Beyond Therapy? Investigating biomedical enhancement in the case of human growth hormone

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ABSTRACT

This project is an investigation of the issue of human biomedical enhancement, taking human growth hormone as a case study. Growth hormone is mainly used to increase the adult height of short children, and is also employed illicitly as an anti-ageing treatment. Both these applications are viewed by bioethicists as going beyond the scope of therapeutic medicine by enhancing normal human traits rather than treating diseases and as such are considered ethically suspect. This project adopts a comparative and retrospective stance, examining the socio-historical development of human growth hormone in the US, where much of the impetus for enhancement uses has originated, and also in the UK where the potential for enhancement uses of pharmaceuticals and other medical technologies is a growing concern.

This project combines a social constructivist approach to bodies and disease categories with science and technology studies theory on the emergence and shaping of new (medical) technologies. Research focuses on the development of growth hormone as a medical technology and the construction of the diagnostic categories that define the illness it is employed to treat. A combination of archive material and contemporary interview data is used to investigate and identify factors that shape the way some applications of hGH have

come to be viewed as legitimate, accepted practices while others remain unstable and controversial.

Enhancement suggests an inappropriate use of biomedicine, but in the case of growth hormone at least, the determination of medical need and entitlement is shown to be more than a matter of instrumental measurements. It is a contingent and socially shaped procedure that is applied in heterogeneous ways at different sites in the networks of healthcare provision. This technique provides a different model for thinking about those biomedical practices labelled as enhancement, which does not share the limitations of that framing.

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CHAPTER 1: Introduction

Introduction

On July 25th 2003 the United States Food and Drug Administration (FDA) announced that it had granted regulatory approval to Eli Lilly's *Humatrope* brand of synthetic human growth hormone (hGH) for treatment of children diagnosed with idiopathic short stature (FDA, 2003). The decision was a significant, if contentious one in the oft-controversial history of growth hormone. The category of idiopathic short stature (ISS) effectively extends the availability of growth-promoting hormone therapy to all children whose height is below a specified statistical cut-off point (2.25 standard deviations below the average, adjusted for age and gender). This decision represents the largest, though not the first, expansion of the patient population for the hormone drug, which was initially approved for small group of patients, numbering not more than a few thousand, whose pituitary glands produced little or no native growth hormone (Tattersall, 1996).

To many bioethicists the use of growth hormone to increase the height of short, but otherwise healthy, ISS children represents the culmination of a worrying progression away from bona-fide therapy towards the ethically suspect terrain of human biomedical enhancement (Tauer, 1995). To others, the expanding use of growth hormone marks the power of the pharmaceutical industry in promoting their products to ever greater sections of the public. The

approval for ISS raises the uncomfortable prospect that short but otherwise normal children are being given an expensive, prescription-only hormone drug to satisfy their or their parents' wish for them to be tall, or perhaps even as a result of pharmaceutical industry pressure on physicians to proffer the drug to likely candidates (Moynihan, Heath & Henry, 2002; Voss & Sandberg, 2004) The FDA's decision to approve growth hormone for ISS can be read as an unwelcome official seal of approval, or at least acceptance, of the desire for human enhancement and an acknowledgement of the power of the pharmaceutical industry.

The problems raised by human growth hormone and the characterisation of certain of its applications as examples of human enhancement form the starting point for this research. The purpose of this chapter is to elaborate the key concepts contained in this brief and the way in which they will subsequently be addressed in this thesis. It is first necessary to present the idea of human enhancement as a phenomenon, and how this relates to the uses of growth hormone. The concept will be illustrated with some examples of contemporary medicines and medical services that are considered enhancements. The specific case of growth hormone will then be set out in a brief review of its development and medical applications, culminating in two uses often considered enhancements; the treatment of short but otherwise apparently healthy children and as an agent to potentially retard the ageing process.

The concept of biomedical enhancement, as distinct from the appropriate, therapeutic uses of medical technologies, comes from the discipline of bioethics. While chapter 2 will address the issues raised by the idea of enhancement from the perspective of social theory, this chapter will focus on elaborating the bioethical framing of the concept, returning to its origins in the bioethics discourse on genetic engineering and gene therapy. Some specific problems with the idea of enhancement as a meaningful distinction from therapy, from a sociological perspective, are raised by way of making the case for this investigation of the topic. The final sections of this chapter set out the benefits of selecting growth hormone as a specific case study to investigate the issue of enhancement, and describe the organisation of the rest of this project and the contribution to an understanding of growth hormone and the issue of enhancement made by each subsequent chapter.

What is Enhancement?

'Enhancement' is a term originating in the discourse of bioethics to describe the use of biomedical technology to improve human performance and boost the capabilities of 'normal' healthy people. Some practices considered 'enhancements', such as cosmetic surgery (appearance enhancement), have been in existence for some time and have become common, if not entirely uncontested, phenomena. More recently, certain blockbuster pharmaceuticals

including Prozac and Viagra have stretched the definition of illness to become ‘enhancements’, where, for example, Prozac is said not only to treat clinical depression but also alleviate unhappiness (mood enhancement), and in doing so have earned the appellation ‘lifestyle drugs’. There is a clear link between the widening use of these medicines and the concern that they are moving beyond therapy into enhancement, a parallel which extends to the broadening application of growth hormone to treat short stature. Other enhancements are somewhat more illicit, relying on off-label prescriptions by physicians or patients selling on parts of their prescribed medication to third parties, to utilise medicines for alternative purposes. Examples include the blood pressure medication beta-blockers being taken by public speakers and actors to hide flushing and other signs of nervousness whilst performing, Ritalin intended to treat hyperactivity reportedly being used by college students as a study aid to improve concentration, and Provigil, an anti-narcolepsy agent being used to help people stay awake and work longer hours (Elliott, 1998; Hall, 2003a). Growth hormone as an anti-ageing treatment is closer to this latter category, as this treatment is only possible through off-label prescribing and is not supported by the majority of mainstream practitioners. Biomedical enhancements have also been used illegally in competitive sports to improve athletes’ performance. Bodybuilders and sprinters have used anabolic steroids to increase muscle mass and professional cyclists have taken the anaemia

treatment erythropoietin to increase their red blood cell count and improve oxygen delivery to the muscles.

The unifying factor linking these practices is that they are construed as the use of medical technologies and practices to augment or affect normal body characteristics. Enhancement is considered distinct from therapy, which is described by many bioethicists as the use of medicine to restore individuals to health and their natural state. In 2003 the United States President's Council on Bioethics published a report entitled *Beyond Therapy? Biotechnology and the pursuit of happiness*, drawing attention to the potential and actual use of biomedical technologies that go 'beyond therapy' in this way. Despite the popularity of some practices - Conrad (2005) reports that by 2003 over six million men in the US had tried Viagra and more than eight million Americans had a cosmetic procedure during the same year - enhancement is often regarded critically. In bioethics, therapy is always considered ethically acceptable while enhancement is generally regarded as ethically suspect (President's Council on Bioethics, 2003). Others, within sociology and elsewhere, see the profusion of lifestyle drugs as part of a detrimental medicalisation of everyday life where biomedicine is used to address social problems while ignoring other social and economic causes (Conrad & Potter, 2004; Moynihan, Health & Henry, 2002).

The issue of enhancement raises questions about entitlement and provision of medical services that cannot be entirely separated from national systems of healthcare provision. The idea of consumer-driven 'lifestyle' medication is more closely linked with neo-liberal models of medical provision where individuals are consumers of healthcare services than with the state sponsored 'social' model of healthcare. Unsurprisingly, as an exemplar of a market-driven healthcare system, much of the debate and practice surrounding enhancement and 'lifestyle' drugs has been centred in the US, although the controversy over NHS provision of Viagra shows this is not an exclusive situation (Klein & Sturm, 2002). There have been signs that the British health system, although significantly closer to the state-managed end of the healthcare spectrum, may be moving towards some aspects of the American model, by promoting greater self-management of individual health through improved access to information, a greater number of medicines, including formerly prescription-only drugs like statins, being made available over-the counter, and comparison of US not-for-profit healthcare providers such as Kaiser Permanente and United Healthcare for ways to improve NHS efficiency and disease management (Blenkinsopp & Bradley, 1996; Bury, 2003; Donaldson, 2001; Dash, 2004; Dixon et al., 2004). Along with this apparent increase in health consumerism has come an upsurge in some of the biomedical procedures considered as enhancements. The private healthcare provider BUPA recently estimated that some 75,000 cosmetic procedures per annum

are carried out in the UK with an additional 50,000 non-surgical procedures such as Botox injections also being done (Aitkenhead, 2005). This raises the possibility that the UK will also experience a greater demand for growth hormone treatment both in idiopathic short stature, and potentially as an anti-ageing remedy. The next section explores the origin of these and other applications of the drug in greater depth.

Human Growth Hormone and Enhancement

Growth hormone is naturally produced in humans and other animals by the pituitary gland, located at the base of the brain, and its role is to stimulate growth during childhood and regulate various aspects of the body's metabolism including the distribution of fat cells. The growth hormone protein can also be synthesised by bacterial or animal cells genetically modified to carry the (human) growth hormone gene. Biosynthetic growth hormone, also known as recombinant[1] growth hormone because of the manufacturing technique, is produced by a number of major pharmaceutical and biotechnology companies including Genentech (who produced the first recombinant GH in 1985), Serono, Pfizer, Novo Nordisk and Eli Lilly. Before the biotechnology to synthesise it was available, growth hormone was harvested at autopsy from the pituitary glands of human cadavers. Unlike other hormones that are employed as drugs such as insulin or oestrogen, growth hormone from animal sources is not biologically active in humans, although like insulin, hGH must be

administered by injection. This meant that, from the time when human growth hormone was first isolated in the 1950s, the supply of cadaveric GH was limited and its therapeutic application was restricted to a small group of children with very short stature believed to result from an absence or abnormally low level of naturally occurring growth hormone. In the mid-1980s a small number of patients in the UK and US, previously treated with pituitary-derived growth hormone, were diagnosed with a form of the fatal neurodegenerative illness Creutzfeld Jacob Disease (CJD). The illness was linked to their GH therapy with supplies of the hormone believed to have been contaminated by infectious material from diseased pituitary glands. As a result all therapy with pituitary GH was suspended in 1985 (Tattersall, 1996). The recombinant DNA-derived growth hormone was in the final stages of clinical testing at this point and, as its synthetic production meant it could not be contaminated by CJD-causing agents, it was rapidly approved by regulatory authorities across the world to treat the pool of children who had previously been entitled to the pituitary-derived hormone.

