Is modern genetics a blind alley?

Genetic research has yet to make the promised impact on medical practice. **James Le Fanu** thinks that it never will, but **D J Weatherall** believes it already has and will continue to do so

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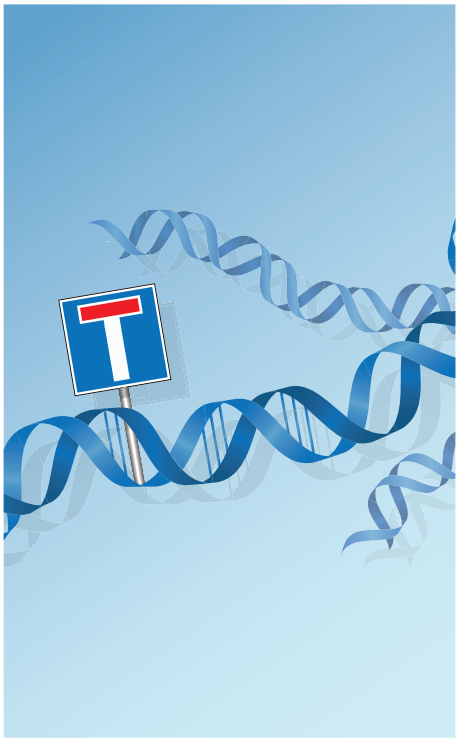

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YES In the 17th century William Harvey's medical contemporaries dismissed his discovery of the circulation of the blood as being of no diagnostic or therapeutic importance. Indeed, it was not till the advent of cardiac surgery nearly 300 years later that the knowledge that "blood is driven into a round by a circular motion" would find practical application.

Given this, and other similar historical precedents, it seems unwise to argue that modern genetics is a blind alley—not least because it might more readily be described as a four lane highway.

Since the discovery of the revolutionary techniques of gene sequencing in the late 1970s, modern genetics—together with neuroscience—has come to dominate the biomedical research agenda. Funding has doubled and doubled again in the recent past, reaching around $100bn (£65bn; €74bn) worldwide.[1] This endeavour is immensely productive, generating billions of bytes of biological data each week and a tidal wave of original studies and scientific journals that occupy an ever greater acreage of library space every year.[2] Modern genetics has become the largest single research field in the history of biology, driven forward by the expectation that "like a mechanical army [it will] destroy ignorance . . . promising unprecedented opportunities for science and medicine."[3]

Practical benefits

And yet for all this cornucopia of new facts and knowledge, its influence on everyday medical practice remains scarcely detectable. This is not to deny that there have been substantial achievements and fascinating insights, but even they fall far short of original expectations. Nearly 10 years have elapsed since the completion of the first draft of the human genome project with its ability to pinpoint the mutations responsible for more than 1000 monogenic disorders. But the realistic prospect of their prevention through antenatal screening remains limited to the thalassaemias and Tay Sachs disease.

Meanwhile the possibilities of their treatment, whether with gene replacement or targeted therapies, remain as elusive as ever.[4] Again, the ingenious techniques of biotechnology may have given us human insulin,

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NO The remarkable developments in molecular biology that followed the discovery of the structure and function of DNA in 1953 are widely regarded as being comparable to Darwin's description of evolution in the 19th century. I was therefore surprised to be invited to discuss the proposition that modern genetics is a blind alley.

Granted, in their enthusiasm some of the early protagonists of molecular biology underestimated the time it would take to bring some of the potential to fruition. Such overoptimism was particularly evident in the reactions of some medical scientists to the completion of the human genome project. They predicted that within the foreseeable future medical practice would be revolutionised; the genome would provide the answer to the causes of many of our common killers, and preventive medicine and therapeutics would become personalised, based on our individual genetic diversity.

However it is already apparent that, because we have fewer genes than expected and the structure of many of them is

"Spectacular advances have followed the application of molecular biology to cancer"

conserved across species, the answers to biological diversity, not to mention why some of us become diabetic, will require a much deeper understanding of the regulation of the genome and of its complex interplay with the environment. But because one aspect of a new field runs into predictable problems, this hardly leads the entire enterprise into a blind alley of complexity.

Benefits are already emerging

The tools of molecular biology started to be applied to the study of human disease in the 1970s.[1] One of the first applications was for the analysis of the molecular basis for monogenic disease. Though many of these conditions are rare, it is estimated that between 300 000 and 400 000 babies are born each year with a serious inherited disorder of haemoglobin. The discovery of their molecular basis provided invaluable information about abnormal gene action and led rapidly to their more accurate diagnosis and prenatal detection, greatly reducing births of affected babies in many countries. The molecular analysis of an uncommon

antiretroviral drugs, herceptin, infliximab, and similar valuable compounds but they remain overwhelmingly the exception in what the chief executive of Genentech has described as "the largest money losing industry in the history of mankind."[5]

The standard response to such observations is to concede that it has all turned out to be much more complicated than previously supposed, which is certainly true. None the less, the presumption holds that the remarkable capacity of modern genetics to generate yet more biological data must eventually, like a bulldozer, drive a causeway to the realisation of those "unprecedented opportunities."

