INTRODUCTION

Therapeutic Promise of Molecular Genetics

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The application of molecular genetics to medicine is based on the observation that even common diseases have both genetic and environmental components. Conventional medicines are often effective in managing environmental components of disease but are generally ineffective in managing genetic diseases or manipulating the genetic component of multifactorial diseases. The development of therapies aimed at the genetic component of disease will require non-conventional medicinal applications of molecular genetics. Various approaches have been proposed such as diagnosing the propensity for disease to facilitate early intervention with conventional therapies, selectively eliminating mutant genes from human populations, correcting mutations in human chromosomes, and using genes as medicines to modify the genetic components of disease. Of these, it is the development of gene medicines that has the greatest practical potential. The combination of conventional medicines, focused on the environmental components of disease, and gene medicines, focused on the genetic components, will provide the clinician with broad options for managing health and disease. The challenge to molecular biology is to develop gene medicines that are effective, safe, and socially acceptable, and therapies that map well to established clinical practice and may be employed efficaciously alongside conventional medicines. Key words: gene therapy/mutation diagnosis/genetic disease/genetic screening. J Invest Dermatol 103:2S–5S, 1994

We are in the midst of a revolution in biology and medicine. It is a revolution brought about by molecular biology, by the discovery of the structure of DNA and the deciphering of the genetic code, by the development of methods for recombination of genetic elements, and by the decision to proceed with sequencing the entire human genome. It is a revolution based on the postulate that by deciphering the genetic code, and learning how it contributes to both disease and the resistance to disease, medicine will acquire dramatic new healing powers. Scientists, physicians, and the public share enormous expectations for a new age of genetic medicine, believing that the genetic understanding of disease will make diseases such as cancer, morbidity, and infection amenable to efficacious medical management.

The genetic approach to disease, however, is not new. The concept that genetic inheritance contributes to both health and disease was expounded in detail by Sir Archibald Garrod, whose studies provided the first conclusive evidence for inherited disease in man. Garrod's landmark studies of Alkaptonuria, the first inborn error of metabolism to be recognized in humans, let him to consider the impact of genetics on human health and disease in general. Garrod's publication of Inborn Errors of Metabolism (1909) and Inborn Factors in Disease (1931) [1] outlined a surprisingly prescient view of human genetics. Garrod recognized that inherited disease was only the most manifest example of the role genetics played in human health and disease. He wrote (1931, p 157)

It might be claimed that what used to be spoken of as a diathesis is nothing else but chemical individuality. But to our chemical individualities are due our chemical merits as well as our chemical shortcomings; and it is more nearly true to say that the factors which confer upon us our predispositions to, and susceptibility from, the various mishaps which are spoken of as diseases, are inherent in our very chemical structure; and even in the molecular groupings which confer upon us our individualities, and which went to the making of the chromosomes from which we sprang.

Since the time of Garrod, the concept that both disease and the resistance to disease have a significant genetic component has been applied to many disorders that do not exhibit classical patterns of genetic inheritance. It is now generally accepted that there is a genetic component to diseases such as arthritis, cancer, and even dementia. In fact, the classical paradigm of allopathic medicine, in which disease is described as a perturbation of normal homeostatic mechanisms by exogenous, pathogenic agents, has been revised to reflect the understanding that most diseases can be described as having both genetic and environmental components. In this model, homeostasis is understood to involve a balance between inherent genetic functions in the patient and the environment. Perturbations in either genetically determined functions, or the environment in which they operate, can disturb this homeostasis resulting in disease.

The relative genetic and environmental components underlying a series of dermatologic diseases are shown in Fig 1. In this representation, the contribution of inherited factors is shown along the X-axis whereas the contribution of environmental factors is shown along the Y-axis. Certain diseases are almost entirely caused by environmental events, for example burns. On the other extreme, disorders such as congenital nevi are almost entirely caused by genetic determinants.* Most conditions, however, can be graphed in the middle of this chart. Even inherited disorders such as epidermolysis bullosa have an environmental component that is an essential

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*Genetic determinants may not be completely deterministic as evidenced by the stochastic component of many disorders as well as the phenomenon of incomplete penetrance or expressivity.

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Inborn Errors by genetic factors as well as environmental factors. The incidence of melanoma is related both to the inherited degree of skin pigmentation and environmental exposures. Disorders such as psoriasis and diabetes, for example, are profoundly affected by both genetic factors and environmental events.

