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Personalised medicine – a revolution in healthcare

> There are few words so widely disseminated and belonging so naturally to modern political vocabulary as the term 'revolution'.
>
> *Reinhart Koselleck (1985:159)*

It was a most peculiar newspaper headline. On 8 December 2003 the British broadsheet newspaper the *Independent* announced: 'Glaxo chief: Our drugs do not work on most patients' (Connor 2003a). The subsequent report covered a conference at which Allen Roses, vice-president of genetics at the pharmaceutical giant GlaxoSmithKline, admitted the 'open secret within the drugs industry that most of its products are ineffective in most patients' (Connor 2003a). Yet rather than this being a cause of outrage and falling share prices, for Roses and others like him in the industry such an admission is the first step on the road to a revolution in the way drugs are developed and, in the long run, how healthcare is provided. For Allen Roses 'is a pioneer of a new culture within the drugs business based on using genes to test for who can benefit from a drug' (Connor 2003a). And it is this use of genetic testing to develop and prescribe drugs, pharmacogenetics, that will drive the coming revolution. As Roses states, 'Pharmacogenetics has the promise of removing much of the uncertainty' that surrounds current drug use (Connor 2003a).

Industry's intense interest in pharmacogenetics and genomic technologies as a whole is relatively recent, dating from around 1997, but it has stimulated considerable investment on the part of pharmaceutical companies. As a report from the investment bank Lehman Brothers (co-researched by the management consultants McKinsey & Co.) notes, 'The excitement over genomics has been far-reaching. The pharmaceutical industry has poured hundreds of millions of dollars into genomics technologies, and investors have poured billions into financing the new industry that has evolved from these technologies' (Lehman Brothers 2001: 8). Although definite figures are hard to come by, one estimate

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suggests that somewhere between 10 and 20 per cent of big pharmaceutical company R&D budgets are now directed towards genomics (Pricewaterhouse Coopers 1998: 9). This puts total annual investment in genomic R&D at between 4 and 8 billion dollars, a figure supported by Lehman Brothers, who suggest that overall investment in 2005 will be 'at about $6 billion' (Lehman Brothers 2001: 81).[1] In terms of individual firms, Roche, one of the industry leaders in pharmacogenetics, claims to be investing about 5 per cent of its total R&D budget in these techniques (Branca 2002). For a company to even join the pack in this new way of developing drugs, 'annual spending on this technology to a certain point (approximately $100 million) appears necessary' (Lehman Brothers 2001: 7). In this context, Allen Roses's admission of the weakness of the modern pharmaceutical industry and its products looks less like an error of judgement and more like a call to arms. The failures and inefficiencies of modern drugs are an opportunity for those companies willing to take the risk, invest in new technology and revolutionise the way in which drugs are developed.

Such excitement on the part of industry has not gone unnoticed. Of course newspapers have covered the development of pharmacogenetics, the move towards personalised medicine; it made the cover of *TIME* magazine, after all (15 January 2001). But academic scientists and medics have also become enamoured. Normally serious researchers can be found spinning futuristic scenarios about the way healthcare will be delivered in the pages of equally serious academic journals. Such vignettes are usually set ten or twenty years into the future, involve the reader going to see a doctor who either samples their DNA there and then or reads their genome off a medical identity card that will have superseded written medical records (see e.g. Phillips *et al*. 2001; Akhtar 2002). Inevitably, politicians and health policy makers have become caught up in this whirl of expectation; the possible benefits of these new technologies are too good to ignore. Responses have varied from the low-key – the US government's funding of a Pharmacogenetics Research Network and Database information resource through the National Institutes of Health – to the high-profile – the British Genetics White Paper of June 2003, which set aside £4 million for research into pharmacogenetics (Department of Health 2003).

Yet however much money is going into research and however excited people in industry and elsewhere become over the promises of personalised medicine, the bright pharmacogenetic future lies tantalisingly out of reach. The aim of this book is to explore the kinds of expectations that have been created around these new technologies, to concepts such as 'pharmacogenetics' and 'personalised medicine', and to show how this technology works its way out in practice.

[1] This $6 billion by 2005 figure is supported by a more recent report from the market research firm Frost and Sullivan (GenomeWeb 2001).

