

Engineering the Human Germline. Gregory Stock and John Campbell (eds). Oxford University Press, New York. 2000. Pp. 169. Price £19.95, hardback. ISBN 0 19 513302 1.

Major scientific advances inevitably incite speculation about their ultimate social impact. When such speculation becomes exuberant it can drift into the realm of science fiction, a form of entertainment that is particularly diverting when predicated upon tangible scientific realities. Take for example the television series *Star Trek*. Released in 1966, just a few years after a man first orbited the planet (Yuri Gagarin in 1961, John Glenn in 1962), this enormously popular programme depicted earthlings of the future gallivanting around the galaxy at velocities exceeding the speed of light, mingling with alien life forms, transporting living beings from one place to another by disassembling and reassembling their atoms, etc. Although these futuristic visions were always understood to be fantasies, humankind's venture into space could not help but make those fantasies seem more like dreams that one day would come true. What made this series and its many sequels all the more enjoyable is that space technology is perceived in a positive light. In fact, it was not at all incongruous to depict the future society of interstellar travellers as manifesting social development to match its technological sophistication.

But what futuristic visions are conjured up by recent advances towards human genetic engineering? Over the past years new reproductive and molecular technologies, concurrent with progress in the human genome project, have provided a scientific foundation for speculation about manipulation of the human genome. In contrast to *Star Trek*, the notion of '*Gene Trek*' evokes far more disquieting images for two main reasons. First, it is more difficult for most people to know where disciplined speculation leaves off and science fiction begins, and second, the notion that people will be genetically designed is widely regarded with suspicion rather than anticipation. Consequently, sci-fi films on the subject such as *Gattaca* (1997) hardly take a sanguine view of human genetic engineering gleefully and, unlike *Star Trek*, the futuristic society of *Gattaca* remains afflicted with degrading, antisocial behaviours such as murder.

In an apparent attempt to address our mixed feelings about human genetic manipulation, the present book is published. This three-part volume tries to address our state of scientific progress in germ-line genetic modification (Part I), presents a panel discussion by eminent scientists, philosophers and physicians on the ethical and scientific aspects of this technology (Part II), and explores ethical and legal aspects of genetic engineering by having ethicists, philosophers and theologians respond to the proposal that their child be endowed with an artificial chromosome that would extend its life span by 10 years (Part III). It is only natural that we hope, after reading this volume, to have attained a more enlightened and coherent view of the scientific, social and ethical implications of human genetic engineering. However, *Engineering the Human Germline* is not designed to meet this expectation.

One of the difficulties with this book relates to uncertainty about its intended audience. Nowhere is this more evident than in Part I, where some fairly sophisticated science is intermin-

gled with prosaic passages that appear intended for a lay audience. For the scientist, the contributions are well written and very interesting, although they fall short of providing a coherent view of the state of the art of genetic engineering technology as it relates to deliberate engineering of humans. A contribution by Lee Hood is exceptionally well written and provides an absorbing explanation of the importance of rapid sequencing and chip technologies in deciphering the human genome. This chapter would be even better if Dr Hood outlined what must be done to actually make sense of the sequencing data. An explanation of the way in which information might be used to map extremely rare traits would have been helpful, as would a brief discussion of problems posed by extensive genetic polymorphism in the human gene pool. A proposal by Mario Capecchi for safe, inducible and reversible gene insertion is also very interesting and provides a good view of at least one strategy for low-risk engineering of the human germ line. Again, this segment would have been more meaningful to the reader if some review of the state of the art of artificial chromosome technology was provided. It would have been useful, for example, to know the stability of artificial chromosomes in mammalian cells and developing systems, and the potential for such chromosomes to exchange genetic material with endogenous chromosomes. If physical exchange occurred and involved *loxP* sequences from the artificial chromosome the result could be devastating. Another paper indicates that selection of appropriate alleles could greatly extend longevity. The assertion is based on experiments with fruit flies wherein animals selected for ovulation at an older age exhibit increased longevity (Rose & Charlesworth, 1980). This finding is consistent with the notion that delayed gonadal function increases life span, and is intriguing in light of similar findings in *C. elegans*, where mutations in *daf-2* (which interrupt progression into the reproductive cycle), or germ cell ablation, lengthen life (Kimura *et al.*, 1997; Hsin & Kenyon, 1999), and in Ames dwarf mice, which are hypogonadal and long-lived (Bartke *et al.*, 1998). Exactly how these observations could be extended to a rational genetic enhancement strategy for humans, however, is not clear.

Other contributions to this section include discussions of somatic gene therapy on the foetus, as well as the adult, and scenarios for how new reproductive technologies such as cloning might be employed in the future. The discussion of foetal somatic gene therapy does not address scientific obstacles that remain before such procedures are workable, and the discussion of cloning, human chimera construction, etc. provides an interesting 'buffet' of embryo manipulations, but is without much justification or rationale for their use, and without mention of other developing technologies that could effectively substitute for them. For example, advances in the human genome project discussed by Dr Hood could readily be exploited for selection of gametes that would confer a genotype on the offspring that was far more favourable than could be achieved by cloning. Since gamete donation is a simple, inexpensive and effective technique, would it not gain favour as the human genome is decoded? These gaps contribute to a sense of incompleteness in this section which leaves the reader anxious for greater development of the topics presented.

