A Century of Mendelism

Edited by
Robert A Peel and
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The Galton Institute

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Proceedings of a Conference organised by the Galton Institute, London, 2000

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PUBLISHED BY THE GALTON INSTITUTE

British Library Cataloguing in Publication Data

A Century of Mendelism : proceedings of a conference organised by the Galton Institute, London, 2000

1.Mendel's law - Congresses

I.Peel,Robert A. II.Timson, John III.Galton Institute

IV.Century of Mendelism. Conference (2000 : Galton Institute, London)

576.5

ISBN 095040666X

First published 2001 by The Galton Institute, 19 Northfields Prospect, Northfields, London SW18 1PE

Printed and bound in Great Britain by The Chameleon Press, 5-25 Burr Road, Wandsworth, London, SW18 4SG

Contents

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Introduction

John Timson

During the 20th century there were many remarkable inventions and discoveries which radically changed our lives. Atomic energy, antibiotics, television, organ transplantation, computers, plastics, aircraft, and the use of pesticides, to name just a few. However as we enter the 21st century it is widely believed that genetics and its offspring, molecular biology, offer the possibility of changes, for good or ill or both, more profound than any of the last century's achievements. Genetics had a slow start after the rediscovery of Mendel's work in 1900 but by the end of the 20th century it was no longer of interest to just a few biologists and some animal and plant breeders. Genetic counselling, the subject of the 85th Galton Lecture by Robert Resta, was widely available in the developed world, genetic testing and fingerprinting became part of medicine and forensic science, genetically modified organisms were the subject of public concern, and the Human Genome Project neared completion. In a single century we learned more about the mechanism of human heredity than in the entire previous history of mankind. And we began, a little hesitantly, to use this knowledge.

The basic facts of reproduction were almost certainly known to every human civilisation. They are simple: like produces like, cats breed to produce more cats, but there is also variation. Features such as eye colour, coat colour, and hair length can vary from one generation to the next. Pedigrees in which breeding has been controlled show that certain features can recur in subsequent generations. In the process of reproduction something is passed down the generations without necessarily showing its effects in each generation. Many civilisations also discovered that with selective breeding strains or varieties could be obtained in which a desired feature bred true or almost so. All our domestic dogs are the same

species. The considerable differences we see in the wide range of breeds we have today are due to mankind's control of dog reproduction over many centuries. Our domestic cats, however, have not had their breeding controlled in the same way[1]. What happened in selective breeding was well known to animal and plant breeders but how it happened and why a character could appear to skip a generation was unknown. There was, of course, no shortage of theories of inheritance of which the most popular was that it was due to something in the blood.

Mendel's seminal work with his now famous peas using seed colour characters showed that they were inherited in a discrete, unblended, manner. Others had indeed done similar work with peas before him but, and here lies his genius, unlike them Mendel recorded the numbers of each kind in each generation. He found that they occurred in simple ratios and that it was possible to forecast the results of future breeding experiments. It was clear that there were factors (what we now call genes) present in both parents which decided the appearance, the phenotype, of the offspring. Whether Mendel himself fully appreciated what he had discovered is rather debatable. Sadly for him his work made no real impact on the biologists of his day partly because the title of his paper "Experiments in Plant Hybridisation"[2] gave no hint of the revolutionary theory of inheritance it contained. There were many other papers on plant hybrids appearing at the time and Mendel's was in a rather obscure journal. It was also published at a time when the debate over Darwin and Wallace's theory of evolution by natural selection was the issue of the day for most biologists and indeed for many others. The irony here, of course, is that Mendelism, had it been appreciated at that time, would have removed one of the weak points in Darwin's argument: just how are the characters on which natural selection operates inherited?

In Darwin's provisional theory of heredity, known as pangenesis, the cells of the body throw off minute particles, gemmules, which circulate in the blood, multiply there, and then collect in the reproductive cells[3]. Francis Galton in a series of experiments with

rabbits was able to show that this did not happen[4]. However, although he made many valuable contributions to our understanding of human heredity[5] Galton had to wait until Mendel's work was rediscovered before, in the last years of his life, he had available a theory of inheritance which, as he probably realised better than most at the time, provided a mechanism which explained his empirical data.

Because the significance of Mendel's work was not appreciated at the time he did not live to see the impact it was to make on the life sciences. It also meant that the 20th century became in fact the Century of Mendelism. The first century but certainly not the last. Unless our civilisation collapses into a new dark age as a result of a manmade or natural disaster, genetics seems set to increasingly affect us all in a wide variety of ways. In a one-day Conference it was not possible to cover every aspect of genetics past, present, and future, but the papers presented here do highlight Mendelism's rediscovery, some of its more important consequences, and, perhaps, give some indication of the opportunities and possible dangers of its future developments.

The Galton Institute has always tried to provide an historical background to the subjects of its Conferences. The Century of Mendelism began in 1900 with the rediscovery of his work and this is usually attributed to three people, De Vries[6], Correns[7], and von Tschermak[8]. But are these claims justified and how much did these men really appreciate what particulate inheritance means? Peter Bowler answers some of the questions in his paper and shows that, when carefully investigated, they, and others, may well have been reading their own ideas into Mendel's paper. Mendel himself may in fact have been looking not for a new theory of heredity but simply at hybridisation as an origin of new species.

Mark Ridley looks at possible future scenarios given our expanding knowledge of the mechanisms of heredity. While acknowledging that forecasting future events is a hazardous process he thinks it is a useful exercise. Copying processes in living organisms are prone to error and, as life becomes more complex, as the number of cell cycles per

generation increases, so the number of errors could increase to such an extent that, in theory, human beings become biologically impossible. Fortunately for us so far evolutionary changes and built-in repair mechanisms have kept error rates down to an acceptable level. However this might not continue. Medical advances could allow errors, deleterious mutations, to build up in the human population and, with natural selection suspended, the future of the human race could be bleak. Designer babies, now politically unacceptable, could, in the future, be the only way for us to avoid extinction.

Robert Resta's Galton Lecture on genetic counselling examines what is probably the most important and direct result of a century of Mendelism as far as individual patients are concerned. Its early development was greatly influenced by eugenic ideas. It was believed that if genetic advice led to fewer births of children with serious genetic disorders this would lead to an improvement of the human gene pool. Mutations would, of course, continue to occur but a least the genetic load would be reduced. However, in Resta's considerable experience this effect, although desirable, is small. Patients seem usually to have quite poor retention of the information given to them in the genetic clinic and in practice do not often change their reproductive intentions as a result of counselling. Genetic clinics do, however, provide a valuable service to families in which there are serious inherited conditions and it is possible that in the future their role may become different and, perhaps, more eugenic. The deliberate selection by patients of embryos known to be free of an already determined genetic defect may become increasingly possible and thus, rather later than the early eugenicists hoped, a reduction of the human genetic load may be achieved.

Colin Tudge's view of the future is one in which genetic engineering in the broadest sense will make many things possible which have, until recently, seemed to be beyond the wildest dreams of all but some science fiction writers. In biology only the laws of physics will set limits to what can be done so who will decide what is right, what is acceptable, and what would be possible but is forbidden? In theory

governments, hopefully democratic, will make laws reflecting the wishes of the people. In practice pressure groups often set the agenda and their concentration on a single issue can all too often prevent a more balanced appreciation of the advantages or disadvantages of what they are for or against. A current example is genetically modified crops. There are good reasons why these need to be introduced with great care if at all in the developed countries where food is abundant. We have to decide if they are worth the risks involved. However in the third World where the choice may often be between GM food or famine the advantages may well outweigh any risks involved in their use. Tudge's stimulating and, at times, controversial views of who we should consult and listen to about the future uses of genetics as we enter a world where almost everything is possible deserve to be widely read.

At the 2000 Conference John Wadham of Liberty (National Council for Civil Liberties) presented a lawyer's view of how the Human Rights Act and similar legislation could affect the use of genetic fingerprinting by the authorities. Unfortunately his paper on this important and contentious topic is not available for this volume but if the Institute has the opportunity to obtain any further contribution from Mr Wadham on this topic it will attempt to publish it in the Newsletter. Professor Raeburn's paper in this volume is based on a lecture presented at an earlier meeting of The Galton Institute.

We would like to thank all the speakers at the Conference for their valued papers and Professor Raeburn for his additional contribution. We would also like to thank Dr John Peel, the Institute's Treasurer, and Mrs Betty Nixon, our General Secretary, for their help in organising this meeting and the Linnean Society for making us welcome.

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1. The Rediscovery of Mendelism

Peter J Bowler

At a recent conference organised to encourage historians of science to play a role in science communication, a number of speakers lamented the difficulties facing academic historians trying to reach a wider readership. There is no shortage of best-sellers featuring the history of science, but most of these books are authored by professional science writers with no training in history – and all too often they merely regurgitate exactly the tired old myths about the history of science that the professionals try to expose as inadequate. A fortunate exception to the latter condemnation is provided by a recent best-seller in the area I wish to discuss: Robin Marantz Henig's *A Monk and Two Peas* provides a popular account of Mendel's work and its subsequent "rediscovery" leading to the foundations of genetics.[1] Henig has read the work of modern historians and has interviewed leading figures such as Robert Olby, so she is aware that the orthodox story of Mendel's work and its reception is problematic. She tells a fairly conventional tale about Mendel's actual research, never really coming to grips with Olby's thesis that he was not (by the standards later adopted) a Mendelian. But on the rediscovery she does a good job of showing how attitudes to the newly emerging discipline of genetics were influenced by biologists' training, background and professional opportunities. Putting it bluntly, the rediscovery of Mendelism cannot be understood as a simple recognition by three scientists independently that a particulate model of heredity self-evidently offered the basis for the complete reformulation of scientific thinking in this area. Something more complex was going on, and it is the historians' job to try and work out what factors lead some biologists to recognise and promote the new approach.

In the conventional story, Mendel discovered the laws of heredity which now bear his name through his experiments with peas, and

published his classic paper in 1866 only to have it ignored, perhaps because the publication was in too obscure a journal, but more probably because the "time was not ripe" for so complete an overthrow of the old-fashioned way of thinking. Then in 1900 his laws were independently rediscovered by three biologists, Carl Correns, Hugo De Vries and Erich von Tschermak, who soon realised that they had been anticipated and enshrined Mendel's name as the posthumous founder of the new science which William Bateson called "genetics."[2] But this model of discovery and rediscovery raises problems for historians, who have long been suspicious of the notion of the "precursor" who anticipates later developments. The trouble with precursors and forerunners is that we now take it for granted that there is an intellectual and social context within which new scientific theories are formulated and refined. It is difficult to see how someone working over thirty years before the founding of the new science could have completely anticipated the ways of thinking that would become characteristic of the later generation. Even the concept of independent discovery is problematic, because two scientists working in different contexts are unlikely to hit on exactly the same idea. In the classic case of Darwin and Wallace, it seems clear that Wallace's version of natural selection was significantly different to Darwin's, and I would defend the claim that Wallace's 1858 paper was advancing a theory of selection acting on varieties or subspecies, not individual differences, and hence missed the real point of Darwin's discovery altogether.[3]

In the case of Mendelism, historical research has shown the problematic nature of the relationship between Mendel's original discovery and the later emergence of the theory which came to bear his name. It is over twenty years since Robert Olby published his provocatively-titled article "Mendel No Mendelian?" in which he questioned whether Mendel had thought in terms of paired material particles corresponding to the characters traced through successive generations in his experiments.[4] Olby was suggesting, in effect, that the rediscoverers had read their own ideas into Mendel's paper, crediting him with theoretical concepts that would only become

available in their own time. He also suggested the Mendel may not have been searching for a general theory of heredity at all – his real motivation was to test the idea (taken seriously at the time) that hybridization might offer a better explanation of the origin of species than transmutation. Re-evaluation of Mendel's contribution lies outside the scope of the present paper, but Olby's thesis certainly forces us to think more carefully about what was going on at the time of the rediscovery.

The events surrounding the rediscovery have also come in for scrutiny by later historians. Tschermak's status as a rediscoverer was challenged as early as 1966 by Curt Stern and is now almost universally rejected.[5] He saw the Mendelian ratios but interpreted them within a still pre-genetical theoretical model of heredity. The Dutch botanist Hugo De Vries' role is still a matter of dispute. He claimed to have observed segregation before reading Mendel's paper, but there is little proof of this and several historians have argued that he did not understand what he was seeing until after he read Mendel's account. Only Correns has emerged unscathed from the analysis; he had clearly begun to think in terms of paired characters because of the new information on the behaviour of the chromosomes, and had observed the Mendelian effect even before becoming aware that he had been anticipated by Mendel. Even so, Correns may not have appreciated the full significance of what he had seen until after he had read De Vries' report, and he still did not accept the results as universally valid. Mendel's work was not equivalent to what the rediscoverers proposed, but his numerical analysis was better than anything they themselves had come up with, so his paper did play a vital role in the formulation of the new theory. It may also be that his name was invoked so eagerly because it helped to head off the possibility of a priority dispute between De Vries and Correns.

My aim in this paper is to look again at the rediscoverers and those who went on to build the science of genetics, and to offer some comments on the factor which may have helped them to recognise the new initiative and promote it. In particular I shall comment on one

factor which is of interest to me because of my background in the history of evolution theory: the theory of evolution by saltations or sudden leaps. Several influences have been identified as contributing to the emergence of a new vision of heredity within which Mendelism could flourish. These fall into two categories: social, economic and cultural factors which helped to focus attention onto the rigidity or determinant character of heredity, and scientific factors which prepared the way for biologists to think in terms of unit-characters derived from both parents. I shall argue that no single one of these factors was, by itself, sufficient to pave the way for Mendelism, although all played a supporting role for at least some of the participants. In the end, I shall suggest that the factor which most interests me (saltative evolutionism) may actually have been the most significant in creating a climate of opinion suitable for the reception of the idea of unit characters.

On the social and cultural side, one must begin by mentioning the growing interest in human heredity promoted by Francis Galton. His insistence that the character of the individual is fairly rigidly predetermined by heredity was taken up with enthusiasm in the closing years of the nineteenth century and led to the creation of the eugenics movement. This view of human nature clearly focussed attention onto the power of what August Weismann called the "germ plasm" to shape the production of individual characteristics in humans, and by implication in animals and plants. Galton was extremely influential in popularising the idea of genetic determinism – but this was not by itself enough to create the idea of unit characters being linked to particular sections of the germ plasm. In America, the claim that many human characters were determined by individual genes became a strong component of eugenics.[6] But in Britain there were social and professional reasons why this did not happen. Galton's disciple, Karl Pearson, was a bitter opponent of the man who became the leading British Mendelian, William Bateson, and although Pearson's rejection of Mendelism may not have been as rigid as we once supposed he was certainly not prepared to use the new genetics as an integral part of his theory of evolution, or his defence of eugenics.[7] Bateson opposed

eugenics partly because it was a component of Pearson's beliefs, and also because his form of elitism regarded the link between heredity and social status as a product of middle class materialism.