Soon after 1985, when the biosynthetic version of the hormone appeared, the pool of short children eligible for growth hormone therapy began to expand to include less severely hormone deficient children and growth failure due to non-hormone deficient conditions such as the genetic disorders Turner syndrome, Prader-Willi syndrome and ailments like chronic renal failure (Ruiz & Tresguerres,

2001). Experimental application of GH in adults, which had previously been theorised but never fully investigated because of the restricted supply of pituitary-derived hormone, also began to be carried out. A new condition of adult GH deficiency was recognised and the hormone was also trialled as a therapy for tissue degeneration in burns victims and AIDS patients. Growth hormone, even before the US approval of idiopathic short stature as a treatment category, had already grown from its humble beginnings to become a blockbuster drug. In 2004 the worldwide sales of recombinant GH were in excess of $2 billion (Martin & Morrison, 2006).

This expanded use prompted some concern amongst clinicians, bioethicists and journalists, particularly with regard to the tactics of the pharmaceutical industry in promoting the use of their new drug. Two applications in particular proved controversial. Along with the expanded treatment of short-statured children was an increasing tendency, notably in the US, to give the hormone as therapy for short children where no discernable underlying pathology was recognised, a category of patients sometimes referred to as having idiopathic (of unknown cause) short stature. Treating ISS children with hGH has been controversial because of the charge that doing so is to medicalise stature itself, and if short stature is not to be considered a disease then increasing height for its own sake is cosmetic medical enhancement of children. In 2003, the same year as the President's

Council on Bioethics report, the US Food and Drug Administration (FDA) contentiously approved Eli Lilly's brand of hGH, *Humatrope,* for treatment of idiopathic short stature. No such approval has been given by the European Medicines Agency (EMEA) or UK regulatory authorities[2] and the case represents a division in regulatory practice between the US and Europe.

Growth hormone use in adults has also expanded into contested areas. In the 1990s a few widely publicised but very small-scale clinical trials suggested that, as growth hormone levels decline with age, injections of the hormone might be useful in retarding some of the symptoms of ageing. While this latter application has not received any significant industry or orthodox medical support, a lucrative trade has arisen in off-label prescription of GH supplied in private anti-ageing clinics or in products of dubious provenance bought unregulated over the internet. No anti-ageing uses of hGH have been granted regulatory approval in America or Europe, and indeed no pharmaceutical manufacturer is openly investigating or supporting this application. However, the emphasis in the outlook and promotional material of anti-ageing proponents such as the American Academy of Anti-Ageing Medicine (A4M) on old age as an inherently negative state places such activity firmly within the realm of enhancement as far as many bioethicists are concerned. It is these two arenas of growth hormone use, in idiopathic short stature and as

an anti-ageing treatment, and their characterisation as enhancements that are investigated in this thesis.

Bioethics and the Origins of the Enhancement / Therapy Dichotomy

Bioethics posits enhancement as a moral problem concerning the proper governance of medical practice and the uses of biotechnology:

> Many medical technologies, new and old, can alter people in ways they desire to be changed. When do we have a social obligation to ensure that such preferences are met? Do rights to health care include entitlements to have those preferences met, resources permitting? What should insurance cover? (Daniels, 1992 p46)

Biomedical enhancement raises questions about equity and resource allocation in healthcare that act at the level of states and institutions but it also concerns the fundamental role of biotechnology in addressing social problems and the type of society that this creates and may create in future. In order to understand why enhancement is considered (ethically) problematic it is necessary to consider the source of the distinction between enhancement and therapy. As stated, this dichotomy has its origins in the discipline of bioethics, and emerged primarily in debates over the possible uses of genetic engineering, especially gene transfer technology.

Bioethics itself is an interdisciplinary academic field, a profession and indeed, an ideological and social movement. It emerged primarily in the US in the mid 1960s in response to a series of medical scandals and ethical quandaries involving the treatment of human subjects in medical research and the application of new technologies to patients[3] (Rothman, 1991). Bioethics in its broad sense acts as a replacement for the older codes of medical ethics and self-regulation by researchers and physicians. In the circumstances of its formation, Rothman (1991) views bioethics as a challenge to previously unchecked medical authority, an extra, external set of checks and balances to protect the public and society from inappropriate, unethical science and technology. Of course bioethics, as a fundamentally interdisciplinary enterprise - the field was essentially founded by collaboration between philosophers, theologians and concerned physicians - is not a monolithic entity but rather incorporates a plurality of views and approaches as befits the diversity of bioethicists (De Vries, Turner, Orfali & Bosk, 2006; Jonsen, 1998). Sociological accounts of bioethics, in tending to portray all bioethical decisions, texts and forms as part of a single, principle-based bioethical orthodoxy have historically caused some friction between the two disciplines (De Vries, Turner, Orfali & Bosk, 2006). The recent pronouncements of the President's Council on Bioethics are a topic of debate within the discipline, not necessarily a representative expression of the field, and still less the voice of an accepted professional hierarchy. Nevertheless the terms

enhancement and therapy have become ‘standard rhetorical tools’ in academic bioethics and are worth consideration as an important line of argument within the field (Juengst, 1997 p125). Although there had been prior attempts in philosophy and elsewhere to define the purpose and remit of therapeutic medicine in moral terms, the therapy/enhancement distinction came to prominence during discussion about the potential new biotechnology of gene therapy.

Genetics and genetic technologies have long proved troubling to ethicists and the public alike, from the 1962 Ciba conference, where the ‘revolution’ in genetics was pronounced and a number of high-profile speakers including Hermann Muller, Joshua Lederberg and Francis Crick[4], espoused eugenic proposals, through to the fears over recombinant DNA technologies in the 1970s and 1980s (Stevens, 2000). Gene therapy describes the proposed use of biotechnology to insert foreign or synthesised DNA directly into human cells to be amalgamated into the host genetic material and effect changes through the production of proteins, etc, in much the same way as genetically altered bacterial cells can be made to produce human growth hormone, insulin and other useful biological components. As gene therapy began to look more scientifically plausible, bioethicists grew increasingly concerned with the ethical considerations of medical technology acting at the genetic level being applied to human subjects (Crigger, 1998). The bioethical debate on gene therapy centred on two fundamental distinctions: somatic

versus germline gene transfer and therapeutic gene transfer versus genetic enhancement (Scully & Rehmann-Sutter, 2001). The first distinction differentiates between gene replacement techniques which affect only a selected body tissue such as the liver (somatic therapy) from germline gene therapy which affects the reproductive tissues and is intended to confer genetic changes that will be passed on to the patient's offspring. The latter dichotomy, of greatest significance here, 'contrasts the use of human gene transfer technology to treat health problems with their use to enhance or improve normal human traits' and thus contains the concept of enhancement *as a contrast* to therapy (Juengst, 1997 p125). Thomas H. Murray, bioethicist and president of the Hastings Centre[5], has stated that in a bioethical view '[a] broad definition of genetic-enhancement technologies, not merely gene manipulation, but also indirect genetic technologies, such as biosynthetic drugs, is needed to capture the full range of possible applications' (Murray, 2002 pS27). This brings the use of human growth hormone in treating short stature, and other technologies beyond gene therapy itself, directly under the remit of enhancement. In many respects the wider debate on human enhancement has now eclipsed the debate on gene therapy as that technology has faltered.

The key to understanding the enhancement/therapy distinction is the notion of normality, which therapy supposedly restores and enhancement improves upon. This distinction draws upon prior

philosophical attempts to discern the limitations of healthcare needs by defining health and disease in biological and statistical terms:

> [D]iseases are internal states that depress a functional ability below species-typical levels. Health as freedom from disease is then the statistical normality of function, i.e., the ability to perform all typical physiological functions with at least typical efficiency (Boorse, 1977 p542).

This type of thinking can be seen in bioethical accounts such as Daniels (1992) who argues that the purpose of medicine is to restore, maintain and compensate for losses, in equality of opportunity to individuals, which result from disability and disease. The role of medicine in this model is not to make people happy, nor to alleviate social inequality. Improving on normal characteristics - enhancement - does not meet a medical need as defined by biostatistical terms, indeed it can be considered a more frivolous desire, and so is not something to which individuals can expect to be entitled.

The Limitations of the Enhancement Model

The effect of the enhancement/therapy dichotomy is to frame a set of biotechnological options in formal moral terms, rendering them accessible to bioethical judgement (Scully & Rehmann-Sutter, 2001). There are however, a number of aspects of this approach that are problematic from a sociological perspective. Bioethics, as a prescriptive enterprise, is inherently normative but the use of normal function models of health to produce enhancement and therapeutic

uses for technology strongly conflates the ideas of ‘normal’ and ‘natural’ (Boorse, 1977; Scully & Rehmann-Sutter, 2001). The average level of biological functioning is held up as the natural human state with all the loaded connotations that term implies. The natural takes on a prescriptive moral weight, sanctioning biotechnological intervention to restore this biological normality, but viewing technologies that may disrupt the natural - from organ transplantation, artificial respiration (as with the Quinlan case), and foetal and embryonic research, to germline gene therapy and pharmaceutical enhancement - as posing a threat to human dignity (Scully & Rehmann-Sutter, 2001). It should be noted that this view of human dignity as being biologically invested is far from universally accepted and opponents of this line of argument against biotechnological intervention and enhancement in particular have labelled this stance as ‘bioconservative’ (Bostrom, 2005). More pertinently from a sociological perspective is the assumption in this strand of bioethics that science and technology can be taken as objective, value-neutral processes, and the model of the human body they produce is an apolitical, acultural reality. Enhancement is viewed as a problem for society, but one caused by a medicine and technology that are distinct from the realm of the social. Indeed the whole dichotomy of enhancement and therapy relies on the idea that biologically appropriate needs are inherently separable from social desires and conditions. Rather than co-opting this stance, this project

does not intend to focus on the problems caused by enhancement, but takes the category of human enhancement as its object of study.

The idea of the enhancement / therapy dichotomy can itself be understood as serving a particular social function. Evans (2002) has argued that state involvement in the ethical regulation of new genetic technologies, especially through the formation of advisory committees and ethics boards, provided a platform for bioethics to thrive. In order to facilitate open, objective-seeming, moral decision making, these bioethics committees eschewed broader, substantive argument about the goals of medicine and concentrated on resolving particular issues by recourse to ethical principles such as justice, autonomy and beneficence, producing a 'thin' debate about which uses of technologies are and are not acceptable. Stevens (2000) views this form of bioethics as a mechanism to diffuse public anxiety about new technological practices, while ultimately legitimising their deployment, by issuing ethical caveats on (and thereby creating) appropriate ways to use them. This can be seen in the case of gene therapy. In order to alleviate public fears over safety, eugenics and other social consequences and allow the first gene therapy clinical trials to begin, enhancement and germline gene therapy, areas deemed to be *prima facie* ethically problematic, were prohibited so constructing an acceptable, therapeutic model of gene therapy. Bioethics in this case provides a justification, an ethical 'fix' to 'a medical demand to push the limits of medical treatment into new

frontiers' (Imber, 2001 p31). When this dichotomic solution was proposed, gene therapy was in its infancy and no capacity for enhancement actually existed so there was no loss of a technical option involved in the ban, but rather it served to initiate the progress of the technology (Scully & Rehmann-Sutter, 2001). A similar perspective can be applied to other cases of enhancement, such as anti-depressants or growth hormone in short stature: some development options are rendered unacceptable while at the same time marking others as within the bounds of normal medical practice and thus morally unproblematic.

