultimately, its standard of living. In his recent provocative book, "Who Will Feed China?", Brown (1995) has marshaled a set of poorly-known, relevant facts. China's recent renewed emphasis on population control undoubtedly stems from the fact that, even with the program enunciated in 1978, the country was projected to add 490 million people between 1990 and 2030, swelling its population to 1.6 billion – the equivalent of adding four Japans. China's balance between population and the agricultural base to support it, already stressed by these projections, was clearly further jeopardized by its drive to industrialization, with the inevitable sacrifice of arable land, plus the diversion to industrial purposes of water important for a predominantly irrigation-type agriculture. In their similar transitions, Japan lost 52 percent of its grain-harvested areas, South Korea 46 percent, and Taiwan 42 percent. Even with successful population control in the near future, China, formerly more or less self sufficient with respect to grain production, will now be entering the world market as a massive importer of grain just as the world production of grain is leveling off. Grain prices are certain to rise, with what that means to countries with marginal resources. But to return to China, to be successful and stable, their transition from a predominantly agrarian to an industrialized nation requires that population

growth be quenched. China is a test case for how far a nation can ethically pressure its people in the interests of the welfare of future generations. If in the face of a perceived military threat to the integrity of the nation, a government can call upon its citizenry to place its lives at risk, why isn't it equally appropriate, in the face of a civil threat perceived to be of equal magnitude, for the government to pressure its citizenry to limit its reproduction?

But while, then, I find it possible to argue that in the long-run, the Chinese effort to control population growth is more humane than the consequences of inaction, and deserves careful study by nations with similar problems, in its recent Law on Maternal and Infant Health Care, promulgated in 1995, the People's Republic of China has introduced clearly eugenic provisions into these efforts. To quote Article 10:

"Physicians shall, after performing the pre-marital physical check-up, explain and give medical advice to both the male and the female who have been diagnosed with certain genetic disease of a serious nature which is considered to be inappropriate for child-bearing from a medical point of view; the two may be married only if both sides agree: 1) to take long-term contraceptive measures or, 2) to take ligation operation for sterility".

Further, in Article 38, we read:

"'Genetic disease of a serious nature' refers to diseases that are caused by genetic factors congenitally, that may totally or partially deprive the victim of the ability to live independently, that are highly possible to recur in generations to come, and that are medically considered inappropriate for reproduction..."

The Law also states that "Sex identification of a fetus by technical means shall be strictly forbidden, except that it is positively needed on medical terms" (Article 32). This presumably reflects an effort to avoid an imbalance in the numbers of males and females in a society where there is a strong preference for a male heir.

This vague and imprecise Law, by any interpretation, constitutes the first return to the slippery slope of eugenics as a national policy since the demise of Nazi Germany, and this on the part of the world's most populous nation. Somehow the genetic community must find a way to open a meaningful dialogue with those in China responsible for these developments,

a dialogue that while supportive of the efforts at population control, is clear on the potential for abuse in the proposed eugenic program¹.

A troublesome issue for the future is the limits to set on 'individual eugenics', i.e., voluntary efforts on the part of individuals to improve the 'quality' of their children (cf. Caplan, 1995). Such efforts can proceed along either of two pathways. On the one hand, there is so-called 'germinal choice', in which a woman elects to be artificially inseminated by the sperm of a 'superior' male (presumably properly screened for various carrier states!). She may elect to do so as a single mother or because of a sterile marriage in which the problem clearly rests with the husband. Anyone who has observed the diversity among his/her own children or those of friends, appreciates what a lottery this will be (even after all possible genetic screenings). The other alternative would be extensive prenatal screening, with the purpose of aborting a child with "undesirable" genetic traits. Such screening is already in wide use (and widely accepted) for such diseases as Tay-Sachs disease (Kaback *et al.*, 1993) or thalassemia major (Cao, 1994); with the increasing ability of the DNA technologies to detect predispositions, the question of the limits to parental choice is sure to receive increasing attention in the future.

The ethical and practical issues that will arise in a planned transition to a sustainable society will be so great that the political establishments, that in so many countries already have shown great reluctance to address this transition, will be tempted to abdicate their responsibilities and let nature take her course. We need, right now, to join other groups in building a record such that, as future events unfold, we cannot be dismissed as a group so mesmerized by the promise of gene therapy for individuals that we neglected our responsibilities to populations.

