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# **NORMALITY AND PATHOLOGY IN A BIOMEDICAL AGE<sup>1</sup>**

## **NIKOLAS ROSE**

In conclusion, we hold that human biology and medicine are, and always have been, necessary parts of an “anthropology.” But we also hold that there is no anthropology that does not presuppose a morality, such that the concept of the “normal,” when considered within the human order, always remains a normative concept of properly philosophical scope.

Georges Canguilhem, *The Normal and the Pathological*, 1951(Canguilhem 2009)<sup>2</sup>

Are you normal? We all know the layers of meaning and judgement conflated within a question like this – the normal as average, typical, physically and mentally healthy, statistically close to the mean in a population. Hence those summoned by its antithesis, pathological – unhealthy, deviant, dangerous. These terms interweave different modes of judgement – statistical, social, medical, moral, ethical. Perhaps most sociologists would accept that the idea of the norm has its place in relation to the body – the vital norms of temperature, of blood pressure, of heartbeat and the like, perhaps of anatomy and physiology more generally. But they – we – tend to look with suspicion when this apparent natural sense of normativity is displaced from the realm that today we call biological (or perhaps biomedical) to that which we term social. Hence they would probably agree with that great historian of the life sciences, Georges Canguilhem, when he differentiated vital norms from social norms. In his doctoral thesis, written in 1943, Canguilhem argued that biological thought derived its ideas of the normativity of the organism from the dynamic normativity of life itself: “It is life itself, and not medical judgment which makes the biological normal a concept of medical value and not a concept of statistical reality” (Canguilhem 1978: 73). In his ‘new reflections on the normal and the pathological’ written between 1963 and 1966, inflected by the radical spirit of those times, he distinguished such vital norms from social norms. Social norms – the norms of docility, legality, productivity, punctuality, civility and the like – were not a reflection of the normativity of a vital order and its struggle against death, but of the normativity of socio-political authorities and their attempts to maintain order and pursue their objectives of control

Of course, this distinction between the organic norms of the body and the artificial norms of society was not accepted by the first sociologists. Sociological styles of thought have long been intertwined with those of biology - indeed biology and sociology were born close together. The Oxford English Dictionary tells us that the term 'biology' for the sciences of life emerged and stabilised in the period from 1820 to 1840; it gives 1844 for the first use of the term sociology for a new science of social ethics. Metaphors drawn from the biology of the time have played a large part in each generation's analysis of social phenomena. For functionalist sociologists it seemed that social norms had the same relation to the healthy functioning of society that vital norms had to the healthy functioning of the human organism: in the former case as in the latter, departure from those norms was evidence of a kind of pathology. Few would accept this today, in the wake of decades of criticisms of functionalism, the rise of the sociology of deviance, cultural relativism and the criticisms of the nature-culture binary, But what, then, of the normal and the pathological, and of the vital and the social. This is the theme I would like to discuss in this paper.

## **The personalised genome**

I don't know how many of you have recently visited the website of [decodeme.com](http://decodeme.com).<sup>3</sup> Those of you who have will have discovered that, "For only \$985, we scan over one million variants in your genome" and that you can "Calculate genetic risk for 18 diseases based on the current literature; Find out where your ancestors came from and compare your genome with others ; get regular updates on future discoveries and a growing list of diseases and traits". You may be surprised to be told, however, that " deCODEme is not a clinical service to be used as the basis for making medical decisions. While the Genome Scan includes genetic variants that have been linked in our own and others' research to risk of certain diseases, we believe that individuals interested in utilizing such information for making healthcare decisions should do so in the context of clinical diagnostic tests." And also that "the deCODEme Genetic Scan does not include genetic variants that have been shown to cause purely genetic diseases or indicate a near certainty of developing any diseases". But there is another way to turn all this "getting to know your genome" into health relevant information, apparently, because deCODE offers to sell genetic tests ordered with the

authorization of a physician at a discount to subscribers, and these may be reimbursable by healthcare providers.<sup>4</sup>

So a new business model is taking shape. And whatever this warning may say, for legal reasons no doubt to do with US FDA guidance on the marketing of genetic tests,<sup>5</sup> the information on risk will have consequences for individuals who receive it. And decodeme is not alone. You could try '23andme' where "genetics just got personal".<sup>6</sup> Or you could go to 'navigenics' for after all it is "my genes, my health, my life".<sup>7</sup> Or, if you are suspicious of commercial motives, visit the site of George Church's Personal Genome Project at Harvard,<sup>8</sup> which comes complete with links to the blog of one of the volunteers, Misha Angrist, GenomeBoy.<sup>9</sup> In Harvard's personal genome project, as with the commercial sites, you participate in a new 'gift relation' – in the very same moment that you deposit your own 'personal genome' and health data into the genome bank to discover your own risks, you contribute your own data to the population on which future risk estimates are based. As these projects gather data from across the world, on a person by person basis, and in doing so collect larger and larger databases to provide the statistical power to discover genetic markers of small effect associated with disease risk, perhaps a new form of global genomic citizenship – individualized and consumerized, is in the making.

## **From tainted germ plasm to genome wide association studies**

In any event, it is clear that something has happened to genomics, to its style of thought, its forms of evidence, its technologies for generating truths, and their implications.

