that the next 50 years will bring a genuine revolution of far greater individual significance than that delivered by genetics over the past 50 years. This is because lifestyle can conceivably be analysed, and in so doing, it should be possible to develop a genuinely personalized medicine.

Researchers can now think seriously about how to identify lifestyle influences: such studies will have to be on an unprecedented scale and one of the first of these, proposed to comprise 500,000 individuals in the United Kingdom, has already started[16]. These kinds of studies are a bold venture into relatively uncharted territory and face substantial technical, biological and science-culture challenges.

Scientifically, it is necessary to understand a deceptively simple equation: genes + environment = outcome. The difficulty here is the uncertainty surrounding both terms in the equation; ideally, one set of genetic factors will interact with one set of environmental influences to produce identical outcomes, but it is unknown whether this is always going to be the case. A far more difficult relationship would exist if multiple genetic factors interacted with multiple environments to achieve the same outcome. The example of glutathione *S*-transferase mutations, smoking and incidence of lung cancer[17] shows it is possible to detect some interactions, but it is unclear how, or even if, statistical methods might be developed for addressing the more complex possibilities.

Perhaps the greatest unknown in undertaking these projects is human psychology; the consequences of smoking have been known for many decades, but people still smoke. Advice does not imply acceptance. How to turn knowledge into practical outcomes must be an increasing focus of attention for both researchers and funding agencies.

Psychology is also in play in the initial decision to undertake this research; for researchers, funding agencies and politicians there is great risk implicit in undertaking a hugely expensive project with complex outcome. People would like to live in a simpler world, with simpler decisions, but the vision of such a project is enormous: once complete, as much will be known about the origins of human disorders as can be discovered by using such epidemiological and genetic studies. Perhaps more important, the beginnings of a new medicine will emerge, one focused uniquely and completely upon the individual, upon the combination of genetic uniqueness and personal choices that are the very essence of individual lives.

If we are collectively bold in our present decisions and accept the risk of action, a world can be created where medicine is a guide, not a place of last resort. If the past 50 years has seen the revolution of DNA, then the revolution cannot be completed without an appreciation of both genetic and environmental individuality; only then will individuals understand the meaning of their inheritance. □

doi:10.1038/nature01401

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The double helix in clinical practice

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The discovery of the double helix half a century ago has so far been slow to affect medical practice, but significant transformations are likely over the next 50 years. Changes to the way medicine is practised and new doctors are trained will be required before potential benefits are realized.

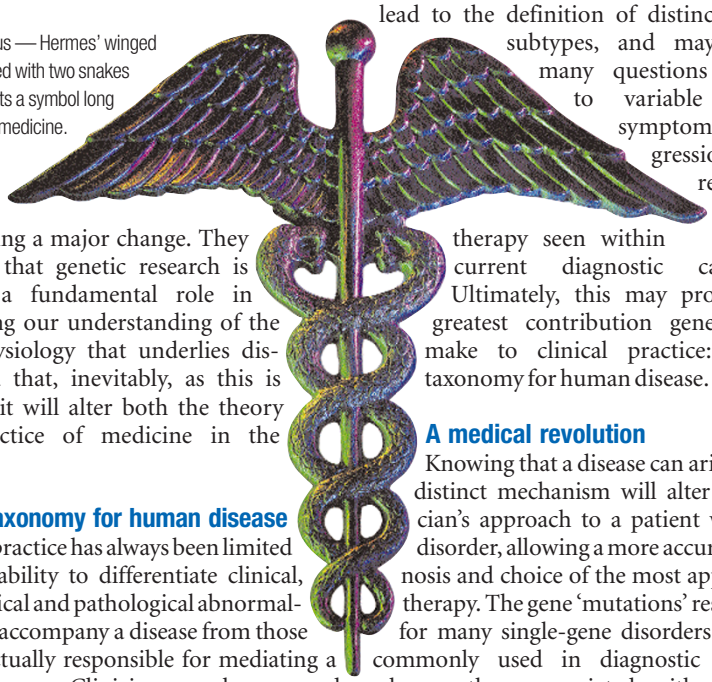
"It is much more important to know what kind of patient has a disease than to know what kind of disease a patient has." Caleb Parry, 18th century physician, Bath.