Garrod was perhaps the first to recognize that inherited diseases represented useful models in which to study the genetic contribution to disease in general. Since the original edition of Garrod's *Inborn Errors of Metabolism* in 1909, which listed four known inherited metabolic diseases, almost 10,000 different inherited genetic disorders have been described. These have been catalogued by Victor McKusick [2]. Whereas considerable progress has been made in the understanding of genetic disease, less progress has been made in developing effective therapies using conventional medical approaches.

CONVENTIONAL MEDICINE AND GENETIC DISEASE

Conventional, allopathic medicine is focused on treating external, environmental components of disease. This approach is effective in dealing with disorders such as infections in which a discrete environmental pathogen may be selectively eliminated. The conventional approach to cancer similarly views cancer as an invading pathogen that can be attacked. The same conceptual approach is taken to diseases such as psoriasis in which invading immune cells or hyperproliferative epidermal cells are seen as pathogenic agents that can be eliminated by therapy.

Conventional medicine, however, is not generally effective in treating genetic disease. The limitations of conventional medicine in treating genetic diseases were demonstrated in a study performed by Dr. Charles Scriver and Dr. Barton Childs and their colleagues at McGill University and The Johns Hopkins University [3,4]. These investigators studied a series of genetic disorders randomly selected from McKusick's catalog [2]. This study asked whether conventional medicines (circa 1986) had a significant impact on the well-being of patients with these disorders. They demonstrated that for greater than 70% of the diseases studied, conventional medicine had no significant effect on the well-being, longevity, appearance, schooling, or growth of afflicted individuals. Thus, though there have been significant improvements in therapy for certain genetic diseases, these data suggested that there was something different about the nature of genetic disease that rendered these diseases less susceptible to conventional medicine.

If genetic disease represents a model for the genetic component of multifactorial diseases, then it might be predicted that contemporary medicines will not be as effective against the genetic components of disease as they are against the environmental components. In considering the diseases shown in Fig 1 this appears to be true. Although there are efficacious therapeutic approaches to those diseases having an extensive environmental component, those having a predominantly genetic origin are poorly addressed by conventional medicine. This is significant. If conventional medicines are generally ineffective against the genetic components of disease, then an improved understanding of the genetic origin of disease may not necessarily lead to improved clinical therapies. Rather, novel approaches to treating disease may be required. The expectation is that these new approaches will arise from the application of molecular genetics to medical diagnosis and therapeutics.

MOLECULAR GENETIC APPROACHES TO THERAPEUTICS

Various strategies have been proposed for using molecular genetics to manage diseases with significant genetic components. It has been proposed that molecular diagnostics will be used to identify the propensity for disease before active pathogenesis is apparent, allowing conventional medicines to be used to greater effect. It has been proposed that population screening might be used to eliminate deleterious genes from the population, therefore eliminating the risk of genetic disease. It has been proposed that genetic technologies might be used to correct the sequence of deleterious genes. Finally, it has been proposed that genes might be used as medicines to directly manipulate the genetic component of disease pathogenesis. Are these measures likely to be clinically feasible, efficacious, and acceptable?

**Diagnosing the Propensity for Disease** The goal of the human genome project is not only to identify diseases caused by mutations in specific genes, but to identify the array of genetic elements involved in common, multifactorial disease processes. Thus, whereas cancer is not caused by a singular mutation, various genetic elements are associated with the predisposition to cancer. Similarly, although inflammatory dermatitis is not caused by a discrete mutation, there are clearly several genetic elements that contribute to the disease. It is likely that as the genetic involvement in such diseases is increasingly described on a molecular level, molecular genetics will allow diagnosis of those individuals who are at risk for these diseases. The expectation is that such diagnostic tests will alter medical practice by allowing physicians to recognize the propensity for disease rather than responding to its progression. The question, however, is whether this recognition will, in fact, lead to effective therapies.

Clinical experience in managing cancer suggests that early diagnosis can have a significant impact on the outcome of disease. This benefit, however, arises not from actions taken to alter the genetic predisposition to disease, but from the application of medicinal and surgical therapies targeted to the environmental component of the disease. There are many examples of conventional therapies that alter the environment in such a way that multifactorial (genetic + environmental) diseases do not progress. For example, the treatment of diabetes with diet, insulin, or oral hypoglycemic agents is an example of manipulating the environment to treat a disease that has a significant genetic component. So too, allergen avoidance for eczema and surgical removal of early melanomas represent effective therapies of diseases that are partially genetic.