Sociologists have long been among the most fervent believers in genetic exceptionalism – that is to say the belief that there is something exceptionally powerful in genetic information. Almost all British sociologists of the first half of the twentieth century had close links with the Eugenics Society – although some of them, notably Titmuss, wanted to shift the emphasis away from genetic improvement and towards environmental and social measures to improve the quality of the population – the approach that would become known as 'social medicine' (Oakley 1991). Sociology in this period was transfixed with problems of fertility, with differential fertility between social classes, and its consequences for population size and quality, and the Eugenics Society was one of the progenitors of academic sociology in Britain as well as of demography (Osborne and Rose 2008).

But when it comes to the social implications of genetic knowledge the contemporary sociological imagination is shaped by hindsight. From the stories of the Jukes and the Kallikaks, with their images of tainted germ plasm coursing down the generations, to the murderous eugenics of the Nazi state and the pastoral eugenics of the Nordic welfare societies, genetics has been associated in the sociological imagination with fatalism, reductionism, individualisation of social problems, and a range of profoundly negative policies for the management of the quality of the population through reproductive control – what contemporary Norwegians call a “sorting society” which divides people in terms of an idea of individual worth fixed at birth in a given genetic complement. Such a genetic imaginary is regularly reinforced by the absurd simplifications of social Darwinists, for whom ‘the gene’ is a black box and selection is accorded a social teleology. Not to mention the occasional outburst by those like James Watson who should know better – you can check out his own personal genome, sequenced in two months in 2007 by 454 Life Sciences – Measuring Life One Genome at a Time – for less than \$1M, and available on the web for all to see, only lightly edited.<sup>10</sup>

Perhaps this perception of genetics as intrinsically linked to a kind of biological determinism was justified in the early years of the Human Genome Project with the regular narratives proclaiming that this was a search for the code of codes, the book of life, and the belief that the genome contained the ‘digital instructions’ for making human beings – the so-called genetic programme approach (Kay 2000). Many suggested that the number of distinct genes, now thought of as coding sequences consisting of strings of nucleotide bases – the Gs, Cs, As and Ts of the three letter code for amino acids that make up proteins – as in the familiar GATTACA- on the 23 human chromosomes was between 100,000 and 300,000 (Gilbert 1993). Estimates of the number of different proteins in the human body vary, but many put this at about 100,000. So it did not seem impossible that there was, indeed, one gene for each protein, together with some additional sequences concerned with the regulation of gene transcription and expression, modelled on the classic studies by Jacob and Monod in the 1960s (Jacob and Monod 1961).

On this basis, one could conceive of a clear genomic distinction between normal and pathological. Most individuals would have ‘normal’ genomes with a common sequence

coding for the proteins necessary to produce health functioning except when disrupted by pathogens from outside. Those destined to sicken would have ‘mutations’ in one or a few genes which would either predispose them, or even determine them, to ill health. This was, indeed, the promise of genomic medicine. Leroy Hood writing in 1992 under the title ‘Biology and Medicine in the Twenty First Century, in the book he co-edited - *The Code of Codes* – believed that, “Once the 100,000 human genes have been identified” it would transform our ways of dealing with human diseases (Hood 1993: 155-157):

The genome project in the twenty-first century will have a profound impact on medicine, both for diagnosis and therapy ... Perhaps the most important area of DNA diagnostics will be the identification of genes that predispose individuals to disease. However, many such diseases – cardiovascular, neurological, autoimmune – are polygenic; they are the result of the action of two or more genes. Human genetic mapping will permit the identification of specific predisposing genes and DNA diagnostics will facilitate their analysis in many different individuals ... Perhaps in twenty years [he was writing in 1992] it will be possible to take DNA from newborns and analyze fifty or more genes for the allelic forms that can predispose the infant to many common diseases... For each defective gene there will be therapeutic regimens that will circumvent the limitations of the defective gene. Thus medicine will move from a reactive mode ... to a preventive mode. Preventive medicine should enable most individuals to live a normal, healthy, and intellectually alert life without disease.

But as this quote illustrates that genomics in the closing decades of the twentieth century, even when it had a rather simple ‘one gene-one protein’ model, was not bound up with fatalism, but with hope. As Carlos Novas and I have argued, even in relation to the most apparently fatal of the single gene disorders, Huntington’s Disease, diagnosis led not to passivity but to activism – campaigning organizations, websites and web-lists for mutual advice and support, fund raising and tissue donation to find the genetic basis of the disorder and the funding of research to develop therapies (Novas and Rose 2000; Rose and Novas 2005). And, more generally, we suggested that we were seeing the rise of what we termed active biological citizenship – a new active consumer-like turn in the strategies of even quite old support groups for those with particular illnesses or disabilities, together with new groups formed around specific diseases, especially genetic diseases, new relations between these groups and medical researchers in which sufferers and carers campaigned for research funding, donated money, tissues and time, and sought to direct research towards cures, a new relation between patients and medical expertise, and indeed new ‘active’ modes of governing the self involving self-education in the nature of a disorder, and self-management – a characteristic combination of autonomization and responsabilization

that one might term 'biomedical prudence'. Many of these contemporary examples have been well studied. Paul Rabinow's work on Association Française contre les Myopathies (AFM) led him to propose the idea of 'biosociality' as a play on the then popular ideas of socio-biology (Rabinow 1999). Carlos Novas's work on Huntington's Disease and PXE international led him to suggest that a 'political economy of hope' characterised this new field (Novas 2006). The work of Deborah Heath, Rayna Rapp and Karen-Sue Taussig on Epidermolysis Bullosa suggested that we were seeing the emergence of new active forms of 'genetic citizenship' (Heath, et al. 2004). And, of course, these new active modes of self-management, part of what I have elsewhere termed 'ethopolitics', led to their own forms of judgment and indeed of exclusion brilliantly captured in the paper by Vololona Rabeharisoa and Michel Callon entitled 'Gino's lesson on humanity' (Callon and Rabeharisoa 2004).