Instead of taking enhancement as an unproblematic category the aim of the project is to investigate the factors that lead to some applications of medical technologies becoming accepted as therapies while others are contested and labelled enhancing. Where the bioethical concept of enhancement proposes an external ethical basis for this division, this study will focus on the construction of indications for treatment within medicine, as the field that has ultimate responsibility for deploying medical technologies. Human growth hormone will be used as a case study to explore the means of legitimisation of medical aims in successful applications of the drug (treating short stature or hormone deficiency in adults) and the elements that undermine the stability of controversial indications (idiopathic short stature and anti-ageing). The next section sets out the reasons for the specific choice of GH as case study.

Human Growth Hormone as a Case Study

The place of growth hormone within the pantheon of enhancements has been explained. The choice of this particular pharmaceutical to act as a case study for the investigation of the phenomenon of biomedical enhancement was made for a number of reasons. The 2003 President's Council on Bioethics report *Beyond Therapy?* was a significant contribution to the enhancement/ therapy debate, not least in terms of raising the profile of the issue[6]. Although human Growth Hormone received only passing coverage, the report did devote two chapters to specific aspects of enhancement - creating 'better children' and anti-ageing - in which growth hormone is involved. GH itself presented an attractive opportunity for study as, when the pituitary era of use is considered, it has been employed in medical practice for a considerable amount of time compared to other more recent enhancement practices such as use of Provigil to stay awake longer or Botox treatment to remove wrinkles. While other pharmaceuticals whose use has spread into lifestyle drug territory such as Ritalin or anti-depressants like Prozac have suitably long medical pedigrees there are ever-present questions about the biomedical model of psychological illnesses and the suitability of drug therapy in these patient populations irrespective of whether the usage is considered enhancing or not. By contrast growth hormone offered a case where a specific physical bodily characteristic is the topic of both established 'legitimate' medical interventions and

controversial enhancement applications, presenting an opportunity to study the relation and possible progression from one to the other.

The two distinct applications of growth hormone, in treating short stature and as an anti-ageing agent, also offered contrasting examples of enhancement technologies. The use of growth hormone in idiopathic short statured children is a controversy within mainstream medical practice, primarily debated (outside of bioethics) by paediatric endocrinologists, in their role as the medical specialists with authority over the application of growth hormone in childhood. In the academic medical literature on hGH in short stature the main concerns are the legitimacy of ISS as a diagnostic category and the efficacy and safety of treatment rather than enhancement *per se*. It is an issue of where the boundaries of appropriate treatment for short stature lie. By contrast the issue of anti-ageing medicine is presented as a clash between orthodox medical science and pseudo-science. Anti-ageing is not supported as a legitimate, medical enterprise in the published discourse of endocrinology or other medical disciplines and proponents of hormonal prolongevity are condemned as renegades or opportunistic entrepreneurs. This is not to say that the potential use of growth hormone in elderly patients is entirely rejected but it remains only an experimental possibility not a therapy. Given that the enhancement/ therapy issue arises as an attempt to make claims concerning the legitimacy or illegitimacy of biomedical technologies, it is useful to be able to investigate how justifications

for or against particular uses differ between separate applications of the same drug as well as within specific indications.

Framework for the Thesis

Having introduced the bioethical concept of biomedical enhancement, as well as some of its limitations, as the starting point of this investigation, the subsequent chapter develops the social theory approach that will be used in this study. Taking a social constructivist perspective, the categorisations and prescriptions of scientific medicine can be viewed, not as neutral, unassailable readings of the objective reality of disease and illness, but as being actively constructed through the practices of medicine. If ideas of what counts as disease (and, by relation, what is therapeutic) can be understood as being socially situated, influenced and shaped by factors such as the interests of the medical profession and governments, this gives analytic purchase to investigate how these ideas become legitimised and, alternatively, why some are rejected. Within this framing the concept of medicalisation is employed to describe the way in which growth and ageing have come under medical control, while the analytical tools of science and technology studies (STS) are proffered as a means by which the mechanics of the process of medicalisation can be studied.

Chapter 3 deals with the methodology, explaining how this theoretical framework can be transformed into a practical research agenda.

Examining the development of growth hormone requires giving consideration to all its indications, legitimate and contested, and this adds a historical element to the study. In order to examine which factors foster or undermine the legitimacy of particular indications, the impact of prior developments, ideas and practices, and especially those existing uses of GH, must be part of the analysis. This attempt to show the impact of the past in the development of the present situation is reflected in the choice and utilisation of data sources. Endocrinologists are the medical specialists with authority for the therapeutic application of human growth hormone: paediatric endocrinologists for childhood growth promotion, and adult endocrinologists for deficient or elderly adults. Two primary data sources are available to access endocrinologists' discourse on growth hormone: academic medical journals and interviews with contemporary endocrinologists. Both of these sources will be utilised to collect data on the previous and current use of GH. The issues of data collection and interpretation, particularly in light of the social constructionist framework, and attendant ethical concerns, will also be addressed in this chapter.

Chapters 4 and 5 recount the social history of growth hormone as a medical technology. This account begins with the birth of endocrinology itself at the end of the nineteenth century in order to illustrate the formative associations between hormones and ideas of rejuvenation. While this early idea of anti-ageing did not survive the

incorporation of endocrinology into orthodox scientific medicine, it was important in setting up the still-prevalent idea of hormone therapy as the biochemical replacement of a deficit inherent in the bodies of afflicted patients. Chapter 5 deals primarily with the development of hGH as a treatment for childhood short stature as this has been the major indication since the first tests of human pituitary GH in 1958. Analytical emphasis is given to the changing networks, institutional and cognitive interests that shaped the technology through the pituitary era and following the introduction of biosynthetic hormone and the subsequent expansion of its use, up to and including the FDA approval for ISS in 2003.

The breadth and categorisation of growth hormone use from severe hormone deficiency to idiopathic short stature in childhood growth failure is also the focus of Chapter 6, which analyses the interview discourse of contemporary paediatric endocrinologists. This material is intended to be analysed and interpreted in view of the historical development of GH recounted in chapters 4 and 5, and aims to gain an understanding not simply of the arguments about idiopathic short stature but of the basis on which discursive rationalisations about entitlement to therapy can be linked to the proposed goals of treatment across the range of diagnostic categories of growth failure.

The last data chapter, Chapter 7, returns to the issue of growth hormone as an anti-ageing therapy and continues the socio-historical

account from Chapter 4 through to the current situation with a resurgence of hormonal prolongevity practice appearing at the end of the twentieth century. This chapter also employs interview material with adult endocrinologists to examine the ways in which anti-ageing is presented as an unscientific endeavour compared to other, accepted adult GH uses, such as the adult growth hormone deficiency syndrome. The principle of symmetry in sociology and science and technology studies favours examining both accepted and rejected cognitive and technological options as a means of examining the social processes that shape these outcomes.

The final chapter will draw together the analysis of historical and current material on GH across the indications for short stature and ageing to answer the core questions of this research project: What are the significant elements in the discursive and technological construction of illness and entitlement to therapy in the uses of growth hormone employed by endocrinologists as the professional custodians of this medical technology? In particular, which representations of scientific medicine are detectable in the way decisions justified as scientific or renounced as unscientific and how has this has affected the development of growth hormone? The key components of endocrinologists' understanding and justification of GH treatment and the boundaries that separate this from inappropriate (unscientific) practices will be compared to the bioethical model of enhancement and therapy and the implications,

particularly of the differences in these accounts, for future use of GH and other controversial enhancement technologies will be considered.

Notes

[1] It is derived from cells which have had a segment of foreign, in this case human, DNA inserted by biotechnological means. This foreign genetic material then *recombines* with the host cell's DNA. The modified cells produce and secrete the human version of the growth hormone protein as if it were one coded-for by their own genetic material.

[2] The case of idiopathic short stature was also formally omitted from the National Institute for Health and Clinical Excellence guidelines on the best use of growth hormone in treating childhood short stature (NICE, 2002).

[3] A series of high profile public scandals for the biomedical establishment included thalidomide-induced deformations in babies, Chester Southam's cancer research using senile and elderly patients in 1963, reporting of the Tuskegee syphilis study in 1972, in which black syphilis patients in Tuskegee, Alabama had been deliberately left untreated since the 1930s to examine the progress of the disease, and the 1975 Quinlan case that centred around the decision to remove life support from a comatose patient (Rothman, 1991).

[4] Each of these speakers was already a Nobel Laureate at the time of the conference (Stevens, 2000).

[5] The first independent institute for Bioethics, founded by Daniel Callahan and Willard Gaylin in 1969 (Guillemin, 1998).

[6] Indeed the report opens by noting that, whilst much of the debate on enhancement to date has been confined to the pages of bioethical literature and conferences, it is worthy of greater public attention and has an import at least equal to the more immediate ethical concerns about medicine and technology (President's Council on Bioethics, 2003).

CHAPTER 2: Conceptual Background

Introduction

The aim of this project is to critically investigate the use of the hormone drug, human growth hormone (hGH), in applications that have been described as constituting human enhancement. The bioethical origins of the concept, along with some of its limitations have been outlined in the Introduction, and the purpose of this chapter is to lay out the components of a more critical theoretical approach to examining the situation. The reason so-called 'enhancement' technologies are controversial is that they are understood in distinction to the 'proper' use of medicines in 'therapy'. In order to examine this state of affairs it is necessary, then, to understand how the targeted conditions, in this case short stature and old age, have come to be considered objects of medical attention in the first instance, and what ends are thought to be served by treating these states. This is problematic if, like the bioethical frame, the natural state of the body and the ways in which it might be altered by (bio)technological means are taken as given, scientifically determined facts. This approach effectively locks the discussion of enhancement into a series of decisions about which medical interventions should be allowed and which prohibited. However, medicine and the knowledge it produces about bodies, health and illness can also be viewed as socio-cultural entities and are amenable to study as such. Rather than casting science and society

as separate domains, in this view, the institutions and practice of medicine are wholly embedded in the social milieu and both affect and are affected by a range of social factors.