The effectiveness of therapy in this model, however, will not relate to the genetic component of disease, but to the extent that homeostasis can be restored in the presence of a genetic predisposition to disease by environmental manipulations. There is no reason to believe that improved diagnosis alone will enable conventional medicine to have a greater impact on the genetic component of multifactorial disease than it has on diseases that are largely genetic in nature.

**Eliminating Mutant Genes From Human Populations** The concept of using molecular genetics to screen for treatable diseases must be clearly distinguished from the eugenic notion of screening for deleterious genes in the population so that these genes can be eliminated through prescriptive matings or selective abortion. Measures to limit the propagation of deleterious genes are still sometimes proposed as a means for eliminating genetic disease. Moreover, concern is often expressed that treating genetic disease could have the opposite effect, that by treating individuals with genetic (or partially genetic) diseases, the normal attrition of deleterious genes will be prevented and these genes will become increasingly prevalent in the population.
This line of reasoning represents the basis of eugenics as originally proposed by Francis Galton and the widespread application of social eugenic practices during the first half of this century. It is a line of reasoning that is scientifically invalid and prone to social abuse. It is invalid because the statistical effect of therapy on the gene pool for most multifactorial or even recessive diseases is likely to be extremely minor. Moreover, it assumes that we understand the complete medical impact of single genes within the human gene pool. In fact, we do not. There are estimated to be greater than 100,000 genes in the human genome, and it has been estimated that everyone carries more than 5–10 genes that could be lethal if expressed in select genetic or environmental circumstances. We do not know, and perhaps cannot know with certainty, the circumstances under which any single gene may induce dyshomeostasis. There are even examples of genes that are deleterious in one environment, but beneficial effect in others such as Hb, which causes sickle cell disease but may also protect against malaria. Other deleterious genes may be closely linked to genes that are advantageous and thus propagate through the population together. Thus, it is virtually impossible to know whether elimination of specific genes through population screening would ultimately improve or impair the genome.

This line of reasoning is prone to social abuse because the perception of whether a gene is deleterious reflects a social, cultural, and environmental context. Anthropologic studies teach that the significance of skin color, body habitus, and longevity varies profoundly in different human populations, in different regions of the world, and at different times in human cultural evolution.

Finally, it is important to reiterate the ethical principles of fairness and individual freedom that make eugenic practices an anathema to modern society. Any practice that compromises the genetic freedom of the individual for social ends, no matter how apparently legitimate the ultimate goal, may trespark down the slippery slope toward eugenics. Conversely, those applications of genetic technologies for preventing or treating genetic or acquired disease that preserve the principles of fairness, individual freedoms, and individual imperatives may not be eugenic in nature and may be acceptable to society [5].

Genetic Correction Therapy It is commonly proposed that once mutations are identified in the genome, it will be possible to selectively repair these mutations by genetic engineering. Methods for homologous recombination have been used to correct defects in inbred mouse lines leading to the perception that this procedure may eventually be applicable in medical practice. It is not difficult to envision that bone marrow stem cells might be grown in the laboratory, that defects such as a thalassemia, Hb, disease, or severe combined immunodeficiencies might be corrected in these cells, and that transplantation of these cells back into the host would lead to effective therapy. Current technologies, however, are not suitable for gene correction in large numbers of somatic cells. Current technologies provide little evidence that such methods might be feasible in the future. If, however, such methods were discovered, they might, in principle, be applicable in clinical practice.

The potential for gene correction in embryonic cells raises both technical and ethical concerns. On the surface, this approach to eliminating genetic disease resembles medical therapeutics and seems less prone to eugenic abuse than measures to eliminate mutant genes by selective mating or abortion. There is concern, however, that while some mutations cause diseases that are obviously pathogenic, gene correction, like eugenics, may be applied to more subjective conditions that reflect social prejudice or power. As with population screening, the major concern relates to the potential loss of individual freedoms, and those therapies applied with due concern for fairness and individual freedoms could be deemed acceptable to society.