This effort to reduce the human gene pool to a sustainable size must be accompanied by efforts to insure that the probable increase in pollution to which populations are to be subjected is not exacting an unacceptable genetic toll. As noted in the Introduction, increased exposures to ionizing radiation have in the past been seen as a particular risk. In 1955, the

uncertainties regarding the genetic hazards of ionizing radiation were such that no less a genetic figure than J.B.S. Haldane (1955) could conjecture that the doubling dose of radiation might be as low as $3r$, this and other uncertainties contributing to the statement by the First International Congress of Human Genetics mentioned earlier. The results of almost 50 years of study of the genetic effects of the atomic bomb exposures in Japan now lead us to suggest that the doubling dose is more of the order of 2 Sv equivalents for acute exposures and 4 Sv equivalents for chronic exposures (Neel *et al.*, 1990), and a reevaluation of all the experimental data from the murine model leads to a similar conclusion for the mouse (Neel and Lewis, 1990). Both these estimates need to be firmed up with the molecular techniques now becoming available (Neel, 1995a). Current exposures to ionizing radiation from all natural sources in such a country as the U.S., up to mid-reproductive age (say age 30), are about 0.09 Sv equivalents. These are technically chronic exposures. Current guidelines call for no more than 0.10 added Sv equivalents from all additional (human generated) sources; the actual increment is much less than this. From the genetic standpoint, there would seem to be a comfortable cushion with respect to radiation exposures in human society but for the occasional accident, such as Chernobyl.

Greater uncertainties exist with respect to the genetic effects of exposures to chemical pollutants, some of whose components have been shown to be chemical mutagens. I would anticipate that as the threat of chemical pollution builds up in the future, and as the potentially much more efficient DNA-technologies for the evaluation of genetic damage come on line, this subject will move from the numerous demonstrations of chemical mutagenesis in cell culture models to population studies. As before, I urge that the most appropriate population for a first study would be the children born to parents potentially heavily mutagenized in childhood in the course of treatment for various malignancies.

The promise of molecular genetics for the future

I have devoted so much of this presentation to the probable environment of the future because I find it impossible to embark upon a discussion of genetic developments in the next several decades, especially with respect to the applications of the new genetics, without some projection of the societal pressures within which these applications will evolve. In addition to the very general pressures that have been mentioned, we must also recognize that in many countries the practice

¹ During the course of the Congress at which this paper was read, the Executive Committee for the Congress drafted a resolution expressing concern over the wisdom of this eugenic legislation. The resolution invited the appropriate representatives of the People's Republic of China to enter into a dialogue with the world's genetic community. This resolution was to be transmitted to the Republic's Minister of Health by the President of the Congress, Prof. Newton E. Morton.

of medicine, under which the clinical applications of genetics will fall, has come under withering scrutiny with respect to cost containment and efficiency, and the moment genetic and gene therapy leave the laboratory and enter the medical arena, the same scrutiny will come to bear on them.

The genetic developments of the past 40 years have resulted in insights into the nature of humankind and, indeed, in humankind's place in the universe, that many scholars have suggested are equaled only by two previous periods in human intellectual history, namely, the developments we associate with the names of Copernicus and Darwin. There can be no doubt that with the momentum associated with the Genome Project, there are many more developments to come. With, however, the approaching economic developments discussed earlier, the research support of the future will not be as lavish as in the past, and an increasing fraction of this support will come from the pharmaceutical industry. The pages of the journal *Nature: Biotechnology* are already reflecting a commercialization of our genetic science that would have been unthinkable a generation ago, with patent battles and proprietary considerations that not only threaten the traditional free discussion among scientists but raise disturbing ethical questions. As, increasingly, the pharmaceutical industry becomes a player in our field, we are witnessing recognition that identifying a gene does not always tell us what its protein product does; these commercial pressures will surely result in a renaissance of interest in protein structure and function. This slowing of the pace of research will not be all bad – time is needed to consolidate and synthesize the new knowledge. It will be tempting during this period to entice funding sources with promises of great practical applications of this new knowledge and indeed, these are already suggestions of this strategy. Neither the Copernican nor the Darwinian revolutions resulted in immediate benefits to society, and I have to wonder whether, in the efforts to keep funding flowing, some geneticists are currently promising too much too fast.

We can certainly diagnose many of the bases for, and changes in, genetic disease with exquisite precision. But it is what the late Lewis Thomas termed 'half-way therapy', to offer a person of 20 found to be a carrier of the multiple-polyposis-of-the-colon allele (APC) or of either of the breast cancer alleles (BRAC1 and BRAC2) a total colectomy or a bilateral mastectomy. Thus far, there does not seem to be a single true instance of the much discussed gene therapy, even for the most simply inherited of the genetic diseases. (I define true gene therapy as the long-lasting introduction into the somatic tissues of an individual with a

genetic disorder, of normal genes in sufficient quantity and functional state to offset the patient's disease). On the other hand, the truly amazing insights into the somatic cell genetics of oncogenesis have already resulted in therapeutic approaches now in clinical trials (reviewed in Bank, 1996).

A disturbing development for the gene therapist of late has been the realization of the complexity of the control of the expression of many genes. In the early years, extrapolating from bacterial models, it was a gene, a promoter, and a few transacting proteins. Now, with the examples in higher eukaryotes of the complexity of control of the hemoglobin loci (Bungert *et al.*, 1995; Fiering *et al.*, 1995), of some transcription factors such as the GABP beta or NRF-2 genes (de la Brousse *et al.*, 1994; Gugneja *et al.*, 1995), and, above all, of the steroid gene family (Beato *et al.*, 1995; Kastner *et al.*, 1995; Mangelsdorf and Evans, 1995; Mangelsdorf *et al.*, 1995; Thummel, 1995), the transfer between individuals of functional genetic complexes is suddenly much more difficult.