Within the canon of social theory on the body and medicine, the literature on medicalisation seems to present an obvious inroad into the territory of biomedical enhancement. Medicalisation examines how areas previously considered outside the remit of medicine come to be treated as medical problems and defined in medical terms, and covers both 'deviant' social practices such as alcoholism and child abuse, as well as 'natural' life processes like child birth and ageing (Conrad, 1992). Many of the same socio-medical phenomena are cited as examples of both enhancement and medicalisation, such as the use of Ritalin to treat childhood (and later adolescent and even adult) hyperactivity, Prozac and other selective serotonin re-uptake inhibitors (SSRIs) to treat depression and anxiety, Viagra for male impotence, and the application of human growth hormone for idiopathic short stature or in anti-ageing (Conrad, 2005; Elliott, 1998; President's Council on Bioethics, 2003). However, taking a social constructionist perspective, bodies and the diseases which afflict them, are viewed not merely as biological phenomena described by medicine, but as claims and conceptualisations made on the basis of specific techniques for producing knowledge (Lupton, 2000; Turner, 1995). Michel Foucault, whose work was instrumental in elevating the study of the body and its construction to prominence in medical

sociology, proffered the following mandate for attempting to critically engage with the pronouncements of modern medicine and the natural sciences that inform it:

> The main point is not to accept this knowledge at face value but to analyse these so-called sciences as very specific “truth games” related to specific techniques that human beings use to understand themselves (Foucault, 2003a p146).

By treating medicine as a discourse – a ‘truth game’- which produces, rather than reveals, facts about the material world, the categories and judgements of medical knowledge can be deconstructed in an attempt to uncover the underlying meanings and values that shape such claims. The knowledge produced by medicine and other sciences relating to human beings such as psychology, psychiatry and many social sciences, is used by people to understand themselves and so creates new identities and social roles based on those labels, ‘that in a certain sense did not exist before’ (Hacking, 2006 p23). This approach provides critical purchase to explore how short stature or old age might come to be understood through a medical model of the body in such a way that makes them potential targets for pharmaceutical intervention.

Like medical knowledge, medical technologies are both products of, and producers of, culture (Van Der Geest, Reynolds & Hardon, 1996). This makes medical technology, as well as the medical

knowledge, ideology and practices that surround it, a valid and useful object of study:

> If medical technology is seen as an embodiment of ideas as well as practices, its uses can be evaluated and explained not by whether or not they conform to government standards, but what they express about medical practice itself (Bell, 1986 p27).

The fact that medical technologies are considered to work (or not) need not be taken as given, but can be analysed to reveal the particular characteristics of the medical contexts in which these technologies succeed or fail. This is directly relevant to the study of human growth hormone where a significant element of the debates surrounding its controversial applications involves arguments about whether it can be said to 'work' or 'work well enough' to justify its use. While the impact of medical technologies has been acknowledged in social studies of medicine, it is an area of study that has historically been underdeveloped (Martin, 1999; Timmermans & Berg, 2003). In contrast, a body of recent work has employed the theoretical perspectives and analytical tools of science and technology studies (STS) to a range of medical technologies from genetic tests to tissue engineering (Clarke & Montini, 1993; Koch & Stemmerding, 1994; Martin, 1999; Martin & Rowley, In Press; Will, 2005). Of particular relevance are a number of in-depth studies which have applied an STS approach to produce critical socio-historical accounts of pharmaceuticals including oestrogen-based hormone drugs and the anti-cancer agent Taxol (Goodman & Walsh, 2001; Lowy, 1996;

Marks, 2001; Oudshoorn, 1994). Given that both share an underlying social constructionist perspective there is potential that the social study of medicine, health and illness, and science and technology studies could be beneficially combined in the study of human growth hormone and its application to short stature and ageing.

To this end, the chapter will begin by introducing some key elements in the development of critical thought about the social role of medicine, from Parsons and Foucault through medicalisation and the modern biomedical era. This theoretical outlook will then be employed to trace a brief account of the rise of modern, scientific medicine from the nineteenth century to the present, highlighting broad social and cultural changes that have shaped and promoted the development of this form of medicine. This will set up the subsequent discussion of the contemporary era and an attempt to produce a model of how enhancement technologies might be understood in these terms. Some difficulties and limitations of the model of enhancement technologies described through the approach described so far will be discussed and the potential of additional perspective from science and technology studies (STS) introduced as a means to provide a more complete analytical basis. Some general theoretical and analytical tools of science and technology studies will then be introduced, highlighting the aspects most relevant to this project; specifically the social shaping of technological devices and their deployment through social networks, with a description of

how these can be applied to medical technologies. The final section of this chapter will explain how these different elements can be combined in the study of human growth hormone and its uses and how this will affect the programme of investigation to be featured in the following chapters.

Theorising Medicine and the Body

This section will introduce the idea that medicine can be thought of as a social practice whose principal concern is managing the human body, especially in times of illness. Some key aspects of a social constructionist perspective will be outlined, along with the way these can be applied to examine how medicine acts as a social practice- how it understands bodies, and the consequences for social structure and ordering that this can have.

Human beings experience the world as 'embodied subjects'; they are aware of themselves as possessing and inhabiting physical bodies with particular configurations and features (Giddens, 1991; Lupton, 2000; Rose, 1996). While bodily awareness, and especially body appearance, are important aspects of identity it is often only through instances of pain or illness that the body (especially the 'inner' body) is brought to prominence as a feature of conscious experience (Lupton, 2003). Sickness has, for human beings, a social, and often a moral, meaning and affects the network of social relations in which individuals are embedded during their everyday life (Lupton, 2003;

Turner, 1995). Being ill affects (usually by reduction) the body's capabilities and an individual's ability to perform social actions such as work or participation in family activities. Sickness can also affect identity, marking a person as someone requiring care or as someone who has transgressed to 'bring the disease upon themselves'. The human body and those instances of heightened awareness about the body which mark the experience of illness and disease, have been the objects of medical attention for centuries, and indeed provide the *raison d'être* for medical practice:

> There has never been a time that men and women have not suffered from sickness, and the physicians' specialised social role has developed in response to it (Rosenberg, 1992 p xiii).

Medicine, in turn, fulfils its social role by producing knowledge and discourses about the body that explain the experiences of individuals who are ill and direct attempts to alleviate their situation. Contemporary attempts to study medicine, health and illness as socio-cultural entities also take as their focus those bodies and experiences of illness, to access the ways in which this understanding is effected and the effects it produces (Lupton, 2000).

At the beginning of the twentieth century, the branch of sociology dealing with medicine and medical practice was mainly engaged in supporting the advance of medicine and was not especially concerned with analysing the socio-cultural content and effects of medicine as a practice (Turner, 1997). Talcott Parsons was among

the first to take a more critical look at the social role of modern medicine, particularly though the concept of the ‘sick role’ (Parsons, 1951). Parsons envisaged medicine as a technique of social control: Through its ability to categorise individuals as ‘well’ or ‘ill’, medicine can sanction the socially deviant behaviour of ‘sickness’ with its attendant components such as abstention from work and other social duties, provided individuals submit themselves to the dictates of the medical regime in following physicians’ guidance to restore themselves to health (Conrad, 1992; Turner, 1995). The theme of medical control in society was also taken up by later writers such as Szasz (1963), Friedson (1970) and Zola (1972) who criticised the increasingly broad remit of medicine in the twentieth century. The process whereby issues and aspects of social life not previously considered medical are redefined as medical problems and brought under the remit of medical authority was termed *medicalisation* (Zola, 1972; 1991).

The medicalisation critique incorporates an implicit (and often explicit) perspective of social constructionism. As Douglas (1969) has argued, all classification systems are essentially social in origin – they do not reflect some inherent ‘reality’ of the object(s) being classified, but rather they are ways in which human beings organise the world in order to make sense of it. Through the study of how this classification system operates and expands in medicalisation it becomes evident that medicine is a social and cultural enterprise as

well as a scientific one- the instance of being sick is as much about (deviant) social phenomena such as inability to participate in work or family care as it is about discrete biological phenomena- one does not prefigure the other (Clarke et al, 2003). A constructionist analysis does not, as has sometimes been inferred hold that 'nothing is real' or that nothing can be truly understood, but rather recognises that the material or 'natural' and the social and cultural aspects of phenomena are intertwined and co-dependant, and cannot be meaningfully separated (Lupton, 2000). The decision as to what constitutes health and disease, does not simply flow from scientific data but is a process of judgement which reflects the influence of broader values, norms, and goals of society (Rosenberg, 1992).

Medicalisation built upon the Parsonian model of medicine as a force for social control, but also challenged it as being overly supportive of the status quo of medical dominance, and drew upon more overtly disparaging accounts such as Illich's (1976) characterisation of scientific medicine as iatrogenic and inefficient (Lupton, 1997). Constructionism lent itself to this critical analysis of medical power because it avoided taking the pronouncements of scientific medicine as objective, unproblematic, representations of physical reality, but rather sought to explore how the labelling and understanding of particular phenomena and behaviours as diseases brought them under medical authority.

> Medicine analyses the failings of the human body and translates them into a series of distinct medical or biological problems, then looks for a technical solution for each problem (Lowy, 1996 p81).

More recent work in the sociology of scientific knowledge (SSK) and science and technology studies (STS) has also sought to show how the practical and conceptual processes of producing scientific knowledge and technological artefacts- the means by which classifications are effected- are themselves influenced and shaped by social factors from localised norms of professional practice to more general cultural values (Mackenzie & Wajcman, 1999; Pinch & Bijker, 1987).

While medicalisation went on to assume a prominent position in the sociology of health and illness during the 1970s and 1980s, the field was further informed by the increased availability of English translations of the work of Michel Foucault (Lupton, 1995; Turner, 1997). Like Parsons and the proponents of medicalisation (a term which Foucault also employed) Foucault saw medicine as part of a system of social control, locating the source of medicine's authority in its ability to categorise human beings in ways which affected their social identity. What is particularly relevant about this body of work is the way Foucault drew attention to the inextricable links between power relations, discourse, knowledge and what is accepted as 'truth' in society (Lupton, 2000). Where orthodox medicalisation theory was

concerned with the expansion of medical authority at its boundaries, Foucault theorised the links between medicine's intrinsic mechanism of operation and the social conditions that favoured it. Specifically, Foucault proposed a convergence between the anatomical model of the body, arising in medicine in the late eighteenth century and the currents- both socio-cultural and material of modernity such as a desire for order and control, and the increasing urban populations of many western countries, which led to a 'take off' in the importance of medicine as a social institution (1973). This perspective has been enormously influential in modern sociology of health and illness and informs much contemporary work, although it also has its limitations (Turner, 1997; Fox 1998).

The ensuing section will draw on the constructionist, Foucauldian standpoint and its modern interpretations, to trace the rise of modern medicine from the nineteenth century to its present dominance, accounting for its changing social role at different stages along the way. This is important because it will provide a more elaborate account of how medicine works as a social institution that can be applied to the study of contemporary applications of growth hormone, but also because the historical aspect of the account is relevant to studying the development of hGH as a medicine. Two important developments of this time- the emergence of scientific medicine as the dominant profession in the field of healing, and a governmental concern not only with public health but especially child health,

occurred during this period and were subject to the socio-cultural influences of the era. Both of these phenomena have come to impact on the use and development of growth hormone. The study of hormones arose as a discipline at the end of the nineteenth century; exactly the time when medicine was struggling to become scientific. Endocrinology was directly affected by, and a key ground for, these struggles. This was particularly noticeable in regards to the selection of which applications of hormones were suitable for scientific consideration and which were not- anti-ageing medicine eventually ending up in the latter category despite significant early enthusiasm. The nineteenth century practices of child health and paediatrics provided the genesis for networks and rationales for medical monitoring and intervention in childhood growth that would later be used to bring short stature to medical attention as a potential indication for hormone therapy. For these reasons, a social account of the rise of medicine is relevant because it will inform much of my subsequent analysis of hGH.