Small component of disease

Perhaps, but the suspicion grows, within the genetic establishment itself, there might be something deeply flawed about the whole enterprise. "The mountain has laboured and brought forth a mouse," observed Steve Jones, professor of genetics at University College London last year.[6] The complexities of those powerful knowledge generating methodologies might explain in part the current paucity of original ideas in medicine. They have diverted attention (and resources) from the more fruitful forms of clinical research that flourished 30 or 40 years ago when the rate of important medical innovations was so much greater than it is now?[7 8]

It is thus conceivable that modern genetics might be a blind alley. There are two further reasons for supposing so. The first, obvious in retrospect, is that natural selection has ensured that genetics is not a particularly important or modifiable factor in human disease. There are only a handful of common genetic diseases, and even they are not very common. And although there is undoubtedly a genetic component to many adult illnesses, this can only be one of several factors, most of which remain as yet unknown. Meanwhile the practicalities of doing something about it—other than for a small minority—remain insuperable.

The further and more substantial constraint on the possibilities of modern genetics is that the power of its techniques in delineating the architecture of the genome has forcibly drawn to our attention our ignorance about the most elementary aspects of gene function. The astonishing revelation, for example, that we share the same modest number of 20 000 genes as the millimetre long worm *Caenorhabditis elegans*

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suggests we know next to nothing about the mechanisms of genetic inheritance.[9] It must thus be highly improbable that the future of medicine might lie in understanding disease at the most fundamental reductionist level of the gene and the proteins for which they code. Those who might doubt this verdict need look no further than the recent findings of the massive sophisticated Genome Wide Association Studies (GWAS), whose investigations show that genetics accounts for less than 5% of the heritability of obesity, diabetes, Crohn's disease, and other common conditions.[10 11]

This takes us to the end of the alley (or highway). There is no way out, and the sooner we recognise it the better because the current dominance of medical genetics threatens to bury the true spirit of intellectual inquiry under an avalanche of undigested (and indigestible) facts.

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form of inherited hypercholesterolaemia led to an understanding of cholesterol metabolism and to the development of new families of cholesterol lowering drugs.[2] The mutations for literally hundreds of other monogenic diseases have now been identified and, although gene therapy for their correction has proved difficult, sufficient progress has been made to suggest that this approach will be possible in the future. Furthermore, it seems likely that, just as in the case of inherited disorders of cholesterol, further studies of rare monogenic diseases will throw light on the causes of some of our common killers.[3]

The application of DNA technology to communicable diseases has also resulted in rapid advances in diagnosis and, at least in some cases, new treatments.[4] We need to think only of the speed at which organisms responsible for new epidemics can be identified to appreciate its role. Similarly, spectacular advances have followed the application of molecular biology to cancer. Since the early 1950s, molecular biology has shown that many common cancers result from acquired mutations of a variety of genes that are normally involved in critical interactions within and between cells.[5] Not only did these discoveries form a link between environmental carcinogens and how they might act, but they have led to new approaches to both screening and treatment of different forms of cancer.

Complex but not insoluble

These examples of the medical applications of molecular genetics, all of which are still progressing in many different directions, certainly do not suggest that modern genetics has reached a blind alley. Perhaps this gloomy prognosis reflects concerns about the value of genome-wide association studies to determine the genetic component of common diseases.[3] Although susceptibility to most of them seems to reflect the action of many different genes with small effects, presumably combined with environmental factors and the biology of ageing, it is early days. In the case of the dementias, for example, provided that great care is taken over the precision of phenotyping, even at the expense of patient numbers, it may still offer important clues about their pathophysiology.

It is true that modern genetics continues to unearth the extraordinary complexity of biological function, both in health and disease. But surely this does not support the concept that it has run into a blind alley. This is not the first time that increasing complexity of a field has led to the pessimistic view that further progress is beyond the scope of human imagination.[6] Indeed, modern physics, with its endless search for a grand unifying theory, seems to be going through a similar phase.

Although genetic research may take longer to produce results than originally estimated, there is abundant evidence that it must remain an integral part of a broader endeavour, ranging from cell biology and the more precise definition of phenotypes of disease by clinical investigation, to the epidemiological and social sciences. To divert a large proportion of its funding towards "translational" medical research, when we have such limited knowledge about the pathological basis of what is to be translated, would be extremely unwise. The remarkable advances that are occurring in evolutionary and developmental biology, and the highly original approaches to tackling the problems of biological complexity discussed recently by Sydney Brenner,[7] show that viewing the young discipline of genetic research as a blind alley would be short sighted.

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