This section would have also greatly benefited by an erudite discussion of the degree to which predetermination of a genotype is likely to result in a predictable phenotype. The book seems to make the assumption that future genetic manipulators will have complete control of human development. This hardly seems likely, given the phenotypic differences between identical twins as regards complex traits, and by the obvious impact of biological and social environment in the development of cognitive, emotional and intellectual capacities. The impact of social environment on human development is exemplified by a comparison between Europe in 1820 and today. In 1820 Europe's population was about 200,000,000, and today it is at least three times higher. Yet in 1820, Europe produced Beethoven (1770–1827), Schubert (1797–1828), Chopin (1810–1849) and Schumann (1810–1856); and Mozart (1756–1791) had only recently died. Statistically, therefore, present day Europe's 'gene pool' has 12–15 composers of this calibre, but the actual number of contemporary composers comparable to those named is far fewer. The difference is unquestionably due to changes in social permissiveness to development of a musical career. It is also obvious that extrinsic biological factors can profoundly affect development. Consider how the aforementioned Beethoven would have developed, for example, had he lost his hearing in his first week of life rather than in middle age. The identification of non-linear behavioural properties of a number of developmental systems (e.g. Mrowka *et al.*, 1996) further indicates that critical developmental processes may be subject to chaos dynamics and, as such, may be intrinsically unpredictable.

Part II is a free-ranging discussion of the ethical and scientific aspects of human germ-line manipulation. Although clearly the views expressed are widely diverse, this section makes some telling points. Importantly, the notion that the human genome is 'sacred' is pretty well dispelled. If no scientific or medical obstacles existed to an effective and beneficial germ-line manipulation, then it hardly makes sense to ban such a procedure solely out of reverence for the human genome. Contributors also remind the reader that complete elimination of risk is not a reasonable prerequisite for performing germ-line manipulation, especially when the procedure is therapeutic. A very important additional point made here and elsewhere in the book is that effective genetic modification will probably be more easily accomplished *via* the germ line than with somatic approaches. Those casually acquainted with the field are probably not aware of this fact.

However, many of the ethical complexities of germ-line modification are not fully discussed. Morbidity and/or mortality in surrogate females who might be needed to carry pregnancies, and whose involvement with the procedure is essentially indirect, is an especially troublesome risk. Another point alluded to only fleetingly is the impact that promulgation of *ex-vivo* reproductive technologies might have on the social status of women. With large numbers of women serving as surrogates (e.g. paid incubators), and many embryos maintained in freezers where they may become subjects of legal disputes, will the respect for a woman's right to control her own body be further eroded? Will reproductive technologists use the anti-abortion fervour to improperly influence or even

intimidate women into selecting such procedures as pre-implantation genetic diagnosis or gene transfer, when a simple abortion is safe, effective and inexpensive? After all, it's hardly in the interest of the gene therapist to have patients elect alternative therapy. In this regard, the discussion would have benefited by the participation of an individual who practices advanced reproductive technologies and who confronts these issues frequently.

Part III presents a full range of opinions on the question of genetic enhancement for prolonged life span. Although several of the contributors avoid the issues by pointing out that older isn't necessarily better, etc., the majority give eloquent justifications for their opinions, which run the gamut. One of the more interesting presentations is by a rabbi who responds to the genetic enhancement proposal according to the canons of the Jewish faith. It would have been very interesting to read similar offerings from theologians representing the other major world religions. This section again does not facilitate a synthesis of the issues into a coherent philosophical position, but it does provide a look at the myriad attitudes surrounding the notion of human germ-line modification.

An important concept alluded to several times in this book, but not formally addressed, is the impact of germ-line modification on human evolution. The suggestion made is that natural selection no longer functions for humans, and that the ability to pre-select the genotypes of progeny negates the natural process whereby biological fitness determines reproductive fecundity. This issue is actually far more complex than is suggested in the scattered allusions to the subject. It may be asserted that evolution has stopped for humans, but there is no scientific analysis presented to support this claim. The fact that a few individuals can be born after genetic pre-selection also does not abrogate evolution, it merely points out that medical intervention can assure survival of individuals with potentially low biological fitness. A related and somewhat amusing declaration made is that humans have about five billion years to perfect germ-line gene insertion, since the solar system will last for about that length of time. Evidently it is thought that human extinction will not occur before the sun burns out. It is perhaps worth noting in this regard that humans have walked the planet for about two million years, a period 15 times shorter than *Tyrannosaurus*. To the extent it could consider the issue, I am certain *Tyrannosaurus* never thought its own extinction possible, and it had a 15-fold better justification for its beliefs than humans. Perhaps the possibility should be considered that evolution selects for beings that imagine their own species exempt from natural selection and possible extinction. If an organism realistically believed in its own species' extinction it might well lose its motivation to reproduce, which would of course be a selectively negative thought pattern. This explanation would at least justify the somewhat whimsical assumption that humans have until the end of the earth's existence to continue their scientific research.

Although many parts of this book makes interesting reading, as a whole it does not provide any novel insights. The issue of human germ-line genetic modification is a very complex one that cannot be examined cogently unless the many related issues are sorted out for systematic analysis. Such

an effort is difficult to undertake within the format of this book, where the eclectic views of numerous experts are solicited. Were it possible to separate ethical issues surrounding gene transfer for therapeutic purposes from those that were entirely elective; were it possible to address issues of informed consent when third parties such as surrogate mothers are involved; were it possible to discuss the issues within the context of a firm knowledge of the technical capabilities and limitations of a technology which still resides within the realm of imagination: this book could give the reader some guidance for forming their own opinion on the subject. However, the format of this book, and the state of the art of germ-line gene transfer make such a systematic analysis overwhelmingly difficult. As such, we are essentially left with an erudite but unfocused exchange on the hypothetical future of human germ-line manipulation.

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