This situation was to mutate again when, in 2001, after much diplomatic negotiation, the draft sequences from both public and private sequencing programmes were simultaneously published, each showed not 100,000 genes, but as few as 30 to 40,000 coding sequences (Lander, et al. 2001; Venter, et al. 2001). As Craig Venter asserted at the time, the basic premise of the genetic programme approach - one gene for one protein - could no longer be sustained: the reductionist approach had to be abandoned in favor of models of complexity: "networks that exist at various levels and at different connectivities, and at different states of sensitivity to perturbation" (Venter, et al. 2001: 1347). When the Human Genome Sequencing Consortium published their final sequence in *Nature* in 2004, (Collins, et al. 2004) we had decisively left what Evelyn Fox Keller termed 'the century of the gene' (Keller 2000) and we also seemed to have moved decisively beyond the 'genetic programme' approach (Neumann-Held and Rehmann-Sutter 2006). There were simply 'not enough genes' for the sequence to be regarded as a 'code of codes' or the digital instructions for making a human being. We were in a much more complicated world, where alternate reading frames could read the same sequence of bases in different ways, where proteins were assembled from sequences spread across many chromosomes, we were in the world of alternative splicing, where parts of one sequence would be connected up with parts of another sequence, in a world where the same sequence could produce different proteins at different stages of development, in a world where, far from the DNA regulating the development of the cell, it appeared that in crucial respects it was the cell, and the humble

RNA previously merely assigned to the role of messenger, that seemed to be in charge of development.

And, if this was not bad enough news for those who had placed such hopes in the future of genetic medicine, the bottom seemed to be falling out of that particular market. By the start of 2007, billions of pounds and dollars had been spent in attempts to 'translate' the results of the Human Genome Project into clinically relevant measures that would improve the health of patients, yet there was little to be shown in the way of new therapeutic options available for the common complex diseases that ail most of us in the developed world, let alone in relation to the burden of disease in developing countries. While companies specialising in biomedical genomics saw their stock market values rise sharply with the initial developments in sequencing the human genome, the downturn began in 2002. Commercial companies whose business plan was predicated on the discovery of the genetic bases for such common disorders saw their share values drop sharply over the opening years of the twenty first century. And by 2005 *Nature Biotechnology* commented that "roughly  $\frac{3}{4}$  of the companies that listed during the 1999/2000 biotech bubble are still not making money", and even in 2006 Genentech and Amgen finished the year down in share value by around 12%. Leroy Hood's hope of finding a few significant alleles of large effect, which would allow clinically meaningful genetic tests for susceptibility to conditions such as diabetes, heart disease, or the dementias had proved largely fruitless, and no effective genetically informed therapies for common disorders were even on the horizon. Where then for genomic medicine?

## **Personalised genomics**

The flurry of publications from Genome Wide Association Studies in Autumn 2007 can be seen as one response to this crisis in genetic medicine (for one influential piece, see Wellcome Trust Case Control Consortium 2007). Economies of scale have come to the rescue, and enabled the emergence of a new way of thinking, a new wave of hope, and a new business model. The industrialisation of the process of sequencing large numbers of SNPS has led to an exponential drop in the prices of sequencing each location – so that it is feasible for researchers with large sample sizes to sequence up to 500,000 SNPs in each subject for less than \$1000. SNP level information from HapMaps has enabled this many

SNP markers to be identified and localised. And case control studies, comparing large numbers of individuals with a disease diagnosis with normal controls have enabled the generation of data showing differences between cases and controls at multiple sites. A new way of thinking – disease susceptibility as the result of interactions between many, maybe two or three hundred, SNPs of small effect, has been made possible. Hypothesis free, it is claimed – no need to opt for candidate genes, no need to begin from functional hypotheses – statistical associations will generate risk assessments with clinically useful consequences.

Not that this approach has been without scientific criticism – for poorly defined phenotypes, poor study designs, and, perhaps most important, for failing to emphasise the low utility of the associations found for assessing the risks of developing complex diseases (effect sizes of the new loci found are modest or small) (Higgins, et al. 2007; Manolio and Collins 2007; Pearson and Manolio 2008). Nonetheless, a new way of thinking is taking shape. For most common complex disorders, the genetic basis, if that is indeed the right word, lies in the highly complex interactions of many ‘genes of small effect’ each of which may, in combinations with others, increase or decrease risk by a small percentage. Perhaps one cannot even call these SNP level variations ‘genes’ of small effect, as many of the signals picked up in these studies actually identify significant differences between cases and controls in regions that were once termed ‘junk’ – that is to say, that do not contain the triplets that code for amino acids at all.