There is, however, another social factor which has been singled out by Robert Olby and others as playing a more direct role in the creation of a niche for Mendelism. This is the ease with which the Mendelian view of heredity fitted into the interests of the powerful horticultural and animal breeding communities.[8] The breeding experiments done by the geneticists were a close parallel to the kind of breeding programmes on which this industry was founded, and the idea of unit characters provided the hope of being able to control such programmes far more effectively. It is no accident that after years of frustration at Cambridge, Bateson eventually took a position at the John Innes Horticultural Institute. Nor is it an accident that his campaign to establish genetics as an independent scientific discipline reached its high point with his speech at the International Conference on Horticulture and Plant Breeding in 1906. In America too, the plant breeders were enthusiastic proponents of Mendelism.[9] So here too we have a powerful social and economic force creating a niche for a new kind of biology that was at first struggling to make its way in the university system. Such factors reveal the extent to which the success of a conceptual revolution may depend on the creation of a professional network dedicated to promoting the new theory. On the other hand, the very antiquity of the plant breeding industry, and its long connection with biologists even before Mendel, suggests that by itself this factor is unlikely to have actively prompted anyone to think in terms of unit characters behaving according to the laws that Mendel discovered. Providing a social and professional niche is not the same as a source of conceptual inspiration.

Among the scientific factors which may have provided such an inspiration, one already alluded to is the development of cytology and the new discoveries made in the late nineteenth century about the role of the chromosomes in the cell nucleus.[10] Weismann had already identified the chromosomes as the location for the germ plasm which

he assumed was the physical bearer of the information from parents to offspring. The paired nature of the chromosomes was obvious and the work of Walther Flemming and Edouard van Beneden had revealed their behaviour in mitosis and meiosis. This information was clearly important to Correns in preparing his mind to accept the process of character-transmission that he (and Mendel) had observed. But these developments were not enough to create a climate in which the relevance of Mendel's laws was obvious to all. Weismann never thought in terms of unit characters for the information stored on the chromosomes and developed an eleborate alternative theory of "determinants" which operated in a much less clear-cut way. De Vries was not very interested in the chromosomes, and his theory of "intracellular pangenesis" – derived from Darwin's earlier ideas – was not based on the claim that they were the sole bearers of heredity. William Bateson, who soon became the leading British Mendelian, resisted the chromosome theory of heredity throughout his whole career, even after T H Morgan and his school had shown how the inheritance of characters can be explained in terms of genes as units on the chromosomes. For Bateson, the notion of the genes as material units was just too materialistic – he thought of them as diffuse patterns of vibration influencing the whole organism, something like the Chladni figures made by a vibrating string acting on a plate.

The influence I want to focus on provides a direct inspiration for the idea of unit characters breeding true from one generation to the next. It seems to me that it is no accident that three of the most important figures associated with the rediscovery and early development of Mendelism were also strong advocates of the theory that evolution occurs by sudden leaps or saltations, rather than by the gradual accumulation of minute individual differences as suggested by Darwin. Hugo De Vries went on to develop his "mutation theory" – the most widely accepted alternative to Darwinism in the early twentieth century. William Bateson had come out in vigorous opposition to Darwinism and in support of saltations in his *Materials for the Study of Variation* in 1894 and maintained this position throughout in

opposition to Pearson's biometrical form of Darwinism. Thomas Hunt Morgan became a supporter of De Vries' mutationism and wrote a viciously anti-Darwinian book, *Evolution and Adaptation,* in 1907 before he went on to do the work that confirmed the true nature of mutations and paved the way for the reinvigoration of the selection theory in the 1920s and 30s. The link between saltationism and Mendelism is fairly obvious: if new characters appear as discrete units then it is likely that they will continue to breed true as units. Indeed, if rare saltations are the source of new species, the new character must breed true without blending or it will be swamped by interbreeding with the unchanged mass of the population – this was the key point made in Fleeming Jenkin's famous review of the *Origin of Species* in 1867.[11] Thus a key element of the Mendelian programme emerges naturally from a belief in saltations (although one need not believe that Mendel's laws explain the whole subsequent process of heredity, and De Vries himself gradually lost interest in the laws). In an important way, those who favoured saltations were preadapted to thinking in terms of unit characters and thus much more likely to take an interest in Mendelism.

The theory of saltative evolution had a pedigree stretching back to the early nineteenth-century speculations of Geoffroy Saint-Hilaire and others. Even T H Huxley thought that Darwin had overstated the case for gradualism and argued for saltations as the true source of new species. Francis Galton, for all that he focussed on breeding within a continuously varying population, thought that saltations were needed to found a new species and took an interest in Bateson's early ideas. In the late nineteenth century saltationism emerged as a major component in what Julian Huxley later called the "eclipse of Darwinism" – the plethora of anti-Darwinian theories which dominated biology until the emergence of the genetical theory of natural selection.[12] Natural selection became suspect in part because of conceptual problems associated with the role of heredity, but also because it seemed incapable of experimental verification in an age when biology was becoming increasingly conscious of the need to boost its

experimentalist credentials. In the later decades of the nineteenth century the Lamarckian theory of the inheritance of acquired characters had become popular. Lamarckism had the advantage of seeming to allow a role for teleology – the animals' own behaviour shaped the course of evolution. But it too was supported mainly by indirect evidence and seemed increasingly unlikely to gain experimental support. Saltationism thus emerged as the most likely alternative to Darwinism, not least because biologists such as De Vries, Bateson and Morgan offered the hope of experimental confirmation.

Saltationism became associated with opposition to Darwinism for two reasons: most obviously, it violated Darwin's commitment to gradualism, but also it undermined his reliance on utility or adaptation. If new characters were produced by some process of mutation arising from within the germ plasm, then they were not under the control of adaptation because natural selection played no role in their creation. Saltationists routinely argued that adaptation was irrelevant in evolution because the characters produced by saltation established new species whether or not they were of any adaptive advantage – all they had to do was to breed true in order to perpetuate the new form. Many of the early Mendelians continued this line of opposition to Darwinism at least until the 1920s.

Hugo De Vries may not have fully appreciated the significance of the phenomenon of character-pairs until he read Mendel's paper, but his own research had already led him toward the idea of unit characters. His theory of "intracellular pangenesis" postulated particles in the cell nucleus responsible for the transmission of characters. In the 1890s his research focussed on the nature of variation and led him to endorse Galton's view that there were two kinds of variation: fluctuating variation within a normal population, and discrete saltations which might establish a new population and, in effect, a new species. He began to study how new characters are introduced and to demonstrate that they are formed as units. He tried to show that such units can be transmitted from one species to another by hybridisation. This led him to the phenomenon of segregation and Mendel's laws –

although he soon abandoned Mendelism because he did not think that the laws threw any light on the origin of the new characters. He went on to develop his mutation theory in which species were supposed to pass through occasional phases in which they throw off numerous saltations capable of establishing new varieties and even new species. He provided evidence for this from the evening primrose, *Oenothera lamarckiana*, although we now know that what he regarded as macromutations were a phenomenon of that species' unusual hybrid character. De Vries certainly insisted that new species were produced without the action of natural selection, but unlike many of his followers, he conceded that only those mutated forms conferring adaptive advantage were likely to survive for any length of time. His followers certainly included many of the early geneticists, who saw large-scale genetic mutations as the source of new characters and hence of new species.

William Bateson began his career as an evolutionary morphologist using anatomical and embryological evidence to investigate the origin of the vertebrates. As it happened, he developed a valid theory linking the early chordates to the acorn worm, *Balanoglossus*, but there were rival theories and it seemed impossible at the time to confirm which was correct because the techniques available were unable to distinguish between genuine homologies indicating common descent and similarities acquired independently through convergent evolution.[13] When he published his conclusions, Bateson indicated his dissatisfaction with the whole enterprise of trying to reconstruct phylogenies and went on to study directly the processes responsible for producing new characters, i.e. variation within species. He rapidly moved toward a position in which he became convinced that many new characters must have appeared suddenly by saltation. If a flower appears in a new form with an extra petal, it is most unlikely that the new petal has been developed over many generations from some slight rudiment – almost certainly the process of variation had triggered a saltation which produced a new petal as a unit by duplicating the existing process of development. Bateson's *Materials for the Study of*

Variation launched a blistering attack on the morphologists' project to reconstruct the history of life on earth and on the Darwinian selection theory. Bateson endorsed both the theory of discontinuous origin of characters and the anti-adaptationist position which assumed that new characters bred true whether or not they were of any use to the organism.

Bateson was now drawn into an increasingly bitter dispute with his one-time friend, W F R Weldon, who had also decided to move beyond the old morphological programme but did so by attempting to study the variation of wild populations with a view to actually measuring the effects of natural selection. Unlike the saltationists, Weldon chose to rise to the experimentalist challenge by actually showing that carefully controlled field observations could provide the demonstrative proof of selection's activity that the Darwinists had always been accused of failing to supply. He teamed up with the statistician Karl Pearson, who provided the mathematical skills needed to analyse data covering large populations. They showed that Darwin was right to postulate a continuous range of variation for most characters and eventually began to accumulate evidence actually showing how the range was affected by changes in the environment through natural selection. Here was a programme of research diametrically opposed to Bateson's, commited to gradualism and adapatationism, and exploiting the sophisticated mathematical analysis of large amounts of variation. Bateson had no mathematical skills, and so was forced to work with small-scale breeding programmes similar to those used by Mendel. The resulting controversy polarised the biological community and may well have been responsible for Weldon's death through overwork in 1906. When he read Mendel's paper (or, more probably, De Vries') on the way to a Royal Horticultural Society conference in 1900, Bateson immediately saw how the new theory could be used to bolster his own campaign to create a scientific discipline based on the analysis of breeding, not on the theory of natural selection. He soon produced an English translation in his *Mendel's Principles of Heredity* of 1902 and went on to

coin the very term "genetics" a few years later. Henig's recent book on Mendel is very effective in telling the story of how Bateson used the rediscovery to create a new professional niche for himself, exploiting his connections with the horticultural community – but she also shows how the debate with Weldon and Pearson shaped his thinking and his receptivity to the Mendelian idea of unit characters.[14] To someone like Bateson, committed to saltations and the tracing of noticeable character differences through into later generations, Mendelism fitted like a glove. It sidelined the biometricians' focus on continuous variation and natural selection, and allowed Bateson to continue ignoring the role of adaptation. Curiously, though, Bateson was not impressed with De Vries' mutation theory, although he remained convinced that saltation rather than natural selection was the key to evolution. But he became increasingly pessimistic about the prospect of uncovering the true cause of evolution, to the extent that he was accused of giving support to the American creationists in the 1920s. He eventually concluded that all mutations represented the destruction of a gene, and implied that evolution was mainly due to the appearance of characters that had always been present, but masked by a gene which prevented their expression. Only when the masking gene was destroyed by mutation did the character appear as though newly formed.

The American biologist Thomas Hunt Morgan also began as an evolutionary morphologist, but in his case the widespread reaction against this programme at the turn of the century led to an interest in experimental embryology. At first he rejected both Mendelism and the chromosome theory of heredity, seeing both as merely a revival of the old preformation theory in which the whole organism somehow already existed in the fertilised ovum. He favoured an epigenetic theory in which germ plasm and environment interacted to produce the successive steps of development. At this time he became an outspoken advocate of De Vries' mutation theory, taking it far beyond De Vries' own position to an outright anti-Darwinism similar to that developed by Bateson in the 1890s. His *Evolution and Adaptation* of

1907 paralleled Bateson's *Materials* in its contempt not only for the selection theory, but also for any notion that adaptation played a role in shaping the course of evolution. Mutations alone directed the appearance of new characters and new species. Morgan initially took up the study of mutations in the fruit fly *Drosophila* to extend the experimental evidence for De Vries' mutations to the animal kingdom. Soon, of course, he realised that mutations did not create new species, but merely extended the range of variability available in the original population. He also came to appreciate how the chromosome theory could explain the transmission of mutated genes in accordance with Mendel's laws. The result was the creation of classical genetics, Bateson alone holding out against the new evidence for the chromosomes as the site of the genes. Gradually Morgan softened his opposition to adaptationism and the selection theory, as he realised that smaller mutations helped to create the continuous variation on which the Darwinists relied, and that the extent to which a mutated character fitted in with the environment would control the rate at which it would spread into the population.

If Morgan eventually conceded the validity of Darwinism, neither De Vries nor Bateson ever relented in their opposition to the idea that evolution could occur through the accumulation of continuous variations. All three had been powerfully influenced by the theory of saltative evolution during the crucial period in which they began to take an interest in Mendelism. Clearly, the assumption that evolution proceeds through the instantaneous creation of whole new characters which must then breed true for them to be fixed in the species helped to create an expectation that existing discontinuous characters should also breed true as units. Mendel's laws go far beyond the mere idea of unit characters, of course, but anyone thinking in terms of unit characters would certainly have their mind prepared to receive the ideas of character pairs and segregation. Although no one factor can explain the explosion of interest in Mendelism after 1900, and there were certainly economic and professional considerations shaping the activities of figures such as Bateson and Morgan struggling to create

new scientific disciplines, the emergence of the saltationist form of anti-Darwinism in the late nineteenth century played a major role in creating a climate of opinion favourable to the introduction of Mendelism. It is one of the great ironies of the history of science that Mendelism subsequently became synthesised with the theory of natural selection to create the neo-Darwinism that now dominates evolutionary biology.

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[1] Robin Marantz Henig, *A Monk and Two Peas: The Story of Gregor Mendel and the Discovery of Genetics* (London: Weidenfeld and Nicolson, 2000).

[2] For the traditional story of the rediscovery see H F Roberts, *Plant Hybridization before Mendel* (Princeton: Princeton University Press, 1929) and Hugo Iltis, *Life of Mendel* (reprinted New York: Hafner, 1966).

[3] Peter J Bowler, "Alfred Russel Wallace's Concepts of Variation." *Journal of the History of Medicine*, **31** (1976): 17-29.

[4] Reprinted as an appendix in Robert C Olby, *Origins of Mendelism*, reivised edition (Chicago: University of Chicago Press, 1985).

[5] Curt Stern and E R Sherwood, *The Origins of Genetics: A Mendel Sourcebook* (San Francisco: W H Freeman, 1966). For more details on modern interpretations of the rediscovery see Peter J Bowler, *The Mendelian Revolution: The Emergence of Hereditarian Concepts in Modern Science and Society* (London: Athlone/Baltimore: Johns Hopkins University Press, 1989).

[6] See for instance Daniel Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity* (New York: Alfred Knopf, 1985).

[7] For a reassessment of Pearson's response to genetics see Eileen Magnello, "Karl Pearson's Mathematization of Inheritance: From Ancestral Heredity to Mendelian Genetics," *Annals of Science*, **55** (1998): 35-94.

[8] Robert Olby, "William Bateson's Introduction of Mendelism into England: A Reappraisal," *British Journal for the History of Science*, **20** (1985): 399-420.

[9] Barbara Kimmelman, "The American Breeders' Association: Genetics and Eugenics in an Agricultural Context, 1903-1913" *Social Studies of Science*, **13** (1983): 163-204.

