At mid-point in the molecular revolution

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Introduction

The papers in this special number of *BioEssays* provide a compelling overview of aspects of the progress in biomedicine over the past 50 years. Truly it has been a Golden Age for biology, the cumulative impact on our view of self comparable to the impact of the Copernican and Darwinian epochs. It is possible – and proper – to revel in the production and synthesis of this fantastic body of knowledge with no thought of its application to human welfare, just as we marvel at the insights into the nature of the universe resulting from modern astronomy. Almost, however, from the first days of molecular genetics, but especially with the demonstration of the ease with which genes can be shifted from cell to cell, even across species, there has been intense interest in how the new knowledge might be used to alter the human condition. I've often wondered, to what extent our species' push toward the innovative use of new knowledge is rooted in our intensely social organization. The guiding principle of social organization in all tribal, preliterate cultures is a kinship system in which all the members of the community have a defined place. In such a community, in general, the adult's concern for one's spouse and children is highest, with concern lessening as one extends outward within the bounds of kinship, but always with a strong sense of who is and who is not kinfolk. To what extent this kinship-oriented behavior has a genetic basis, now under siege, an expression of an ingrained desire to 'help the family', and to what extent it is a cultural adaptation by an unspecialized animal who for various reasons would have great difficulty going it alone, is unclear. No matter the biological basis of our behavior, no sooner does new knowledge become available to our species than – repeatedly in history – ways to exploit it are vigorously investigated.

The hallmark of the biological science of the next decade will be efforts to derive practical applications from this new body of knowledge. With increasingly limited resources (see below), although the momentum of the Human Genome Project and related activities will dominate many biological developments of the immediate future, it is more and more clear that long before all those 3×10^9 nucleotides are put in their proper place, long before all the 80,000 genes and their mutational variants have been described, considerations of the use (and potential misuse) of even the present body of knowledge will have come to dominate the field of molecular biology. This investigator-driven push will be strongly reinforced by the sources of the lavish research funding of the past 50 years – ultimately, the people – who, in the pragmatic societies of the world, will increasingly be looking for tangible returns from society's investment. While I personally – and most scientists – might feel that the corpus of knowledge created is sufficient return, society as a whole will not see it that way. But as the full complexity of the genome shaped by four billion years of evolution unfolds, will history see the present efforts to manipulate this complexity as foolishly premature, driven by our poorly understood biology and a world impatient to realize its investment?

The world the next generation will face

There has always been a certain tension in society between the 'doers' and the 'dreamers' (the latter, in this context, being most of those elaborating molecular insights that are too difficult for all but a few to comprehend). Now, for all society's lip service to 'science', these tensions are about to be exacerbated. Many people, as well as myself, have in recent years been documenting the oncoming crunch between the world's ballooning population and the diminishing resources to meet the needs of that population. Space constraints do not permit even a brief enumeration of the more salient facts. To an approximation, in another generation, the world's population may have risen from its present 5.8 billion persons to some 8 billion, even as the various resources to support that population – agricultural, hydrological, oceanic and mineral – decrease by at least 25%. That simple statement implies that in 2020, there will be half the resources per person as at present, but with a more appallingly unequal distribution of these resources than at present.

Human ingenuity may delay the precise day on which the necessary clear consensus is reached concerning the gravity of these developments, but that the situation will call for a dramatic readjustment, both with respect to population growth and to resource consumption, cannot be doubted. In another 20 years, even the most obtuse will be forced to recognize the gravity of the human dilemma. If the biological community does not assume its share of the necessary thoughtful leadership soon, the 'doers' will be more precipitous.

Perhaps the clearest portent of the economies the future holds is the current effort to rein in medical expenses in the United States. In this country, with its enthusiastic embrace of all things new, and the recent research support to improve old and explore new medical technologies, the cost of medical care had far outstripped the cost in any other country. Now the practice of medicine in the United States is convulsed by efforts to rein these costs in. The guiding principle of the 'new' medicine is cost effectiveness, a difficult principle to apply when so many of medical expenditures involve prolongation of a waning life. The same pressures may overtake the new genetic medicine as its fruits come on line.

The primary argument of this essay, very simply, is that at best reaping the full potential benefits of the new knowledge is decades away, and this millennium will never be realized unless society puts its population/resource house in order – and soon.