This way of thinking has been central to the new buoyancy of the market in genomics. Consider the words of Steven Burrill, whose group acts as biotechnology consultants to the industry:<sup>11</sup>

The transition to a more personalized medicine world is creating the need for molecular diagnostics, biomarkers, genotyping assays, etc. and so companies specializing in these areas have received positive investor attention ... Sequenom, for example, a provider of fine mapping genotyping, methylation and gene expression analysis solutions, saw its share price rocket and closed the year up 588%.

This, to return to our starting point, is the kind of research that animates Navigenics, 23andme, and decodeme. Indeed decodeme is an attempt, by those who carried out one of the first population wide studies of the association between genomic information, medical records and genealogy in Iceland, to develop a new business model. The one on which they had placed their bets – that one could use this method to develop tests for common complex

disorders and ultimately therapeutics that targeted their genetic basis - had generated few if any medically useful findings. Hence the new target audience is less pharma companies and medics than it is you - your own personal genome. You are to be empowered, to discover your own levels of genomic risk, to become an active participant in genomic research, and to have to make your own kind of sense of the new spectrum of risk data with which you are provided - it is "your genes, your health, your life" and hence in your power to use genetic information to assemble a pathway to optimal health. And, in the moment when you accept the obligations of this new offer of genomic freedom, you enrol your own genome in the database that will eventually, or so the companies hope, provide the statistical power necessary for more and more pronouncements of more and more sites associated with small variations in population risk for particular disorders. Indeed, according to *Nature* in February 2008, over the five and a half months since October 2007, the number of diseases for which genetic tests were available to patients had grown by 8.4%, to 1,236 (Editorial 2008).

But what has become of the notion of normality - the healthy, the average, the absence of pathology? At the genomic level, the answer may seem surprising - NONE OF us - none of you - are 'normal'. We are all at risk, of higher risk for some conditions, of lower risk for other conditions, but all of us harbour, in those three billion base pairs that make up our 23 chromosomes, multiple minor variations that are potentially knowable, and which appear (although I would like to stress that word) to render our future risks of everything from Alzheimer's disease to obesity knowable and calculable. We are all asymptotically, presymptomatically ill - and perhaps all suitable cases for treatment. Now of course this is not itself a radical shift. On the one hand it just extends what we already know about the emerging landscape of risk susceptibility, presymptomatic and asymptomatic diseases etc. Most of you - at least those of a certain age - will be personally familiar with procedures for the allocation of individuals to risk groups, on a genealogical basis, in terms of a family history of illness or pathology, and/or on a factorial basis, in terms of combinations of factors statistically linked to a condition. Men presenting to their doctors with high blood pressure are risk profiled in terms of age, weight, family history, smoking and so forth, are allocated to a risk group using a scale based on epidemiological and clinical research, and if at high risk, may be advised to make changes to behavior, diet or lifestyle, or preemptively placed on a drug regime intended to reduce the risk of the occurrence of such disorders.

Pregnant women are risk profiled by their doctor or midwife, and if allocated to a high risk group for miscarriage, premature birth or associated difficulties are subject to enhanced surveillance by midwives and gynecologists (Weir 1996). And so on.

Many of us working in these areas have drawn attention to the apparently illimitable expansion of this territory of risk under pressures from several directions. Preventive medicine, of course, prioritises identification and intervention, both at the collective and at the individual level, prior to the emergence of frank disease. The growing precautionary principle, coupled with foresight and horizon scanning exercises, predicts the future burden of current health trends and demands early interventions into conditions such as obesity not previously encompassed within the territory of treatment; pharmaceutical companies seek products that will treat chronic conditions, as these make more sense in a business model, and what could be more profitable than medications used for a lifetime to treat a pre-disease – high lipid levels, for example – that is to say, to treat parameters that are not themselves diseases but are thought to increase the likelihood of future disease. And patients themselves, enjoined to be prudent about their own health, to manage their bodies in the name of health, willingly or unwillingly are coming to ally themselves with such presymptomatic measures in the name of health.

As I have said, none of this is without precedent. In some recent papers the fine historian Charles Rosenberg has pointed out two important senses in which nothing much new was happening (Rosenberg 2003; Rosenberg 2006). First, that there have always been disputes about the boundaries of disease, or perhaps better, the boundaries of the territory of medicine and the legitimate activities of medics – from back pain to pregnancy, the characterization of disease has been disputed. Second, what Rosenberg terms ‘technocrep’ has a long history: diagnostic tools elicit signs that are taken as evidence of pathologies that were previously invisible – generating what Rosenberg terms ‘protodiseases’ (Rosenberg 2003). What changes, when, when we move to the molecular scale, the scale of molecular genomics? The prediction was that gene sequencing would identify the genomic bases of diseases at birth, if not before, with all sorts of consequences. Sequences were identified that coded for the defects causing rare and often fatal diseases – such as the famous or infamous ‘Jewish Genetic diseases’ such as Tay-Sachs, Canavan Disease and Fanconi Anemia - known to be more common among Ashkenazi Jews – these became the subject of a

controversial genetic register, run by communities themselves, that tests young people for their carrier status before they entered into marriage and advised them whether or not it was genetically appropriate for them to marry and procreate. But attempts to discover diagnostically meaningful genetic information for common complex disorders were largely unsuccessful – even the much publicized ‘breast cancer genes’ BRCA1 and BRCA2 – account for only a small proportion of the heritability of breast cancer, let alone for the bulk of the condition that is not known to be linked to family history. And so, although with a few exceptions again for simple and rare conditions, attempts to develop genetically targeted treatments or clinical interventions were similarly unsuccessful. But nonetheless, the idea that genetics held the key to future risk, to susceptibility, was hard to dislodge – as witness the number of people seeking to have those tests when they first became available on the web.