[10] See Bowler, *The Mendelian Revolution*, chap. 4.

[11] See Jean Gayon, *Darwinism's Struggle for Survival: Heredity and the Hypothesis of Natural Selection.* Cambridge: Cambridge University Press, 1998.

[12] Peter J. Bowler, *The Eclipse of Darwinism: Anti Darwinian Evolution Theories in the Decades around 1900* (Baltimore: Johns Hopkins University Press, 1983); on

saltationism, including the views of De Vries, Bateson and Morgan discussed below, see chap. 8.

[13] See Peter J. Bowler, *Life's Splendid Drama: Evolutionary Biology and the Reconstruction of Life's Ancestry, 1860-1940* (Chicago: University of Chicago Press, 1996) chap. 4.

[14] Henig, *A Monk and Two Peas*, chaps. 16 and 17.

2. Genetics in the New Millennium

Mark Ridley

Introduction

The new genetic and reproductive technologies that we are starting to see signs of may prove to be a turning point in genetics and evolution. My discussion of these technologies will be futuristic, but I do not really believe in futurology as predictions about the future. I do believe in it as a way of understanding the present, trying to distinguish the things that will be of long-term importance from distractions and ephemera, as a way of distinguishing the wood from the trees.

I have been thinking for the past four or so years about error: genetic error, or mutation. The result is a book (Ridley 2000) which contains references for the assertions later in this paper. Errors matter because they place an upper limit on the complexity of a genetic message. The reason is closely analogous to the loss of meaning that takes place in verbal messages in the children's game of Chinese whispers. When a message is repeated, occasional mistakes are made. In Chinese whispers the result is that the message is corrupted over time. Life, however, has been saved from this fate because each DNA message is repeated more than once, and only error-free messages are used to perpetuate living systems into the next generation. (I am ignoring advantageous mutations.)

Even so, the error rate has an upper limit. At least one error-free offspring is needed per parent. This criterion corresponds approximately to an upper limit on the error-rate of one per offspring. (Non-mathematicians can see that this is about right, in the following way. If the error rate is 0.6, then about 3/5ths of the offspring have errors. If a parent produces five offspring then two of them will be

error-free, and the system is viable: the next generation can be produced from the error-free offspring without any net decay. Take the error rate up to 0.8 and 4/5ths of the offspring have errors. One of the five offspring is error-free. We are not at the limit of the possible. If that one error-free offspring does not have an accident, it can perpetuate the system. But take the error rate up to one and all the offspring have errors and we are back with the same unsustainable set-up as in the original Chinese whispers game. There is an inevitable meltdown of meaning. Mathematicians will see that the upper limit of one is crude. With a Poisson distribution of errors, for instance, some error-free offspring will be produced even with an error-rate of one; but still the error-rate cannot go far above one. One is a good memorable figure for the upper limit on the error rate.)

Error rates in life so far

Let's look at error rates in the history of life so far, from the origin of life until us (Table 1). The Table shows two things that have happened as life has evolved increasing complexity. One is an increase in the length of the DNA message – complex life forms such as ourselves are coded for by a larger number of genes than are simple life forms. The other is the increase in the number of times that the DNA is copied per generation. In biological terms, this corresponds to the number of germ line cell divisions. In many species, it differs between males and females. In humans, it is 33 in women, independently of age; but the number goes up with age in men. My figure of 200 in the Table is an average for a woman and a man in his late twenties, when he has 400 or so cell divisions behind each sperm.

The error rate per letter, or per nucleotide, reduced from the origin of life to the bacterial stage. It is about one in 100 for an enzyme-free replicating system. It reduces to about one in 10,000 with a copying enzyme but no proof-reading or repair enzymes (a number that is supported both by measurement (Drake et al. 1998) and theoretical argument (Crick 1989, [1990 edn, p. 111])). And to about one in 10,000,000 when the full battery of error-correcting enzymes have evolved at the bacterial stage. The suggestion that the unit error rate is

constant after that is only an approximate, order of magnitude, claim. The actual figures in the table follow Drake (Drake et al 1998) and are based on observed spontaneous mutation rates. They could be up to ten-fold lower if based on mutation rates deduced from evolution rates (Ochman et al. 1999, Keightley & Eyre-Walker 2000).

The combined result is that life was limited by error up to the bacteria stage. The evolution of repair enzymes then hugely raised the limit of possible complexity. But those possibilities may have been exhausted by the time we humans had evolved. This conclusion stands no matter whether we use mutation rates from spontaneous mutations or rates of evolution. Indeed it is something of a puzzle how we can exist with the number of mutations we make. Two hundred is a big number. We do need to know what fraction of them are harmful, and that is uncertain. But the lowest estimates are about 2 (Eyre-Walker & Keightley 1999) and a plausible estimate, from the number of sites that are conserved between mice and men is more like 20 (Kondrashov 1995): either way it is above 1. Moreover, the 200 or so mutations specified in Table 1 are only the copying mistakes. On top of that are the chromosomal mutations that underlie Down's syndrome, declining fertility with age, and possible menopause. It has been estimated that 50% of human conceptions have a chromosomal error (Boué & Boué 1973).

If humans are near the limit of the biologically possible, then the reprogenetic technologies that are – or may be – on the way could be the key to future evolutionary increases in complexity. Let us look at the mechanisms that have enabled evolutionary increases in complexity so far and their possible future-technologies (Table 2). I should say that I am going to be casual about the practicalities of developing and implementing these technologies, and the gene testing skills they will require. I shall also be casual about the ethical questions they raise. These matters are discussed in other papers in this book.

Coping with error

Life has evolved to cope with error in three or four ways. One is to avoid it, by lowering the mutation rate. Mutation rates in life are

lowered, for instance, by copying enzymes – polymerases – and by the use of DNA, which is an exceptionally stable molecule. One technological development of this sort is the possibility of gamete preservation, for instance by gamete freezing. Mutations accumulate with age. Women (or men) in the future may preserve a few eggs (or sperm) in youth, for later reproductive use at a time of their own choosing. This would lower the effective mutation rate. (Or perhaps I should say 'could' lower the mutation rate: if gamete preservation techniques cause mutations it could have the opposite effect; but I suspect preservation can be done in such a way as to lower mutation rates.) Most of the mutations that accumulate with age in women are non-disjunctions, in which both copies of a chromosome go into an egg, instead of one copy. If gamete preservation reduced these mutations, it would be a cultural mechanism for preserving Mendel's law of segregation.

A second way that life copes with errors is to correct them. This is done in the DNA by proof-reading and repair enzymes. It may be done in the future technologically by gene therapy. Gene therapy is an elusive technology, obstinately remaining beyond the frontiers. But if (or, as I suspect, *when*) it is developed it may be the first improvement in DNA repair technology since the evolution of repair enzymes in bacteria, and those enzymes could have evolved over 3000 million years ago (Schopf 1999).

A third way I'll skate over briefly. Our bodies have various means of preventing errors from doing damage, without correcting the underlying DNA codes. For instance, a cell with damaged DNA can be killed. The technological analogue is normal old medicine – which I am skating over not because it is unimportant but because it is obvious, and because it has been around for ages and is not particularly futuristic. Unlike reprogenetic technology, it is not a possible revolution that is unfolding beneath our eyes. But in so far as we become better able to conceal error medically, we shall be able to withstand higher error rates.

Finally, there is good old natural selection. That is the way such errors as make it through the detection-and-repair machinery are purged. Natural selection itself differs from the other mechanisms that I mentioned in that it did not evolve for the purpose of coping with error. Natural selection simply happens. For natural selection alone there are two futuristic possibilities to look at. One follows from medicine, and is the possibility that technological improvements relax the force of natural selection, both by specific medicines and by a general easing in the demands of life. I, like many others, am sceptical about whether technological advance does relax the force of selection (the transportation struggle to reach Piccadilly from Oxford would have ruined the health of our ancestors). Natural selection can still work against mutations in gametes and early embryos, and also (as I shall mention later) in the mating market. However, to be fair, it is worth pointing out that the case for some relaxed selection in wealthy nations is not incoherent and there is some evidence in support. The best evidence comes from the frequency of red-green colour-blindness. There is huge amounts of data. In samples of 8000 people from 13 different traditional societies – that is, hunter-gatherers and simple farmers – the frequency of red-green colour-blindness is 2 per cent. In samples of 440,000 people from wealthy nations in Europe and East Asia, the frequency is 5 per cent (and over 10 per cent in some localities). Red-green colour-blindness is undoubtedly a genetic trait, and its frequency seems to have more than doubled in wealthy societies. The increase in this case is probably because of a general relaxation of selection, not a specific prophylactic. Therefore, some relaxation of selection may have occurred.

I suspect that if this conference had been held a century ago, any futuristic talk would have been mainly concerned with genetic decay and relaxed selection. The technological outlook now is by no means ethically uncharged, but the relation between genetic decay and technology is more optimistic than a century ago. The technologies down the line may enable us to correct error, rather than simply

relaxing selection and triggering a mutational meltdown. Some relaxed selection may be going on, but I doubt that it is a threat.

By 'eugenics' in Table 2 I mean a socially sponsored program to discourage or prevent people with mutations from breeding. If enacted, such a program could enhance the power of natural selection. However, I doubt whether any such program will contribute to any future human error reduction. There is almost unanimous political opposition to eugenics, including from me. Natural selection is a morally questionable process, and eugenics (in the sense in which I am using it) compounds the problem.

Although natural selection itself has not evolved to fight error, various adaptations may enhance the power with which natural selection operates against error. Sexual reproduction, as opposed to clonal reproduction, is one such possible adaptation. It is a story in itself, and I do not have space for it, but I shall notice one future-tech possibility. If sex does exist to help purge error – indeed if sex exists for any positively beneficial reason – cloning is unlikely to have much of a part in our reproductive future. If we went in for cloning, we should lose the benefits of sex. A clonal line plays Chinese whispers with its errors, and cloned offspring would be more than twice as likely to die of genetic disease than sexually reproduced offspring. Sexual recombination of genes is embodied in Mendel's second law, the law of independent assortment. Our ancestors' genes have obeyed that law for 2000 million years or so; I predict our descendants will continue to.

About the only technology that is in this category and that may be used is DNA profiling, or other genetic information, in mate choice. The force of natural selection against mutational error has probably been evolutionarily enhanced by sexual selection – there is good evidence from several species that individuals with inferior genes are discriminated against in the mating market. There is some – but not convincing – evidence that it goes on in humans. There is also evidence that genetic information (I mean culturally acquired scientific genetic information) may be made use of in such a way that genetically diseased offspring are less likely to be born; but the evidence is not for

liberal decision-making. So I can imagine that the force of sexual selection could be tuned up by enhanced genetic information in the future. I am not advocating it – merely remarking the possibility.

Exploiting the error-reduction technologies

So we have several potential technologies – I am particularly stressing gamete preservation and gene therapy – that may effectively drive down our mutation rate. If so, they could be one of the big evolutionary breakthroughs in 4000 million years of Earthly life. I shall now move on to the most speculative part of my paper, and ask what evolutionary consequences the technologies may have in the future. A technologically reduced error rate could be evolutionarily exploited in two ways – and I am not talking here about the next 1000 years but the next 1000s of 1000s of years (though the seeds of those long-term changes may be planted in the next 1000, or even 100, years).

One thing our descendants could do would be to economise on our existing anti-error devices. The first devices in the firing line might be natural selection, and (perhaps) sex. I remarked earlier that clonal reproduction would be unlikely to replace sexual reproduction. However, if we had technological means of reducing our error rates that argument would be relaxed. Our descendants could exist with perpetual virgin birth if they balanced the error-enhancing technology of cloning against error-reducing technologies such as gene therapy. Notice, though, that does assume sex exists to purge error. If sex exists for some other reason, such as dealing with parasitic diseases, then gene therapy and gamete preservation will less obviously enable cloning.

More straightforwardly, error-reduction technologies would enable us to relax the force of natural selection against genetic error. Fewer people would die prematurely of genetic disease, and that would be a good thing. In theory we could also economise on our proof-reading and repair enzymes. I doubt there will be any conscious force in favour of it – though there may be a Darwinian force.

That is one way our descendants might exploit error-reducing technologies. It is a sort of negative exploitation, in which our descendants stay roughly where we are in term of biological complexity but relax the forces used to maintain that complexity. A second use of the technologies could be more positive, more creative. Our descendants could evolve to be more complex than us. We may be limited to something like our generation lengths and DNA size, but in the future the limit may be relaxed.

What might a future life form, more complex than ourselves, look like? The usual speculation is to think about creatures that live longer and are brainier than ourselves – a sort of extrapolation from tendencies in our own society, or in the subsector of our society that is doing the speculating. That may be right. But to me a more interesting line of speculation is that it might enable life to become more flexible. I learned this idea from W D Hamilton – and if I have short-shrifted him (or his shade) on his theory of sex, maybe I can finish with this less well known idea of his.

Error limits not only the amount of our DNA, but also how rarely it can be used. We cannot have back-ups of genes to cope with very rare contingencies, because the DNA would be mutated away before it was put to use. We know what happens to the genes that code for eyes in subterranean life forms: they are mutated away and in a few thousand generations they have evolved to be blind. (There is also an active advantage to the loss of useless organs, from trade-offs (Cooper & Lenski 2000).) Life forms now do have some unexpressed genes. Gender is an obvious example. A male human contains all the genes to build a female human body, and vice versa. We can get away with it because the genes for each sex are presented to selection on average every other generation. Mutations accumulate in the unexpressed female-organ-coding genes in a male body, but those mutations may be expressed in a daughter in the next generation, and purged. But there is an upper limit on how much unexpressed genetic material we can carry, and for how long. The limit is tight; the differences between

male and female bodies are not large and they are only held in reserve for on average one generation.

As a lead into Hamilton's idea, it is best to think not of a life form like us in which gender is determined by X and Y chromosomes. Think instead of one of those species with environmental sex determination. In some sessile invertebrates, for instance, the larval dispersal stage is ungendered. If it settles alone, it becomes female; if it settles on, or next to, a female it becomes male. They have the ability to assess their environment and then pick the best way to grow up.

A life form with reduced error-rates could extend this idea marvellously. Imagine a flexible life form that contained the genes for a number of our existing species – the genes, perhaps, for a barnacle, a phytoplanktonic creature, an oak tree, a bird, and a human being. That might take 250,000 genes, against our 60,000 or so. Early in life, the flexible life form would assess the environment and see where the best opportunities for future reproduction lay. If photosynthesis in the sea surface looked best, it would switch off its human, avian, and barnacle genes and grow up as a phytoplanktonic creature. If the air looked best, it would grow up as a bird. Its Darwinian fitness could not be lower than a fixed species life form of the sort that currently dominates Earthly life. Its fitness could be increased, as it could exploit a greater range of opportunities. So the technologically paved road to our evolutionary future may not lead to super-geriatric humanoids with bulging cortexes but to a kind of flexible life, in which the observable life forms are not more complex than anything we see now but are collectively the next stage up in Earthly life complexity.