The Birth of Modern Medicine: A Scientific Medicine, a Social Medicine

Medicine, as described above, exists to serve the social function of dealing with ill and diseased bodies, and has done so for a considerable part of human history. However it is a mistake to over-emphasise the continuity in this account: medicine has not followed a systematic process of enlightenment, arriving at its present

conjunction by a gradual elucidation of the truth while progressively discarding incorrect theories. Rather, medicine has existed in a series of different, discontinuous forms each with its own epistemological regime and related practices. Following Ackerknecht's (1967) categorisation, Armstrong has described the form of medicine preceding the eighteenth century as "library medicine" 'in which the classical learning of the physician seemed more importance than any specific knowledge of illness' (Armstrong, 1995 p393). During the eighteenth century this was supplanted by a medicine displaying greater concern with managing and classifying illnesses, especially through the work of English doctor Thomas Sydenham, who promoted the idea of diseases as distinct entities recognisable by common patterns of symptoms (Reiser, 1993). Finally at the end of the eighteenth century and primarily in Paris, a new form of medicine arose, based on the anatomical model of the body and located in the hospital[7] (Armstrong, 1995; Foucault, 1973). Foucault called this form of medicine the medicine of 'The Clinic'; it has also been called biomedicine, western medicine and scientific medicine (Armstrong, 1995).

This is not to suggest that medicine suddenly 'became' scientific at the beginning of nineteenth century or at some other arbitrary point. Medicine and science have been associated with one another at least since the scientific revolutions of the sixteenth and seventeenth century and very few 'orthodox' physicians of the early modern era

would have described themselves as unscientific or espoused explicitly unscientific grounds for their treatments (Bynum, 1994). There was, however, competition from 'irregular' and folk healers from outside orthodox medicine, and some considerable separation between the scientific investigation of the body in the laboratory and the daily clinical practice of most doctors within orthodox medicine (Bynum, 1994; Curth, 2006; King, 2006). Prior to the advent of hospital medicine, illnesses were seen as idiosyncratic phenomena, understood in terms of the symptoms reported by the patient- thus a complaint of stomach pain by the patient meant that stomach pain was the disease to be treated by the doctor and therapeutic efforts were often individually tailored (Armstrong, 2006; King, 2006;Reiser, 1993). Given that the discourse of science relies for much of its authority on the assumption that the knowledge it produces is objective, universal and acultural, this reliance on patients to provide personal (and thus subjective) accounts of their symptoms and illness was seen as an obstacle to the progress of scientific medicine (Lupton, 2000, Reiser, 1993).

The introduction in the nineteenth century of a range of technologies for physical diagnosis- first the stethoscope and ophthalmoscope, and later x-rays and laboratory tests- removed the physician's dependence on the patient's account in making diagnostic judgements (Ibid.). Instrumental measurement is so central to

modern biomedicine that Foucault's asserted that before these developments medicine was;

> [N]ot a true science, but rather a rhapsody of ill-founded, poorly established and unverified sets of knowledge (Foucault, [1974] 2004 p9).

Through its instrumental techniques and anatomical understanding of the body, the medicine of the clinic, which Foucault termed the 'medical gaze', assessed the body of the patient, the physician detecting signs, rather than the patient's self-reported symptoms, of illness and using these to diagnose the underlying cause of the disease, which was usually an internal lesion in the tissues of the body (Armstrong, 1995). In this way the physician could now 'read' the body to produce knowledge about disease which could not be determined by the patient alone- it required the application of specialised, scientific techniques and it was this ability to produce 'inside information' which gave practitioners of hospital medicine their authority (Chrysanthou, 2002; Foucault, 1973). The ability of scientific medicine to produce seemingly objective categorisations of disease resonated with the modern ethos of reason, rationality and post-enlightenment progress, and made science the core around which the professionalisation of the discipline could occur (Bynum, 1994; Nettleton, 1997).

> In effect, within a few years in the middle of the 19th century two new 'bodies' materialised, two new identities that were to form the bedrock of clinical encounters over the following centuries.

> It was the patient as anatomical body that entered medical practice – a site for the diagnosis of pathology and an object for observation and examination in the hospital bed. And it was the newly professionalised body of the physician that crystallised out of the mass of heterodox healers: a lifetime identity and vocation that constituted the new practitioner in the clinical setting (Armstrong, 2006 p870)

The announcement and success of Pasteur and Koch's germ theory of disease also gave support to the idea of diseases as specific entities with common features, and thus providing a basis for categorisation, existing outside the bodies of individual patients, and demonstrated the value of medicine grounded in a scientific knowledge base (Turner, 1995).

These changes in medicine and medical practice can be understood in the context of significant changes in the organisation of western society such as secularisation, rationalisation and the rise of bureaucratic states, industrialisation, a post-Enlightenment orientation towards progress, and the rise to prominence of scientific methods following the scientific revolutions of the sixteenth and seventeenth century (Bynum, 1994; Chrysanthou, 2002; Gruman, 1966). In particular, the desire for control and order is seen as a defining characteristic of modernity:

> One of the most dominant logics organising ways of thinking and acting in Western societies at the end of the twentieth

> century is that of control. Individuals constantly engage in activities in the quest for control over their lives…Nowhere is this desire for control more evident than in the ways in which people conceptualise embodiment, health, and illness (Lupton, 2000 p56-7).

Within this context the centrality and authority of medicine, understood as an agent of social control makes sense. Foucault described modern, western medicine as a 'social medicine' which, although it can act on individuals and individual (anatomical, physiological) bodies, does so with the chief aim of maintaining the health of society and which seeks to increasingly rationalise and standardise, rather then individualise, the human body (Foucault, 2003 b). In this way it is different to the previous forms of medicine which essentially took each patient's illness as an idiosyncratic property of that specific body and its (subjective) symptoms. For Foucault, modern medicine does more than standardise bodies into categories of health or types of disease, it simultaneously establishes the boundaries of what is normal and what is abnormal within (a) society; medicine does not simply sanction and control deviant social behaviour, it produces specific categories through which normalcy and deviancy are defined and understood (Brown & Webster, 2004; Foucault, 1973). Medicine does this by taking the body as an anatomical object to be monitored, measured, and divided into categories which that measurement creates: normality and an "other"

against which that normality is distinguished and judged (Foucault, 2003b).

By defining individuals' problems- for example as a result of hidden lesions within the body- and providing solutions for them, medicine exerts a moral authority which patients become subject to in a form of 'normative coercion', that is, they are directed to follow certain prescribed courses of action in order to become 'right', normal, and acceptable again (Turner, 1997). Medicine is thus, following Foucault's terminology, disciplinary, although this does not necessarily mean that it acts in an authoritarian or violent way. Rather it is a discourse which constitutes particular ways of portraying, treating, writing about, and thinking about bodies that creates new identities for people based around their bodily configurations (Hacking, 2006; Lupton, 2000). The power of medicine lies in the way individuals come to understand themselves in medical terms- adopting these new identities- and voluntarily subject themselves to its behavioural, moral, prescriptions (Turner, 1995; 1997). This internalisation of norms and judgements in order to guide ones own behaviour for the purpose of self-improvement and achieving happiness were termed by Foucault 'technologies of the self' (Foucault, 2003 a). The ordering, guiding ability of scientific medicine made it not only useful to those wishing to use science as a means to establish the dominance of physicians as the foremost providers of healthcare but also to the burgeoning interests of

modern states in controlling their populations. This second factor also needs to be included in an account of the formation of the modern medical landscape.

The Birth of Modern Medicine: Biopolitics and Public Health

The emergence in the eighteenth century of modern industrialised cities and large urban populations such as Paris and London provided new challenges for the government of these populations, which Foucault called biopolitics (Foucault, 2003 c). The concerns of biopolitics are quite literally, the problems of bodies dwelling in close proximity - such as disease, sanitation, birth and mortality rates, race, and lifespan. The earliest biopolitical issues were primarily the problems of environmental public health: such as poor water supply or disposal of corpses, but by the middle of the nineteenth century the focus had shifted to the health of the labouring classes and the poor:

> [T]here appeared in the nineteenth century –above all in England- a medicine that consisted mainly in a control of the health and the bodies of the needy classes, to make them more fit for labour and less dangerous to the wealthy classes' (Foucault, 2003b p336).

Accompanying the urbanisation and industrialisation of western society, a range of social changes including state-applied universal age markers for the beginning and end of school attendance, voting age and qualification for public pensions brought greater visibility (not

least in institutional terms) to the different elements of the lifecourse (Cole, 1992). Such techniques of social stratification allowed the development of medical classification systems detailing:

> [L]ists of illnesses that are more closely associated with the body at certain times during life – diseases of childhood and of the elderly, and the different diseases of men and women in 'mid life' (Brown and Webster, 2004 p4).

This in turn allowed the structuring of public health provision around these general categories. The idea of a standardised lifecourse provides a basis for models of 'normal' development and 'abnormal' variation, which can be used as the rationale for medical intervention (Vincent, 2006). Towards the end of the nineteenth century new medical specialities such as paediatrics and geriatrics emerged, dedicated to the health of such groups, defined by age range and socio-cultural status, as children or the elderly (Haggerty, 1997; Mahnke, 2000; Morley, 2004).

The processes of medical categorisation were amply aided by that other great tool of public health- statistics. Two nineteenth century pioneers of public health, Louis-Rene Villermé and Adolphe Quetelet had already begun the application of statistical means to study the effects of living conditions on health, primarily assessed through measurement of physical characteristics including height and weight (Tanner, 1981). Quetelet is chiefly renowned for adapting the normal distribution curve of Laplace and Gauss[8] to describe the distribution

of such characteristics in a population in terms of deviation from a central, average (normal) set of values (Hacking, 2006; Tanner, 1981). Francis Galton, eugenicist, anthropologist and statistician among other occupations, introduced further statistical refinements to the analysis of populations, including the concepts of standard deviation which describes the extent of difference from the average, and the correlation co-efficient which allows normally distributed characteristics to be to other quantitatively measured traits (Hacking, 2006; Hall, 2006). Statistical calculations could link population segments classified by age, socio-economic status, or behaviours not only to the incidence of illness, but to the *risk* of illness and the *potential* of individuals in those categories to pose a threat to health (Hacking, 2006, Nettleton, 1997).

> Disease became constituted in the social body rather than the individual body, and deviant types were identified as needful of control for the sake of the health of the whole population (Lupton, 2003 p31).

