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Rett Syndrome, Rare Diseases and UK Research

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Biography

Helen Crompton is a full-time PhD student with the Innovation and Entrepreneurship group. Funded by a Faculty studentship, Helen is currently researching innovation processes through knowledge networks within high-technology SMEs. Prior to joining the Business School, Helen studied at the Department of Information and Communication (MMU) for her BA Information Technology, and at PREST (Manchester University) for a MSc funded by the ESRC.

Abstract

This paper examines policy issues surrounding patients who suffer from rare diseases and the implications of the biotechnology 'revolution' in relation to priority setting and rationing in the National Health Service. It shows how the key players in rationing decisions - politicians, bureaucrats, managers, consumers and the media, are shaping research into rare diseases and the threat to autonomous researchers by the increasing centralisation of NHS R&D. It also shows the increasing power of patient and professional lobby groups to influence policy decisions, aided by the new information and communication technologies. The lack of government support for the nascent UK biotechnology industry, in contrast to the USA, not only impacts on industrial success but may also hinder medical advances. The recent European Orphan Drug Regulation (2000) and the supporting Framework V programme may have an impact on treatments for rare diseases. Orphan drugs are defined as medicinal products for the treatment of rare [orphan] diseases, whose costs of development are inevitably disproportionately high in relation to the volume of products likely to be sold, since there are only a few sufferers needing treatment.

Key Words: Biotechnology; Orphan diseases; Technology assessment

Introduction

According to Leneghan (1998, pi) the issues that the new genetics will raise for the NHS have hardly been identified, let alone debated. More recently, Ron Zimmerman 1999 (see Kent 1999), the Director of the Public Health Genetics Unit, reported that many publications and conferences over the years:

> "have recognised the impact of genetics but most, if not all, have focused on the broader ethical, legal and social implications of genetic science rather than its consequences for clinical practice".

Various bodies have produced reports on a variety of policy issues surrounding screening, cloning, insurance, patenting and genetic [social] discrimination. Wider issues surrounding research funding, especially for rare diseases, and links with the pharmaceutical industries and the issue of the development of genetic medicine in an environment of rationing and priority setting has had little coverage. According to Hunter (cited in Leneghan, 1998, p1), it is time for a thorough appraisal of the policy implications of genetic medicine. Even though the technology may be ten years or so away it is critical for policy makers, managers, practitioners and the public to have an understanding and knowledge of what lies ahead. It has been agreed that rapid advances in medical technology will ultimately result in increased rationing (The Kings Fund 1998, Ruddle 1991, Office for Science and Technology [OST] 1993, Seedhouse 1994) due to the expected increased expenses of new medical and therapeutic interventions. Judge 1978 (in Leneghan 1998) identifies five key players in rationing decisions - politicians, bureaucrats, managers, professionals and consumers, to which the writer will add the media. Patients suffering from rare diseases and the non -profit organisations representing them often feel like the orphans of the healthcare and social systems. Using Rett Syndrome as a case study this paper will explore how a minority population is placed to generate basic research, be of developmental interest to pharmaceutical companies and the barriers to treatment within the NHS under 'unwritten' policies. To determine the scale, scope and direction of this research a wide literature and Internet search was conducted on rationing in the NHS, orphan drugs legislation, Rett Syndrome, gene therapy and the biotechnology and pharmaceutical industry. This search will need to be ongoing as the area of medical developments changes fast. Lofland's 1984 'puzzlements' technique (see Gilbert 1993, p136) was used to categorise problematic

and interesting themes around the subject area. From this areas of interest were identified, which had not been attended to in previous research. The respondents chosen are the target population of a particular, narrow, research population who are not known - identification is one of the research aims.

The paper gives the background to the UK National Health Service (NHS) resources dilemma, and rationing, and the role of the National Institute for Clinical excellence in technology assessment. NHS access and increased public demand are discussed and the background to the UK pharmaceutical and biotechnology industry is compared to that of the United States. The case study, Rett Syndrome, is followed by the preliminary findings of the paper in respect of the European Orphan Drug Regulation (2000).

The Resources Dilemma in the UK National Health Service.

> ‘’The government has made it clear that there should be no clinically effective treatments which a Health authority decides as a matter of principle should never be provided’’ (Health Care UK 2000, [1995], p39).

The King’s Fund (1998) suggests this use of semantics is politician speak for ‘rationing is not inevitable’, that is, rationing defined in this way does not exist. Whilst NHS funding has increased in real terms, demand is still outstripping supply. This is not new, first year expenditure estimates of £176m in 1948 spiralled to spending of £225m (Ruddle, 1988, p3). It could be argued that as long as services are provided at zero cost to the consumer, then demand is potentially infinite. Added to these demands are powerful economic and cultural pushes towards a technological ‘quick fix’. New technologies and techniques, whilst reducing costs in some areas such as key-hole surgery, are mostly cost increasing rather than cost-reducing (Ruddle, 1988). They may turn out to be ‘flat of the curve’ (Fuchs, 1993, p180) medicine providing minimal or no health benefits. According to Leneghan (1998, p123) the problem for policy makers is that the high costs of new genetic technologies have not been studied thoroughly. A resources dilemma is defined as the gap between finite resources and infinite demand, which appears to be growing within health services internationally. Rationing, (usually expressed as ‘prioritisation’, ‘allocation of resources’, ‘cost-effectiveness’ etc), is described by

Hall (1974) as a process by which a balance "between an excess of demand for services.... and a limited supply of resources" is achieved (quoted in Ruddle, 1991, p1). The King's Fund (1998, p89) suggest that priority setting is a synonym for rationing and that beneficial treatments will continue to be denied, whilst decisions to allocate funds are often the result of political battles over budgets.