In recent years, buoyed by the indisputable success in elucidating the molecular basis of the simply inherited monogenic disorders, there is increasing discussion in the genetic literature concerning similar molecular attacks on the inherited multigenic disorders of later life – diabetes mellitus, hypertension, cardiovascular disease, emphysema, asthma, and the mental diseases and Alzheimer's, with strong hints from some geneticists that with this understanding should come nothing less than genetic therapy. The full complexity that these efforts to understand the molecular basis of multigenic inheritance must assume is only now becoming apparent. Without question, some simply inherited sub-types of these diseases will be teased out, as seems to be occurring with respect to Alzheimer's disease and non-insulin dependent diabetes (NIDDM). However, the genetic component in the majority of patients with these diseases is probably multi-factorial, with a strong environmental overlay. When several factors are involved in a given phenotype, complex interactions between them, these influenced by environmental variables – so-called epigenetic effects – are almost to be expected; these are a serious impediment to quantitative genetic analysis (Sing *et al.*, 1992, 1994, 1996; Strohman, 1993, 1995). Furthermore, for many continuously distributed polygenic traits, the environmental component in the total variance is some 50%. The ability to detect the contribution of a single major segregating allele to the remaining (50%) genetic variance depends on many variables (discussion in Cannings and Thompson, 1977; Thompson, 1981; Boehnke *et al.*, 1988; Boehnke and Moll, 1989; Moll, 1993;

Risch and Zhang, 1996) but with studies of the size usually envisioned, the effect of any single locus that in a top-down segregation analysis does not contribute some 10% of the remaining variance is not apt to emerge as statistically significant. This limits the number of gene effects that can be detected in a single study. When there is so-called "saturation" of the genome with markers, say one every 10 cM, in an effort to detect linkages with loci involved in quantitative traits, or where there are candidate loci, now smaller effects can be detected (cf. Tanksley, 1993), but now there will be many false positive associations in any single study, and apparent cross conflicts across studies, some real, some due to genetic heterogeneity, all of which must be sorted out. Finally, for many continuously distributed traits, such as blood pressure or blood glucose, the definition of the phenotype that medicine arbitrarily declares to be 'disease' (hypertension, diabetes mellitus) is arbitrary, but just where the defining diagnostic cut point is made can have a strong influence on the view of the prevalence of the "disease" and its association with other diseases. There is no doubt we will shortly learn a great deal more about the genetic component in many of the common diseases of adulthood, but progress will be slower than anticipated, and the applications of this knowledge, problematic.

The concept of a complex epigenetic nexus, invoked in the preceding paragraph, does not often appear in the literature of the molecular geneticist and needs a little explanation. For a recessively inherited disease due to the absence of a critical enzyme, epigenetic phenomena do not enter into the manifestation of this deficiency in any very significant fashion. In complex multifactorial inheritance, the situation is quite different. I would like to illustrate with an example that goes back more than 50 years, to my days as a *Drosophila* geneticist. At that time, I was interested in the phenotypic effects of combining non-allelic mutations causing extra hairs or bristles (microchaetae or macrochaetae) in *Drosophila melanogaster*. Table I illustrates some of the results of combining three different mutant genes, the flies being raised under carefully standardized conditions (Neel, 1941, 1943). Note that the mutants in almost all combinations exhibit more than additive effects. This indicates the action of epigenetic factors. All these interactions were studied on an isogenic background, achieved by repeated backcrosses to a standard line – without this the range in the expression of the various genotypes would undoubtedly have been even greater. In addition, as one altered the temperature at which the flies were raised or the amount of food available, bristle number was dramatically affected (Neel, 1940, 1943). For instance,

pyd flies raised at 14°C had twice the number of supernumerary dorsocentral bristles observed in flies raised at 29°C. Finally, as Table I illustrates, the various groups of microchaetae – macrochaetae that were studied revealed different degrees of non-additive effects. Although this is admittedly a somewhat contrived example, imagine attempting to sort out the genetics of a similar quasi-continuous trait in a human population in which three such genes plus modifiers were segregating and the general and individual environments could not be controlled.

As geneticists strive to develop therapies based on understanding the genetic basis of complex diseases, in these times of concern with medical costs, the question of cost effectiveness must constantly be borne in mind. The pharmaceutical industry may be prepared to give the genetic approaches stiff competition. Let us consider only one example, the emergence of

Table I - The phenotypic interaction of three mutations responsible for excess hair-bristles in *D. melanogaster* (Neel, 1941). Note that combining these mutations in all possible combinations almost always results in a bristle or hair number greater than if the mutations were simply additive in their effects.