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Politics

As its title suggests, this book adopts a broadly political approach to the topic of pharmacogenetics. Such a position covers issues such as healthcare rationing, the economic effects of expensive drugs and the relation between pharmaceutical companies, regulators and researchers. But following Bruno Latour's (in)famous rephrasing of von Clausewitz – that science 'is Politics by Other Means' (Latour 1988: 229) – this book also explores the politics of the way in which scientific ideas progress, develop, fail and get rejected. At this level, the participants involved are not political parties, electorates and parliaments, but researchers, clinicians, genes and drugs. At the core of this position is the idea that 'The political need not only be associated with the control of political institutions, the activities of the state or the fermentation of social movements. Instead I take the political to refer to the ways in which artefacts, activities, or practices become objects of contestation' (Barry 2001: 5–6). Theoretically then, this book comes out of broad research traditions within Science and Technology Studies, starting with the constructivist sociologies and histories of science of the late 1970s and early 1980s, moving through approaches variously described as the Social Construction of Technology (SCOT), the Social Shaping of Technology (SST) and Actor Network Theory (ANT).[2]

At this point, it must be confessed that this book does not address the most political (however one defines it) aspect of pharmacogenetics: race and ethnicity. In the growing ethical and social literature in this area, there is acute concern that genetically based differences in reactions to certain drugs might be mapped onto ethnic categories and serve as a basis for the biologising of race. For example, in a recent collection edited by Mark Rothstein, four out of fifteen chapters looking at the social and ethical impact of pharmacogenetics focused on ethnic or group-based differences (Rothstein 2003). Even Craig Venter, the 'arch-privateer' of the Human Genome Project (Rose 2003), 'hope[s] your goal in life isn't just to find genetic variation to identify ethnic groups. That would get us all in trouble pretty quickly' (Venter 2000: 17). This book does not address these issues because they simply did not arise in the two case studies that formed the core of my research. The analysis of pharmacogenetics offered in this book is rooted in the empirical setting of the two drugs I focus on. In neither one were ethnic differences relevant to variations in response to the drugs. There is a book to be written on the racial politics of personalised medicine, but this is not it.

[2] For a broad introduction to these approaches, see Bijker, Hughes & Pinch 1987, Bijker and Law 1992, MacKenzie & Wajcman 1999. For a recent review focused on medical technology, see Timmermans & Berg 2003.

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Terminology

The word *pharmacogenetics* is derived from 'pharmacology' and 'genetics', and has traditionally been defined as: 'genetically determined variability in drug response' (Wolf, Smith & Smith 2000: 987). For over forty years the term remained uncontroversial, with little dispute over what people meant when they spoke of a pharmacogenetic reaction to a drug. In 1997 a new word appeared in the literature, 'pharmacogenomics', the meaning of which was less clear than in the case of pharmacogenetics, with competing definitions of the term vying for recognition.[3] Recently there has been a move towards a consensus on the differences between the two terms, coming into line behind the idea that pharmacogenetics is about testing individuals for drug response,[4] whereas pharmacogenomics is used more broadly to describe the 'the concept of using whole-genome information to predict drug action' (Roden & George 2001: 37). As Roche's Klaus Lindpaintner puts it, pharmacogenetics is about 'one drug, many genomes' while pharmacogenomics, with a focus on how the same genome may vary its expression in the face of a variety of different products, concerns 'many drugs, one genome' (Lindpaintner 2003: 317–18).

Surrounding discussions of pharmacogenetics and pharmacogenomics are less technical, perhaps more publicly acceptable terms; 'tailor-made treatments', and, of course, personalised medicine (Cockett, Dracopoli & Sigal 2000; Mancinelli, Cronin & Sadée 2000; March 2000; Murphy 2000; Ginsburg & McCarthy 2001; Liggett 2001). Because of disagreement and doubts over the exact meaning of the word *pharmacogenomics*, in this book I tend to talk about pharmacogenetics, with 'personalised medicine' as something of a catch-all, covering a range of approaches currently being developed. Stripped of any obvious terminological link to potentially off-putting words such as 'genetics', personalised medicine might seem a perfect example of pharmaceutical industry marketing speak.[5] Perhaps because it seems less like jargon, or because it does not obviously invoke ethical issues, personalised medicine has been enthusiastically adopted in newspaper coverage of these new technologies.[6]

[3] For a fuller analysis of these debates, see Hedgecoe 2003.