The structure of DNA established the basic framework that would develop into the field of molecular genetics. The information gleaned from this scientific endeavour continues to have a profound influence on our understanding of biological systems[1]. As most human diseases have a significant heritable component, it was soon recognized that the characterization of the genetic determinants of disease would provide remarkable opportunities for clinical medicine, potentially altering the way disease was understood, diagnosed and treated.

But despite the obvious potential applications to medicine, the development of significant genetic advances relevant to clinical practice could take generations. This is in marked contrast to many other medically related discoveries that occurred around the same time and which were translated rapidly into clinical practice. For instance, the development of penicillin by Ernst Chain and Howard Florey in 1941 was saving thousands of lives within months of their discovery of how to efficiently produce the antibiotic[2]. Discoveries relating to disease aetiology, such as the recognition in 1950 of a relationship between smoking and lung cancer, have had a profound effect on mortality[3]. This was despite the convictions of at least one distinguished statistical geneticist who argued against the causality of this observation, implying that a common genetic factor caused both lung cancer and a predilection to smoking cigarettes[4]!

Although other important discoveries have had demonstrably more impact on health care at the time of their fiftieth anniversaries than has the double helix, its slower transition from discovery to clinical implementation will be balanced by its potentially profound impact across all medical disciplines. Progress has been slow, but mounting evidence suggests that, while public health and antibiotics produced important healthcare outcomes in the past 50 years, the next 50 are likely to belong to genetics and molecular medicine.

The potential impact of genetics on clinical practice has been questioned by some observers[5] who believe that the positive predictive value of genetic testing for most common disease genes will be insufficient to provide the beneficial effects seen with single-gene disorders, which affect only a tiny proportion of the population. Many advocates of genetics argue, on the other hand, that our understanding of disease is



The caduceus — Hermes' winged staff entwined with two snakes — represents a symbol long adopted by medicine.

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undergoing a major change. They contend that genetic research is playing a fundamental role in improving our understanding of the pathophysiology that underlies disease and that, inevitably, as this is applied, it will alter both the theory and practice of medicine in the future[6].

A new taxonomy for human disease

Clinical practice has always been limited by its inability to differentiate clinical, biochemical and pathological abnormalities that accompany a disease from those events actually responsible for mediating a disease process. Clinicians may have moved on from calling 'fever' a disease[7], but they still rely on phenotypic criteria to define most diseases, and yet these may obscure the underlying mechanisms and often mask significant heterogeneity. As Thomas Lewis pointed out in 1944, diagnosis of most human disease provides only "insecure and temporary conceptions"[8]. Of the main common diseases, only the infectious diseases have a truly mechanism-based nomenclature.

An understanding of the genetic basis of maladies is providing a new taxonomy of disease, free from the risk that the diagnostic criteria related to events are secondary to the disease process, rather than to its cause. Genetic information has allowed us to identify mechanistically distinct forms of diabetes, defining an autoimmune form of the disease associated with human leukocyte antigens (a highly diverse complex of immune-system genes), and recently has implicated dysfunction of factors that affect both expression and modification of gene products in mediating the adult form of the disorder[9]. Similarly, we are now aware of a range of molecules and pathways previously not recognized in the pathogenesis of asthma[10–12].

A clearer understanding of the mechanisms and pathways that mediate disease will lead to the definition of distinct disease subtypes, and may resolve many questions relating to variable disease symptoms, progression and response to therapy seen within current diagnostic categories. Ultimately, this may provide the greatest contribution genetics will make to clinical practice: a new taxonomy for human disease.