Genotype	Mean number of dorsocentral bristles		Mean number of scutellar hairs	
	Observed	Additive expectation	Observed	Additive expectation
+	4.04 ± 0.02		0.0 ± 0.00	
<i>pyd</i>	5.76 ± 0.07		0.0 ± 0.00	
<i>h</i>	4.03 ± 0.01		24.1 ± 0.23	
<i>Hw</i>	7.42 ± 0.12		4.5 ± 0.11	
<i>h pyd</i>	5.68 ± 0.07	5.75	24.25 ± 0.24	24.06
<i>Hw pyd</i>	9.81 ± 0.16	9.13	4.61 ± 0.11	4.50
<i>Hw h</i>	8.37 ± 0.07	7.41	40.51 ± 0.24	28.56
<i>Hw h pyd</i>	12.68 ± 0.12	9.12	54.92 ± 0.33	28.56

Genotype	Mean number of scutellar bristles		Mean number of hairs on second longitudinal wing vein	
	Observed	Additive expectation	Observed	Additive expectation
+	4.00 ± 0.01		0.0 ± 0.00	
<i>pyd</i>	4.38 ± 0.04		0.0 ± 0.00	
<i>h</i>	4.23 ± 0.03		8.46 ± 0.24	
<i>Hw</i>	4.14 ± 0.03		11.05 ± 0.28	
<i>h pyd</i>	5.19 ± 0.06	4.60	10.82 ± 0.29	8.46
<i>Hw pyd</i>	4.87 ± 0.06	4.52	11.07 ± 0.30	11.05
<i>Hw h</i>	5.54 ± 0.05	4.37	33.10 ± 0.37	19.51
<i>Hw h pyd</i>	7.02 ± 0.09	4.74	38.35 ± 0.45	19.51

psychotropic agents of great specificity, directed in disease states at a specific molecule that is directly or indirectly a gene product. Although more than 100 distinct chemicals have been identified as involved in the complex transactions of the brain, three of the most major players are surely dopamine, serotonin, and norepinephrine, and drugs specifically targeted toward each of these are now available. We have time to mention only one of the serotonin-directed agents. This is Prozac (fluoxetine hydrochloride), now widely prescribed for depression and obsessive-compulsive disorder, in both of which diseases a strong genetic component has been identified. The mode of action is thought to be interference with the uptake of released serotonin at central nervous system neuronal synapses, this accompanied by little or no effect on the reuptake mechanisms for norepinephrine, dopamine, or acetylcholine (reviewed in Messiha, 1993). Serotonin is a gene product; this manipulation of the system is very close to genetic therapy, i.e., therapy designed to alter the amount or availability of a gene product. The action of Prozac is already a very specific action, but there are different types of serotonin receptors, and the possibility of even greater specificity through developing agents to block specific receptor types is obvious. In addition to its major therapeutic uses, Prozac seems also to be remarkably effective in relieving in some people some of the minor "hang ups" that drive people to psychotherapy – "hang ups" that in some instances may be "minor" genetically determined biochemical disorders – and the question of the limits to what is close to enhancement therapy in the genetic sense is under active discussion (Kramer, 1993). It is developments like this against which the cost effectiveness of some of the new genetic therapy will be judged.

Geneticists: do not overlook euphenics

The environment in which human beings currently function is very different from the environment in which they evolved, but there is no evidence that in the relatively brief period since humankind abandoned the hunting-gathering-scavenging ways of our tribal ancestors, there have been significant corresponding genetic adaptations. As noted earlier, there is currently great interest in the genetic component in the so-called "diseases of civilization", such as hypertension, NIDDM, or atherosclerosis. In appropriately studied unacculturated tribal populations, those diseases are quite rare, in part because of the relative youth of the population, but also on an age-adjusted basis. For instance, in our own studies of relatively unacculturated American Indian populations, only very rarely did we

encounter gross obesity, NIDDM, or hypertension (Neel, 1971, 1977). On the other hand, in Tecumseh, Michigan, a reasonably typical American town, among males ≥ 40 years of age, the frequency of obesity (body mass index ≥ 27) was 38%, of hypertension (sitting diastolic blood pressure ≥ 90 mmHg), 40%, and of NIDDM, 15%. The corresponding figures for females were 41%, 42%, and 16% (Neel, in press). Since we all have tribal antecedents, we must presume that the alleles with which these diseases will ultimately be associated are in fact part of the normal genotype, but now labeled "disease-predisposing alleles". Given the emerging complexities of multigenic inheritance, it is by no means clear what genetic or gene therapy will have to offer as we come to understand the situation better.

Much more of practical value in relation to these diseases may come from the euphenic approach, and at a lower cost. The term euphenics, coined by Lederberg (1963), refers to a conscious effort to structure the environment in the interests of optimizing the expression of the genotype. In the early days of human genetics, there was a great deal of discussion of the relative importance, for complex traits, of heredity vs. environment, of nature vs. nurture. The field we now term 'genetic epidemiology', with its predominant interest in complex traits, can be viewed as the successor to that traditional interest. In many studies, about half of the variance associated with these diseases is non-genetic. In the ultimate understanding of the etiology of those diseases for which we strive, sorting out how the environmental component interacts with the genetic is as important as understanding the detailed genetics, and appropriate environmental intervention, using the term in the broadest possible sense, may be as important as measures based on genetic knowledge.