[4] 'how to characterize a person with respect to disease susceptibility, severe adverse events . . . or whether the medicine is effective for treatment or prevention of disease' (Roses 2002b: 1472).

[5] The need to make clear in the public mind the difference between pharmacogenetics and traditional, disease genetics is a consistent feature of the debates around this technology. As the first half of this book will show, this distinction is not always that easy to make.

[6] Bonnor 1998; Connor 1999; Kolata 1999; McKie 1999; Pilling 1999a; Pilling 1999b; Pollack 1999a; Connor 2000; Griffith 2000; Pollack 2000; Independent 2000; Weiss 2000; Abate 2001a; Abate 2001b; Bowe & Pilling 2001; Griffith 2001; Highfield 2001; Kendall 2001; Lappin 2001; Moore 2001; O'Connell 2001; Feltham 2002; Highfield 2002; Jenkins 2002; Pollack 2002; Griffith 2003b.

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A familiar caveat at this point is to note that personalised medicine in the form of pharmacogenetics is not personalised in the same way a car number plate can be personalised. Misleadingly, some authors make comparisons with

> Health clubs [that] offer personal trainers; TC[2] and Levis offer personalized body scanning and custom-made clothing: Gateway and Dell computers advertise the customization of a personal computer based on the user's needs. This adaptation of this strategy within the healthcare industry would be personal pills.
>
> *(Anderson, Fitzgerald & Manasco 1999: 266)*[7]

But it is perhaps more accurate to say that personalised medicine is about putting people into treatment groups; certainly these proposed groups will be smaller and more predictable than the current division of patients. But to regard them as personalised, in the sense of being shaped and structured around an individual's specific needs (as opposed to the needs of the group that she or he has been assigned to) is to have an idiosyncratic definition of what the word *personalised* means. If we consider the parallel concept of 'tailor-made medicine', then what is being proposed is more a case of buying a small, medium or large T-shirt from The Gap than being fitted for a Savile Row suit.[8]

Interviews

The empirical 'core' of this book is based on interviews with sixty-six people involved in either Alzheimer's disease, breast cancer or broader issues to do with drug regulation or development.[9] Interviewees' names were gathered from internet searches, a review of scientific articles and snowball sampling. The interviews were carried out between April 2001 and July 2003, and most were taped and transcribed and lasted between 20 and 80 minutes. Specialist interviewees were asked to classify themselves as either clinicians, researchers or clinician researchers, with most clinician researchers (in both case studies) classifying themselves as such due to involvement in clinical trials (rather than laboratory-based research, for example). In writing up this material, I have

[7] Such comparisons frequently occur in the literature: 'Customized products, from personal computers to cars, are becoming increasingly popular' (Bracco 2002: 166).
[8] Thanks to Steven Rose for this comparison.
[9] There were twenty-seven Alzheimer's specialists (4 clinicians, 15 clinician researchers and 8 researchers: three were US-based, the rest from the UK), four people from companies involved in developing Alzheimer drugs, and one AD policy person. One researcher, one clinician and one clinician researcher were US-based. For breast cancer there were twenty-five specialists (2 clinicians, 20 clinician researchers, 1 researcher, and 2 oncological pharmacists), two policy-based interviewees, one regulator, one person from a company and two people from breast cancer charities. There were also three regulators.

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chosen to use a significant number of excerpts from these interviews, rather than paraphrasing or summarising the general themes that emerged. In practical terms, I hope this approach brings out the interviewees' voices: they say things far better than I could.

The stories that this book explores, stories from the clinical coalface (to use a term that cropped up in a number of my interviews), are not ones that get told in debates around personalised medicine. Strange as it may seem, clinicians who are beginning to use this technology, an apparently powerful group with important things to say about its use and impact, are almost totally excluded from discussions in this area. The ethical debates around pharmacogenetics have tended to focus on the issues raised by pharmacogenetic research: informed consent; the encryption of DNA and medical records; who has access to this data; do the results of such research get fed back to participants?[10] These are all vital topics that need to be explored if we are to regulate the development of pharmacogenetic products appropriately, but it is not enough to assume that a focus on pharmacogenetic research means that such technologies are not being used at the moment, or that the impact they might have on clinical practice is not at least as great as that on drug development. Two recent comprehensive reports, one by the US-based Consortium on Pharmacogenetics (Buchanan *et al*. 2002) and the other by the British Nuffield Council on Bioethics (Nuffield Council on Bioethics 2003), have gone a long way towards redressing the balance in terms of questioning the ethical issues surrounding the clinical use of pharmacogenetics. Yet even in these reports there are necessarily gaps in terms of the 'complexity of the empirical'. Coming from STS, it is natural to see the ethical issues raised by pharmacogenetics as socially constructed, in the same way that technical, scientific issues are. This is an obvious point, but not one that is necessarily highlighted in philosophically rooted bioethics literature. Thus just as my political approach sees scientific debates as inherently sociotechnical, so are ethical discussions socioethical. This book provides the means to make messy current consideration of the ethics of personalised medicine.