Rationing can be formal, explicit and overt through a prioritisation of need and positioning on waiting lists or through eligibility rules like breast screening for the over 50's. Rationing by geography is where a treatment is only available at one centre, limiting those able and willing to travel. Rationing can be unofficial and covert through delays in, or deterrence from seeing a consultant or through a dilution of services. Rationing by price occurs in the decisions on which technologies or drugs to buy from pharmaceutical companies. Simply not purchasing a specific drug rations its use. There may be variations in availability as a result of legitimate clinical disagreement about the practical effectiveness of laboratory tested drugs. Most rationed drugs are not cures but may alleviate symptoms, or prolong life, in chronic incurable degenerative conditions, therefore non-treatment affects quality of life. Clinicians increasingly have to prioritise resources. Rationing via public relations means the growing reliance on charitable or private fund-raising to pay for expensive medical treatment. This dependence is seen as disturbing and deeply problematic. A report from the Health Advisory Service (1997), reported in the Kings Fund (1998), found that the most dynamic force for change was the existence of a clinical team with a special interest, the absence of which meant health, as well as social services, had to rely on local charities as the main source of expertise, equipment and the funding of specialist provision. This may be analogous to the 'special interests' across the range of medicine, including Rett Syndrome (see below). Practitioners within R.S. speak of the 'family of Rett' to include sufferers, carers, families, researchers and clinicians. The government will come under increasing pressure as public knowledge, gleaned via the new media technologies, increases and consumerism grows.

Health Technology Assessment

The National Institute for Clinical Excellence (NICE) was launched in March 1999. Its remit is to assess new drugs and techniques and advise ministers on which treatments are too expensive or insufficiently cost-effective for the NHS to afford. It will also offer 'authoritative guidance' throughout the NHS, whilst disseminating innovation quickly and effectively (Timmins 31.3.99). NICE will consult a Partners council, comprising stakeholders (including patients) and will advise on whether new treatments, drugs or technologies should be adopted. However NICE will not cover the private sector, which accounts for between 10-30% of medical treatment, so therefore 10-30% of the data will be missing in any assessment of 'best practice' (Timmins 15.3.99). The Commission for Health Improvement (CHIMP) will enforce clinical governance, to ensure doctors follow NICE guidelines, unless in certain cases there are good reasons not to (Timmins 15.3.99).

In launching NICE and talking about the future NHS service, Frank Dobson, the Health Secretary (www.coi.gov.uk/coi/depts/GDH/coi3738f.ok) did not use the 'rationing' (allocation/ priority) word once. Perhaps these terms have been replaced by 'the spread of good value', 'the degree of clinical benefit' and 'good value for money.' The medical respondents in this paper suggest that there would be no problem of NICE recommending treatments for rare diseases, however the treatment has to be developed first and this thesis has attempted to show the barriers in this development. The UK Licensing Authority licences any drug shown to be safe, efficacious and of good quality, with no weighting on cost. It is up to the purchasing Health Authority whether to purchase expensive drugs passed by NICE, thereby dictating to clinicians what is available. Health technology assessment can be defined as the assessment of the costs, effectiveness and broader impact of all procedures used by health professionals to promote health, to treat and prevent disease and to improve the rehabilitation of patients.

There is national interest in innovation and technology transfer. Advances in health related technologies promise the UK competitive advantage in a global market. The underpinning of this advantage depends on the rock-bed of basic research, the exploitation of biotech sciences and the diffusion and adoption of proven advances in

order to offer new treatments, or to replace less effective treatments or procedures. Technology assessment is a tool of health economists to gauge the cost-effectiveness of treatments, in the diffusion of technologies gleaned from advances in R&D. The implementation and exploitation of new technological innovations is paramount to patient's health needs and industrial competitiveness. Technology assessment, as a policy guide, is necessary to evaluate short and long-term safety, efficacy and outcomes, comparison with any existing options, indications for use, quality and cost-effectiveness of novel procedures. Technology assessment may be a complex re-iterative process requiring re-evaluation, for example if new data emerges or the cost of technology reduces (making it more cost-effective). Pharmaceutical companies and developers of diagnostic techniques may disregard a promising treatment if they cannot see a market for it, ethical arguments are therefore very influential.

Researchers cross multi-disciplinary activities, each with its own focus in interest and levels of skill. Complex areas of research require a multi-disciplinary element in assessments, which are now more broadly disseminated and under public scrutiny via the mass media.

Randomised trials are still the preference of many clinicians being critical of technology assessment's scientific credibility. However according to Fuchs (1993, p182)

> "Even expertly designed clinical trials...may not yield clear, quantitative answers concerning the effectiveness of a new diagnostic or therapeutic intervention".

Complexity invites errors, even with the greatest care. Multi-disciplinary research means evaluators reliance on other 'experts' such as journal reviewers, who might fail to detect errors due to a lack of essential data, inadequate analysis or misinterpretation of results. The value of technology is dependent on the clinical setting and consumer preferences, requiring consideration rather than a yes or no response. Non-physiologic factors like quality of life, ethics etc. are difficult to incorporate into an analysis, which may lead to errors in evaluations.