Table 1 **Molecular genetics in clinical practice**

- Mechanistically based diagnostic criteria
- Predisposition testing and screening
- Rapid molecular diagnostic testing of pathogens
- Pharmacogenetics
- Identification of new drug targets
- Tools for molecular medicine (for example, recombinant DNA methodology)
- Recombinant expression of therapeutic proteins
- Gene therapy

A medical revolution

Knowing that a disease can arise from a distinct mechanism will alter a physician's approach to a patient with that disorder, allowing a more accurate prognosis and choice of the most appropriate therapy. The gene 'mutations' responsible for many single-gene disorders are now commonly used in diagnostic practice, whereas those associated with common complex diseases are just being characterized. Although their predictive value will be less than with single-gene disorders, their contribution as risk factors will be similar to other risk factors such as blood pressure, cholesterol levels and environmental exposures. Because much of clinical practice involves evaluating and acting on risk probabilities, the addition of genetic risk factors to this process will be an important extension of existing practice. The overall effect of genetic risk factors is likely to be significant. For example, recent estimates in breast cancer suggest that the attributable genetic risks are likely to exceed the predictive value of a range of existing non-genetic risk factors[13].

Other potential applications of genetics in health care may be realized in a shorter timeframe. Individual variation in response to drugs and in drug toxicity is a significant problem, both in clinical practice and in the development of new therapeutic agents. Clear examples now exist of genetic variants that alter metabolism, drug response or risk of toxicity[14,15]. Such information provides an opportunity to direct therapy at individuals most likely to benefit from an intervention, thereby reducing cost and toxicity, and improving methods for drug development.

The discovery of the structure of DNA not only led to an ability to characterize genetic determinants in disease, but also provided the tools necessary for the revolution in molecular medicine that has occurred in the past 25 years. The description of the double helix was the first important step in the development of techniques to cut, ligate and amplify DNA. The application of these molecular biology and DNA-cloning techniques has already had a profound impact on our understanding of the basic cellular and molecular processes that underlie disease.

Molecular biology has improved our ability to study proteins and pathways involved in disease and has provided the technology necessary to generate new sets of targets for small-molecule drug design. It has also enabled the creation and production of a new range of biological therapeutics — recombinant proteins such as interferon, erythropoietin and insulin, as well as therapeutic antibodies, which are one of the fastest growing classes of new treatments. Further extensions of this methodology will see the inevitable introduction of DNA-based therapies that will produce proteins of interest in the appropriate cellular setting. DNA-based vaccines represent the first wave of such novel gene-therapy approaches to disease and many more are expected to follow.

We are undergoing a revolution in clinical practice that depends upon a better understanding of disease mechanisms and pathways at a molecular level. Much has already been achieved: an enhanced understanding of disease-related pathways, new therapies, novel approaches to diagnostics and new tools for identifying those at risk. But more remains to be done before the full impact of genetics on medicine is realized. Complex disease, with multiple susceptibility determinants (both environmental and genetic), will take time to dissect. This information must then be moved into the clinic and evaluated for its benefits.

As the practice of medicine moves to one more scientifically founded in disease mechanisms, many aspects of clinical practice will need to be transformed. Individual genetic variation is likely to explain a significant part of the heterogeneity seen clinically in the natural history of disease and in response to therapy. Tools to tailor medicine to an individual's needs rather than directing it at a population will inevitably become available. Similarly, as predictions of risk improve, early or preventative therapy of high-risk populations will become a reality, with screening programmes targeted to those at particularly high risk.

Transforming clinical practice

For fundamental changes to take place in clinical practice, sweeping transformation will be needed to healthcare provision, economic management and training. It is currently difficult to predict the cost–benefit ratio for such changes — certainly the present impact of molecular medicine has not made medicine less expensive. Few medical schools adequately train their students to think mechanistically about disease; indeed, the trend towards pattern-recognition medicine, away from basic science training, means that we are still far from educating the next generation of clinicians to apply the knowledge and tools bequeathed to us by the double helix. The evolution in health care that will incorporate these new principles of early diagnosis and individualized therapy will be a daunting

challenge in an era of uncertainty for healthcare systems worldwide.