CREATURE	ERROR RATE PER LETTER	DNA LENGTH	CELL CYCLES PER GENERATION	TOTAL NUMBER OF ERRORS	NUMBER OF HARMFUL ERRORS
original life	10^{-2}	[10^2]	1	[1]	[1]
RNA virus	10^{-4}	10^4	1	1	1
bacteria		10^6	1	<<1	<<1
worm	10^{-9}	$2x\ 10^8$	10	2	0.5 - 1 ?
fruit fly	10^{-10}	3.6×10^8	20	4	1
human being		6.6×10^9	200	200	2 – 20

Table 1. Error rates in various life forms. More complex life forms have more cell cycles per generation and more genes. Unit error rates decreased from the orgin of life to the bacterial stage but then are approximately constant. The total number of errors, and harmful errors, increases from bacteria to human beings. After various sources: see Ridley (2000).

ERROR CAN BE:	BIOLOGICAL MECHANISM	FUTURE-TECH POSSIBILITIES
AVOIDED	DNA, not RNA Polymerase	Gamete preservation
CORRECTED	Proof-reading and repair enzymes	Gene therapy
CONCEALED	Diploidy developmental trouble-shooting (e.g. apoptosis, p53, hsp 90)	Medicine
PURGED	[normal natural selection] sex mate choice	Relaxed selection, eugenics cloning DNA profiles

Table 2. The technology of error reduction: the table gives examples of biological mechanisms in four main categories, and possible future technological mechanisms

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3. The Galton Lecture 2000: Genetic Counselling – Its Scope and Limitations

Robert G Resta

Johann Gregor Mendel was not a genetic counsellor, nor, I suppose, could he have ever imagined that the field of genetic counselling would develop from his studies of the humble garden pea. Nonetheless, one could draw a branched, if not straight, line, from Mendel's Augustinian Monastery in Brno to the offices of today's genetic counsellors across Europe and North America.[1]

Despite dramatic advances in genetics over the last 100 years, it is still Mendel's 1:2:1 segregation ratios that form the core of many genetic counselling sessions and play an important role in many couple's reproductive decisions. The genetic diseases that we commonly test for today – familial breast/ovarian cancer, Huntington disease, cystic fibrosis – are simple Mendelian traits. And perhaps the most valuable genetics text/website is Dr Victor McKusick's *Mendelian Inheritance in Man*, a catalogue of thousands of human Mendelian traits and diseases.

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[1] For those who are interested in a wonderful fictional account of Mendel's life that does draw a direct connection between Mendel and today's genetic counselors, I heartily recommend Simon Mawer's entertaining novel *Mendel's Dwarf*, published by Penguin Books in 1999. For a more factual account of Mendel's life see Robin Marantz Henig's recent biography of Mendel, *The Monk in the Garden.*

Some of the standard tools of today's genetic counsellors were developed to illustrate and explore Mendelian inheritance. For example, the Punnett square, used by genetic counsellors to predict Mendelian ratios, was developed by the British geneticist R C Punnett (Punnett was interested in identifying "silent" carriers of genetic conditions to help further eugenic goals). And of course, the pedigree, the classic genetic tool used to investigate and demonstrate Mendelian inheritance and eugenic principles, is a *sine qua non* of virtually every genetic counselling session (Resta, 1993).

Historical Influences On the Development of Genetic Counselling

The rediscovery of Mendel's work by Correns, DeVries and Tschermak in 1900 did not lead directly to the development of genetic counselling. Mendel and his rediscoverers were not particularly interested in human genetics, though Bateson and other scientists were quick to grasp the implications of Mendel's principles for human traits. While many scientists believed that most human characteristics – such as height, intelligence, body shape – were inherited as continuous rather than discrete traits, there was little doubt that at least some human traits followed Mendelian patterns. Farrabee's 1905 report of autosomal dominant inheritance of brachydactyly is thought to be the first formally described human Mendelian trait.

Although Galton had defined eugenics well before 1900, it was the growth of genetics at the turn of the century that allowed eugenics to flourish in the UK and the United States. Many of the scientists prominent in eugenics such as Karl Pearson, R A Fisher, H J Mueller, Madge Macklin, Charles Davenport, and Raymond Pearl, were also the intellectual forefathers of modern day medical genetics and genetic counselling.

It is true that genetic counselling has been influenced by eugenics. However, this view simplifies a complex history. The development and practice of genetic counselling has been directly and indirectly shaped by many social, medical and technological factors. Some of these factors include:

Obstetrics: Modern obstetrics has been particularly interested in reducing the maternal and fetal morbidity and mortality associated with pregnancy and childbirth. After the medical interventions and innovations of the 19th and early 20th century helped dramatically improve maternal outcomes, the health and well-being of the fetus became the next natural focus of the discipline (Speert, 1980). Throughout the 20th century, obstetricians realised that some birth defects and developmental disabilities were due to avoidable environmental factors, such as alcohol, rubella, thalidomide and cigarettes.

Obstetricians were aware that genetics also played some role in birth defects, and felt that selective breeding could help improve the health of new-borns. John William Ballantyne, often regarded as the father of modern obstetrics, states in his classic 1904 book *Manual of Antenatal Pathology and Hygiene:*

> "It need hardly be said that it will likewise be well for the individual ... to make no matrimonial alliance endowed with the sad legacy of family ill health ... Eugenesis or well-begetting is one of the world's most pressing problems – it is far from being a hopeless one, but it must be attempted before it can be solved."
>
> – Ballantyne, 1991, p.658-9

In the mid-1950s, the first amniocenteses were performed for assessment of Rh-sensitized pregnancies and for assessing fetal lung maturity. In the mid-1960s, physicians performed the first amniocenteses for the detection of genetic and chromosomal abnormalities. Perhaps not coincidentally, the first genetic counselling training program was established in 1969 at Sarah Lawrence College in New York. Many of the first genetic counsellors were as likely to be employed by obstetrics departments as by genetics departments. In fact, to this day, the majority of genetic counsellors work in prenatal diagnosis clinics within obstetrics departments.

Medical Genetics: In the 1940s and the 1950s, medical genetics departments and clinics began appearing in the US and UK (although

the phrase "medical genetics" was coined by Canadian geneticist Madge Macklin in the 1930s). Many of the first medical geneticists were in fact eugenicists, even though these geneticists tried to deny their intellectual heritage when eugenics became less fashionable after World War II. For example, the American Society of Human Genetics was founded in 1948. Five of its first 6 presidents served simultaneously on the Board of Directors of the American Eugenics Society (Paul, 1995).

Laboratory Medicine: The 1950s saw the discovery of the structure of DNA and the identification of the modal number of human chromosomes (46). In 1957, Lejeune discovered the chromosomal basis of Down syndrome. Improvements in cell culturing techniques enabled amniotic fluid cells to be cultured for karyotypic and biochemical analysis. The development of electrophoresis and isoelectric focusing helped identify protein variants associated with human disease, such as the hemoglobinopathies and alpha1-antirypsin deficiency. Patients were now faced with struggling to understand complex genetic test results such as amino acid substitutions and unbalanced translocations. Many physicians did not have the training or skills to help their patients understand this information or to grasp its medical and reproductive implications. The need for individuals with special training in medical genetics and counselling in part grew out of this situation.

Paediatrics: In the 1950s and early 1960s, paediatricians such as David Smith, Josef Warkany, and Victor McKusick, helped bring together the fields of dysmorphology, genetics and embryology. Their work enabled physicians and patients to understand the genetic and developmental factors that led to birth defects and mental retardation. Their clinical work, and their respect and compassion for patients, influenced a whole generation of medical geneticists and genetic counsellors.

Counselling and Psychotherapy: In the late 1960s, the first program in genetic counselling was established by Joan Marks at the unlikely location of Sarah Lawrence College, a small Fine Arts college

just outside of New York City. Joan Marks was not a geneticist, but she recognised the need for specially trained individuals - genetic counsellors - who could work with families at risk for genetic disease. She incorporated the client-centred therapy of psychologist Carl Rogers into the training of genetic counselling.

In 1976 Seymour Kessler took over what was then called the "Genetic Advising Option" at the University of California at Berkeley. Kessler was a classically trained geneticist (he was one of the last students of Theodosius Dobzhansky at Columbia University in New York) who switched his professional interest to psychotherapy. Kessler drew attention to the psychological and psychotherapeutic implications of medical genetics, and over the last 25 years has written some of the most important publications on the psychological aspects of genetic counselling (Resta, 2000).

Radiology: In 1896, the discovery of x-rays heralded a new era in medicine, and the new technology was rapidly applied to obstetrics. By 1916 Dr J T Case reported, as far as I can tell, the first prenatal diagnosis of a fetal disorder - anencephaly - using an x-ray, and over the next 60 years a variety of other fetal defects were identified by this technology (Resta, 1997a). By the 1970s, static and then real-time sonography dramatically improved the ability to visualise the fetus. Today, nearly all pregnant women receive a sonogram, leading to a dramatic increase in the identification of fetal abnormalities of known or uncertain clinical significance.

Social Trends: The practice and availability of genetic counselling has also been influenced by social factors. The Feminist Movement has allowed women to take a more active role in making reproductive decisions. The Patients' Rights movement has resulted in patients demanding more medical information and questioning the once supreme authority of the physician. The availability of safe abortions and the social acceptability of contraception have given couples more reproductive freedom to make choices about when and if to have children. Indeed, these social factors were probably as influential as

advances in medical technology and knowledge in the growth of the genetic counselling profession.

Hence, genetic counselling in one form or another can be, and has been, practised by individuals from a variety of medical backgrounds – obstetrics, paediatrics, medical genetics, laboratory medicine, radiology, psychiatry and specially trained genetic counsellors. Each of these professional disciplines brings their own history and philosophy to the practice of genetic counselling.

Genetic counselling as a medical specialty developed after World War II. Sheldon Reed, a non-physician, defined the term genetic counselling in 1947 as "a kind of genetic social work" with training in classical genetics. Reed and other geneticists in the US and the UK described their patients who were desperately seeking information about their own and their children's rare disorders (Reed, 1955; Coventry and Pickstone, 1999; Neel, 1994). Such families had often spent years in the medical system, frustrated by physicians who could not explain what problems their children had, why the abnormalities happened, how parents could prevent the problems from recurring, and what the implications were for the health and well-being of the patient and family. Once they began working with families, Reed and his colleagues realised the deep-rooted psychological implications of diagnosing a genetic disorder in a child, and the need to address the psychological as well as medical aspects of genetic disease (Reed, 1955; Tips and Lynch, 1963).

Indeed, the origin of the genetic counselling profession was in part patient-driven. That is, whether or not there had been a Eugenics Movement there would still be a need and demand for genetic counselling.

The Scope of Genetic Counselling

What is genetic counselling? Some people view genetic counselling as synonymous with reproductive counselling. In such a view, genetic counselling involves making a diagnosis, educating couples about the clinical details and inheritance of the disorder, and then determining

recurrence risks so that couples can make "informed" choices (where the word informed implies that the couple have the recurrence risk memorised and that risk will guide their reproductive behavior). Another approach to genetic counselling is to view it as a sugar-coated form of eugenics, where the primary goal is to improve the genetic health of the population.

In practice, though, genetic counselling is neither strictly clinical medicine nor a modern day form of eugenics. In its simplest and purest form, genetic counselling is the process of helping patients and their families cope with the effects of genetic disease on their lives. Genetic counsellors do not work only with pregnant couples or couples planning a pregnancy. They also co-ordinate new-born screening programs, paediatric clinics for specialised metabolic diseases, run teratogen information services, work in adult cancer and neurogenetics clinics, interface between DNA laboratories and physicians, and participate in research.

The goals of genetic counselling are:

1. Establishing a diagnosis and explaining the implications of that diagnosis for the patient's health, reproduction, social and psychological functioning, as well as the implications for relatives (Walker, 1996). It may be just as common to be unsuccessful in establishing a diagnosis.
2. Help patients improve their emotional well being and to adapt to the medical, psychological, reproductive and socioeconomic consequences of genetic disease (Biesecker, 1998; Marteau and Biesecker, 1999; McConkie-Rosell and DeVellis, 2000).
3. Provide patients with some sense of control and understanding of their situation, and to empower them to make decisions that reflect their personal goals, beliefs and values (Berkenstadt et al., 1999; McConkie-Rosell and Sullivan, 1999; Schwartz et al. 2000; Shankar et al., 1999).
4. Guiding patients through the process of decision making about undergoing genetic testing, help arrange appropriate testing,

deal with the effects of their decisions to undergo or decline testing, and explain test results to patients (Walker, 1996).

Given these goals, genetic counselling is not strictly a medical discipline in the classic sense of trying to cure, treat or eliminate diseases. Of course, genetic counselling is usually carried out in a medical setting and genetic counsellors probably support the idea of curing and treating most genetic diseases. However, treatment and cure are not primary goals of genetic counselling. Indeed, many genetic counselling patients are not affected with a disease; they or their offspring are at risk for *developing* the disease.

The skills a genetic counsellor should possess are:

1. Clinical skills, such as the ability to recognise disease symptoms and traits, interpret results, calculate risks, etc.
2. Administrative skills - clerical abilities performed in a timely manner, such as making phone calls; keeping orderly, complete and accurate records, etc.
3. Practical social work skills, such as knowledge of support groups, identifying appropriate government agencies to help patients with financial and other assistance, working with insurance companies to cover testing, etc.
4. Basic educational and counselling skills, such as the ability to:
   - Educate patients about complex medical and genetic information.
   - Assess the psychological needs of patients.
   - Understand the psychological meaning of clients' behaviors.
   - Communicate that understanding in ways that leave clients emotionally enriched, psychologically stronger and more competent to deal with their own lives.

Should Genetic Counselling Be Nondirective?

Most genetic counsellors in the UK and US profess a philosophy of non-directiveness. Nondirectiveness is usually taken to mean the

genetic counsellor should make no attempt to overtly influence a client's decisions or behavior (Elwyn et al., 2000; National Society of Genetic Counselors, 1992).

The origin of nondirectiveness is usually traced to a rejection of eugenic ideologies, based on the mistaken notion that post WW II geneticists rejected eugenic ideologies. In fact, while most geneticists publicly rejected traditional eugenic methodologies such as sterilisation, prohibition of mixed race marriages, and immigration restrictions, there was still strong support for eugenic goals (Paul, 1995; Resta, 1997b). For example, note the following quotations from some of the leading geneticists of the 1950s (Table I). Geneticists may have rejected the methods of eugenics, but they did not reject the goals of eugenics.

Given the philosophy of nondirectiveness, it is ironic that perhaps the most common questions fielded during a genetic counselling session are "Doctor, what would you do if you were me?" or "Doctor, what do you think I should do?" Patients are pleading for direction in the face of complex medical and genetic information. Thus, these are not unreasonable questions. After all, patients go to a specialist to benefit from the advice and expertise of that specialist. Often, the information explained to patients is overwhelming and they tend to throw up their hands in frustration, and rely on the wisdom and clinical judgement of the specialist. Patients do not want to feel they made a foolish decision, that the counsellor might shake his or her head in disbelief at the patient's choice.