There are fears amongst medical researchers and the medical technology and pharmaceutical industry that technology assessment will inhibit the development and diffusion of new products (Fuchs 1993, p182)

NHS Access

Private health insurance is available to those who want to (or can) pay. Many government reviews have surrounded the implementation of an insurance based system, similar to the US system, of healthcare but has been rejected as being a viable alternative (Ruddle 1988). Meanwhile patients are 'locked in' to what is 'available' under a state monopoly. According to the Office of Health Economics the UK health expenditure, as a percentage of GDP, in 1999 was less than half that spent in the US. Other EU countries spend far more of their wealth on healthcare, although some of the difference can be accounted for by private health insurance schemes. According to the Pilling (13.4.99) it appears that the US health insurance industry appears more willing to pay for treatments than governments, leading to a boom in the US domestic drug market over the last twelve months.

Politicians take macro-level decisions but are also involved in micro-level conditions, when called upon to intervene on a constituent's behalf or to enhance public relations. The media increasingly bring pressure to bear on decisions concerning high profile cases, especially cases involving children denied treatment or suffering delays. In these cases resources may have to be diverted from elsewhere, denying some-one else treatment to retain the veil of political 'correctness'.

In the UK there is no legal right or precedent to treatment. Test cases have been brought under the 1977 NHS Act but the courts, in general, have not found for the plaintiff. The legal system cannot be used successfully unless the government issues more explicit rules about how the NHS should 'set priorities' ('ration', 'allocate') and the specific responsibilities of the NHS. Healthcare 2000 (1995) suggests it is generally agreed that the principles of the NHS are:

- Universal access.
- Highest quality, professional standards applying up to date knowledge.

- Treatment based on clinical need without regard to the patient's ability to pay.
- A service responsive and sensitive to the needs and wishes of patients and carers.

The issue is how do you define need as distinguishable from wants and demands. The whole definition of the NHS ethos is in crisis. Ruddle (1998, p21) suggests that:

> "The incommensurability of values means that it would be impossible to develop a rational model for rationing resources in the NHS"

Ruddle (1998) also suggests this is why rationing decisions are usually made in an ad-hoc reactive way, which supports Richardson (1994 p.65). Resources, at the micro-level, are allocated from the top down to different competing services. Each service then has to decide on the budget allocation. This allocation mechanism will directly affect decisions taken on the 'front line' by consultants and doctors, who face an ever increasing level of expectant demand from an ever more aware, knowledgeable and belligerent consumer. It is on this micro-level front line that rationing is most overt. Macro level rationing decisions are covert, there are no written rules so according to Ruddle (1991, p13) the issue is 'fudged', in the sense that there is "no co-ordinated, consistent, national criteria for rationing", perhaps because of the risk of a public backlash. Doctors are between a rock and a hard place, they want to do the best for their patient and retain clinical freedom, whilst relegated to acting as a gatekeeper to limited resources in what is, in effect, a local monopoly or 'closed shop'. There is a flood of information in the media on diseases and medical advances. On the Internet there are medical sites, chat rooms and virtual pharmacies. Pharmaceutical companies are advertising their 'wonder products' to an ever increasing audience (Pilling 20.3.99). Consumers may demand, with combined pressure from relatives and Non Government Organisations (NGO's) the 'very best' new treatments.

The UK Pharmaceutical Industry and Biotechnology

According to the Financial Times Biotechnology Survey (6.10.98) we are in the first stage of a biotech revolution, the aspiration of which is to find the cause of diseases and develop cures and enabling therapies. Pre-1993 all drug discovery by all the

pharmaceutical companies put together had worked on an estimated 400 ‘keyhole’ drug targets. Today they work on 400 per. year, due to an explosion in new technologies. The issue is the pace and breadth of this revolution and how quickly we can harness the results.

In 1999, the UK pharmaceutical industry was the third largest exporter in the UK with exports of about £7b, employing 30,000 people (OST 2001) This global industry is hampered, in competition with the US, by different patent laws. The US advantage allowing a twelve month breathing space before the lodging of a patent, UK scientists are pressured to patent immediately - leading to restrictions on interactions between academia and industry. There also appears to be a development gap between research and industrial application in the UK. The cause of this gap appears to be ‘differences in perception between academia and industry in what constitutes an exploitable invention’ (OST 1993). Academia, industry and the NHS need a successful partnership in order to exploit all possibilities. Collaborative ventures, as found in the US, leading to a greater understanding of the potentiality, may be engendered especially in newer areas of research, such as gene therapy. OST (1993) points to comparisons of the UK industries reticence, and the US enthusiasm for, new product innovation and keen approach to long-term investment. US pharmaceutical companies, whilst having strong links to US research centres, have also set up parallel research programmes alongside UK universities, for ‘mutual support’. The US operates what is essentially a market-based health care system, reforms driven by powerful market forces. Competition and free market entry are said to allow consumer choice. Prices tend to settle at a level people are willing to pay and products are designed to meet consumer needs. In the U.S. whilst costs *are* rising again it is thought that regulations and restrictions, imposed top-down, via government policies, are not in the interests of patients (who are becoming more educated and vocal about restrictions in health care). It is suggested that policies should be introduced that make the market work better. The rapid acceleration in medical technology is leaving policy makers behind. An open, informed and competitive market, within which patients are not passive recipients but have rights responsibilities and choices, may require an expansion of the private health sector in order to cope.

According to the Pilling (13.4.99), by 2002 only three of the world's top 25 drugs will be of European origin, as opposed to 50% a decade ago. The reason is seen, not in research but in the squeezing of drug budgets, forcing downward pricing, and the malaise in the approval of new (more expensive) treatments - giving a poor rate of return on research investment and creating a disincentive to innovation. Pharmaceutical companies are currently investing up to 20% of their overall R&D budgets (typically 20% of revenue) in increasing symbiotic alliances (see Appendix B) and joint ventures with, or equity stakes in, biotech companies, whilst embracing some of the platform technologies such as genomics, combinatorial chemistry and high throughput screening.