The influence of genetic and molecular medicine on the health of patients is already sufficiently ubiquitous that it will have an impact on most common diseases. Its influence will grow over the next few decades (Table 1). It will not, however, answer all of the questions about human health, nor will it provide all the answers for optimizing clinical practice. The reductionism that accompanies molecular genetics will identify the pieces in the jigsaw, but assembling these to understand how complex systems malfunction will require a substantially more integrated approach than is available at present.

The crucial role played by environmental determinants of disease will perhaps become more tractable when combined with an understanding of genetic susceptibility. Sceptics, rightly, will wish to see more data before they acknowledge that molecular medicine will be truly transformed over the next 50 years, despite the fact that its influence on diagnostics and new therapeutics is already clearly apparent. A transition is underway, the direction of travel is clear, but managing the change in clinical practice may prove at least as challenging as resolving the original structure of the helix. □

doi:10.1038/nature01402

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BRIDGEMAN/GETTY IMAGES

The *Mona Lisa* of modern science

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No molecule in the history of science has reached the iconic status of the double helix of DNA. Its image has been imprinted on all aspects of society, from science, art, music, cinema, architecture and advertising. This review of the *Mona Lisa* of science examines the evolution of its form at the hands of both science and art.

"A monkey is a machine that preserves genes up trees, a fish is a machine that preserves genes in water; there is even a small worm that preserves genes in German beer mats. DNA works in mysterious ways." Richard Dawkins in *The Selfish Gene* (Oxford University Press, 1976).

History has thrown up a few super-images, which have so insinuated themselves into our visual consciousness that they have utterly transcended their original context. This is epitomized by the *Mona Lisa*, painted by Leonardo da Vinci around 1503. The double helix of DNA is unchallenged as the image epitomizing the biological sciences. Both images speak to audiences far beyond their respective specialist worlds, and both carry a vast baggage of associations.

In the worlds of popular image diffusion, particularly on the Internet, the double helix is beginning to rival the *Mona Lisa* as a playground for eccentrics and obsessives (Fig. 1). There is an apparent difference, of course. Leonardo's panel painting is the product of human artifice, whereas DNA is a naturally occurring, large organic molecule. But Leonardo claimed that his art represented a systematic remaking of nature on the basis of a rational understanding of causes and effects. His painting is the result of a complex, nonlinear interaction between concept, subject, plan of action, acquired knowledge, skill, medium and the evolving image itself. In *The Art of Genes*[1], Enrico Coen argues that "biological development and human creativity are highly interactive processes in which events unfold rather than being necessarily pre-planned or anticipated. In other words, in both cases there is no easy separation between plan (or programme) and execution."

Looking at the investigation and representations of the double helix, we can say that they are cultural activities no less than any painting. Behind the discovery lies the vast infrastructure of a scientific culture that led to the development of the knowledge, theories, institutions, techniques and equipment that made the quest both possible and desirable. The very natures of scientific models and representations, using whatever technique, are integral to the vehicles of science communication. Their visual look is compounded from a complex set of factors, ranging from technical to aesthetic. But, in case anyone should be getting the wrong impression, I acknowledge that the cultural vehicles are designed to deliver non-arbitrary information that is open to rational scrutiny as a way of working towards real knowledge of the physical constitution of the world.

Looked at from a popular perspective (and even from the standpoint of reputation within science), James Watson and Francis Crick are identified with DNA no less than Leonardo is identified with the *Mona Lisa*. The researchers were in a very real sense the 'authors' or 'artists' of the acts of visualization that generated their models of the molecule. But their brilliant achievement was not necessarily of a higher order than that of the other pioneers of molecular modelling, such as the Braggs, John Kendrew, Max Perutz, Maurice Wilkins and Linus Pauling. Rather, they were uniquely fortunate that their molecule was both visually compelling, as a supreme example of nature's 'sculpture', and