Of course, as I have suggested, the new ventures in gene sequencing also hold out that idea that your genome carries variations that may affect your future disease susceptibility – that tiny SNP level variations in sequences increase or decrease susceptibility to all the ills that flesh is heir to. And Craig Venter, one of the few individuals who has had his whole ‘diploid’ genome sequenced, peppers his recent autobiography *A life decoded*’ with inserts letting the reader know that he does or does not carry the specific variant that would increase his risk of developing a particular disorder (Venter 2007). But this simply makes the point - there is NO normal genome – at the genomic level, no-one is ‘normal’, at least in the sense that this term acquired from the nineteenth to the twentieth century, overlaying a statistical average, a judgment of desirability, and an idea of health and illness. The developments in the genomics of disease that I have outlined suggest a different way of thinking, one that is perhaps difficult to comprehend – that of pathology without normality. I want to propose that, in the area of disorders of body and mind at least, we are moving from dividing practices based on the binary of normality and abnormality to practices based on the idea that all individuals vary, and that most, if not all, carry from molecular variations that can in particular circumstances lead to disorders of body or mind, but which, once known, are potentially correctible. In the human genome, ‘the normal is rare.’<sup>12</sup> Or rather, there is no normal human genome - variation *is* the norm. In this new configuration, what is required is not a binary judgment of normality and pathology, but a constant modulation of the relations between biology and forms of life, in the light of genomic knowledge.

## **Is my brain normal?**

Let me turn from genes to brains. Is my brain normal? Of course, the validity of psychiatric diagnosis of abnormality or mental disorder has long been contested and not just by sociologists – although sociologists will remember the famous paper by David Rosenhan, ‘On being sane in insane places’ which concludes that sanity is hard to diagnose (Rosenhan 1973). But you might be forgiven for thinking, given all the popular hype about brain scanning, that we now had technologically sophisticated ways of seeing at least if your brain was normal, if not your mind. Images of brains of people with Alzheimer’s and other disorders that appear to have a firm neurological aetiology often seem to confirm this. However things are not so simple. Take the case of Alzheimer’s. Many clinicians consider that imaging of persons thought to be showing symptoms of Alzheimer’s can be helpful in ruling out other causes of dementia such as tumours, if it is carried out when the behavioural and cognitive signs of disorder are quite marked,. However, imaging the brains of those persons with mild symptoms which might indicate that they are at an early stage in developing the disorder is not helpful diagnostically. Perhaps, then, we might pause for a moment on brain imaging.

The work of anthropologists who have done field work among the brain mappers has shown us that such images are not simple representations of the living brain, but are highly mediated inscriptions of changes in blood flow, measured not in ‘your brain’ itself – since they have little idea of the size of the scanned brain or its actual configurations until post-mortem, but in terms of pixels in a three dimensional space which is mapped onto a ‘standard’ brain space, and coloured according to certain conventions (Beaulieu 2000; Dumit 2003). A lot, then, is ‘black boxed’ in that image, and brain mappers themselves view with some concern the proliferation of these images as if they were simple photographs or X-Rays, and their utilisation in popular and professional discourses. Nonetheless, the images have undoubted power. Scans of the brains of children from Romanian orphanages, for example, have been deployed to give us hard proof at last of the importance of early mother-child interaction – it is written in the brain (Nelson, et al. 2007). Defence lawyers have used scans of the brains of those accused of impulsive or violent conduct to indicate that their brain was maladaptive and so their responsibility for the act was mitigated: while

this has largely been unsuccessful in the courtroom it is the focus of much ongoing research (I discuss this in Chapter 8 of Rose 2006b). And so on. Now I do not want to cast doubt on the importance of scanning technology, the great advances in resolution, and its potential role in diagnosis of some conditions. But we should pause for a moment to consider the relation between the state of your brain – the wet, meaty stuff – and your mental capacities.

Again, we can refer to Alzheimer's – and I am drawing extensively on the excellent work of Margaret Lock on this issue (Lock 2007). Now Alzheimer's is one of the rather rare psychiatric conditions that appears to have a clear neurological basis – the neurofibrillary tangles and amyloid plaques that Alois Alzheimer identified in the first decade of the twentieth century – using novel staining techniques - in tissue obtained from the brains of a number of patients who died with the condition that Emile Kraepelin would later name after him. This is not the place to go into the tangled history of this condition and the rival claims for its discovery.<sup>13</sup> The point for our purposes is what it might reveal about the relation between pathology in the brain and pathology of conduct. And to put it simply, the answer is this: there is *no* simple relation between the numbers of plaques and tangles in a person's brain and the symptoms of dementia.