Background and Context to Rett Syndrome

This paper concentrates on a specific condition, Rett syndrome, (the sufferers of which may benefit by new interventions in the future). Rett syndrome (estimated to affect 1: 20,000 of the population) is a rare neurological condition, which overwhelmingly only affects females, caused by a mutation on the X chromosome at site Xq28 on the human genome, usually lethal to male foetuses. The incidence of Rett Syndrome is the same across all the social, racial and cultural groups of the world. Life expectancy, in the affluent Western countries is into the 40's, however there are cases of sudden death, caused by respiratory arrest and heart failure together with deaths from other causes such as pneumonia or seizures.

Rett Syndrome was first reported in 1966 by Dr, Andreas Rett, an Austrian clinician. His attention was drawn to two young female patients, sitting in his waiting room, exhibiting similar 'behaviour'. Dr Rett unfortunately published his findings in German, therefore his paper was not widely read. Rett Syndrome was 're-discovered' in 1983 by Bengt Hagberg, a Swedish paediatrician who, when presented with a patient displaying certain characteristics, recalled an earlier meeting with Dr Rett and realised his patient displayed similar symptoms to those described by Dr Rett. Dr. Hagberg then published an article in English on this 'new' syndrome, which he referred to as Rett Syndrome (see appendix A). New techniques in molecular genetics with the identification and diagnosis of genetic disorders, with pharmaceutical innovations, offer a future potential treatments whilst genetic tests can be used for

prenatal and presymtomatic diagnosis, carrier identification and DNA profiling. It appears protein based pharmaceuticals would seem to be the most expedient hope for Rett Syndrome sufferers, using recent innovations such as combinatorial chemistry, high throughput screening and bio-informatics. Genomics, pharmacogenomics and proteomics will enable the proteins produced from genes (once identified) to be studied and tested for therapeutic use, using tailored drugs. According to Kent (1999) where interest has been shown by biotechnology and pharmaceutical companies, it has been in the common genetic disorders.

Research Design and Methodology

To determine the scale, scope and direction of this research wide literature and Internet searches were conducted on rationing in the NHS, orphan drugs legislation, Rett Syndrome, gene therapy and the biotechnology and pharmaceutical industry. From this areas of interest were identified, which had not been attended to in previous research. The respondents chosen are the target population of a particular, narrow, research population. There is still major debate regarding the virtues of qualitative research as compared with quantitative methodologies. I chose to use qualitative methods to conduct non-standardised, semi-structured, in-depth interviews. This method was chosen based on the limited resources and time available. A control sample cannot be compared with an ‘affected’ sample due to the emotional issues involved. Although using questionnaires, to elicit information from carers, would elicit rich information this was felt to be unethical. Questions concerning research and possible treatments may raise false hopes in a vulnerable population. Such complicated issues are not amenable to questionnaires or structured interviews to gain sufficient depth amongst a minority population, who may be difficult to identify. The subject matter in this case excludes the vast majority of the population.

A simple design, at micro-level was needed that parallels social conversational ‘norms’ - allowing a more in-depth investigation (see Lofland, 1971, ‘guided conversation’, in Gilbert, 1993, p136). Also this approach may allow the ‘study’ of participant’s motivations. There was a need for a flexible approach to a complicated, perhaps sensitive, area. This required a strategy for discovery of detail. One-on-one

interaction reduces suspicion, allowing a genuine interplay between researcher and respondent. Pilot interviews were not felt practical as the respondents selected were high status professionals whose time is very valuable, although returning to respondents may be possible for clarification if needed. The approach involved informal interviews with a professor of genetics, a leading clinician and a representative from the biotechnology industry. The standardisation of interview 'discourse' may be problematic, each respondent is a unique individual, representing a different discipline and background. It may not be possible to isolate cause and effect, or to generalise from the outcome due to the specific nature of the topic. However transcripts were made of each interview, to enable a full and accurate record for scrutiny during later analysis and, following Gummesson (1991), to enhance the reliability and generalisability the accuracy and credibility of the findings were confirmed by the interview subjects.

Preliminary Findings: NHS Priorities, R&D and Increasing Accountability of Regional Genetic Centres (RGC)

In the UK the NHS is the major purchaser and consumer of health care technologies and the main beneficiary of medical and health related R&D achievements. Clinicians in the NHS provide a dual role as users of new technologies and the development of innovative basic research, together with researchers in Higher Education Institutes (HEIs) which is fed to industry for further development. Successful partnerships between academia, industry and the NHS are the seed-bed of UK competitive strength and provide future benefits in the quality of life of UK citizens.

In the UK there are currently on average only 1.4 consultant clinical geneticists per million population. There are around 5000 diseases that are individually rare but collectively represent a significant number of patients. The workload of RGCs is increasing due to an increase in recognised genetic conditions and an expanding demand from patients (or relatives) having an increased awareness and expectation brought about by media reports.

There is no official definition of what genetic services should comprise however the activities of the Regional Genetic Service include running genetic clinics, counselling, maintaining genetic registers, the training of clinical geneticists, undergraduate and postgraduate education, research, liaison with genetic laboratories and providing expert advice to clinicians in other specialities.