The most obvious area in which to begin to 'think euphenically' is with respect to diet. Paradoxically, the problems in this arena are of two diametrically opposed types. In the industrialized nations, the issue is overalimentation, with its concomitants, the so-called diseases of civilization. But in the developing nations, the nutritional problem is primarily under-alimentation, with estimates that at least half a billion persons are seriously undernourished, the most spectacular example of which is the Kwashiorkor of Africa. The remedy for the latter – improved nutrition – is obvious, but how best to approach the former is not equally obvious.

Just how food-adaptable are we? The literature on eating healthy and what it will do for you is becoming enormous but cannot be reviewed in this presentation. Especially impressive is the experimental evidence on the role of dietary restriction in reducing

the incidence of various malignancies in rodents (see Grasl-Kraupp *et al.*, 1994); the results of similar studies on primates now in progress under the sponsorship of the National Institute of Aging will be of great interest. However, while improving the diet appears to be a relatively simple undertaking compared with other undertakings we are discussing, this is not so. Efforts to control cardiovascular (i.e. atherogenic) disease have had a high priority in recent years. One prime approach has been the substitution for dietary butter and lard of polyunsaturated vegetable oils that have been rendered semi-solid by catalytic hydrogenation. Now Mann (1994) is arguing that the reason for a sub-optimal result in attempts to ameliorate atherogenesis with the use of these oils is that partial hydrogenation is accompanied by a shift in the position in the fatty acid of many hydrogen ions, from *cis* to *trans*, and these predominantly *trans* fatty acids cannot be metabolized as well as the more usual *cis* fatty acids. If this thesis proves to be correct, it will indicate the care with which diets must be realigned. In this particular case, what seemed an obviously appropriate modification was never really tested out before massive promotion.

A second arena for euphenic thinking is with respect to the environment of the mind. This is a vast topic that we have no time to discuss properly. Suffice it to say that there are again complex heredity-environmental interactions that we must understand better if we are to alleviate the aggressions that result in the fratricidal tragedies recently witnessed in the former Yugoslavia, or in Somalia, or in Liberia. Speaking as a citizen of the United States, I feel strongly that the glorified violent solutions of human problems that so permeate commercial television are inappropriate representations to our young of how the world functions.

Euphenics can proceed on an individual or population basis. While the two approaches are not mutually exclusive, society may, in the interests of efficiency, attempt to emphasize one or the other. As an example, elevated blood levels of homocysteine (sometimes elevated for genetic reasons) appear to play a role in the etiology of vascular disease. These levels can be reduced by the administration of folic acid. Physicians could screen patients considered at risk for vascular disease and if hyperhomocysteinemia is encountered, initiate folic acid therapy on an individual basis. On the other hand, Boushey *et al.* (1995; see also Motulsky, 1996) have calculated that 9% of male and 54% of female deaths from coronary artery disease could be prevented by fortification of flour and cereal products with 350 µg of folic acid/100 g food. Morbidity and mortality from coronary artery disease, strokes,

and peripheral vascular disease should also be reduced. In addition, such fortification might prevent upward of 50% of neural tube defects in newborns (Centers for Disease Control, 1992). Incidentally, this dietary fortification may only be restoring folic acid intake to levels characteristic of many early human populations, in which case the dietary folic acid supplementation is truly euphenic (rather than medicinal). There is thus a strong argument for routine dietary fortification, which would probably be less costly than individual tests and pharmaceutical prescriptions for those with elevated blood homocysteine levels, i.e., the population approach to euphenics would be less costly.

It should be noted that the euphenical approach offers few quick fixes. Dietary supplementations, as just discussed, place no personal strictures on the individual. However, there are many aspects of euphenics that require an individual commitment: total calorie uptake, proportion of calories derived from fat, fibrous content of diet, etc. Let us assume that by dietary manipulation society could decrease obesity, NIDDM, and hypertension by at least one half. Perhaps by a thorough understanding of the genetics of these diseases, genetic therapies might lead to a comparable result. The former approach would entail a fraction of the expense to society as compared with the latter approach as now envisioned. If the government in a democratic society assumes, under increasingly straitened circumstances, responsibility for the health care of its citizens, we may expect a lively debate in the future over the allocation of resources, between public education directed at altering life styles conducive to the realization of genetic predispositions and the genetic therapies for those same diseases in that population.

There is, however, an unfortunate "catch 22" to euphenics, as, indeed, there also is to the various genetic (gene) therapies in place and under consideration. All over the world, but especially in the industrialized nations, the proportion of elderly citizens is increasing. In the United States, for instance, the number of persons over 65 years of age is projected to increase from the current 30 million to 58 million by the year 2030. Nations are already having difficulty adjusting to the various issues created by the increasing number and proportion of, usually, non-productive citizens. To the extent that improved genetic therapies and euphenic measures contribute to a worsening of this situation, a current social problem can only be exacerbated.