Themes and structure

As chapter 2 makes clear, pharmacogenetics is a heterogeneous technology. For some people it is about avoiding adverse drug reactions, for others it is about discovering the genetic basis to common diseases. Based on the experiences,

[10] For a review of the literature, see Møldrup 2001. For examples: Chadwick 1999; Issa 2000; Clarke, English, Harris & Wells 2001; March, Cheeseman and Doherty 2001; Thomas 2001; Robertson 2001; Rothstein & Griffin Epps 2001; Issa 2002; Vaszar, Rosen & Raffin 2002; Lipton 2003; Vaszar, Cho & Raffin 2003.

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attitudes and beliefs of the clinicians and researchers interviewed, several themes arise and run through this book, which can best be presented as contrasting ideas, or dichotomies. The first is between the way those at the clinical coalface view particular examples of pharmacogenetics, and the kinds of expectations created around these examples in the broader pharmacogenetic literature. At its most crude, those industry scientists and academic geneticists and pharmacologists who cite the two case studies I use in this book, Alzheimer's disease and breast cancer, have a greatly simplified, almost unrecognisable, view of these examples, when compared to the technically complex, ethically messy, position taken by those who actually use the technology.

The second comparison I wish to highlight is between the view of pharmacogenetics as an ordinary, as opposed to a revolutionary, technology. The standard view of pharmacogenetics is that it will revolutionise the contexts within which it is applied. While this may well be the case for drug development, it seems to me that the clinical context is far more resistant to revolution than many commentators assume. When a pharmacogenetic drug arrives in the clinical setting, as in the case of Herceptin and the breast cancer clinic for example, then the drug and its test become incorporated into clinical practice, compared with other treatments and tied into networks of funding, testing and professional practice. The pharmacogenetic treatment becomes 'ordinary'. Rather than pharmacogenetics arriving and revolutionising the clinic, new treatments arrive and are redefined in terms of ordinary clinical practice.

The final dichotomy is between knowledge and resistance. A regular feature of discussions around the movement of new genetic technologies into the clinic is the need for clinician education. Educating clinicians, giving them knowledge about new technologies this argument goes, will increase acceptance of the new technology and lead to faster, wider uptake. Based on the research in this book, it seems quite clear that lack of knowledge is *not* the main cause of clinical resistance to pharmacogenetics. The reasons why clinicians are reluctant to adopt such apparently beneficial technologies vary from technical uncertainty through financial limitations to the usefulness of interventions and the morally risky nature of some pharmacogenetic tests. We need a more socially nuanced understanding of how technologies move into clinical practice.

This book is structured as follows. Chapter 2 gives details about the history and context of pharmacogenetics and personalised medicine, and sketches out the theoretical framework for my research; the sociology of expectation. Next, two case studies in pharmacogenetics are presented. Chapters 3, 4 and 5 discuss the relationship between Alzheimer's disease, a gene called APOE4 and the anti-Alzheimer's drug Tacrine. The story follows APOE4 from the discovery in the early 1990s that it is associated with increased risk for developing Alzheimer's