Unfortunately, such an approach can backfire if the course of action suggested by the geneticist results in an adverse outcome, such as a miscarriage, psychological harm or loss of employment opportunities due to genetic testing. Everybody loses in such a situation – patients are upset over the quality of care they received, referring physicians feel like they made a "bad" referral and geneticists feel professionally threatened and legally vulnerable.

One way to address this dilemma is for genetic counsellors to be directive when and where appropriate. Counsellors should make it

clear to clients when there might be good clinical reasons to make a particular choice. For example:

- Prenatal diagnosis of spina bifida can alter pregnancy management and long term prognosis, i.e. C-section and high-risk management of the delivery may increase the child's chances of not being in a wheelchair.
- Prenatal diagnosis of alpha-thalassemia will almost uniformly result in fetal death and a high chance of maternal preeclampsia
- DNA testing for juvenile polyposis in a child may result in interventions that lower the chances of the child dying from cancer.
- Diagnosis of Marfan syndrome can lead to treatment and surveillance that lowers the risk for aortic aneurysm.
- Testing for Huntington disease should be delayed if it dangerously increases the suicidal ideation's of an already unstable individual.

But often the clinical and psychological benefits are not clear-cut, even to geneticists. Genetic counsellors often don't know what the "right" choice is either. Should a 38-year-old woman undergo amniocentesis? Should a 45-year-old woman have BRCA testing given her family history of breast and ovarian cancer? Should a couple have cystic fibrosis screening if there is no family history of the disorder?

When the immediate clinical benefits are not clear cut, the counsellor needs to use counselling skills to work with families to help them clarify their own goals, needs and values. Once those issues are addressed, the counsellor can then work with the family to help them arrive at a decision that is appropriate for their situation, taking into account the unique psychological, social and medical background of the patient. For example:

A childless 45-year-old woman is diagnosed with advanced ovarian cancer several years after she was diagnosed with breast cancer. Her oncologist offers her BRCA testing but she declines, stating that it won't do her any

good since she will likely die soon and the test results won't affect her treatment and besides the DNA analysis often yields ambiguous results.

For this woman, BRCA testing offers little medical benefit. However, knowledge of her BRCA mutation could allow other relatives to choose to undergo (or not undergo) accurate genetic testing so that they may learn their own risks and potentially lower their risk of breast and ovarian cancer. Thus, the patient may derive psychological benefit in that her cancer and decision to undergo testing could help other relatives. Or perhaps the patient chose to avoid testing specifically so her family would not get the information, perhaps as a way of "getting back" at her relatives over a long-standing family dispute about other issues altogether. The genetic counsellor, perhaps with the help of a family therapist, could help the patient and her family work through their problems so that the patient can make a decision that is satisfactory to both her and her family.

A pregnant 16-year-old girl undergoes amniocentesis after a sonogram reveals multiple fetal abnormalities, and the fetus is subsequently diagnosed with trisomy 18. Despite the pleas of her parents and obstetrician, she does not terminate the pregnancy.

For this girl, a forced decision to terminate the pregnancy could have serious long-term psychological consequences. Simply informing the patient of the serious consequences of trisomy 18 will likely do little other than alienate her. The counsellor should explore with the patient why she does not want to terminate. Is it simply to "get back" at her parents for rejecting her boyfriend? Does she have a deep-rooted philosophical or theological opposition to abortion? Or is she confusing trisomy 18 with Down syndrome? Once her understanding and motives are clarified, then the patient could make a decision appropriate to her life situation, one that her physicians and relatives could better understand and perhaps support.

In this context, nondirectiveness becomes irrelevant. One of the main goals of genetic counselling is to help families make decisions that are appropriate for that family. Therefore, the genetic counsellor needs to have good counselling and education skills to work with

patients to ensure that patients have a good understanding of the genetic and medical information, as well as to help the patients elucidate their own goals and motives for their decisions about genetic testing.

If a patient makes a "bad" decision, the counsellor needs to clarify if the decision is "bad" because it conflicts with the counsellor's values, or if the decision is "bad" because it conflicts with the family's values. If the decision conflicts with the counsellor's values, then this is a professional issue for the counsellor to work through, ideally with the help of a clinical supervisor (Kennedy, 2000). If patient's decision conflicts with his or her goals and values, the counsellor should point out this conflict to the family. The counsellor should also make sure that the patient decision is not based on a misunderstanding of some complex clinical issue, such as poor comprehension of complex clinical issues or the subtleties of DNA analysis.

Limitations of Genetic Counseling

Ironically, some of the limitations of genetic counselling are the very things it attempts to achieve. For example, risk communication and anxiety reduction is universally acknowledged goals of genetic counselling. Yet most studies of risk perception and anxiety have found that despite the best education and counselling, most patients perceive their risk as higher than the actual risk. Or even if the patient has a better understanding of the risk, anxiety is not necessarily reduced (Marteau, 1999; Croyle and Lerman, 1999; Lippman, 1991; Kessler, 1989). Risk perception and anxiety are influenced by many inter-related factors beyond the counsellor's control – patients' personal experiences with genetic disease, psychological stress, education, and familial relationships. Indeed, the very act of risk communication is almost doomed to failure from the outset because most of these extraneous variables are beyond the counsellor's domain.

Genetic counsellors have also had limited success in achieving adequate education of patients (Sorenson & Wertz, 1986; Kessler, 1989; Lippman, 1991). Most counsellees demonstrate minimal long-term retention of information. Studies have shown that some patients

can, for up to a few months, retain some of the technical information. But even with summary letters, multiple sessions, and the information communicated by several different health care professionals (e.g. nurses, GP's, genetic counsellors, surgeons, obstetricians, etc.), and through different modalities (brochures, CD ROM, videos) most patients eventually forget most of the information. This is not surprising. Patients have lives beyond genetics, and most of the technical information – like the lifetime risk of breast cancer in the general population, the likelihood of carrying a particular mutation, or the specific risks associated with carrying a balanced chromosomal translocation – are not relevant to their day to day lives, and thus patients are not likely to retain these various statistics.

In fact, some studies suggest that patients don't actually forget the information that was imparted to them. Instead, patients weave authoritative medical information into the context of their own experiences, beliefs, lives and other sources of information (Lippman-Hand and Fraser, 1979; Lippman, 1999). Many geneticists and researchers approach the assessment of genetic counselling as a sort of final exam in which patients must recall complex medical and genetic information that was communicated to them at a time when patients were undergoing psychological distress (e.g. after an abnormal ultrasound exam or shortly after the unanticipated birth of a child with multiple defects). In reality, patients do not necessarily forget the information so much as shape it into a form that is appropriate and suitable to their lives (Lippman, 1999). Until genetic counsellors recognise this, efforts at education and at measuring the "success" of genetic counselling on the patient's ability to recall complex and probabilistic information are doomed to failure and inadequacy.

Another limitation lies in the ability - or more precisely the inability - of genetic counsellors to influence patients' reproductive choices. While counsellors may sometimes influence patient decisions about some aspects of genetic testing (Wroe and Salkovskis, 2000), genetic counsellors are not very effective at altering or influencing patients' reproductive behaviour. Most studies have suggested that genetic

counselling usually reinforces reproductive decisions that have already been made by the patient prior to the counselling session (Frets et al., 1990; Lippman-Hand and Fraser, 1979; Lippman, 1999). When counselling does influence reproductive choices, the tendency is for clients to have more children rather than fewer (Kessler, 1989).

This implies that genetic counselling is unlikely to have a significant success as the basis of a eugenics program or ideology. Let me state it again - we cannot influence the reproductive behaviour of our patients. People are going to do what they are going to do; sometimes the reproductive outcomes will be influenced by genetic information and counselling, but often other factors will affect patient decisions – the severity of the disorder, desired family size, the availability of abortion and prenatal diagnosis, and basic human lust.

I would further argue that attempting to influence the reproduction of other people is, in the context of most Western cultures, ethically and morally wrong.

Having said this, I acknowledge that genetic counselling can have eugenic effects, such as prenatal screening for Down syndrome. While most families probably do not think of eugenics when struggling with the very difficult decision of whether to continue a pregnancy in which the fetus is known to be abnormal, the end result of prenatal diagnosis is eugenic, i.e., a reduction in the incidence of fetuses with mental and physical impairment.

The availability of widespread prenatal screening reflects the values and ethics of the social milieu (Fenner, 1996; Terrell White, 1997; 1999). A sizeable portion of the population must believe that it is undesirable, and difficult, to raise a physically and mentally impaired child. Nor has society chosen to allot significant money and resources into improving the lives of people with disabilities. This suggests that some narrow and limited aspects of eugenics may be socially acceptable.

However, the focus of prenatal decisions is on the implications of a handicapped child for the family rather than the burden for society,

and in this sense is not concordant with traditional eugenic goals. In fact, eugenic goals are largely irrelevant to the daily practice of genetic counselling. And while it may be argued that the availability of prenatal diagnosis further diminishes the social acceptability of people with disabilities, it is also true that some people with disabilities support prenatal diagnosis (Chen and Schiffman, 2000).

Lowering the incidence of some disabilities is not an inherently bad goal. After all, who wants to add to human suffering? However, there are ways of achieving this goal that do not involve eugenics (See Table II).

The relationship between eugenics and genetic counselling is complex, and I do not intend to untangle it here. However, reducing all of genetic counselling to a latter day form of eugenics only serves to inaccurately simplify that complex relationship, and result in name-calling that serves to amplify hostilities and gets everyone nowhere fast. Genetic counsellors cannot deny the eugenic ramifications of their work but clearly eugenics is not the business of genetic counselling. This acknowledgement is a starting point for an open-minded discussion among genetic counsellors, physicians, ethicists, the disability community, and rest of society that can hopefully result in the delivery of empathic, humanistic genetic services. I like to think that Mendel would agree.

Table I. Eugenics and Medical Geneticists[2]

Parents should make their own decisions after they have all the facts possible. (Oliver, 1952b, p.343)
A geneticist should prevail upon some persons to have at least their share of children as well as to show a black picture to those with the potentiality of producing children with undesirable traits. (Oliver, 1952a, p.31)
We try to explain thoroughly what the genetic situation is but the decision must be a personal one between the husband and wife, and theirs alone. (Reed, 1955,

[2] Adapted from Resta, 1997b.

p.14)

If our observation is generally correct, that people of normal mentality will behave in the way that seems correct to society as a whole, then an important corollary follows. It could be stated as a principle that the mentally sound will voluntarily carry out a eugenics program which is acceptable to society if counselling in genetics is available to them. (Reed, 1952, p.43)

In no case, however, should the geneticist presume to tell a couple whether or not they should have a child. (Dice, 1952a, p.5)

We must give due concern to the possibility of eliminating, or, perhaps, of perpetuating, undesirable or desirable genes. We must not only be concerned with the particular family concerned, but also with whether or not harmful heredity may be continued or spread in our population. (Dice, 1952b, p.346)

Table II. Non-Eugenic Means of Lowering Disability Rates

- Testing and surveillance of medications and other environmental exposures for teratogenic potential, and adequate education of couples. Some disabilities are preventable through the avoidance of environmental exposures, such as rubella, alcohol, certain medications, tobacco, and infections.
- Newborn screening for treatable diseases such as galactosemia and PKU (though newborn screening can engender its own problems – See Paul, 1999).
- Folic acid supplementation to lower the incidence of spina bifida and anencephaly.
- Better prenatal and neonatal care to help reduce incidence and effects of prematurity and low birth weight, two factors that significantly contribute to long term physical and mental disability.

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4. Problems of Genetic Engineering

Colin Tudge

The new biotechnologies are taking us into a new phase of our history – indeed they promise or threaten to transform the entire world; and in such new times as these we need to take stock. We should go back to first principles and ask what technology and science are actually *for* – what we want them to achieve. We should ask, too, whether the economic forces that now drive the world, and the multitudinous and largely vague ethical principles that are adrift in it, really meet the needs of the immediate and distant future. To judge from what has been said so far in public places, people in general – including or perhaps especially those in the higher echelons of society, who tell the rest of us what to do – have not truly grasped the enormity of what's afoot: how momentous, and how momentously different, our present age really is. Many, including some who are very clever, seem content simply to allow the new biotechnologies to follow their course, guided by nothing more nor less than market forces – which, so they blithely suggest, can be relied upon to produce appropriate outcomes. Many others, though – including me – do not feel comfortable with this at all.

In this essay I want to pursue two lines. First, I will try to show *why* present technologies are qualitatively different from all that has happened in the past: what they promise, and what they threaten. Then I want to outline the moral principles that really could serve to ensure that those new technologies do serve the best interests of human beings and our fellow creatures. You might think it highly pretentious of me – not to say hubristic – to set myself up as a prophet of morality, and of course you would be right if that is what I was

doing. But I do not intend to be a moral innovator. I merely want to draw attention to the principles that have been identified by the great prophets of the past. In this context at least, it is very hard to improve on ancient wisdom. To begin, then:

What are the new biotechnologies – and why are they qualitatively different?

Three biotechnologies have come on to the world's agenda in the past 30 years. The first to appear chronologically, and the most significant, is known colloquially as 'genetic engineering', which came on line in the early 1970s. Genes – functional stretches of DNA – are transferred directly between organisms without the medium of sex.

The second new technology is that of cloning by nuclear transfer – a technique that has been around in primitive form since the 1950s but truly came of age at Roslin Institute near Edinburgh in the mid 1990s. The first outstanding success was Megan and Morag, who were cloned from cultured embryo cells in 1995, and then more famously came Dolly, cloned from an adult mammary gland cell in 1996.

The third great, modern biotechnology is genomics – the craft and science of sequencing all the DNA, and eventually identifying all the genes, in a creature's genome. Again, genomics has been with us in various primordial forms for some decades but it truly came of age in 2000, when the Sanger Centre in Cambridge presented their first draft of the entire human genome.

Each of the three technologies is significant in its own right. Cloning technologies can be used in many contexts – notably in the immediate term to culture cells for tissue replacement. Knowledge of the human genome has enormous implications throughout medicine – not least in preventive medicine, as we learn to identify individuals who are especially at risk for particular disorders.

But it's when we put the three technologies together that they become truly powerful. So powerful, indeed, that we should not speak of them merely as a 'trio' of techniques, or a trio, or a triad. Truly they form a Trinity: though whether holy or unholy has yet to become clear.

Of the three, genetic engineering is the most startling. Biologists refer to all the genes possessed by all the creatures in a given population as the 'gene pool'. In nature (with just occasional exceptions) a creature's gene pool extends only to the limits of its own species. So black, white, brown, and yellow people all partake of the same gene pool – that of *Homo sapiens*: but bears, cats, and dandelions partake of different pools and – traditionally – the pools of each species remained separate from all the others. With genetic engineering, however, any gene can in principle be taken from anywhere, and put into any other organism. Thus, with genetic engineering, *all the creatures now on Earth become members of the same gene pool.* I find this thought extraordinary. I cannot have sexual relations with a mushroom (and neither do I want to) but I could, with the aid of a genetic engineer, partake of its genes: or it of mine. Or I or any of us could swap genes with a seaweed, or a bacterium: what you will. Furthermore, functional genes can be and already are synthesised in the laboratory: genes that have never existed before, and very possibly would never have appeared in the course of natural evolution, no matter how long this Earth persists. The thought is weird, and worth dwelling upon.