It has been difficult to determine reality from media hype as industry and some researchers have been quite happy to fuel these expectations, thereby increasing their profile and share prices or easing access to research grants. According to the geneticist the media also play on the publics emotions, for example highlighting campaigns for increased resources for premature babies. The response of the NHS is seen as a 'knee-jerk' response to media reporting, allocating resources to popular diseases. Finite resources mean that for every decision made about resource allocation there is an opportunity cost. Money spent on 'popular' diseases cannot be spent elsewhere. It appears that research into rare diseases is still being done regionally on an ad-hoc autonomous basis, dependent on the researchers particular interests based on knowledge of, or association with, a patient or patient group (which supports Blank 1988). It has been suggested that less of this research is being done due to the NHS priority in service delivery and research into common diseases, rather than focused biomedical research. This has reduced the funds available to specialities such as the Regional Genetic Services, creating immense problems for an 'orphan' service, which continually has to justify research. Getting actual research funds is described as a nightmare, having to try national bodies like the Medical Research Council or numerous outside charitable organisations. This means if you are a member of an organisation representing a rare disease you are unlikely to have enough funds to either 1) be approached or 2) be able to pay for research.

Research is done on an *ad hoc* basis by researchers who are allowed a measure of autonomy within the NHS or by academic and medical researchers funded by government research institutions like The Medical Research Council or charitable bodies such as the Wellcome Trust. The writer has previously shown that there are no formal projects undertaken into rare diseases or Rett Syndrome in particular by the research councils or the NHS. So rare diseases will have a low priority, even if they

are more debilitating than certain common diseases that may already have some form of treatment.

Rare diseases, at least at the regional level are not prioritised (other than perhaps through investigators interests - there must be some level of discrimination due to human nature). The accepted method in applying for funding is to look at groups of similar disorders as experience has shown that applying for funding in this way has a better outcome. The power of small associations is through collective lobbying as shown by EURORDIS, NORD and GIG (see appendix A) and professional organisations like the JCMG (see appendix A). One must question who 'shouts loudest' even within this. There is bound to be a dominant group pushing personal self-interests. There is an emotional lobbying power in that genetic disorders affect children, which can be a powerful media projection. However, perhaps not as appealing as premature babies or children with cancer. The RGC know the pressing needs of families with genetic disorders but it is difficult to get that across to an increasingly cash-strapped health service administration when there are so many other priorities.

The advances in genetics may soon threaten RGCs specialisation in rare diseases as the emphasis on genetic research is concentrated on the causes and cure of common conditions found to have a genetic cause. As medical researchers in the NHS become more accountable to the Central Research Council (CRC) autonomous research may disappear, with pressure to move to NHS priority areas in common disorders (for example cancer, Alzheimer's and heart disease). The RGC is already constrained by limited NHS funds, creating opportunity costs. In addition to maintaining established services for rare diseases they are faced with new projects such as the genetic component of the multidisciplinary provision for cancer genetic services.

The Regional Genetic Service has no current joint research projects with pharma or biotech companys, which may, in the future, be an avenue worth exploring. However the feeling is at the moment that pharma / biotech companies are only interested in the 'big hits'. Hopefully the recent European Orphan Drug regulation may encourage new links between industry and the research base, at the genetic service level. A small biotech company would do well to collaborate with researchers in the Regional

Genetic Services. The background research to this thesis uncovered a vast amount of research ongoing in the US, into rare diseases. There may well be research being done into Rett Syndrome in the UK that is subsumed under 'umbrella' projects but information is either not available or impossible to untangle.

It was felt to be impossible for NICE to devise a national service framework for every single speciality, for every single disease but that a kind of generic standard will be set. If a treatment came available for a rare disease it might actually be funded. Standards for situations are being drawn up by the genetic profession to present to NICE as a *fait accompli*. It seems that if a treatment is discovered for Rett Syndrome that as long as NICE is not backlogged with other work it may well be fully endorsed and available with no geographical bias. However there would be nothing to stop a clinician prescribing treatment without NICE's blessing. CHIMP, the NHS inspectorate is very unlikely to influence the use of such (hypothetical) treatment. However the possible closing down of autonomous research under centralisation may hinder a treatment being found for a rare disease in the first place.

NICE has proven controversial in its conclusions regarding various drugs, devices and technologies it 'tests', however it may allow the NHS progressively to set priorities in a much more rational way than has been possible to date. Policymakers need to be predictive if not prepared, in their approach, in order to understand the ways in which patients may react to the potential choices offered by new technologies. It may be impossible to predict how genetics and biotechnology develop. Planning for the future involves uncertainty but requires a clear understanding of the principal factors that shape policy making. The less that is known about the future pressures on NHS resources the greater the need for inclusive debate on rationing and the principles of the NHS. According to Hunt (cited in Leneghan, 1998, p5), the subject has hardly been considered by those who advise on, or formulate, national health policy.

UK Research and Industry Links UK Funding of Genetic Research

The Human Genome Project (HGP) is not an end in itself and it could be argued that this project has taken resources from the basic biological research needed to interpret

the information it has produced. Assessment of the total funding for genetic research is difficult as genetic research crosses the broad range of science. Little funds are allocated to genetic research by the NHS due to the MRC contribution. The NHS R&D programme only spent £1.1m in 1995/6 on research into diseases of genetic origin and their consequences. The NHS does however provide some of the infrastructure costs of clinical research, which allows the universities, the MRC and medical research charities to operate within the NHS. The Wellcome Trust has been recognised by the House of Commons Select Committee on Science and Technology (1995) as sustaining both basic and applied research in the UK, contributing more than £400m a year overall to medical research, conducted in academia, hospitals and pharmaceutical companies. The committee acknowledges that 'without the support of the Wellcome Trust and other charities genetic research in this country would be severely under-funded'. In the increasingly competitive climate for research funding researchers are chasing ever-shrinking resources. Funding agencies currently only support 15-20% of applications. According to Goldblatt (1997) the MRC is more interested in grants to centres and collaborative funding to UK research projects. This may deplete funds available to 'isolated' research interests or international networks. There are approximately ninety-six charities that fund medical research in the UK. Many support single rare diseases, with an average budget of less than £1m. The smaller charities (like the RS Associations) have budgets measured in £1000s.