Final comments

These past 50 years have been a time of intellectual excitement and advance in the field of

human genetics that, because of the magnitude and heterogeneity of the discoveries, few of us truly understand. Although dramatic discoveries will continue, we are now entering into a period of integration and consolidation, in which the ethical and practical implications of this new knowledge will provide the foci for intense debate. But increasingly, I suggest, we geneticists will (and should) also be drawn into questions of population limitation and how it is to be accomplished. Even if none of molecular genetics bore any practical fruit for another generation, the genetic health and well-being of the human gene pool would not deteriorate on this account. But I absolutely guarantee you, that if we geneticists do not join kindred souls in seeking to reconcile population growth with sustainable resources, and present trends continue, the gene pool will be affected in ways we cannot foresee, ways apt to impoverish that gene pool, even as the quality of life deteriorates. We will also, as the limitations of gene and genetic technology become apparent, and cost-benefit ratios get sorted out, almost surely find ourselves devoting more time to euphenic considerations, and especially the balance between individual and group euphenics. The Proceedings of this beautifully planned and executed Congress should provide a document that catches, at this critical time in the development of the study of human genetics, the full complexity that field has assumed.

REFERENCES

- Bank, A.** (1996). Human somatic cell gene therapy. *Bioessays* 18: 999-1007.
- Beato, M., Herrlich, P. and Schutz, G.** (1995). Steroid hormone receptors: Many actors in search of a plot. *Cell* 83: 851-857.
- Boehnke, M. and Moll, P.P.** (1989). Identifying pedigrees segregating at a major locus for a quantitative trait: An efficient strategy for linkage analysis. *Am. J. Hum. Genet.* 44: 216-224.
- Boehnke, M., Young, M.R. and Moll, P.P.** (1988). Comparison of sequential and fixed-structure sampling of pedigrees in complex segregation analysis of a quantitative trait. *Am. J. Hum. Genet.* 43: 336-343.
- Bongaarts, J.** (1994). Population policy options in the developing world. *Science* 263: 771-776.
- Boushey, C.J., Beresford, S.A.A., Omenn, G.S. and Motulsky, A.G.** (1995). A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: Probable benefits of increasing folic acid intakes. *JAMA* 274: 1049-1057.
- Brown, L.R.** (1995). *Who Will Feed China?* W.W. Norton and Co., New York, pp. 163.
- Bungert, J., Dave, U., Lim, K.C., Lieuw, K.H., Shavit, J.A., Liu, Q. and Engel, J.D.** (1995). Synergistic regulation of human beta-globin gene switching by locus control region elements HS3 and HS4. *Genes Dev.* 9: 3083-3096.
- Cannings, C. and Thompson, E.A.** (1977). Ascertainment in the sequential sampling of pedigrees. *Clin. Genet.* 12: 208-212.
- Cao, A.** (1994). 1993 William Allan award address. *Am. J. Hum. Genet.* 54: 397-402.
- Caplan, A.L.** (1995). What is wrong with eugenics? In: *Moral Education V.* (Rosenthal, J.H., ed.). Carnegie Council on Ethics and International Affairs, New York, pp. 17-33.
- Centers for Disease Control** (1992). Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *Morb. Mortal. Wkly. Rep.* 41: 1-7.
- de la Brousse, F.C., Birkenmeier, E.H., King, D.S., Rowe, L.B. and McKnight, S.L.** (1994). Molecular and genetic characterization of GABP beta. *Genes Dev.* 8: 1853-1865.
- Ehrlich, P.R. and Ehrlich, A.** (1990). *The Population Explosion.* Simon & Schuster, New York, pp. 320.
- Ehrlich, P.R. and Ehrlich, A.H.** (1991). *Healing the Planet: Strategies for Resolving the Environmental Crisis.* Addison-Wesley, Reading, MA, pp. xv & 366.
- Federation of American Scientists** (1996). FAS hosts climate change conference for World Bank. *J. Fed. of Am. Sci.* 42: 1-11.
- Fiering, S., Epner, E., Robinson, K., Zhuang, Y., Telling, A., Hu, M., Martin, D.I., Enver, T., Ley, T.J. and Groudine, M.** (1995). Targeted deletion of 5'HS2 of the murine beta-globin LCR reveals that it is not essential for proper regulation of the beta-globin locus. *Genes Dev.* 9: 2203-2213.
- Flavin, C.** (1996). Facing up to the risks of climate change. In: *State of the World, 1996* (Brown, L.R., ed.). W.W. Norton and Co., New York, pp. 21-39.
- Gleick, P.H.** (1993). *Water in Crisis: A Guide to the World's Fresh Water Resources.* Oxford Science Publications, Oxford, pp. 473.
- Goldsmith, E., Allen, R., Allaby, M., Davol, J. and Lawrence, S.** (1972). A blueprint for survival. *The Ecologist* 2: 2-43.
- Grasl-Kraupp, B., Bursch, W., Ruttkey-Nedecky, B., Wagner, A., Lauer, B. and Schulte-Hermann, R.** (1994). Food restriction eliminates preneoplastic cells through apoptosis and antagonizes carcinogenesis in rat liver. *Proc. Natl. Acad. Sci. USA* 91: 9995-9999.
- Gugneja, S., Virbasius, J.V. and Scarpulla, R.C.** (1995). Four structurally distinct, non-DNA-binding subunits of human nuclear respiratory factor 2 share a conserved transcriptional activation domain. *Mol. Cell. Biol.* 15: 102-111.
- Haldane, J.B.S.** (1955). Genetical effects of radiation from products of nuclear explosions. *Nature* 176: 115.
- Hardin, G.** (1993). *Living Within Limits: Ecology, Economics, and Population Taboos.* Oxford University Press, New York, pp. 339.
- Hayes, B.** (1993). Balanced on a pencil point. *Am. Sci.* 81: 510-516.