Although Roslin's work on cloning is useful in its own right, its greatest significance is to make genetic engineering routinely possible in animals. Without the Roslin technique, genetic engineers who wanted to work on animals were obliged to inject DNA into young embryos. But there is, of course, only one embryo per animal; and since the injected DNA is more likely to fail than to be incorporated into the recipient's genome and become operative, the success rate was, and is, extremely low. But the Roslin scientists produced entire animals from the nuclei of *cultured* cells. So genetic engineers no longer have to work with whole embryos. They can, in principle, add DNA to cultured cells – and cells in culture can in principle be multiplied indefinitely, until there are 1000, 10,000, or many millions of copies. So instead of having one attempt per animal, the engineer can have as many attempts as he or she chooses, to produce a cell that incorporates

and expresses the new DNA in the way that's required. Furthermore – and just as importantly – when cells are in culture it is possible to delete bits of their DNA, or to alter them – which hitherto has not been possible in whole animals. Thus, by introducing the cell-culture technique that was developed for the purposes of cloning, it becomes possible in principle to apply to animals the full gamut of genetic engineering techniques which hitherto have been applicable only in bacteria or (sometimes) in plants. With Roslin's cloning technique, in short, the genetic engineering of animals comes of age. In 1997 Roslin's commercial associate PPL produced Polly – a sheep created from cells that had been genetically transformed in culture. The theory clearly works.

However, although genetic engineers over the past few decades have developed many wonderful techniques for transferring DNA between organisms their successes have been limited largely because they had very little knowledge of which bits of DNA they ought to be transferring. Genomics provides this information. As the decades unfold the scientists will reveal many hundreds, indeed thousands, of different genes in scores of different organisms and show what they do.

Thus it is that genetic engineering, cloning, and genomics form the Trinity, and I like to argue that this Trinity brings us into a new age of applied biology: that it represents a *qualitative* shift. On a purely practical level we can point out that now – as has never been the case in the past – every organism has become part of every other organism's gene pool; and indeed that any organism might be fitted with functional DNA that has been created *ab initio* in the laboratory. In principle – roll the clock forward a few centuries – it will be possible in principle to design and build entire organisms in much the same way as Ferrari now build racing cars, or Toshiba make computers.

We can put the matter more broadly. Thus, when I was taught biology formally in the 1950s and '60s we learned that certain procedures were 'biologically impossible'. It was impossible to transfer genes between organisms without the medium of sex – yet this was

achieved in the 1970s. Or then again, the great German biologist August Weismann declared in the late 19th century that once cells had differentiated (become specialised as stomach or muscle or whatever) then they could not be de-differentiated again; they could not revert to an embryonic state. Therefore, it seemed, it was 'biologically impossible' to create whole organisms from differentiated cells. A century after Weismann, a distinguished modern German embryologist declared in *Nature* that it was 'biologically impossible' to clone mammals using DNA from differentiated cells. Yet this is precisely what the Roslin scientists achieved in the mid 1990s.

People at large, over the past two decades in particular, have been keen to ask biotechnologists where their work is leading. Might we cure genetic diseases by transferring genes? Might we clone babies? Might we produce 'designer babies' – fashioned to the last gene, just like Ferraris? Commonly, however, the biotechnologists (doctors, scientists, agriculturalists) have simply declined to enter such discussions. The stock response has been – not necessarily in these words but there was no mistaking the meaning – 'You are simply fantasising. There is no point in discussing (say, designer babies) because this is impossible. The issue therefore is not on the agenda – and never will be!' Thus the notion that some things simply cannot be done has been used as a duck-out – for in truth we do not need to discuss, or have misgivings about, phenomena that are simply not possible.

But now there can be no such duck-out. Biotechnologists should feel themselves obliged to answer *any* question that society at large may throw at them. We cannot say, *a priori,* that no new biological impossibilities will ever be discovered. We might at any time find some reason why some particular ambition cannot be realised, for insuperable reasons of biology. But it is no longer safe to assume *a priori* that the things we might care to fantasise about can definitely *not* be achieved. If we can so readily overcome the two apparently insuperable barriers that were recognised until the late 20th century – the inability to transfer genes between unrelated organisms, and the

inability to cause cells to de-differentiate – then we ought, I suggest, to consider that for practical purposes the expression 'biologically impossible' no longer has meaning. To reject it as a concept is not to indulge in philosophical dogma, but simply to exercise proper caution. We can now see that it's not 'safe' to hide behind the concept of 'biological impossibility'.

In other words, biotechnologists should now be considered capable of doing *anything* provided only that they do not attempt to break the laws of physics, or offend the rules of logic. Thus they will never produce elephants that fly like Walt Disney's Dumbo, because real elephants (as opposed to cartoon elephants) have weight, and cannot be born aloft by a mere flap of the ears. They will not produce clones from mammalian red blood cells because mammalian red blood cells have shed their nuclei, and hence have no DNA to work from. But anything that is not so obviously daft, should now be considered to be on humanity's agenda.

At least until the 1970s, biotechnologists of all kinds – in medicine, agriculture, whatever – were obliged to recognise *biological* barriers to progress, and in a sense they were safe behind those barriers. They could do remarkable things – the green revolution was brought about by advanced plant breeding, rather than by genetic engineering for example – but the limits seemed clearly circumscribed.

Now, although there may still be limits to what might be done, we cannot perceive any. Until proved otherwise we should work on the assumption that *anything* is achievable in the name of biotechnology, provided only that it does not transgress what Sir Peter Medawar called 'the bedrock laws of physics'. That, I suggest, is a huge and obvious qualitative shift. I have been surprised and alarmed recently to come across very clever people who argue that in fact there has been no such qualitative shift – that genetic engineering is merely advanced breeding – and that even if there were, this would not be important. I don't know what more to say – except that if the (theoretical) ability to build organisms as if they were Ferraris is not a qualitative shift, then it is

hard to envisage what might be; and if qualitative shifts do not demand a certain measure of re-thinking, then it is hard to see what would.

So what do we need to re-think? Just about everything, I suggest, from the nature of government to the nature of ethics and whether and to what extent we can really understand nature itself.

Rule by expert: a matter of mandate

Many technologies in recent years – nuclear power, fluoride in drinking water, as well as genetically modified crops (organisms) commonly known as 'GMOs' – have raised disquiet among people at large (I hate the peremptory expression, 'the public'). Sometimes the objections have been so strong and focused that entire technologies have been withdrawn or severely cut back, at least locally – like nuclear power in Scandinavia, and high-rise flats in much of Britain. Whoever 'wins' such discussions, however, the arguments go through a phase in which 'experts' are seen to be at odds with the rest of the populace (or at least a significant slice of them). The experts sometimes respond by arrogance – 'We know best! Don't meddle with things you don't understand!' and sometimes wring their hands in frustration and despair – partly because they see their own careers in tatters and partly for commendable social reasons: genuine regret that other people should fail to see the benefits that are on offer, and how humanity as a whole might gain. The 'engineers' who are making GMOs, and their employers and political defenders, are currently showing all those responses. High-handedness has been all too evident. But most of the applied biologists that I know really do want to make a better world; really do envisage that their own technologies could lead us into better times; and are saddened and horrified that society at large seems to reject the new way forward. Surely people would see how good and beneficial the new technologies were if only they knew more – and if only they had not been frightened off by foolish superstition! Hence the unfortunate vocabulary that frustrated experts so often give voice to: that 'the public' are 'ignorant'; and that 'the media' are guilty of 'hype' – 'whipping up' public disquiet in order to sell newspapers. But

there is a lot more to the public objections than this – much of which the experts seem almost invariably to miss.

To begin with, whether we are talking about fluoride in drinking water, or GMOs, or particular additives in animal feed, or vaccination programmes, or whatever, the general structure is the same: A group of specialists – experts – propose to introduce some technology or other that will affect the lives of society at large.

Surely the very first question we ought to ask – a matter of ethics, economics, politics, and personal survival – is *by what right* does anybody, however expert, elect to do anything at all that might affect the health or well-being of any third party, or indeed of society as a whole? For example, most of us accept that water engineers have a right to put chlorine into our drinking water (even though it sometimes has a nasty taste, and even though we know that chlorine in large doses is poisonous) but if I, say, proposed to put barley sugar into the reservoirs on the grounds that it would make the water taste nice, I would be widely condemned and indeed locked up. What's the difference?

We can of course address such issues by risk-benefit analysis or whatever, and we certainly should do this, but before we get this far there is a more general issue – the most general of all: which is to ask why *anybody* has a right to do *anything* that affects third parties.

In the end it all comes down to mandate. I, and other citizens, have given the water engineers a mandate to add chlorine to the drinking water, and I for one am very grateful that they do so. But nobody has given me a mandate to add barley sugar. *Before* we discuss whether chlorine is good (in this context) or barley sugar is bad, it's a question of whether or not society at large (or whichever individuals are affected) has given the person who proposes to intervene, the right to do so. If they have, then the interventionist has a perfect right to do whatever he or she has been licensed to do, however crazy some outsider might consider the intervention to be. If not, then the interventionist has no right to do anything at all, however salutary the intervention may seem.

As I see it, the general relationship between the expert who wants to intervene (add chlorine to water, introduce GMOs into the food chain, etc etc) and society at large is that of customer/contractor – the principle that Lord Rothschild spelled out in his report on government research in the early 1970s. Society is the customer, the expert is the contractor. More broadly, the relationship is generically the same as Thomas Hobbes described in the context of monarchy: a monarch (said Hobbes) has the right to rule (to do what he thinks fit) insofar as the subjects give him license to do so – and only insofar as they give him license. The monarch has no right to take matters into his own hands, and exceed his specific brief.

In practice, of course, in a complex society like ours, we are all 'experts' in some context, with special skills to offer: plumbing, preventive medicine, writing, painting pictures, whatever. But in most contexts all of us are customers (or subjects), eliciting and dependant upon the expertise of others. But none of us has a right to impose our expertise upon others unless specifically asked to do so; and all of us have a right to object if an expert imposes some change on our lives without being specifically invited.

But mandates – licenses and invitations to act – are specific. An expert who is contracted to do one particular thing must not assume that he or she thereafter has *carte blanche* to do whatever he or she thinks fit. If experts propose to do something qualitatively different from what they were first contracted to do, then they must negotiate afresh.

In practice, too, the extent of a mandate has to be tempered by common sense. Thus we (society) have given potato breeders a mandate to produce potatoes that are more resistant to blight. But if they seek also to breed more mildew-resistant potatoes, or more waxy or floury potatoes, we do not expect them to re-apply for a licence for each fresh enterprise. Effectively, society has given plant breeders the freedom to breed whatever they think is worthwhile.

It is tacitly understood, however, that plant breeders by and large use standard techniques that we all know and understand, and have

been tried and tested over millennia: essentially, those of crossing and selecting. To be sure, since the early 20th century they have added a few bells and whistles – including the wholesale transfer of chromosomes that transformed the breeding of wheat from the 1960s onwards, or induced mutation to increase genetic variation. But essentially, until about the 1980s, plant breeding was the same in principle as it had been for centuries (although, thanks mostly to Gregor Mendel, it had become more precise). The point here is *not* that the 'traditional' methods were 'good', simply because they were traditional. The point is simply that techniques that have been tried in the field for thousands of years, in many thousands of contexts, can be considered to be safe: or at least, we can be as confident as it is possible to be that we know the dangers. So provided plant breeders work within the parameters of what 'plant breeding' is normally taken to mean – then yes indeed, they have *carte blanche*. We may object to some of their products – tasteless tomatoes, for instance – but there is nothing here that cannot be put right by simple market forces (ie, 'customer resistance'). No very deep issues are raised. But when the plant breeders change the nature of the game – make the qualitative shift into genetic engineering – then they need to ask again whether this is what society really wants them to do.

But why shouldn't society want the traditional breeders to graduate into engineers? If the engineers are merely souped-up breeders – doing the same things as before but more quickly – why shouldn't they simply carry on as they always have?

One answer is that in this context, society – the customer – does not have to give reasons. If people at large feel disquiet, then in a democracy they have a right to call a halt, without explaining themselves. Most people, however are reasonable, and would want to give reasons. One good reason is that genetic engineering could raise new dangers: one of which is that genes introduced into rape, say, might spread to wild plants and affect their biology, and hence the ecology of the whole region, or even the whole world. This kind of misgiving raises a whole new swathe of issues that have to do with

hazard and assessment of risk, and the extent to which, in the end, we can really understand the world.

Hazard, risk, and the limits of human understanding

It is easy for experts to make light of other people's fears. Why should a particular gene introduced by a genetic engineer spread more easily to wild plants than any of the 10s of thousands of genes that the crop contains already? Realistically, what damage might be wrought by such a gene? Most ecosystems world-wide are already shot through with entire organisms introduced as 'exotics' from foreign places, from groundsel in Hawaii and gorse in New Zealand to rhododendrons in Welsh woodlands. What difference would a few more genes make?

But although such arguments may seem fair enough – the sweet voice of reason, putting hysteria to shame – they contain deep flaws. Thus it is abundantly clear that *all* forms of technology, even the most tried and tested, do not always produce the results that are expected. Civil engineers bring a great deal more experience and data to bear upon their bridges and their office blocks than genetic 'engineers' are able to bring to their novel crops. In truth, genetic 'engineering' is a bad metaphor. It is much more like genetic gardening: light the blue touch paper and retire (as I argued in my book of 1990, *The Engineer in the Garden*). But however precise the civil engineers may be, however established the basic physics (it mostly comes straight from Archimedes and Newton, after all) every now and again (surprisingly often, in fact!) their bridges fall or at least wobble, and their tower blocks collapse (or shed their giant plate-glass windows like snowflakes, as on one famous occasion in Boston Mass. in the 1970s). The reasons are clear: it is theoretically impossible to predict all the exigencies that the bridge or the building might encounter. Some novel combination of factors might arise that the engineer simply didn't think of – and could not have thought of.

There is a deeper point than this, too. High technology, by definition (or at least by the definition that I like to promulgate) is the kind of technology that is rooted in, and depends upon, science. Mediaeval windmills are not high-tech, wonderful though they are,

since they were built without theoretical knowledge of aerodynamics. But modern aeroplanes certainly are high-tech, because they were.