The Clinician's Viewpoint

The clinician confirmed that the current prevalence of Rett Syndrome (1:10,000) may well now be just the tip of an iceberg. Rare diseases and Rett Syndrome in particular may be an attractive proposition to pharmaceutical or biotechnology companies who, whilst developing a drug for a minority disease may hit the jackpot if, as may be the case, that Rett Syndrome is the greatest cause of mental handicap in females. Diagnostic tools may also find more boys who have a form of Rett Syndrome. The clinician has approached drug companies who have helped fund dinners, host scientists meetings and helped with travel expenses. They seem rather reluctant in offering R&D or clinical trials even where drugs have been identified as possible candidate treatments by independent Rett researchers. The clinician suggested that research is frequently based in the NHS, with many practitioners working on specific

interests in their own time. The NHS also supports research by establishing joint posts where holders divide their time, in a symbiotic relationship, between hospitals and universities. The NHS benefits from the research resources available at the universities and the universities benefit by a steady stream of medical tutors and the knowledge, which comes from practical experience. Genetic research is often based in Universities, the balance covered by private initiatives. Interested researchers in rare diseases are geographically dispersed and as in Rett Syndrome for example are often international. Individual clinicians encourage networking and collaboration. These net-workers not only share information but also tissues (from the rare cases of Rett Syndrome that result in sudden death), donated by next of kin who have taken the brave step of organising special autopsies.

Increasing numbers of diseases previously thought as non-genetic in origin are being found to be linked to certain genes. Biotechnology companies are increasingly involved in this process but are constrained by a shortage of R&D funds. Whilst collaboration between academia and industry and within industry itself is critical to the success of the UK biotechnology industry according to the House of Commons Select Select Committee (HCSSC 1995) two of the key factors impeding the development of the biotechnology industry in the UK are:

1. The relative ease and enthusiasm with which US researchers, as opposed to UK researchers, sought application of their research and collaborated with industry.
2. The reluctance of pharmaceutical companies to collaborate with British companies or academics.

The clinician has had little support from industry, which may show that little improvement in collaboration, on rare diseases in particular, has been made possible since the Select Committee report in 1995.

There is evidence of how dedicated professionals use their own time to pursue their research and how informal networks have been set up which cross international borders. There is evidence of the barriers researchers (identified in the writers research) face in obtaining either funding or industrial interest and how important charities, especially the Wellcome Trust, are to the UK medical research base.

Industry's Perspective

European patient groups played a major role in negotiations in the passage of the European Orphan Drug Regulation through the political process, having gained a larger voice by uniting into lobby groups, similar to the American experience, which merits an introduction here (see Appendix C). In the US, under the Orphan Drug Act of 1983 and subsequent amendments, incentives are given such as:

- Exclusive marketing rights for 7 years after the approval of the orphan drug developed for a disease that affects < 7.5: 10,000. (The Japanese Orphan Drug Act of 1993 relates to diseases that affect < 4: 10,000).
- Tax credits (up to 50%) for clinical testing of orphan drugs.
- Grants and contracts to support clinical and pre-clinical orphan drug research.
- Flexibility and assistance in regulatory processes.

Prior to 1983 only ten drugs had been developed for orphan diseases in the previous decade. In 1991 there were 189 in development. Some of these drugs have since proved to be extremely profitable, being found useful in more common disorders. The European Orphan Drug Regulation came into affect in June 2000. The regulation allows an exclusive ten year distribution right as an incentive to pharmaceutical companies to develop 'orphan drugs' for the cure or alleviation of diseases that affect <5: 10,000. EU authorities will also assist in clinical trails and help to obtain licences and cover designation fees. It is hoped that this regulation will stimulate interest in the orphan drug market in Europe, similar to the effect of the US and Japanese initiatives. This will be discussed later.

Research and Development Within Biotechnology Companies.

Within biotech companies contacts, or association with a patient, patient group or family member are becoming an important catalyst to R&D. Orphan drugs or possible treatments for rare diseases often result from personal contact, or association with, a patient or patient group or family member. Within larger pharmaceutical companies R&D for orphan diseases more often arises from the testing of established drugs which are found to have an unexpected effect (serendipitous discovery) which

might be useful in specific situations. However even with orphan drug incentives some diseases are too rare to ever interest a company unless the enormous market prices were passed on to the patient or provider. It is possible that the treatment may be later found applicable for a commoner disease but the financial risks are too high. Most basic research is not done by the actual company (that may develop a treatment), but is usually done within government institutions. It would appear the research done is reflected (again) by a researchers particular interest.

> "Some researchers even look specifically for rare diseases because they think that through a rare disease finding they can then go to a common disease later on and find similarities there" (respondent).

There have been accusations in the media about companies exaggerating the potentialities of new drugs and being completely profit oriented. However in discussion with patient groups, the biotechnology industry has agreed to approach the press in future only over realistic expectations. Companies are in business to make profits, to attract investors, to expand. However, there is no necessary conflict between altruism and being profit oriented. Industry is itself a component of society, which contributes to society. Industry is not separate from society, it is a part of it. Industry has a responsibility therefore to that society. Corporate governance means more and more companies are looking at their societal role as being an important part of their integrated development.