It is no coincidence that this era saw the rise of accounting, actuarial attempts at rational calculation of risk and the insurance industry (Brown & Webster, 2004).

Modern forms of government presuppose that the object of their government- the population- is comprised of a certain type of 'selves' (the subjects of their government), and increasingly this type of self is understood and framed in the discourses of the human sciences

especially psychology and medicine (Nettleton, 1997). Scientific medicine can produce selves understood as standardised, ordered anatomical bodies, and whose own understanding internalises this self-concept and is willing to act upon its dictates. Thus the requirements of government form a link between the need for control at the individual and collective levels and the utility of medicine at both. The rise of modern government (bureaucratic, rationalising etc) and its concern with bodies is thus one of those social changes linked to the development and rise of modern medicine. The need for governments to control, guide and regulate risky elements makes the body a site for social contests and the application of power (Brown & Webster, 2004; Lupton, 2003). The ability of medicine to exert a voluntary, coercive control over bodies makes it a useful biopolitical tool:

> '[T]he body is a biopolitical reality, medicine is a biopolitical strategy' (Foucault, 2003b p321).

At the same time, the duty of modern governments to secure the economic and social health and wellbeing of its subjects can also be enacted through the provision and supply of medicine and healthcare (Nettleton, 1997). Ideas of control in modernity are also linked to ideas of progress[9] and meliorism- that civilisation can and should be guided in a positive and desirable direction, and this spirit underlay much of the public health reforms of this period (Gruman, 1966). An obvious example, would be the deprivations and sickness 'revealed' by the statistical techniques of military records and factory surveys in

the eighteenth and nineteenth centuries and the drives to increase the health of the urban, labouring population (and especially working children) that resulted (Tanner, 1981). These actions served to provide assistance to the poor that would otherwise be beyond their means, while at the same time allowing control of these classes which would protect the wealthy and privileged from disease or social unrest (Foucault, 2003b).

The utility of medicine for biopolitical regulation of bodies has led to it becoming institutionalised within the apparatus of state, which oversees matters of its regulation, administration and often financing (Bodewitz, Buurma & DeVries, 1987; Brown & Webster, 2004).

> The medical gaze provides an organising principle for looking at the problem of sickness at the level of the individual body, the growth of institutional regulation and control at the level of the clinic and the hospital and finally the emergence of biopolitics of populations (Turner, 1995 p219).

This in turn has aided the consolidation of medical authority, practices and forms of knowledge over both individual bodies and the social body that typifies the modern age:

> With a base in the hospital and in all these social controls, medicine was able to gain momentum, and clinical medicine acquired totally new dimensions (Foucault, [1974] 2004 p14).

From the Health Services and the Health Office established in Britain in the 1870s through the milk depots for infant care of the early twentieth century, as the state gradually assumed greater responsibility for health and welfare so it required greater monitoring, surveillance and record keeping (Foucault, 2003 b; Lupton, 2003). These in turn increase the dispersion of the concepts and understandings of scientific medicine throughout society- medicine 'escapes' the clinic in the sense that health is increasingly a matter for everyday concern rather than something only applied to those who have already been hospitalised (Armstrong, 1995). The pervasiveness of scientific medicine is such that by the end of the twentieth century, at least in western society, the anatomical, biological (and increasingly genetic) way of conceptualising the body and its diseases was by far the most dominant understanding of these phenomena, to the extent that it was barely considered a serious option to conceive of an alternative perspective (Lupton, 2003).

The Era of Medicalisation and Enhancement

Having produced the above account of the rise of modern medicine in terms linking the nature of the new, scientific, medicine and the social circumstances which favoured it, this section will deal with the further development of medicine through the greater part of the twentieth century to the present. In particular, attention will be paid to changes in medicine's social role in response to its increased

economic status, changing political ideologies and the rise of consumer society. The trajectory of modern medicine will provide a frame to conceptualise how 'enhancement' technologies might be understood as manifestations of medicine and health as contemporary socio-cultural entities.

The period after World War II has been described as a second 'take off' in medicine (Armstrong, 1995; Clarke et al, 2003). Clarke et al (2003) characterise the first phase, begun in the nineteenth century (as described above), as defined by the professionalisation, institutionalisation and specialisation of scientific medicine, along with the accompanying technological developments – antibiotics, x-rays etc- that shaped the medical practice of the era. However, post-war, the emphasis has shifted to the expansion of medical surveillance from its base in the hospital bringing ever more of the population under its gaze through public and community health initiatives, health promotion, education programmes, and socio-medical surveys (Armstrong, 2006). This growth was accompanied by an increased economic and cultural import accorded to medicine:

> [A]fter World War II, medicine, as a politico-economic institutional sector, and a socio-cultural "good", grew dramatically in the United States through major investments both private (industry and foundations) and public (e.g. the National Institutes of Health [NIH], Medicare, Medicaid) (Clarke et al, 2003 p163).

Foucault identified a similar shift in European medicine, taking the announcement of the Beveridge Plan, which set up the British National Health Service, in 1942 as a symbolic reference point (Foucault, [1974] 2004). He argued that prior to this, state control of health had mainly consisted of preserving the strength of the workforce (and the pool of potential military recruitment), but that the post-war era represented a qualitative change in biopolitical orientation of governments and in the social role of medicine. The state now guaranteed health not for the benefit of the population but as an entitlement of individual subjects, and, at the same time health then entered the field of macroeconomics becoming a major source of state expenditure to achieve this goal.

In the later part of the twentieth century, health and medicine have become increasingly central to western society as more aspects of human life have come to be understood as medical problems and come under the authority of medical practitioners. This growing dominance of medicine as a force for ordering and regulating society has not been without critical attention and resistance. The medicalisation critique drew upon, and in some ways was a component of, the wider social and cultural upheaval of the 1960s and 1970s, where a variety of movements from civil rights to feminism challenged established authority, of which the institutions of medicine formed a significant part (Lupton, 1997; Rothman, 1991; Stevens, 2000). These circumstances that (as detailed in the

introductory chapter) led to the formation of the discipline of bioethics, also provoked the sociological response of medicalisation theory. Both discourses shared a certain anti-authoritarian view of the medical establishment[10] but where bioethics, in the main, focused on formulating ethical rules to regulate the conduct of doctors and scientists in areas such as human subjects research or 'end-of-life' care decisions, medicalisation examined *how* medical practices, from intra-professional organisation to 'claims making' activities in medical journals could bring ever more areas of social life under medical dominion (Conrad, 1992). In part, medicalisation took as its core the study of what Conrad (1975; 1992) has termed the 'definitional issue':

> Medicalisation consists of defining a problem in medical terms, using medical language to describe a problem, adopting a medical framework to understand a problem, or using a medical intervention to treat it' (Conrad, 1992 p211).

This is reflected in the early case studies of medicalisation, which dealt with the way contemporary issues, notably alcoholism, hyperactivity (later Attention Deficit Hyperactivity Disorder/ ADHD), post-traumatic stress disorder (PTSD), menopause and child abuse, often seen as social or moral problems, were being (re)described as medical, usually biological, phenomena (Conrad, 2005). The medicalisation authors generally took a negative view of this process; an anti-authority stance being reflected in criticism of the power relations displayed in the traditional doctor-patient relationship, where

the medical definition of problems was seen to be enforced upon individuals[11] and society, but also from a socio-political standpoint, arguing that medical, biological definitions acted to individualise and depoliticise what might otherwise be seen as collective social problems (Conrad, 1992; Lupton, 1997).

Although the definitional issue takes preference in medicalisation studies, the influence of broader socio-cultural factors in promoting and driving the medicalisation process are also pertinent. Contemporary accounts propose an intensification in medicalisation fuelled by the convergence and increase of three factors: consumerism in healthcare, the cultural importance of medicine and health, and the dominance of biomedicine as a key component of modern self-identities. In the modern (western) era, the role of government is no longer to guide its subjects to spiritual salvation, but to provide 'worldly goods such as health, well-being and security' (Nettleton, 1997 p211). The project of neo-liberal medicine, especially predominant in the US, is a product of the political ideology which places supply of healthcare and medical services within the 'for profit' corporate sphere and encourages a consumer-service provider relationship rather than a doctor-patient one:

> This commercial agenda makes it increasingly commonsensical to understand medical services as *products*. Health maintenance organisations refer to the "product lines" that they sell, and that language diffuses into the way people think of

> delivering and receiving services (Frank, 2006 p70 emphasis in original).

As healthcare seemingly becomes more corporatized and privatised, healthcare services- from health insurance plans to medical consultations and screenings, pharmaceuticals, and hospital care become commercial products to be competitively advertised and sold (Conrad, 2005). Concurrently, individuals come to act more like consumers of healthcare rather than patients or state-entitled recipients (Conrad, 2005; Greenhalgh & Wessely, 2004).

Recent trends in medical science such as genetics, genomics and brain-imaging techniques propose biological origins for ever more aspects of human life including behaviours, personality traits and even emotions (Clarke et al, 2003; Novas & Rose, 2000; Rose, 2004). At the same time, information about health available to the population at large has never been more accessible or provided in such quantity, through television, magazines, public health initiatives, direct-to-consumer advertising of pharmaceuticals and the internet (Blenkinsopp & Bradley, 1996; Henwood, Wyatt, Hart & Smith, 2003; Woloshin, Schwartz, Tremmel & Welch, 2001). As biomedical concepts become an ever-greater component of western culture so more aspects of life become understood as having a biological component:

> Biomedicine has become a potent lens through which we culturally interpret, understand, and seek to transform bodies and lives (Clarke et al, 2003 p163).

More broadly, other authors, often following a Foucauldian perspective, have highlighted the importance of the physical body, most commonly understood through these discourses and practices of scientific medicine, as a primary locus for individual identity and action in contemporary western society (Chrysanthou, 2002; Lupton, 2003; Novas & Rose, 2000; Rose, 2004; Turner, 1992). In particular more aspects of social life, especially its problems, become understood as located in the body and thus requiring action at the site of the body to ameliorate them.

In a culture where the body is the primary site of individual identity, and that body is understood primarily in biomedical terms, people are led to seek self-control and self actualisation through techniques in accord with that understanding – i.e. through medicine, and if this has become a commercial service, then it must be worked for and bought like other products in a capitalist system. As medicalisation spreads into ever increasing aspects of human life, it produces at its expanding edges, those phenomena classified by bioethics as enhancements and lifestyle medication. For Gruman (1966) any community based on science, technology and industry must continue to follow an agenda of progress and meliorism or it will face collapse. The energy of modernity is thus always towards ‘more’ and ‘the

cultural impetus is to expand what it is legitimate to crave' (Frank, 2006 p70). Ultimately modern medicine, or the economic-medical-industrial complex;

> [R]aises the illusory prospect that people are entitled to a life not just free of disease, but also free of symptoms, with the social, psychological and physical all in harmony (Greenhalgh & Wessely, 2004 p201-2).