There are, however, convincing logistic reasons to believe such therapy may not be applicable to medicine. Although gene correction in human embryos or embryonic stem cells in culture may prove to be technically feasible, the medical imperative to do no harm will remain predominant. Thus, the profound risks of genetic engineering of the germline must be compared to alternate approaches including preimplantation diagnosis or treatment of affected individuals. It seems unlikely that gene correction will ever prove to be the procedure with the least potential for harm.

Gene Medicine The potential for using genes as medicines to treat the genetic component of human disease arises from the identification and cloning of genes involved in various diseases as well as the ability to transfer genetic material into human cells. There are several ways in which gene medicines could be used in clinical therapeutics. Gene medicines can be used to replace expression of essential gene products in inherited disease. Gene medicines can be used to express gene products capable of restoring normal homeostasis in the presence of multifactorial and environmentally induced disease. Finally, gene medicines may be used to re-engineer cells in the body making these cells less prone to disease or more sensitive to conventional medical therapeutics.

Unlike conventional medicines, gene medicines will be directed explicitly at manipulating the genetic component of disease. The combination of conventional medicines, aimed at the environmental component of disease, and gene medicines, aimed at the genetic component of disease, may provide comprehensive therapeutic opportunities and could have an enormous impact on the management of health and disease.

There has been extensive social debate on the use of genes in medical therapeutics. Despite sometimes rancorous debate, no government or religious body has objected to gene therapies as long as the genetic therapy is directed only at somatic cells and conventional principles of balancing risk and benefit, obtaining voluntary informed consent, and adhering to the principles of fairness [6]. Because of the high visibility of gene therapy and level of social concern, a distinct review process has been established for gene therapy in which the Recombinant DNA Advisory Committee, acting in an advisory role to the Director of the NIH, performs a public review of all gene therapy applications in addition to the review performed by the FDA. To date, over 40 protocols for experimental gene therapy in human subjects have been proposed and approved. It is likely that within the decade hundreds of potential therapies will be proposed and that the first commercial products for gene therapy will be approved. The challenge is to derive clinically efficacious and acceptable gene medicines from the promise and the power of molecular genetics.

FROM GENES TO GENE MEDICINES

The combination of conventional medicines and gene medicines promises to provide physicians with broad instruments for managing health and disease. Thus, gene medicines need to be developed that can be used in clinical practice in conjunction with conventional medicines. Gene medicines will need to be administered by conventional routes of drug administration. They will need to provide a predictable therapeutic effect and appropriate duration of action. They will need to be acceptable to physicians and patients and to provide a balance of risk and benefit appropriate for each disease. Gene medicines need to be developed with the understanding that they will be prescribed in routine clinical practice where diagnoses is often incorrect, where compliance is poor, where patients have concurrent diseases, where patients often take multiple medications simultaneously, where adverse experiences are often inexplicable, and where the cost of health care is an increasingly important factor in the selection among alternate therapies.

These perspectives are essential in identifying appropriate methods and strategies for gene therapy. The ideal gene medicine for clinical application will be one that can be administered like a conventional medicine to express therapeutic levels of the gene product at a specific site in the body for a finite period of time. Ideally, gene
delivery can be achieved using non-immunogenic materials to avoid the potential for interactions with other gene therapies, infections, or vaccines. Ideally too, genes will not incorporate into the genome of the host cell, but can be engineered to persist for a discrete, controlled period of time in an episomal state. This will eliminate any risk from insertional mutagenesis, allow the therapy to be stopped if adverse experiences are encountered, and provide a means for controlling the level of the gene product by adjusting the dose and schedule of administration. Although this picture of a gene medicine may differ from the theoretical ideal of a one shot cure for genetic disease, this picture embodies the attributes that will make such medicines useful in clinical practice.

CONCLUSION
Molecular genetics holds considerable therapeutic promise. The realization of this promise, however, requires critical analysis not only of the technical potential of molecular genetics, but how this potential maps to clinical practice. Ultimately it is not the elegance of the genetic approach to disease that will find acceptance in clinical practice, but simply the development of therapeutic strategies and products that are effective, safe, facilitate compliance, and are cost effective. The development of gene medicines that may be used in conjunction with conventional medicines to deal with the genetic as well as environmental causes of disease will provide the physician with new and powerful therapeutic options for many common diseases. It is this approach that will allow patients and society to realize the therapeutic promise of molecular genetics.

REFERENCES