Discussion and Conclusion

Biotechnology companies (being small enough to concentrate on smaller projects) may be the salvation of sufferers of rare diseases. The European Orphan Drug Regulation has to be followed by the UK government and may be the stimulus UK biotechnology companies need to compete with US biotechnology companies in the orphan drug market. The evidence given in Appendix C shows the American Orphan Drug Act was more an act of the people and the media rather than any 'policy decision'. European lobby groups contributed greatly to the progress of the European regulation. This shows the power of united lobby groups and the media the writer has alluded to previously.

As Information and Communication Technologies (ICTs) have proved powerful organising tools for scientists, in the new bio-informatics, so too have they become an organising tool for public concerns. ICTs and the media are allowing mass communication, synchronously and asynchronously, facilitating organised mass lobbying. Rather than ICTs disenfranchising citizens in a decline of the public sphere (Habermas 1997) it can be argued that ICTs have allowed disenfranchised citizens to become better informed within a high-speed public sphere of communication never witnessed before. As these networks become more accessible and attract interested parties we may witness a decentralisation of government policy setting, to powerful lobbyists combining public, charitable and scientific communities. The strength of these lobbies will be a reflection of the 'strength' and determination of its members. The champions of rare diseases are 'angry' and therefore very determined, as can be seen in the American execution of the Orphan Drug Act (1983) and the influence of NGOs in the implementation of the European Orphan Drug Regulation (2000). As more patients obtain more information about their medical condition and what is available world wide, politicians and managers will need to become more explicit about priority setting and include society in the policy process.

The UK system of government is representative, as opposed to the US system of participation, which is perceived as having created a more open climate and improved scrutiny of public decision making. The US gave its citizens a statutory right to access official information in 1966. The 1999 UK Freedom of Information Act has been accused of being littered with catch-all exemptions and a gross dilution of the radical 1997 White paper which promised to make the UK one of the world's more open governments. Science and politics remain a closed shop, remote from 'humanity' or the 'citizens' they purport to represent. The media meanwhile, often sensationalising a story, supply 'information' to the public.

The US system of democracy is much more open than the UK, allowing citizens to address the Senate. These include Kathy Hunter, the President of the International (US based) Rett Syndrome Association (IRSA), who has learnt to use the media to good effect. She has recently been elected to the National Advisory Neurological Disorders and Stroke Council, the major advisory panel of the NINDS. It would be interesting to suggest this is why Rett Syndrome is a priority in the US, where a

mother of a Rett Syndrome child who, like Abbie Meyers the Tourette syndrome mother, ‘got mad’ and decided to do something not possible in the UK where the government is closed, dismissive and remote. For a cure for a rare disease to be found research has to be done and I hope I have shown that this is being done, probably on a larger scale than officially known and recorded, whereas much information is not available and many researchers may be doing this research in their own time.

The EU Orphan Drug Regulation came into force in June 2000. Medicinal products in this case are those products intended for the diagnosis, prevention or treatment of a condition affecting <5:10,000 persons in the European Community, where no other product is in existence. However, according to Article 3 Paragraph 1 of the regulation, a candidate may be given orphan status even when other methods of treatment are available, provided that the candidate will be safer, more effective or otherwise clinically superior. It is thought that commercial incentives under the Regulation, in the form of exclusive marketing rights and tax incentives may encourage increased commercial investment in products for rare diseases, in line with successes in the US and Japan who have established orphan drug policies.

Rare diseases have also been identified as a priority area for Community Action (1999-2003) within the Framework V Programme. Decision no. 1295/1999/EC includes actions to provide information, to deal with clusters of rare diseases in a population and to support relevant patient organisations. The Framework V Programme for R&D funding promises to provide substantial funds for research into rare diseases and ensuring a consistency and complementarity of action between Community Action and the Orphan Drug Regulation. Member states are invited to introduce incentives for R&D work on orphan medicinal products and for placing such products on the market, within the framework of their own powers and responsibilities. In the US it has been found that most applications for Orphan Drug status are filed by small firms, specialising in biotechnology and genetic engineering, since the vast majority of rare diseases are developmental genetic disorders.

How policy decisions will incorporate EU regulation and the Framework V programme is not known. What appears evident is the need for involving the public,

industry, academia, the media and government, the NHS and research councils in a public sphere of debate.

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Appendix A: Overview of Organisations and Associations

EURORDIS (www.eurordis.org) is the European Association for Rare Diseases. A supportive, collaborative group of 126 patient associations throughout Europe which advocates for the development and access to new therapies. It also seeks to promote research and accessible information for those it represents.