The pervasiveness of self-surveillance and a discourse of risk where absolute health (zero risk) can never be attained mean that for the 'worried well' any aspect of the self which is less than optimal can and will be brought into visibility as a biomedical problem (Armstrong, 1995; Clarke et al, 2003; Lupton, 2003). In this way the socially sub-optimal situations where an individual is unable to concentrate sufficiently to take an exam or drive long distance, where a child is shorter than its peers and perceived as less sociable or less likely to succeed, or obese, or poorly behaved, or when the signs of ageing begin to show in physical appearance and reduced capacity all become occasions for medical intervention to restore the state which is desired. The techniques of biomedical enhancement are thus attempts restoration, or at least progress, towards bodily, and so social, success and affirmation.

Limitations in this Framing and the Relevance of STS Theory

While the previous section set out an account of how so-called enhancement uses of medicine can be understood in the context of

modern medicine as a socio-cultural phenomenon, there are a number of weaknesses in its construction that make it unsuitable to serve as the entire analytical approach to the study of human Growth Hormone. One set of difficulties arises from the conflicts and disagreements inherent in the different component bodies of work. Some authors have described the contemporary situation as a post-modern one where individuals use medicine to transform their (bodily) selves in unique and personal ways representing a fragmentation of order and control (Clarke et al, 2003: Chrysanthou, 2002). This resonates with some 'technoluxe' cosmetic surgical procedures such as the surgical reshaping of feet to make them a better fit for designer shoes offered by some New York podiatrists (Frank, 2006). For others, e.g. Lupton (2000), however, the project remains a modern one of control and a drive towards normalisation. Evidently normalising procedures such as hormone and surgical interventions to assign particular genders to intersexed children or surgery for cleft palates seem more in concert with the latter model (Morris, 2006; Aspinall, 2006). Conrad (1992) has also stated that the definitional issue remains at the core of medicalisation and health promotion and the 'new morality' of personal responsibility for health and lifestyle are related but secondary phenomena. By contrast others have placed the expansion of health as a cultural good and goal of self-actualisation as a major, even central, element of the contemporary situation (Clarke et al, 2003; Crawford, 1980; Lupton, 2000). The increasingly individual-orientated nature of the

consumptionist model also seems to undermine some aspects of the classical Foucauldian model of a social medicine in the service of a controlling state, although more recent syntheses such as Rose (1996) have argued that self-government can be aligned with the objectives and concerns of (neoliberal) political objectives.

In some respects these conflicting interpretations reflect a paradox in the current medical system. By acting as individualist consumers people are behaving in the way expected by modern governmental models of the self-as-subject but at the same time, with health remaining a major component of state spending, the interests of states have shifted from issues of access to healthcare to issues of cost containment (Mechanic, 2002). Many aspects of the modern state medical apparatus- healthcare technology assessment (HTA), evidence based practice, bodies like the UK's National Institute for Health and Clinical Excellence, and even managed care organisations- are actually designed to reduce medical costs and restrict the amount of medicines consumed. US-style Health Maintenance Organisations (HMO's) can further medicalisation, for example of psychiatric problems, by covering the costs of drug therapies, but not alternative modes of treatment, but they also place restrictions on access to medicine through their coverage decisions (Conrad, 2005).

There is other evidence to suggest that the case for medical consumerism is overstated. Lupton (1995) has found that while individuals in an Australian survey did exhibit some consumerist-style behaviour in preferring to have a choice of doctor, they did not, in general, position themselves as medical consumers, especially when faced with an episode of relatively serious disease or illness. Mechanic (2002) also found that individuals in the US, while adopting a more consumerist position, thought of healthcare mainly in terms of the quality of personal physicians and access to specialists while they had 'limited comprehension about even the most basic differences among health care plans' (p461). Thus there are a number of limitations and sites of resistance to the pharmaceutical industry-consumer cycle of medicalisation outlined above. Individuals may choose not to act as consumers, or ignore the recommended lifestyle options proposed by public health promotions, financial restrictions on doctors or health insurance plans may restrict individuals' access to medicine, or in the case of the poor and uninsured, disenfranchise them almost entirely (Clarke et al, 2003; Hedgecoe, 2005). Greenhalgh and Wessely (2004) also contend that individuals who do exhibit consumerist, healthist behaviour are also likely to consider alternative practitioners and remedies, potentially removing them from the realm of orthodox medicine and the pharmaceutical industry. Rather than focusing on overt consumerist behaviour as a driving force of medicalisation, the appropriate analytic goal would appear to be an understanding of how medical

need is constructed to incorporate previously non-medical problems such as short stature or social anxiety.

There are also conceptual weaknesses in the current formulation of the 'enhancement as medicalisation' model. Medicalisation has been criticised for a tendency to paint an overly 'black and white' representation of western medicine by dwelling exclusively on its negative aspects (Broom & Woodward, 1996; Fox, 1977; Lupton, 1997; Williams, 2001). In regards to the 'definitional issue' it can appear as if physicians, or latterly pharmaceutical companies, act solely in the interests of furthering their own authority and status and ignores the fact that individuals can and do benefit from medical care (Broom & Woodward, 1996). The power to define also appears to reside in the hands of particular groups, such as pharmaceutical manufacturers and doctors, which is problematic on two counts. Firstly, it tends to portray these social groups as monolithic entities, acting with impunity in wielding the power to define illness and disease thus producing a rather deterministic account (Williams, 2001). Secondly, there is insufficient explanation of the mechanism by which definition occurs and is disseminated to create new social divisions, understandings, identities etc.

The resolution of these issues lies in an examination of medical technologies. In modern, scientific medicine, technologies-pharmaceuticals, imaging devices, diagnostic implements, quality-of-

life questionnaires and more- suffuse all levels of medical practice. Modern medicine is increasingly, thoroughly, a technological medicine; technologies not only embody scientific knowledge they are inherently involved in the production of medical knowledge from experimental apparatus in the laboratory to diagnostic devices in the clinic (Waldby, 2000; Will, 2005). A more detailed study of the technology of medicine then, is required to address the analytic gaps in the enhancement model: What role do measuring technologies play in making previously non-medical bodily attributes visible as medical problems? How do pharmaceuticals convey ideas of illness and medical need about the conditions being treated? And how are these understandings shaped by those involved in producing and applying the technologies- regulators, industrialists, doctors and patients? Given the utility of Science and Technology Studies theory to address these issues of technological construction, a more complete account of how STS can be applied to medical technologies and particularly those areas relevant to the study of growth hormone will be presented in the next section.

Medical technologies in an STS Perspective

Biomedicine, in common with other scientific disciplines, has been deeply intertwined with the creation and use of technologies to facilitate its major functions: detecting, diagnosing, treating and preventing disease and disorder in the body (MacKenzie & Wajcman, 1999; Waldby, 2000). A useful critical perspective on this aspect of

modern techno-medicine can be provided by the interdisciplinary field of science and technology studies (STS). There are a number of different approaches within STS including the social construction of technology (SCOT) exemplified by the work of Bijker & Pinch, Hughes' large-scale systems approach to technological development and actor-network theory (ANT) formulated primarily by Callon, Latour and Law (Bijker, Pinch & Hughes, 1987; Law & Hassard, 1999). What unites these approaches is a shared commitment to moving away from a simple, deterministic view of how technology is created and deployed in society (Martin, 1999). The standard model posits technology as 'applied science' resulting in the creation of an object or procedure in a simple linear path where:

> '[S]cientists discover facts about reality, and technologists apply these facts to produce useful things (MacKenzie & Wajcman, 1999 p6).

STS adopts a constructionist approach where technologies can be understood as complex entities incorporating physical objects or artefacts, processes and (practical) knowledge which embody the human activity that creates them and which develop through a process of interactions between different social groups (Bell, 1986; Mackenzie & Wajcman, 1999).

Two aspects of the STS outlook are particularly relevant to the study of medical technologies being attempted here. The first of these is the co-construction of medical technologies and medical knowledge:

If, as described above medical knowledge takes the body as an object to be measured and categorised as normal or abnormal, it is through technologies that much of this measurement occurs (Timmermans & Berg, 2003). Early technological innovations such as the stethoscope, the scalpel and, later, x-rays were central to the project of visualising the body as a standardised anatomical entity (Lowy, 1996). Biomedicine has, if anything, become more bound up with technological means in the present (Clarke et al, 2003). More recent understandings of the genetic body or the biochemical brain are only possible through the use of novel technologies such as genetic tests or MRI scans. This is not to suggest that technologies determine or create medical practice- the stethoscope or scalpel did not force recognition of the anatomical model of the body upon practitioners of the nineteenth century- but nor are technologies merely passive facilitators of medical agendas and knowledges. Medical technologies and knowledge are shaped by, and also shape in return, the perspectives of different groups involved in healthcare as new ideas or technologies spread out from their point of origin in an attempt to become accepted as part of medical practice. This forms the second important aspect of an STS perspective. The intricate networks of healthcare actors include hospitals, patients (and by extension the public), doctors, laboratories, governments, regulatory agencies, pharmaceutical manufacturers, and healthcare funders as well as the organisations and institutions of different medical disciplines and specialities. As techno-knowledge is

disseminated through this network, its acceptance or rejection can depend, not merely on its content but on how compatible it is, or how it can be shaped (translated) to suit, the interests of the different parties involved (Koch & Stemmerding, 1994). Of particular relevance to the story of growth hormone in this respect are the translations between laboratory and clinical practice, at the junction of state/ regulatory approval, and especially the interface of doctor-patient encounters.

The Social Shaping of Medical Technologies

A specific analytic gap identified in the model of enhancement technologies produced so far was a means of conceptualising how disease categories are constructed and how social entities come to be understood in medical terms. From an STS perspective, science and technology are systems of knowledge production which are not only interdependent, but co-related to the extent that it is difficult to clearly delineate one from the other (Brown & Webster, 2004). That is, medical technologies are one of the primary means by which scientific knowledge is produced and scientific claims are made, and hence provide a means to address the social construction of medical categories. At the same time medical technologies also embody scientific concepts and so provide a means by which these concepts can be transmitted and disseminated- for example the use of antibiotics disseminated knowledge of the germ theory of disease,

not only among scientists and doctors but also among state officials and the public (Bynum, 1994; Rosenberg, 1992).