Brain state, that is to say, is not correlated with mind state – if I can use that old fashioned term for a second – in any simple way. First, such plaques and tangles are found in several other conditions, not in senile dementia or Alzheimer's alone. Second, and more importantly, one cannot predict brain state – the quantum of plaques and tangles present at autopsy - from the degree of cognitive decline of the person when alive. Although in the 1960s and 1970s many researchers, research institutions, patient support groups and others coalesced around the hypothesis of the cerebral basis of the disorder – and hence agreed on the direction for research into aetiology, prevention, treatment, perhaps even cure – doubts have continually resurfaced about the coherence of the diagnostic category of Alzheimer's, about the role of the best known 'risk factor' – carrying one or two copies of the allele APOE4 (which I won't discuss here). More important for our purposes, there were continual doubts about the relation between the brain state and the mental state. The much quoted Nun's study makes the point most clearly. Almost 700 Catholic sisters from The School Sisters of Notre Dame in the US participated, agreeing to have neuropsychiatric assessments regularly from age 75, and to donate their brains for autopsy after

death. Despite the fact that pictures posted by the researchers, on their website,<sup>14</sup> seem to show clear gross anatomical differences between the brain of a normal centenarian and an “Alzheimer Brain”, as the autopsy evidence accumulated, it seemed that a proportion of the nuns who performed rather well on the test battery, actually had extensive plaques and tangles in their brains, while some of those who had few anatomical changes in their brains performed badly on the tests and exhibited the behavioural signs of dementia. What, then, predicted cognitive performance or decline, if not the state of the brain? It appeared that this was ‘cognitive reserve’ - for each of the nuns had written an account, at admission, of their reasons for wanting to join the order and these had been preserved – when analysed, there was a negative correlation between the elaboration and complexity of the account and the level of cognitive decline shown by the neuropsychiatric tests.<sup>15</sup>

So is Alzheimer’s linked to plaques and tangles in the brain? Probably. If one could visualise those plaques and tangles in the living person, would that predict their cognitive capacities? No. Indeed many of those living perfectly normal lives unto death would, on autopsy, show brain abnormalities. Despite all the research, and the very important basic science that has been done, the relation between brain anatomy and cognitive capacity remains mysterious. While research continues to focus on Alzheimer’s as a ‘brain disorder’, the multitude of environmental, social and cultural supports for the disorder – its ecological niche, to use Ian Hacking’s nice term, remain relatively unstudied. As Margaret Lock has put it “dementia will not be better accounted for without consideration of the embodied, minded, self having a unique life history embedded in singular social and environmental contexts”<sup>16</sup>

So what is a normal brain? Brains are not, of course, routinely scanned for early signs of dementia. Nonetheless, one does see the spread of a new diagnosis, not based on brain scanning, called Mild Cognitive Impairment. MCI is a diagnosis made by clinical judgement usually requiring memory loss and perhaps unexpected decline in other cognitive functions. There is controversy over the status of this diagnosis and of its utility (See the papers collected in Macher 2004). Some claim that the diagnosis can be made with relative certainty, others say that the phenotype is too blurry to be of much clinical or predictive use. Estimates of prevalence in those aged over 65 range from 5.2% to 16.8% (Golomb, et al. 2004: 354). Some claim MCI is an early stage of Alzheimer’s and will progress to full

Alzheimer's, others dispute this inevitable progression. Some claim that recent advances in brain imaging enable the visualisation of plaques and tangles at an early stage, and hence allow prediction of which among those who meet the behavioural criteria of MCI will progress to Alzheimer's, although the evidence from the Nun Study and elsewhere suggests we should be wary. Some say that the diagnosis enables early treatment which will slow progression, others doubt that such treatment is available. There is much to be said, here, given the blurry character of Alzheimer's itself, of the apparent capacity of a diagnosis of MCI to shift an individual onto a social and experiential pathway to Alzheimer's. Nonetheless, since the naming of this phenomena in 1988 re-organised a complex and competing field of categories and definitions, citations have increased exponentially – according to the Institute for Scientific Information's Web of Science, there was one article on this topic in 1990, 158 in 2000, and 943 in 2007. But here I can only focus on one issue that relates to my opening question – what is it to be normal?

Of course, there are many reasons for this renewed interest in this condition on the borders of normality: as Golomb et al put it “this explosion of interest reflects a shift in dementia research away from established disease and toward early diagnosis” (Golomb, et al. 2004: 353) linked to the hope of early therapeutic intervention – for who could argue with the view expressed in the introduction to the edition of *Dialogues in Clinical Neuroscience* in which their article appears; “Earlier is almost always better” (Lebowitz 2004: 350) . The logic of preventive medicine is a press towards early diagnosis – surely it is better to know early and intervene early in disorders such as Alzheimer's. Hence the increasing use of diagnostics in the clinic to identify patients with MCI, and perhaps to treat them with the one drug that is currently suggested to delay the development of Alzheimer's – donepezil, marketed as Aricept – “Does spending time with your loved one mean everything to you? If your loved one has Alzheimer's, Aricept may help.... Aricept may help your loved one be more like themselves longer.”<sup>17</sup> In the face of the fear of such a devastating condition, and with such a possibility, who could resist this hope.