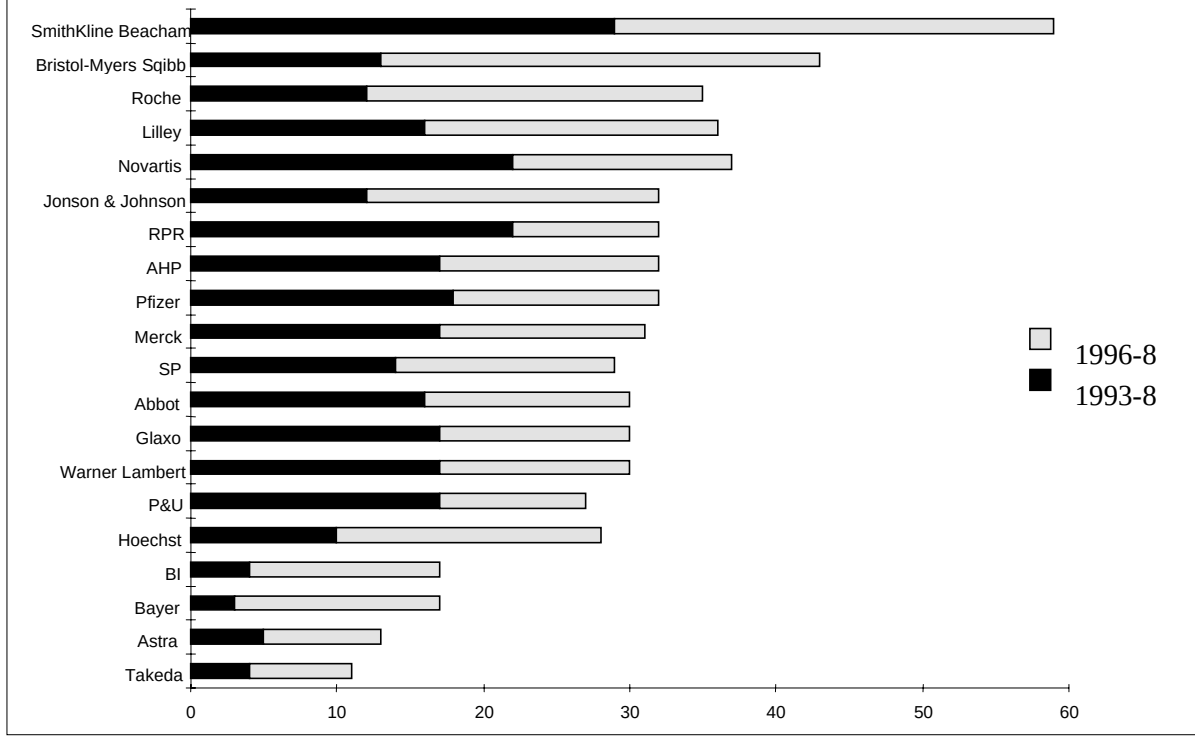
NORD (www.rarediseases.org) is the National Organisation for Rare Diseases in the US, a coalition of rare disease organisations. Acting as an information clearing house it deals with around 700,000 calls and letters together with an additional 210,000+ enquiries to its Internet site. NORD has become a powerful patient representative group with alliances with manufacturers, voluntary organisations and the US government - NORD has become a potent political force in the US Congress, where public participation in debate is commonplace. NORD was founded in the early 1980's by 'one mother {Abbie Meyers} who got mad' about the non-availability of necessary drugs for her sons condition.

GIG (www.gig.org.uk) is the Genetic Interest Group which is a UK alliance of over 120 charities that support children, families and individuals affected by genetic diseases. GIG lobbies on behalf of its members to promote awareness and understanding of genetic disorders, to stimulate R&D and service development.

JCMG (www.bshg.org.uk/jcmg.htm) is the Joint Committee on Medical Genetics which represents the Royal College of Physicians, the British Society for Human Genetics and the Royal College of Pathologists. Part of its remit is to "discuss and co-ordinate advice to government and other bodies on policy and service issues relating to genetics in medicine".

RSAUK is the Rett Syndrome Association UK, a registered charity and support group for sufferers and carers.(www.rettsyndrome.org.uk)

Appendix B: Number of announced R & D alliances by top 20 drug firms



Source: Financial Times 13.4.99.

Appendix C: A Brief History of the US Orphan Drug Act

Mar-1980	Senator Henry A Waxman of the United States Congress was approached by a constituent whose son's condition (Tourette syndrome) required treatment with a drug called Pimozide. The drug was approved in Canada but not in the US, so the son's drugs had been confiscated by US Customs. The mother, Abbie Meyers, asked Mr Waxman "I have only eight days of Pimozide left for him. What are you going to do about it?"
Jun-1980	Senator Waxman began a series of Congressional hearings at which citizens with rare diseases addressed Congress regarding the problem of unavailable treatments for their conditions. Newspaper and magazine stories appeared, explaining the dilemma of people suffering rare and often debilitating if not deadly illnesses.
Mar-1981	A famous television star, Jack Klugman, who starred in 'Quincy' as a medical examiner had been moved by the orphan disease dilemma and, knowing the power of the media, produced an entire episode surrounding Tourette syndrome. Members of Congress began to be lobbied by the public. The Congressional hearing drew national media attention to orphan drugs.
Mar-1982	Survey results on orphan drugs were presented, engendering public support but opposition from the Pharmaceutical Manufacturers Association (opposed to any government intervention) and the Reagan administration (opposed to financial incentives from treasury funds).
Sep-1982	The Orphan Drug Bill was put together by politicians, patients and other interested parties and passed by the House of Representatives but was hindered in its journey through the Senate by senators opposed to tax credits. Again, Jack Klugman (Quincy) intervened using the passage of the Bill as a storyline.This brought increasing pressure on the Senate who then passed the Bill unanimously. However there was still the risk of a Presidential veto, recommended by the Treasury Dept. When word was leaked, of a possible veto, patient organisations (now united under NORD) another nation-wide media focused campaign strengthened public support. "Over forty news-papers wrote editorials supporting the Act. Radio stations carried hourly reports on the fate of the Bill. Thousands of letters and phone calls poured into the White House. On the tenth day, the last possible day for the President's action, the Act was signed and became law" Henry A Waxman (1982)

Source: Adapted from Scheinberg & Walshe (1986)