The fact that a particular piece of high tech performs as expected to some extent vindicates the scientific theorising that gave rise to it. But not entirely. Thus Ian Wilmut and Keith Campbell produced Dolly at Roslin in 1996 on the back of ideas about the possibility of re-programming the genomes of cells that had differentiated in culture. Dolly was a success – so does this vindicate the underlying theory? As Professor Campbell is the first to point out – only up to a point. The cloning of Dolly probably worked for the reasons he thought that it worked. On the other hand, as he himself points out, other scientists in other labs did carry out more simple forms of cloning in the 1980s: and to some extent (as can be seen with hindsight) the theory on which they based their techniques was undoubtedly flawed. What they thought was happening, wasn't; and what was happening, they did not at the time suspect. In short: the success of a particular piece of high-tech does not and *cannot* vindicate the underlying science beyond all reasonable doubt. *Ergo*, if you try out a totally novel technology on the back of a novel piece of science, it might go off in directions you simply had not dreamed of. That is always a theoretical possibility.

But there are worse difficulties even than this. Scientists at any one time tend to have the illusion that they understand the world – at least in principle: just a few i's to dot and t's to cross and then we'll know all that is really worth knowing. Such claims have often been made, and have always proved ludicrous. The point is not to laugh at our over-confident forebears, but to note the general lesson: that at any one time there will always be areas of ignorance; and – much more to the point – that it is theoretically impossible, *logically* impossible, to gauge the extent of that ignorance. It may be that modern science effectively floodlights the whole Universe, give or take a few black corners. Or it may be that science so far has simply illuminated a few meandering paths across the darkness. Looking out from the areas of illumination, it is impossible to see the difference.

Such problems are disturbing enough when applied in the context of GMOs. They become truly horrifying when applied to the designer baby. We might compare each gene to a word, which has a specific meaning; and soon, thanks to the brilliant success of the Human Genome Project, we will have a complete dictionary. But if genes are words then the genome as a whole is language, and language is more than a string of words. It has syntax, wit, puns, cross-references, allusions to the past. A language works as a whole. The language of the human genome is at least as esoteric – surely by orders of magnitude – than, say, mediaeval Chinese or Linear B. Would you undertake to edit an epic poem in mediaeval Chinese if all you had was a somewhat cursory dictionary? Of course not. Neither would anyone who was halfway sane. Yet that is what would be implied if we took the notion of the 'designer baby' literally. The possibilities for error are obviously prodigious; and the slightest incongruity could produce a monster. Yet as we have seen, it is theoretically impossible to anticipate all the possible hazards, for we cannot tell what Nature is really like until we look. With the designer baby, then, it seems we lose both ways. If the technologies perform only as well as all technologies seem bound to do, then there would be many a hideous and to a large extent unpredictable disaster along the way. Indeed the genetic manipulation of babies will always be hazardous – as all technologies are: which of course is why Ferrari, for all their experience, brilliance, and precision, must still employ test-drivers. But we cannot scrap failed babies in the way that mechanics scrap failed cars. On the other hand, if the technology succeeded beyond all reasonable expectation and precedent then our descendants could, in principle, design the present-day rough-and-ready but altogether wonderful *Homo sapiens* out of existence. Whether a species is wiped out by some ecological disaster, or evolves into something else – or in this case is transformed into something else – it disappears: and extinction is extinction.

All in all, then, we now have a body of genetic theory, and very wonderful it seems and undoubtedly is. On the back of it biotechnologists are already growing GMOs in the field, and marketing

them; and others contemplate cloned babies, and designer babies. What astonishing self-confidence! We can all of us envisage a shortlist of possible disasters – and the biotechnologists *cannot* say *a priori* that those disasters will not happen. Much worse: we should raise the theoretical possibility that a whole swatch of disasters might ensue which, at present, we cannot envisage at all. We cannot know in advance all the science that might turn out to be pertinent or know, as a matter of logic, how much of what we ought to know we simply don't know. But evidence abounds that even when we think we do understand the science, and the technology is well tried, things go wrong. Bridges continue to wobble.

It ought to be obvious, then, as a matter of common sense (backed up by logic) that we must proceed with caution: the 'precautionary principle' should apply. Of course, if our ancestors had never taken chances, then we would still be living in caves (assuming we had got that far); and caves are not attractive. So we should modify or tighten up the general principle of 'caution' and think more precisely of 'risk-benefit analysis'. What might we gain from the new technology? To what extent can we envisage the risks? And what reason do we have for thinking that there could be dangers that we are not yet able even to envisage?

Risk-benefit analysis applied to GMOs or to the genetic engineering of babies gives the kinds of results a sensible person might predict: that genetic engineering in some contexts does indeed seem to have a lot to offer – the discernible benefits sometimes seem to outweigh the risks, even the unknowable risks. But this emphatically does not suggest that genetic engineering can be deployed lightly, in any instance when the benefits are not absolutely obvious, and the risks relatively slight. Thus it seems clear that farmers in the Sahel would benefit enormously from a mildew-resistant sorghum. Sorghum is the staple, and mildew commonly takes half the crop, and fungicide is too expensive and brings problems of its own. But it seems impossible to breed a mildew-resistant sorghum by conventional techniques because the sorghum gene pool contains no suitable genes. Genetic engineering is

necessary, to introduce a gene from some other grass. Yes, there are risks: but in this case, the technique could save a great many lives, and an entire economy. The herbicide resistant rape that was being tried in the UK offered no comparable advantages. It would merely have clipped a few fractions of a penny off the price of a commodity that is already cheap. But the risks would be at least as great as in the Sahel.

Then again: it really does seem worthwhile to apply the techniques of genetic engineering to repair the tissues of children with cystic fibrosis, as has been mooted since the 1980s. Genes introduced *ad hoc* would not be passed to the next generation: although most children with cystic fibrosis could safely reproduce (if they were healthy enough) because, although their offspring would be carriers, grandchildren could be selected at the embryo stage that did not carry the mutant gene at all. This seems a benevolent and low-risk use of a truly wondrous set of technologies. But to introduce genes into a person that *could* be passed to the next generation – and to all generations beyond; and to do this furthermore when the person has no specific, damaging pathologies, simply in the hope of adding a few IQ points to the dynasty, seems a serious chancing of arm.

These are the kind of arguments that were sometimes made explicit (though not always) in the fracas over GMOs. The people who went out into the fields and pulled up the genetically modified rape and maize in the English counties were not all mindless vandals or simple, primitive luddites, and they were not in any pejorative sense 'ignorant'. Many pointed out that the perceived benefits from those crops were simply not commensurate with the conceivable – and the unknowable! – hazards. They pointed out, furthermore, that the biotechnologists, farmers, commercial companies and government simply had no right to put these plants into the countryside and the market place without asking specific permission to do so. Whoever attempts something novel that affects the rest of us, requires a new mandate. The simple principles spelled out by Thomas Hobbes were being flouted. Such insouciant high-handedness is, in principle, at least as dangerous as the

technologies themselves. Uncritical rule by expert is a serious threat to democracy.

Yet, I suggest, the principles that could guide the new technologies are straightforward. They are ancient, and widely – almost universally – acknowledged.

New high-tech and ancient morality

When Dolly first became known to the world in 1997 people at large began naturally enough to speculate on human cloning. Many biologists entered the fray and some at least – though not Wilmut and Campbell, the principal players! – were sanguine about it. One well-known professor said he would like to be cloned out of curiosity, as if this were justification enough, and another said that human cloning 'raises no new questions of ethics'. He challenged the world to show otherwise. Let's see if we can rise to the challenge.

To begin with, cloning a human being or conferring novel genes upon the next generation certainly raises the ethical ante. The reasoning is simple. No-one can be held morally responsible for eventualities over which he or she has no control. (This is not universally accepted – not for example by those who believe in the doctrine of original sin – but it is a good common-sense rule of thumb that is certainly recognised as the basis of law). On the other hand, what you can control, you should take due care over.

Normally, people have only very limited control over the genetic makeup of their own children. We all of us exercise mate choice – and it seems morally proper to do so. At least, most of us would consider that it was irresponsible to produce children in partnership with a dangerous psychopath, if the psychopathy was thought to be genetically rooted. In detail, however, the genetic makeup of our own children is outside our control. It depends on the vagaries of meiosis and genetic recombination, and which gamete meets which; and if anything is in 'the lap of the gods' then it surely is this. So – we are responsible for the genomes of our children insofar as we can, should, and generally do exercise mate choice. But after that, if anything goes

wrong, we really cannot be held to moral account (even though, distressingly, people often do feel guilty when their children, out of the blue, suffer some genetic setback).

But if we clone a baby, or if we engineer the embryo *in vitro*, then we are *prescribing* its genes. What we presume to prescribe we *are* responsible for. No-one believes in 'genetic determinism' but it's true nonetheless that everything that happens to us, the bad as well as the good, to some extent is rooted in our genes. To prescribe another person's genes is to some limited but significant degree to prescribe their lives. It makes us morally responsible for that person's fate and welfare to an extent that is quite outside the experience of all previous humanity. Again, I am inclined to suggest, if that is not a new moral scenario, then it is hard to know what would be.

Clearly (although this is an aside) there are many psychological considerations. Even if the designer child were eminently successful – a star at basket-ball, the brightest lawyer ever – he or she would still have grounds to feel fiercely resentful. Many children are angry with their parents simply for sending them to what they perceive to be the wrong school, however well they fare subsequently. How much more aggrieved would they be if their parents had prescribed their genes! They could well feel that they had been robbed of their individuality. Intelligent children born by AI have been known to say that they do not feel quite 'real'. Designer children might well say this with interest – and however 'irrational' the rationalists might tell them this is, the feeling surely would not go away. People who suffer such feelings may be 'counselled', but they cannot simply be talked out of them. The parents of the genetically enhanced lawyer might well be shocked to find that their super-bright son sues them for all the mental anguish he has been put through. A few such cases would surely take the edge off the technophilia.

To return to the ethical challenge, we might simply point out that it is at least premature to suggest there will be 'no new ethical principles'. It is impossible to predict what new scenarios will arise – including the strange turns of psychology, even in successfully cloned or tailored

children – just as it is impossible in principle to predict precisely the outcome of new high technologies. This is unknown territory, and we will just have to wait and see. There are no *a priori* statements to be made.

Or – and this I find most interesting – we might simply point out that cloning will raise no more *principles* because there are no more deep principles to be raised. The deepest principles of ethics which most of us acknowledge are probably at least in part evolved: adaptations to help us get along with our fellow human beings. Those deep principles have been made explicit, time and time again, not by professional moral philosophers (though many have certainly been helpful) but by prophets, the various representatives of the great religions: Moses, Jesus, Mohammed, and such Hindu luminaries as the 19th century mystic Ramakrishna. Their approach was not to practice formal philosophy, but to seek what they took to be truth by revelation. Their method has invariably been to seek solitude, and contemplate 'in tranquillity'.

Out of such contemplation three great principles have emerged – which have most succinctly been summarised by Ramakrishna. The first is that it is good to be personally humble (a virtue also emphasised by Aristotle). The second is that we should have 'respect' for fellow human beings and for fellow, sentient creatures. The third is that our attitude to the Universe as a whole should be one of reverence.

This is not the occasion to discuss whether these notions do in fact represent 'revealed truth': whether, as the prophets themselves believed and maintained, they are the literal word of God. Pure pragmatism is enough to suggest that as general statements of attitudes of mind, they work. All ethics in the end is rooted in feelings – emotional responses – as David Hume pointed out in the 18th century. The arguments of moral philosophers are secondary: to tease out and explore the motives behind the emotional responses, and the likely consequences of actions that are based on them. Feelings drive morality, while the intellect merely talks about it. It is religion, rather than formal moral philosophy, that seeks directly to refine and cultivate the emotions on

which the ethical arguments are based. In secular societies the underlying attitudes are left to hazard – even though they underpin the entire ethical fabric. Secular societies have thrown out formal religions, and so they have thrown out the prophets who represent and largely define them. But those prophets, collectively and individually, have provided what seem to me to be unimprovable principles. The ultimate source of their wisdom I am happy to leave to the theologians. But the content – humility, respect, reverence – seems to me to say almost all of what needs saying, in all contexts.

Thus, if we were personally humble, would we think of cloning ourselves? If we had such humility, and truly had respect for others, would we for a second entertain the idea that we might impose our own taste in genes upon our children? For although we call them 'our' children for convenience, there is no ownership. They are their own people. If we truly regarded the Universe as a whole with reverence, and the life it contains, would we take such risks with our fellow creatures, just to knock a few quid off a tonne of maize? Surely not. Surely if we just remembered the simple roots of morality, as spelled out over the past three-and-a-half thousand years – and undoubtedly were acknowledged for many thousands of years before that – we would deploy the new technologies with a much surer touch. It would still be necessary to frame careful laws and codes of practice (for example on the culture of embryo cells for tissue repair) but the general shape of those laws, what they and we should be trying to achieve, would be obvious.

I feel that people at large – the peremptory 'public' – know all this perfectly well, even if the arguments are not always made explicit. It's the scientists and philosophers steeped in their own specialties, or at least many of them, who seem to have trouble. This is yet another reason for not accepting rule by expert; and why experts would do well to listen, far more than they are inclined to do, to what their critics are actually saying, and not assume that it's all the baying of ignoramuses. The notion that all criticism springs from lack of appreciation may be comforting, up to a point, but it just isn't so.

5. Genetic Issues in Insurance and Employment: How to Prevent Unfair Discrimination[1]

Sandy Raeburn

Introduction

In this new Millennium, genetic issues will be of great importance in almost all medical specialities. The Human Genome Project has mapped all important disease-causing genes and most of these will have been sequenced. This creates theoretical possibilities to identify pathological abnormalities in these genes (Collins, 1999). Also, technological advances will mean that specific genetic tests (eg. looking for the commonest mutation of the CF gene in Caucasian populations, ΔF508) could be carried out on large numbers of samples relatively inexpensively. Because tiny quantities of DNA are required for such tests, there will be pressure to perform groups of tests, simultaneously, searching for several mutations in one gene or for mutations in many genes. Gene chip technology means that several hundreds of mutations could be sought using a single drop of blood. Already there have been biotechnology conferences at which geneticists were asked for suggestions as to which specific mutations should be included in such a screening process.

Another feature of our knowledge in this Millennium will be increased recognition of the interplay between the genotype (or genetic

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[1] Based on a talk to the Galton Institute in the Conference entitled "Man and Society in the New Millennium". Presented in September 1999 and updated in March/April 2001.

constitution of an individual) and the environment. Changes in our world will certainly influence the phenotypic expression of particular genotypes (Kitcher, 1996). Completion of the draft map of the Human Genome in June 2000, was an important landmark. The surprise of the work was the accompanying evidence, suggesting that the human genome may only contain about 32,000 genes, rather than the 100,000 genes previously deduced. This suggests that more genetic variation is due to interactions between genes than to single mutations in specialist genes. This gene interaction is probably more efficient and more conservative. It is certainly more complex.

An obvious application of new genetic knowledge would be to collect accurate data on the prevalence of particular genotypes (possibly anonymously, eg. after neonatal testing). That would mean that public health departments could estimate the future health needs of a community with greater precision. The caveat though is that whilst "genotype prevalence" could be measured, it would not always be easy to predict the likely future prevalence of "phenotypes".

Looking ahead

It is instructive to imagine the possible situations 15 years on as regards a) genetic knowledge; b) funding for health care; c) opportunities for intervention; and d) the societal/political climate (Collins, 1999).