- Heilbroner, R.L.** (Ed.) (1974). *An Inquiry Into the Human Prospect*. W.W. Norton, New York.
- Hodges, C.A.** (1995). Mineral resources, environmental issues, and land use. *Science* 268: 1305-1312.
- Kaback, M., Lim-Steele, J., Dabholkar, D., Brown, D., Levy, N. and Zeiger, K.** (1993). Tay-Sachs disease – carrier screening, prenatal diagnosis, and the molecular era. *JAMA* 270: 2307-2315.
- Kastner, P., Mark, M. and Chambon, P.** (1995). Nonsteroid nuclear receptors: What are genetic studies telling us about their role in real life? *Cell* 83: 859-869.
- Kramer, P.D.** (1993). *Listening to Prozac*. Viking Penguin, New York, pp. xix & 409.
- Lamm, R.D.** (1985). *Megatraumas: America at the Year 2000*. Houghton Mifflin, Boston, pp. xii & 290.
- Lederberg, J.** (1963). Molecular biology, eugenics, and euphenics. *Nature* 198: 428-429.
- Mangelsdorf, D.J. and Evans, R.M.** (1995). The RXR heterodimers and orphan receptors. *Cell* 83: 841-850.
- Mangelsdorf, D.J., Thummel, C., Beato, M., Herrlich, P., Schutz, G., Umesono, K., Blumberg, B., Kastner, P., Mark, M., Chambon, P. and Evans, R.M.** (1995). The nuclear receptor superfamily: The second decade. *Cell* 83: 835-839.
- Mann, G.V.** (1994). Metabolic consequences of dietary *trans* fatty acids. *Lancet* 343: 1268-1271.
- McKibben, B.** (1989). *The End of Nature*. Random House, New York, pp. ix & 226.
- Meadows, D.L. and Meadows, D.H.** (1973). *Toward Global Equilibrium: Collected Papers*. Wright-Allen Press, Cambridge, MA, pp. x & 358.
- Meadows, D.H., Meadows, D.L., Randers, J. and Behrens III, W.W.** (1972). *The Limits to Growth: A Report for the Club of Rome's Project on the Predicament of Mankind*. Universe Books, New York, pp. 205.
- Meadows, D.L., Behrens III, W.W., Meadows, D.H., Naill, R.F., Randers, J. and Zahm, E.K.O.** (1974). *Dynamics of Growth in a Finite World*. Wright-Allen Press, Cambridge, MA, pp. xi & 637.
- Meadows, D.H., Meadows, D.L. and Randers, J.** (1992). *Beyond the Limits: Confronting Global Collapse, Envisioning a Sustainable Future*. Chelsea Green Publishing Co., Post Mills, VT, pp. x & 300.
- Messiha, F.S.** (1993). Fluoxetine: A spectrum of clinical applications and postulates of underlying mechanisms. *Neurosci. Biobehav. Rev.* 17: 385-396.
- Moll, P.P.** (1993). Biometrical searches for new genes with effects on quantitative risk factors for atherosclerosis: Problems and prospects. *Curr. Opin. Lipidol.* 4: 144-151.
- Motulsky, A.G.** (1996). Nutritional ecogenetics: Homocysteine-related arteriosclerotic vascular disease, neural tube defects, and folic acid. *Am. J. Hum. Genet.* 58: 17-20.
- Neel, J.V.** (1940). The interrelations of temperature, body size, and character expression in *Drosophila melanogaster*. *Genetics* 25: 225-250.
- Neel, J.V.** (1941). Studies on the interaction of mutations affecting the chaetae of *Drosophila melanogaster*. I. The interaction of hairy, polychaetoid, and Hairy wing. *Genetics* 26: 52-68.
- Neel, J.V.** (1943). Studies on the interaction of mutations affecting the chaetae of *Drosophila melanogaster*. II. The relation of character expression to size in flies homozygous for polychaetoid, hairy, Hairy wing, and the combinations of these factors. *Genetics* 28: 49-68.
- Neel, J.V.** (1970). Lessons from a "primitive" people. *Science* 170: 815-822.
- Neel, J.V.** (1971). Genetic aspects of the ecology of disease in the American Indian. In: *The Ongoing Evolution of Latin American Populations* (Salzano, F.A., ed.). C.C. Thomas, Springfield, IL, pp. 561-590.
- Neel, J.V.** (1977). Health and disease in unacculturated Amerindian populations. In: *Health and Disease in Tribal Societies, Ciba Foundation Symposium 49* (Elliott, K. and Whelan, J., eds.). Elsevier North Holland, Inc., Amsterdam, pp. 155-177.
- Neel, J.V.** (1991). Priorities in the application of genetic principles to the human condition: A dissident view. *Perspect. Biol. Med.* 35: 49-67.
- Neel, J.V.** (1994). *Physician to the Gene Pool*. John Wiley & Sons, New York, pp. ix & 457.
- Neel, J.V.** (1995a). Invited Editorial: New approaches to evaluating the genetic effects of the atomic bombs. *Am. J. Hum. Genet.* 57: 1263-1266.
- Neel, J.V.** (1995b). An open letter to the American Society of Human Genetics: The neglected genetic issue – the why and how of curbing population growth. *Am. J. Hum. Genet.* 56: 538-542.
- Neel, J.V.** Looking ahead: Some genetic issues of the future. *Perspect. Biol. Med.* (in press).
- Neel, J.V. and Lewis, S.E.** (1990). The comparative radiation genetics of humans and mice. *Annu. Rev. Genet.* 24: 327-362.
- Neel, J.V., Schull, W.J., Awa, A.A., Satoh, C., Kato, H., Otake, M. and Yoshimoto, Y.** (1990). The children of parents exposed to atomic bombs: Estimates of the genetic doubling dose of radiation for humans. *Am. J. Hum. Genet.* 46: 1053-1072.
- Nelson, T.** (1996). Russia's population sink. *World Watch* 9: 22-23.
- Pimentel, D., Harman, R., Pacenze, M., Pecarsky, J. and Pimentel, M.** (1994). Natural resources and an optimum human population. *Popul. Environ.* 15: 347-369.
- Potter, V.R.** (1988). *Global Bioethics*. Michigan State University Press, Lansing, MI, pp. xvi & 203.
- Risch, N.J. and Zhang, H.** (1996). Mapping quantitative trait loci with extreme discordant sib pairs: Sampling considerations. *Am. J. Hum. Genet.* 58: 836-843.
- Royal Society of London and U.S. National Academy of Sciences** (1992). *Population Growth, Resource Consumption, and a Sustainable World*.
- Scientific American** (1989). *Managing Planet Earth*, Scientific American, September.
- Sing, C.F., Haviland, M.B., Templeton, A.R., Zerba, K.E. and Reilly, S.L.** (1992). Biological complexity and strategies