Now MCI, and Alzheimer's, are linked together by organizations such as the European Brain Council under the heading of 'brain disorders' – a category that, for them, includes Anxiety disorders, Addictive disorders , Affective disorders, Psychotic disorders, Multiple Sclerosis, Dementia, Parkinson's disease, Migraine and other headaches, Stroke, Epilepsy, Brain

trauma and Brain tumour. Their 2004 study on “The Cost of “Brain Disorders” estimated that across 28 European countries (the EU plus Iceland, Norway and Switzerland) with a total population of 466 million, 127 million people or 27% are affected by at least one brain disease. and that the total cost of brain disorders amounted to 386 billion Euro, of which the largest cost component was indirect costs totalling 179 billion Euro (47%), with a direct healthcare cost is 135 billion Euro (35%) and a direct non-medical cost is 72 billion Euro (18%).<sup>18</sup> Such figures act as powerful mobilisers of public health agencies, repeating the arguments made by the World Health Organization, epidemiological estimates made in the United States of the prevalence of psychiatric disorders among the general population – not just those in touch with psychiatric services and in Europe by such organizations as the European College of Neuropsychopharmacology (Kessler, et al. 2005; Wittchen and Jacobi 2005; Wittchen, et al. 2005; World Health Organization 2004).

Of course, these numbers don't merely represent – they create realities – they create a world of mental states, of mental normality and abnormality, that is made intelligible, practicable, governable through numbers. We could say a lot about the specific ways in which these numbers were generated, assembled, framed and rendered public, notably about the ways in which diagnostic manuals are transformed into checklists that invite members of the general population to transform their feelings of malaise into symptoms that then appear as indicators of the presence of undiagnosed disorder. But these numbers, however ‘constructed’, have consequences and index something about our forms of life – such numbers mark out what is salient and to who; as in the case of psychiatric diagnoses, they group us into categories and divide us between categories, transform moral and political judgments into impersonal and technical data upon which they confer the moral authority of objectivity. Numbers legitimate, and make demands, and here we can especially see what Anthony Hopwood termed ‘the power of the single figure’ (Hopwood 1987) . Numbers render a space governable yet contestable – indeed these very numbers open a contest between those who proclaim the challenge of the rising ‘burden of mental illness’ and those who proclaim the challenge of the “medicalization of normality” – as in the recent book by Horwitz and Wakefield on the extension of the diagnostic category of depression entitled *the Loss of Sadness* (Horwitz and Wakefield 2007).

Nonetheless, these numbers seem to show is the birth of what I have termed elsewhere “disorders without borders” (Rose 2006a). And we can find other indicators than these. Take, for example, rising rates of the use of psychiatric drugs – data that I have discussed extensively elsewhere (Rose 2003; Rose 2004). You will probably not be surprised by the data on the use of stimulant drugs for the treatment of ‘Attention Deficit Hyperactivity Disorder’ in children – rates of diagnosis in different areas range from around 2% of schoolchildren to around 17% in some states in the USA. And you probably won’t be surprised, given all the public debate, at the figures, even in Europe, for the rising use of the selective serotonin reuptake inhibitors – drugs initially marketed for depression, but whose remit has widened to anxiety disorders such as Social Anxiety Disorder and Panic Disorders. But you may be surprised at the rising rates of diagnosis of young children in the United States with bipolar affective disorder and of course the list could go on.

Sociologists are not short of explanations. Today they seldom cite social causes, as was the case for an older sociological psychiatry. On the contrary, they favour constructionist accounts in terms of medical imperialism, medicalization of social problems, energetic proselytising by parents and support groups, the egregious power of the drug companies with their disease awareness campaigns, the suborning of psychiatric and clinical judgement and so forth. I don’t want to evaluate these different accounts here – my purpose is rather different. What I have tried to gesture towards, with these selected data is the strange fact that in the most wealthy sector of our globe, in the century when more human beings are living longer than ever before, we seem beset by a virtual epidemic of disorders – not just of mind or psyche, but of brain. Madness, we were once told by sociologists, was a residual category, to be deployed when all other accounts of deviant conduct failed (Scheff 1966). But no longer – it appears that a lifetime without mental disorder, at least in this expanded definition, and now mapped onto the brain, would be somewhat abnormal – or to put it another way, mental abnormality has practically become normalised – simultaneously a condition to be treated and a mode of existence to be expected.

Think back, for a moment, to the message that accompanies these medications – because it’s a message to you. It is a certain image of a form of life to which you should aspire, and which the drug will aid you to achieve – you can get your life back, you can become yourself

again – you too can say “I feel like myself again, I feel like me”. Actually, if you Google “feel like myself again” you will find this phrase repeated over and over, not just in psychiatric drug testimonials, but in websites for drugs to promote female libido, dietary supplements, breast augmentation testimonials, menopause treatments, plastic surgery and much more. Normality has to be worked at, or at least this version of normality as an ideal of autonomous self-fulfilment of the self. In fact most of the quotes come from women, so perhaps this is a specific gendered normality, although the images in the pharmaceutical advertisements are of both sexes and all races and ethnic groups. Here as elsewhere we see the rise of the obligation to manage ones self as a kind of enterprise of itself – a continuous work of modulation of the self in relation to an ideal. The critics are wrong in saying what is promised here is a shallow, illusory happiness in a pill (President's Council on Bioethics (U.S.) and Kass 2003). The work on the self that is enjoined is multiple – diet, exercise, self-reflection and self monitoring, goal setting and evaluation, not to be displaced, but to be supported, with the aid of medication. And you can see here, I hope, why some of the recent ‘neuroethical’ discussion of enhancement technologies rather misses the point – for what is involved here cannot be divided according to the binary logic of treatment versus enhancement – it is, in general, a constant work of modulation of the self in relation to desired forms of life.