Genetic knowledge (about genes and genotypes) will be fairly complete for some single genes which can have mutations of major effect (such as Huntington's disease, cystic fibrosis, myotonic dystrophy, polyposis coli or hereditary breast cancer). Knowledge will be fairly complete, even about the relationship between genotype and phenotype. However, there will still be insufficient information about the types of mutation occurring in sub-groups of the population. Only if we act now will the knowledge on which to base services for important population sub-groups be adequate (Darr, 1999).

All indicators suggest that, within the next 2 decades, funding for health care will pose major problems in most countries of the world.

Even the most wealthy states do not allocate more than 10-15% of their gross national product for Health Care. Some have developed Health Care based on compulsory insurance. In the UK, it is clear that all possible Governments support the concept of the National Health Service, but all are looking to maximise the benefits. Increasingly this means applying pressure on health care providers to use available technologies to increase effectiveness. There are additional pressures alongside the financial constraints to ensure that health care strategies are evidence-based.

Although much discussed, as an exciting future consequence of genetic research, the opportunities remain scanty for intervention in families affected by a genetic disease. To the patient and family the interventions wished would be those which can prevent or reverse the adverse effects. For the foreseeable future though, most interventions will be based on genetic screening to identify future risks followed by strategies to alter the natural history.

Society will also change over the next 15 years. This is the least understood aspect of any exercise looking to the future. In the UK, the development most likely to be favoured would be for individuals to be given more opportunities to make their individual choices. For this to happen, the community must provide a background of knowledge about all choices available. The individual then explores the preferred options. If this model develops, then the individual and families will be making personal decisions within a community which accepts a range of quite different options. The variation between the extremes of ethical decision-making within society may be considerable; individuals will have a narrower range of choice, based on their own ethic and culture. An additional ethic required that is essential is that people and communities are tolerant to views different from their own.

Discrimination

Unfair discrimination regarding insurance or employment needs to be set in context. People affected by disorders like Huntington's Disease, cystic fibrosis or Down's Syndrome are already discriminated against in terms of their personal relationships, their opportunities to

make friends and (perhaps) to choose partners. These human issues may outweigh the consequences of any discrimination with regard to the financial issues relating to job and salary, or to a pension and life or health insurance. When I ask people with genetic disorders what are the matters that distress them most with regard to discrimination, they frequently mention that the so-called "normal people" discount them and plan for the disabled person without that individual's input. This is exemplified by the question posed by the title of the BBC Radio programme, "Does he take sugar?". Professionals, unaffected relatives and health care planners alike, often make (expensive) assumptions about the needs of the disadvantaged people rather than asking what would be useful. As the chairperson of the Huntington's Disease Association has written "It is the responsibility of society as a whole to ensure that people, disadvantaged by their inheritance, should be protected from further hardship" (Watkins, 2001).

The insurance industry has always needed to assess the degree of risk for a particular contract or portfolio. Groups of policies which have higher risks are assessed and underwritten so that the premiums received balance likely future successful claims. It is similar with life and health insurances. People who have greater risks would be charged more, commensurate with their extra risk. Present data show that, for life insurance, less than 5% of people who apply will be charged extra premiums. Unfair discrimination in this insurance context would be if premiums were increased in excess of the extra required to cover any added risk. People with genetic disadvantages form only a small proportion of the 5% of individuals offered insurance at higher rates.

The Genetics/Insurance interface

During the past decade, geneticists have become increasingly anxious that their work, intended to improve the circumstances of people with genetic disadvantage, might be mis-applied in non-medical areas to the patient's detriment (Harper, 1997). In the early 1990s the response to this suggestion from either insurers or employers was minimal. It was the insurers who received most criticism (Harper,

1997; Select Committee Reports 1995 and 2001). Geneticists assumed that if they were to identify the future likely risk of an individual getting a serious genetic condition, that it would lead to uninsurability or prohibitively high premiums. Insurers took little action; the evidence they had from applications for new policies was that genetic issues played only a tiny part of their overall turnover. The Nuffield Council on Bioethics reported in 1993 and emphasised the need for clarification (Nuffield Council on Bioethics, 1993). When little seemed to have happened from within the insurance industry by 1995, the UK Parliamentary Select Committee on Science and Technology suggested that the insurance industry should be given one year in order to answer the criticisms and develop systems to prevent unfair discrimination (Select Committee, 1999).

Genetics/Insurance - Rapid change - 1996 to 2001

From 1996 the insurance industry, via the Association of British Insurers (ABI) took major steps to correct previous lack of action. First, they formed a Genetics Committee composed of members from the industry (a minority) plus independent members with experience and skills in law, ethics, clinical genetics, oncology and epidemiology. Amongst the members of this Committee, *ex officio*, was the ABI Genetic Advisor, a new and unique position created by the ABI and taken up, part-time, by a clinically committed academic (Raeburn, 1999).

During 1997 the ABI Genetics Committee developed the ABI Genetics Code of Practice. This was published in December 1997. The principles are set out in Table I. The Code of Practice also outlined the duties of the Genetic Advisor, of the Consultant Medical Officer of insurance companies and of the "nominated Genetics Underwriter". Compliance with the Code of Practice was necessary as a condition of ABI membership.

In February 1997, the ABI had restated the policy of **not** using any genetic test result, if the life insurance applied for was less than £100,000 and was being used to cover the purchase of the individual's own house with a mortgage.

At the same time as the Code of Practice was released, the first report of the Human Genetics Advisory Commission (HGAC) was published (HGAC Report, December 1997). This had many recommendations; some were already addressed by the ABI Genetics Code of Practice. The HGAC report recommended a moratorium on the use of any genetic test information by insurers for a period of two years, a recommendation in which there was significant conflict with the ABI approach.

The UK Government's response

In December 1997, along with the published Code of Practice, the ABI also issued a list of 8 conditions for which there was reasonable validation data for the insurance use of specific genetic tests (Table 2). The selection criteria included recognition of the prevalence of the disorders, the extent to which genetic services for these disorders were available via the NHS genetic centres and especially the positive predictive value of any genetic test result. **Because** the Genetics Code of Practice dictated that no insurer would force an individual to have a genetic test carried out against their wishes, the focus was on the request for insurance access to the result of a test, previously performed for clinical reasons. The availability of pre-existing results to the underwriter was the issue. Epidemiological issues about genetic testing such as the sensitivity and specificity of genetic tests would already have been considered by the genetic laboratory. From an insurer's viewpoint if a particular test showed a positive result, then the important issue was the positive predictive value, ie. the likelihood that an individual, considered in the family context and with a positive test, might later develop the disease.

The new Labour Government came into power in May 1997. It noted both the ABI Code of Practice and the HGAC report on insurance. In November 1998, it issued its response (summarised in Table III). The most important conclusion was that the UK Government undertook to establish a Genetics and Insurance Committee (GAIC) with the following Terms of Reference:

- to develop and publish criteria for the evaluation of specific genetic tests, their application to particular conditions and their reliability and relevance to particular types of insurance;
- to evaluate particular tests against those criteria and promulgate its findings; and
- to report to Health, Treasury and Department of Trade and Industry Ministers, on proposals received by GAIC from insurance providers and the subsequent level of compliance by the industry with the recommendations of GAIC.

In April 1999, GAIC was established under the chairmanship of Professor John Durant, an academic experienced in the "public understanding of science". The other members were recommended by the ABI (2 people, one a clinical geneticist and the ABI's Genetic Advisor), by the Institute of Actuaries (1 person), by the British Society of Human Genetics (2 people, 1 a clinical geneticist who also advises the Chief Medical Officer, the other a genetic epidemiologist) and by the Genetic Interest Group (GIG) representing patient perspectives (2 members). GAIC met 3 times during the summer of 1999 and published details of its progress on the world wide web.

Responding to the Government report, the ABI made an undertaking to accept all findings of GAIC. The ABI promised that if a test result not approved by GAIC had already been reported to an insurer, and had been used to calculate a different from standard insurance rate, then the insurer would:

- re-rate cases where a loading was applied because of the test result and
- underwrite cases which were previously declined.

Media reports, however, (from August 1999 onwards) indicated that many journalists and some geneticists remained critical of the insurance industry.

During 1999 and early 2000, GAIC developed criteria for assessing whether a genetic test results could be requested by an insurer; GAIC

also carried out a public consultation on the proposals. After relevant modifications, submissions to GAIC by insurers were invited and the first one was submitted in July 2000. This was refereed, considered and validated by October 2000. The application concerned Huntington's Disease and Life Insurance only.

By the end of 2000, applications for different insurance products with respect to Huntington's Disease, hereditary Breast Cancer, and the small element of presenile dementias which is due to specific changes in the genes, presenilin 1 and amyloid precursor protein genes, were submitted. Meanwhile, the Government responded to the media hostility to the concept of insurance access to genetic test results by asking the newly formed Human Genetics Commission (HGC) (and the Science and Technology Committee) to review the wider social and ethical issues of genetics and insurance. The HGC embarked on public consultations on this and other 'genetic privacy' issues (HGC, 2001). The Science and Technology Committee prepared and published a report. Both HGC and the Select Committee implied or stated strong criticism of the insurance industry's policy on genetics and insurance.

Part of that criticism is based on the fact that other countries have banned access to genetic test results for the purpose of underwriting (Murthy et al, 2001). However, before the UK follows such countries (eg. Austria, France, the Netherlands and Norway), it is important to establish the aim of such a ban. If the aim is to show that there is solidarity with families with a genetic risk and a will to help them, then the outcome of such a ban in other countries should be evaluated. I am not aware that people with genetic disadvantages in the 4 countries mentioned above that do not allow insurers access to test results, have actually benefited. If that is so, then there are better ways to show solidarity and to support the genetically disadvantaged. If the aim of banning insurance access is "to draw a line in the sand", then some consequences must be appreciated. Banning access to genetic test results will weaken the principle in Law of "*uberrimae fides*", utmost good faith. Would this lead to a lesser standard for a contract, based

on "*caveat emptor*" or "*caveat venditor*"? The benefits of the UK approach are that the evidence from clinical, actuarial, legal, social and ethical assessments can be independently and then collectively, examined.

Genetics/Employment

In contrast to the considerable conflict between geneticists, social scientists and insurers over the issue of genetics and insurance, there was little conflict with employers about the genetics/employment interface. This was possibly because existing legislation (the Disability Discrimination Act, 1996, plus other Acts involved with racial or sexual discrimination) was felt to provide sufficient protection. The Human Genetics Advisory Commission issued a consultation document in April 1999 and published a report in August 1999, summarising the conclusions. More recently, the European Group on Ethics in Science and New Technologies (EGESNT) have published proceedings of a debate on Genetic Testing in the Workplace (EGESNT, 2000).

How to prevent unfair discrimination

Overt discrimination on the basis of a person's genetic risk is obviously wrong. This would be against ethical principles. If a person is able to carry out a particular job, then they should not be penalised because of a future problem. One of the discussions that has taken place concerns whether people with genetic disadvantages should be discriminated for positively to give them a better chance of achieving a job (or of getting insurance). The opinion of many self-help groups involved with the disabled, is that they would not wish such positive discrimination for employment. They state that the job must go to the best applicant, whether disabled, possibly disabled in the future or able-bodied. To ensure that unfair discrimination in employment does not take place, individuals should be assessed by an independent organisation rather than by a department within a particular employer's company. In that way, confidentiality can be best maintained. It is clear that many consider there should be positive discrimination with regard to insurance.

Conclusions

The history of genetics has always thrown up controversies. Since Francis Galton (1869) published his book on Hereditary Genius, the use of genetic methods in improving the health of the population has always been seductive. Viewing history and the present opportunities from the standpoint of a practising clinical geneticist I see that there are certain strategies and principles which could protect vulnerable sub-groups of the population from any excessive zeal to alter population structure. Individual informed choice and recognition of the importance of variation between individuals, will protect society from unwise centralised controls.

The first principle recognises that a healthy community **should** show a high degree of genetic variation. Policies which prefer and discriminate for one particular community sub-group rather than others will ultimately be dysgenic. (A world populated only by Professors of Clinical Genetics would not be healthy and would be unlikely to survive!)

The second principle is that politicians and leaders of public opinion must respect the views of individuals, who have experienced specific disabilities and traumas. People who have confronted a risk of inheriting the mutation predisposing to Huntington's Disease will have robust views about how their life should best be planned. There will be different viewpoints; each viewpoint must be respected. In a partnership with insurers and employers such individual options could be facilitated.

The closing words of this chapter should be from a Scottish poet who was well aware of the philosophers of the Enlightenment, including David Hume and Adam Smith.

Then let us pray that come it may –
As come it will for a' that —
That sense and worth, o'er a' the earth
May bear the gree, and a' that;
For a' that, and a' that,

It's coming yet for a' that
That man to man the world o'er
Shall brothers be for a' that!

from ***Is There, for Honest Poverty,*** **Burns, 1784**

Table I

Principles of the Genetics Code of Practice

- Insurers will not force individuals to have genetic tests.
- Confidential handling of all clinical and genetic information.
- Insurers will only request access to results of tests for which reliability and relevance has been established
- An Appeals Procedure was established.
- Insurers must not offer lower than standard premiums on the basis of Genetic Test results.
- Insurers have responsibilities
  - to give reasons for decisions
  - for monitoring and certifying compliance

Table II

Genetic disorders for which tests were valid for certain insurances

* An Alzheimer's Disease Sub-group

* Hereditary Sub-group of Breast/ovarian cancer

Hereditary Motor/Sensory Neuropathy type I (HMSN)

Huntington's disease (HD)

Multiple Endocrine Neoplasia (MEN)

Myotonic dystrophy (MD)

Polyposis coli or familial adenomatous polyposis (FAP)

** Adult type polycystic disease (APKD)

* These sub-groups are a low proportion (<5%) of the complete disease group, involving known mutations in one of 3 genes which can cause Alzheimer's disease or of 2 genes (BRCA1/BRCA2) which predispose to familial breast/ovarian cancer.

** At the end of 1997 it was expected that mutations in the gene causing adult polycystic kidney disease, type I (APKD1) would be available for NHS families at risk. This did not happen and therefore, despite being valid, this condition was withdrawn from the matrix of 8 conditions (ABI, August 1999).

Table III

Government's Response to the HGAC report (November 1998)

- Predictive value of genetic test results is of primary importance.
- Government agrees with HGAC (and the ABI) that for monogenic conditions actuarially significant associations are known to exist.
- Agrees too, that genetics of multi-factorial disease is not yet understood enough to use in risk assessment.
- Concurred with the HGAC that a permanent ban on the use of genetic tests by insurers would not be appropriate.
- Noted that test results could be used to an individual's advantage (eg. negative HD tests).
- Took responsibility for establishing a "Genetics and Insurance Committee" (GAIC).

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Declaration of Interest

Professor Sandy Raeburn is a Clinical Geneticist, Genetic Advisor to the Association of British Insurers (ABI) and a member of the Government's Genetics and Insurance Committee (GAIC).

Index

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