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The human genome, in proportion

Even the most sceptical critic of genetic thinking in medicine would be hard pressed to resist a shiver of high expectation when faced with a research article entitled "The sequence of the human genome". That is how J Craig Venter and colleagues presented their findings in *Science* this week (see p 531). The International Human Genome Sequencing Consortium opted for a more self-effacing headline in *Nature*, calling its own efforts an "initial sequencing and analysis". The vast technical achievement by so many scientists around the world deserves to be applauded without either reservation or, despite still simmering arguments concerning public access to these data, any residual resentment. Yet, irrespective of the variable measures of modesty running through these first reports, both groups make extravagant speculations about the practical importance of their work for human health.

The public and private initiatives justify their hugely expensive research programmes on the basis of the likely benefits to medicine. The Consortium writes of the "profound long-term consequences for medicine, leading to the elucidation of the underlying molecular mechanisms of disease and thereby facilitating the design in many cases of rational diagnostics and therapeutics targeted at those mechanisms". The promise may indeed be great, but there is "a major surprise"—Venter and colleagues' words—within these latest results. The complement of human genes is far smaller than most observers originally thought: no more than 38 000 protein-encoding regions and possibly as few as 26 000. Commentators on the impact of this finding for medicine have tended towards gloom.

Some see the much smaller than predicted number of genes as offering fewer targets for pharmaceutical companies to exploit. Others argue that the incredible complexity of the human genome will drive up the average cost of developing new drugs, thereby increasing commercial risk and so perhaps diminishing rather than expanding innovation. One report even claims that the drug industry could bankrupt itself over trying to find ways to manipulate such an impossibly complex biological system. This early guesswork misses the point of why the human genome matters to medicine. It matters because the

human genetic signature finally reveals what it cannot tell or do for us. Its true relevance becomes clear only when set in the context of the global predicament of those with disease and disability.

The major risk factors for human illness are not likely to be affected by the range of applications that knowledge of the human genome will bring forward. Malnutrition, poor water and sanitation systems, unsafe sex, tobacco, and alcohol make up the top five risk factors for human disability. Beyond these priorities, physical inactivity, occupation, drug misuse, and air pollution are additional important contributors to disease. Only hypertension, a substantial cause of stroke and heart disease in developed and now developing countries, might succumb to the power of genetic understanding. But even for hypertension there is no simple gene-disease correlate.

It is these determinants of human disease that should be having "profound long-term consequences for medicine". Since the questions they pose for health fall largely within the realm of politics rather than science, they are all too easily marginalised. Politicians will trumpet the genome and pay homage to the science that has uncovered its message. But they will do so while too often ignoring public health, their own responsibilities to wider and more influential causes of disease, and the dangers that a simplistic genetic understanding of disease will foster.

Venter was therefore right to emphasise the value of the human genome for personal rather than public health, and he was also correct to counsel against the twin "fallacies" of determinism and reductionism. Perhaps the most intriguing report this week came from the International Single Nucleotide Polymorphism (SNP) Map Working Group. A SNP is an inherited DNA sequence variation that occurs about every 1000 to 2000 nucleotide bases. SNPs produce human genetic variation and the SNP Working Group found 1.42 million of them in the human genome. This enormous diversity proves how limiting it is—for medicine as well as for evolutionary science—to think about *the* human genome. Such humility is perhaps no bad thing at the end of a justly important week for human biology.

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