## **Social norms and vital norms today**

Where does all this leave us, in relation to the normal and the pathological, the social and the vital today? I am not sure that I have an answer, or rather I am quite sure that I do not! I have suggested that recent developments in medical genomics lead us into a world where there is no norm, no single standard or reference ‘normal’ genome, but rather a world of multiple molecular variations of small effect shaping for each individual a specific profile of risks in relation to which prudent life choices are to be made – in the name of the newly empowered autonomy of – and obligations of - the contemporary genomic biological citizen. And I have suggested that, in the new world of molecular neuroscience and psychopharmaceuticals, a perception has taken shape of the burden of mental disorder, as brain disorder, which makes abnormality into a new kind of norm, and requires a continual work of the self on the self in order to manage that constant lure by the will, by lifestyle, by drugs, in order to achieve an ideal form of life - which is the life of the autonomous self.

I am, however, certain of one thing. The distinction made by Georges Canguilhem with which I began, is difficult to maintain – the distinction between the vital norms of the body and the disciplinary norms of society. On the one hand, those vital norms, of height, weight, longevity, fertility, obesity etc. are much more historically and socially variable than this formulation suggests. On the other hand, today the norms of the body itself have been opened to re-engineering at the molecular level in the name of a certain kind of freedom. It would be facile to try to judge these changes with a reference to some naturalness which we modern human beings have now lost. We humans have never been natural. So the question that confronts us is perhaps an ethical one. Perhaps we need to ask, not just the question of historical ontology - what kinds of human beings have we become – but a question of ethics as *Lebensführung*: “what kinds of creatures do we think we should become”?

## FOOTNOTES

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- 1 This paper was written for a keynote lecture entitled *The Normal and The Pathological: Managing Bodies and Minds in the Age of Molecular Biomedicine*, to be given at the Annual Conference of the British Sociological Association, in March 2008. In the event, it could not be delivered. In revising it for this publication, I have kept to the style of a spoken, speculative talk, rather than a formal paper, and it should be read in that light.
- 2 Canguilhem originally published an article titled "Le Normal et Le Pathologique" in 1951, and a version of this was included in the original French edition of *La Connaissance de la Vie*, published in 1965. I have quoted this passage from the forthcoming translation of this text under the title *Knowledge of Life*.
- 3 <http://www.decodeme.com/> - since the time this paper was written, the costs have reduced and the numbers of risk conditions have increased – both considerably.
- 4 <http://www.decodeme.com/> accessed 17 February 2008.
- 5 <http://www.fda.gov/cdrh/oivd/guidance/1549.pdf> accessed 18 February 2008.
- 6 <https://www.23andme.com/> accessed 18 February 2008
- 7 <http://www.navigenics.com/corp/Main/> accessed 18 February 2008.
- 8 <http://www.personalgenomes.org/> accessed 18 February 2008.
- 9 <http://thepersonalgenome.com/> accessed 18 February 2008. For Misha Angrist's pages, see <http://www.genomeboy.com>
- 10 <http://www.454.com/> accessed 18 February 2008 – the sequencing of James Watson was announced in their press release dated May 31, 2007.
- 11 [http://www.burrillandco.com/pdfs/q4\\_12\\_2006.pdf](http://www.burrillandco.com/pdfs/q4_12_2006.pdf) accessed 18 February 2008.
- 12 'In his 1997 book, *Pharmacogenetics*, Wendell W. Weber quotes from Somerset Maugham's account of his experiences as a young medical student. ..."I have always worked from the living model. I remember that once in the dissecting room when I was going over my 'part' with the demonstrator, he asked me what some nerve was and I did not know. He told me; whereupon I remonstrated, for it was in the wrong place. Nevertheless he insisted that it was the nerve I had been looking in vain for. I complained of the abnormality and he, smiling, said that in anatomy it was the normal that was uncommon. I was annoyed at the time, but the remark sank into my mind and since then it has become forced upon me that it was true of man as well as anatomy. The

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normal is what you find but rarely. The normal is the ideal. It is a picture that one fabricates of the average characteristics of men, and to find them all in a single man is hardly to be expected." Maugham's observation -that the normal is rare -is at the heart of the challenge and promise of pharmacogenomics' (Wendell W. Weber (1997) *Pharmacogenetics*, Oxford: Oxford University Press, quoted in Norton, 2001: 180). Thanks to Oonagh Corrigan for this quote.

- <sup>13</sup> There is actually some disagreement about priority here but this is not pertinent to this paper.
- <sup>14</sup> <http://www.mc.uky.edu/nunnet/> accessed 14 February 2008
- <sup>15</sup> For a list of publications from the Nun Study, see <http://www.healthstudies.umn.edu/nunstudy/scientific.jsp> accessed 14 February 2008.
- <sup>16</sup> Quoted from p. 23 of the MS of "Seduced by Plaques and Tangles" given by Margaret Lock at the Workshop of the European Neuroscience and Society Network held in Harvard in May 2008, see [www.neurosocieties.eu/pdf/Harvard\\_2008\\_Programme.pdf](http://www.neurosocieties.eu/pdf/Harvard_2008_Programme.pdf)
- <sup>17</sup> <http://www.aricept.com/index.aspx>, accessed 14 February 2008
- <sup>18</sup> <http://www.europeanbraincouncil.org/projects/CDBE.htm> accessed 14 february 2008.

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