- for finding DNA variations responsible for inter-individual variation in risk of a common chronic disease, coronary artery disease. *Ann. Med.* 24: 539-547.
- Sing, C.F., Zerba, K.E. and Reilly, S.L.** (1994). Traversing the biological complexity in the hierarchy between genome and CAD endpoints in the population at large. *Clin. Genet.* 46: 6-14.
- Sing, C.F., Haviland, M.B. and Reilly, S.L.** (1996). Genetic architecture of common multifactorial diseases. In: *Variation in the Human Genome, Ciba Foundation Symposium 197* (Chadwick, D. and Cardew, G., eds.). John Wiley & Sons, Chichester, pp. 211-232.
- Strohman, R.C.** (1993). Ancient genomes, wise bodies, unhealthy people: Limits of a genetic paradigm in biology and medicine. *Perspect. Biol. Med.* 37: 112-145.
- Strohman, R.C.** (1995). Genetic simplicity, epigenetic complexity. In: *The Human Genome* (Fischer, E.P. and Klose, S., eds.). Piper, Munich, pp. 147-191.
- Tanksley, S.D.** (1993). Mapping polygenes. *Annu. Rev. Genet.* 27: 205-233.
- Thomas, L.** (1992). *The Fragile Species*. Scribner's, New York, pp. x & 193.
- Thompson, E.A.** (1981). Optimal sampling for pedigree analysis: Relatives of affected probands. *Am. J. Hum. Genet.* 33: 968-977.
- Thummel, C.S.** (1995). From embryogenesis to metamorphosis: The regulation and function of Drosophila nuclear receptor superfamily members. *Cell* 83: 871-877.
- Turner II, B.L., Clark, W.C., Kates, R.W., Richards, J.F., Mathews, J.T. and Meyer, W.B.** (1990). *The Earth as Transformed by Human Action*. Cambridge University Press, Cambridge, pp. xvi & 713.
- Union of Concerned Scientists** (1992). *World Scientists' Warning to Humanity, Statement Signed by 1600 Scientists*.
- Weiner, J.** (1990). *The Next One Hundred Years*. Bantam Books, New York, pp. 312.
- Wilson, E.O.** (1992). *The Diversity of Life*. Belknap Press of Harvard University Press, Cambridge, MA, pp. 424.
- World Commission on Environment and Development** (1987). *Our Common Future*. Oxford University Press, Oxford, pp. xv & 383.
- World's Scientific Academies** (1993). *Population Summit of the World's Scientific Academies, A Joint Statement by Fifty-eight of the World's Scientific Academies*.