Applications of the new genetic knowledge

It is against this background that we consider some of the potential applications of the new genetic knowledge. Many of these do not of course involve medicine, but those that do will have to meet the same scrutiny that is now being accorded other medical procedures. Disease prevented is disease that not only does not have to be treated but also does not bring grief to the individual and family involved. Where catastrophic genetic disease that can be detected prenatally is involved, it will be necessary to work out the relative effectiveness of prenatal diagnosis with abortion as contrasted with presumably life-long genetic therapy, all with due regard for the mounting ethical issues. First and foremost among these issues is the right of a woman carrying a grossly defective fetus to have a first-trimester abortion. Unfortunately, at present only a small fraction of simply inherited diseases seems, for theoretical or practical reasons, amenable to prenatal diagnosis and subsequent abortion.

Most of the discussion of the other uses of this new knowledge have been along interventionist lines. The appropriate studies reveal a malfunctioning gene, and the requisite steps are taken to offset the abnormality of that gene or even to implant into the somatic tissues of the individual a sufficient quantity of normal genes that the individual's functioning is restored to adequate levels. For all the gaudy publicity, there is not yet a single example of successful gene therapy as this was originally defined. The greatest immediate promise for the application of the new genetic knowledge seems to rest with engineered vectors directed against the genetic abnormalities that characterize a mutationally based acquired disease, cancer.

As, however, knowledge of the human genome and how environmental factors influence its functioning unfold, there may evolve a supplementary but very powerful approach to these genetic therapies. Many of the diseases involving the citizens of the 'advanced' (i.e. technologically sophisticated) countries are so-called 'diseases of civilization': e.g. hypertension, obesity, non-insulin-dependent diabetes, cardiovascular disease and intrinsic bronchial asthma. The extensive studies of the genetic basis for these diseases now in progress should reveal much about the inherited predisposition to these diseases. Current thinking about the use of these new insights seems to be dominated by considerations of genetic (including gene) therapy. These same insights, however, should vastly improve understanding of the gene-environmental interactions which bring these 'diseases of civilization' into prominence.

Perhaps the greatest ultimate contribution of molecular genetics to this approach to these diseases will be through its incorporation into sophisticated genetic epidemiology, resulting in an understanding of gene-environmental interactions that will lead to euphenic developments that create an environment in which the complex genotype we are slowly coming to understand will better express its physical and mental capabilities. To be sure, euphenics can proceed without a detailed understanding of the genotype, but one would like to believe it would proceed more efficiently with that knowledge. The most obvious point of attack is dietary, but the psychological should not be far behind. Unfortunately, the utilization of the new genetic knowledge for euphenic purposes would appear to require a degree of self-discipline not much in evidence these days – it is far easier to trust science to come up with a technical fix, than to discipline oneself to a life style which lessens the probability of realizing genetic predispositions. As, however, the future unfolds, with governments intent on holding medical expenses down, we will see more emphasis on euphenics. The current effort in many countries to curtail cigarette smoking, although not thus far involving a genetic principle, is an example of how government may intervene.

My secondary argument in this essay is, then, that there may for some of the genetic problems of humankind be more economical and low-tech alternatives to the high-tech solutions being envisioned, involving the manipulation of the environment – but they demand personal discipline rather than magic genetic bullets.

Back to basics

Finally, we come back to the general question of the milieu in which molecular genetics will find itself in another 10-20-30 years, as the harsh realities of the consequences of the population having overshot its sustainable resource base become so apparent that they can no longer be ignored by the body politic. I have for some years been arguing for a worldwide policy in which a strong effort is made to limit family (sibship) size to two, with no constraints based on parental attributes. Without some such policy, especially in the face of dwindling agricultural, mineral and hydrological resources, our children and grandchildren cannot possibly enjoy our present standard of living. All segments of society will suffer, but if the Golden Age of genetics is prematurely terminated by harsh realities, genetics and related disciplines will suffer disproportionately.

Such a program of population control will qualitatively essentially preserve the human gene pool in its present condition. It is as genetically neutral as can be, and yet I find colleagues who see eugenic overtones in any effort to influence human reproduction, and feel geneticists should not get involved. It is a great irony, that the efforts at gene therapy and other applications of the new genetics, by altering the prospects for survival and reproduction of genetically impaired individuals, already have implications for the qualitative composition of the gene pool of the future. These implications – small though they be – are dysgenic. It would be hypocrisy, for geneticists to ignore this fact, while backing away from a strictly non-eugenic approach to population control.

The author will be happy to document any of the statements in this piece upon request.

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