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and the professional debates that surrounded its use in the clinic (chapter 3), through its link to the reduced effectiveness of Tacrine and clinicians' attitudes towards this putative pharmacogenetic association (chapter 4), to the role of APOE testing in research and the attitude of industry towards APOE4 and the possibility that it may play some pharmacogenetic role in prescribing drugs (chapter 5). The second case study – chapters 6, 7 and 8 – concerns the breast cancer drug Herceptin, which is used to treat tumours with too much of a certain gene, called HER2. I follow the drug as the pharmaceutical company Roche tried to overcome clinical resistance and persuade UK clinicians to adopt both Herceptin and the HER2 test that accompanies it (chapter 6), through to more formal hurdles, as Herceptin was assessed by the UK's National Institute for Clinical Excellence in an attempt to make it eligible for NHS funding (chapter 7), until finally, we see how a pharmacogenetic drug works in the clinic, how it impacts on the doctor–patient relationship, and how, in this context, it needs to be seen as an ordinary technology (chapter 8). Chapter 9 ties these various themes together and shows how this research can be of use to regulators, policy-makers and the wider public in debating pharmacogenetics.

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Pharmacogenetics, expectation and promissory science

> In an age when people in developed societies expect individual treatment in all spheres of life, the provision of drugs often appears clumsy.
>
> *Andrew Marshall (1998)*

A brief history of pharmacogenetics

The aim of this chapter is to briefly set out the debates about personalised medicine in the professional literature, outline theoretical ideas that might help us get to grips with these arguments, and introduce the two case studies used in this book. As a sociologist of science, one of the interesting things about coming to personalised medicine is the sheer range of people who are willing to write about it and tell you how they think it will develop. The profusion of reviews, editorials and opinion pieces in scientific and medical journals (what we might collectively call 'commentaries') that speculate about how medical practice and drug development might look in a few years' time provides a wonderful resource for sociological analysis. What follows is an attempt to unpack some of the claims being made about pharmacogenetics by academic scientists, company representatives and other commentators. Although it is not a comprehensive, quantitative review such as those found in the scientific literature, it does provide a detailed outline of the kinds of concerns that form the context within which pharmacogenetics will move into clinical practice.

Depending on one's source, pharmacogenetics was either founded by Pythagoras, with his observation of adverse reactions to fava beans in 510 BC (Nebert 1997; Ensom, Chang Patel 2001; Rusnak *et al*. 2001) or Freud, with his discovery in 1885 that different people have different pharmacological reactions to cocaine (Pfost, Boyce-Jacino & Grant 2000). The term *pharmacogenetics* itself was coined by Friedrich Vogel in 1959, following groundbreaking work

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by Arno Motulsky two years earlier (see Weber 2001 for a detailed historical review).

At the core of pharmacogenetics is the idea that humans differ one from another in their reactions to drugs. Individuals may differ in the way in which they metabolise drugs, the way in which the drugs actually operate within their bodies, and the rates and extent to which products are removed. The results of these variations mean that some people metabolise a standard dose of a drug so fast that they do not gain any therapeutic benefit from it; others who are slow metabolisers run the risk of adverse drug reactions (ADRs) and have to be prescribed much lower doses of particular drugs.

Although in the early years of the discipline, important discoveries were made, such as Glucose-6-phosphate dehydrogenase (G6PD) deficiency in 1956 and the genetic variation in ethanol metabolism in 1964 (Kalow 1990), pharmacogenetics expanded slowly, with specific drug–gene relationships becoming clear as and when investigators came across them, rather than there being any active search for such links.

The emergence of molecular biology provided the means for improved investigation of the genetics of drug response, with the 'molecular turn' in pharmacogenetics dating from 1988, when Frank Gonzalez and his colleagues isolated several alleles of the human CYP2D6 gene, part of the P450 cytochrome complex of genes responsible for drug metabolism in the liver (Gonzalez *et al.* 1988). This study opened up the field to the 'new genetics'. The 1990s brought the Human Genome Project, and new technologies gave scientists a greater understanding of genetic variation and gave rise to an increased interest in pharmacogenetic studies.

Industry

Any discussion of the rise of personalised medicine has to set industry ('big pharma' as well as small biotech firms) at the centre of the story. Industry involvement dwarfs any investment from governments or charitable institutions. Company concerns shape the timing of our increased interest in this technology, the scientific debates that are taking place over the shape pharmacogenetics will take in the future and even the ethical discussions going on around personalised medicine (Hedgecoe & Martin 2003).

Traditionally, pharmaceutical companies have adopted a 'one size fits all' principle with regard to different people's reactions to drugs (Mancinelli, Cronin & Sadée 2000; Liggett 2001). Although acknowledging variations in dosage (because of age, sex and body size), the general approach has been the

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