Since scientific knowledge and technology are co-produced it is proper to consider the generation of both facts and artefacts in similar terms. SCOT in particular draws upon previous work in the sociology of scientific knowledge which operationalises Foucault's injunction not to take systems of knowledge at face value , by arguing that scientific knowledge both 'true' and 'false' does not arise directly from human rationality but rather is shaped by material, cognitive and social input (Bijker & Pinch, 1987; MacKenzie & Wajcman, 1999). The process of social shaping can occur in two main ways; Firstly, observations made by scientists are rarely value free; Lowy (1996) and Oudshoorn (1994) have drawn upon Ludwig Fleck's theory of pre-scientific ideas to explore the way in which existing cultural values and concepts can influence the interpretation of experimental data and resulting scientific tenets while Callon (1987) has depicted the way in which engineers must first create a conception of the particular social universe into which a proposed invention will be deployed. Biomedical science constructs bodies, diseases and interventions (medicines, devices) through the practices of the laboratory research and clinical experimentation but, as Rosenberg observes:

> Explaining sickness is too significant –socially and emotionally- for it to be a value-free enterprise (1992, pxiv).

The language used to frame models of the body and its diseases is not neutral but invested with the socio-historical and cultural context in which it is developed (Oudshoorn, 1994). Both laboratory research and clinical experimentation are social processes where the production of new knowledge about bodies and disease is shaped by material constraints, institutional settings, academic background and prior cognitive commitments, political influences (including public policy decisions about health), existing cultural ideas, local factors and wider developments in healthcare and industry (Lowy, 1996; Rosenberg 1992). This process is rendered invisible because science, perhaps more than technology,[12] stakes its authority on the claim that the facts it produces are a direct mirror of reality which could not be otherwise, by hiding and denying the social contexts of its generation (Oudshoorn, 1994).

As well as external values and ideas, there is also a significant influence exerted by existing organisational and technical arrangements. Hughes' theories of large technical systems has highlighted the fact that technologies often develop within existing socio-technical regimes where they do not form in isolation but as parts of an integrated system (MacKenzie & Wajcman, 1999; Brown & Webster, 2004). Will (2005) observes that technological devices including experimental apparatus and techniques for measuring or producing images are used to create scientific data from observations, and that these devices are themselves the products of

previous, stabilised innovations in techno-knowledge. In medicine, one critical realm where technologies are heavily interdependent on other existing technologies is diagnosis/disease construction. Diagnoses, and thus technologies of measurement, play an important role in producing and deploying disease concepts, with all the associated implications for patient identities.

> The diagnostic technique does not simply reflect the meaning of illness in a patient's biography but actively constitutes those existential meanings (Timmermans & Berg, 2003 p105-6).

Measuring technologies embody particular conceptions of what parameters define a disease and thus can strongly influence both what sort of remedial technology, such as a pharmaceutical, should be applied and how the impact of that intervention should be understood and followed (Oudshoorn, 1994; Timmermans & Berg, 2003). Diagnostic and therapeutic technologies are thus closely interdependent. MacKenzie & Wajcman (1999) have posited that there are parallels between Hughes' approach and Kuhn's theory of scientific paradigms, in the first sense of a paradigm as an exemplar that stands for:

> [A] particular scientific problem-solution that is accepted as successful and which becomes the basis for future work (MacKenzie & Wajcman 1999 p9).

The technological equivalent of such an exemplar would be a particular technical achievement which acts as a model for

subsequent development work. In medical terms once a particular model of a disease-therapy (problem-solution) such as vaccination for infectious diseases, has gained acceptance other interventions or techniques which appear to embody or follow the same logic will be more readily accepted than a development which disrupts existing ideology. This process of acceptance- the spread of new medical knowledge and technologies is also a key part of the shaping process.

Networks of Health

The non-linear process of development emphasised by STS holds that a fact or artefact has the potential to exist in a variety of different ways and it is the influence of the relevant social groups which eventually shapes and selects a particular form to be stabilised (Bijker & Pinch, 1987).

> Scientific procedures and certified knowledge do not emanate from a social vacuum; they, too, are outcomes of social processes of acceptance (Bodewitz, Buurma & DeVries, 1987 p258).

Acceptance and stabilisation as a 'scientific fact' or a new technology occurs when there is a consensus amongst the interested social groups that both the problem and the solution have been constructed in ways which are comprehensible and satisfactory to them (Bodewitz, Buurma & DeVries, 1987; Bijker & Pinch, 1987). In order to thrive, new facts and artefacts must leave their site of construction

and spread out through the broader networks of medical practice. According to Lawrence (1992) this process of translation across professional and disciplinary boundaries and between heterogeneous professional groups is the key to understanding the growth of modern medicine. This also provides an account of knowledge construction more in keeping with Foucauldian models of power. Rather than a deterministic interpretation where power- for example the 'definitional' power to describe social issues in medical terms- is held by a particular social group such as physicians or the pharmaceutical industry, new definitions, in order to achieve acceptance, must spread out through a network of actors that interpret and shape the ideas according to their own interests and conceptions. Power, as Foucault argued, is thus held in the relations between different elements in networks and in mundane practices rather than by any social group (Lupton, 1997). Using the changing iterations of renal disease as a case study, Pietzman has illustrated how the process of translation involves ongoing shaping across domains and heterogeneous meanings given to a disease concept:

> [F]irst, individual physicians, then, the community of scientific medicine, and finally government or society, fashioned both conceptions of this disease and the labels given the conceptions (Pietzman, 1992 p5).

A conception of a disease or a new medical technology is shaped because different groups in a network interpret in their own epistemological terms- that is, they create different meanings for the

idea or technology within their own domain. The process of interpretation is the translation of techno-knowledge. Owing to the diverse range of actors in health networks, it is possible to conceive different types of social shaping occurring at different interactive boundaries in the network. Three boundaries which are relevant to the socio-historical study of growth hormone are the transition between the laboratory and the clinic, the convergence of state, industry and institutional medical interests in the regulation of drugs and ultimately at the doctor patient interface.

One such translational boundary, which has received a certain amount of STS interest, occurs where laboratory research meets clinical practice (Oudshoorn, 1994; Lowy, 1996; Martin & Rowley, In Press). In standard accounts this is a site where the flow of pure scientific knowledge is supposed to be transformed into improvements in practical applications. Sociological study, however, suggests that rather than an unproblematic flow of knowledge, laboratory-clinic interactions are a primary site of (often fraught) social negotiation between different actors over the content and shaping of medical techno-knowledge:

> The laboratory and the clinic belong to different social worlds, and have different institutional settings, different professional norms, and different forms of knowledge. Consequently, resulting knowledge has been shaped differently (Martin & Rowley IP p9).

Rosenberg (1992) suggests that physicians draw on existing cognitive resources particular to their discipline, position and generation when constructing disease explanations. Different professional groups- such as clinicians and researchers, tend to interact mainly with others within their particular ‘silo’ of professional culture and have difficulty relating knowledge across disciplinary boundaries (Currie, 2006). Deployment (and translation) can be bolstered if uptake of a new technology is beneficial to the authority or prestige of a particular medical specialism or sub-speciality (Lowy, 1996; Pietzman, 1992).

In order for a social system of healthcare provision to function successfully, patients have trust in the prescriptive actions of doctors and, in turn, doctors must have confidence in the medicines and medical devices they employ (Bodewitz, Buurma & DeVries, 1987). From an STS perspective, establishing trust is vital for mediating acceptance across social groups and the stabilisation of artefacts and facts within a network. In modern networks of health, the function of producing trust has been institutionalised primarily in the form of national and international regulatory regimes. Because the authority of modern medicine (and indeed many other areas of governance) is so closely bound up with its scientific character:

> The reception and use of medical technology are thus bound up with assessments of its scientific basis (Bodewitz, Buurma & DeVries, 1987 p246).

In most regulatory systems, assessment of drugs and other medical technologies is enacted through the scientific calculation of two key indices: efficacy and safety. Efficacy is generally assessed through the procedure of controlled clinical trials- by preference with patients split into two groups at random, one receiving a placebo the other receiving the medicine or procedure being tested, arranged so that neither the treating physicians nor the patients are aware of which group they are in until after the trial- designated the 'randomised controlled trial' or RCT. Safety is subject to somewhat more controversial production through animal testing data, human trials and post marketing surveillance of new technologies. Similar 'evidence-based' procedures also form part of the regulation of medicines supply through healthcare technology assessments (HTA) favoured in systems of healthcare which are 'free at the point of access' such as that in the UK[13] (Brown & Webster, 2004; Will, 2005).

There is room for localised social shaping at this junction too. The regulation of new medical technologies has historically emerged as a nexus where physicians, regulators and pharmaceutical companies collaborate and negotiate to decide which features of a disease should be measured to decide upon the efficacy of a treatment being tested, what severity and incidence of adverse effects are acceptable for particular socially stratified patient populations (e.g. the elderly or women) in relation to the disease being treated, which chemical

substances are legally recognised as drugs and to which disease entities they are formally attached (Bell, 1986). If regulatory activities embody a microcosm of the prevalent values and ideas in health networks, then the evaluation of medical technologies is less a matter of whether or not they meet government specifications and rather a measure of how well they reflect dominant ideas about medical practice (Bell, 1986; Bodewitz, Buurma & DeVries, 1987). Many of these contingent, value-laden decisions are obscured by the presentation of scientific evidence as the basis of the decision making[14]:

> The rhetoric of the standard empiricist view of science presents itself as particularly suited for this purpose. Scientific rationality promises an Archimedean point outside the social world, from which the acceptability, and hence survival, of technological artefacts can be decided (Bodewitz, Buurma & DeVries, 1987 p258).

Where public concerns, especially over safety or ethical aspects of a new medical technology cannot be assuaged by regulatory oversight, the work of institutionalised bioethics can be seen as offering a second bastion of acceptance mediation. This follows Evans (2003) and Stevens (2000) argument (See Chapter 1) that the technology-wary stance of early bioethics was ultimately eroded by the need to co-operate with medicine, at least to an extent, to ensure institutional survival. In this model bioethics accepts technologies as objective, value-neutral products of science, ignoring ‘the interconnectedness

between science, society, and the technocratic megamachine' (Stevens, 2000 p29) and instead designating 'ethical' and unethical' ways to utilise new technologies, finally sanctioning their deployment while allaying public fears about their use (Martin, unpublished manuscript).

Ultimately, all of the negotiations and contingent understandings around diseases, bodies and technologies impact, in some way, upon the doctor-patient relationship (Rosenberg, 1992). This is a crucial junction in the network of healthcare; it represents the site at which the social purpose of medicine was founded and where medicine fulfils its social role and interacts with individuals in a population. It is the location- whether in a hospital ward, the office of a general practitioner or specialist consultant, or other socially sanctioned space- where bodies are measured, diagnostic technologies applied, judgements of normality or abnormality made, classification by age, gender, and other socio-medical criteria employed, where risks are calculated, need assessed and the moral injunctions of remedial, therapeutic action prescribed. By the time medical technologies reach this junction they will have been shaped by the interests and concerns of laboratory researchers, state regulators, industrial manufacturers, insurers, and physicians. However, the social shaping of medical knowledge and technologies during their development does not end with a deterministic imposition of disease concepts on the patient. Although, as Rosenberg (1992)

notes, the specialised nature of medical knowledge and the authority conferred on its practitioners means that lay patients and the public are more likely to take diagnostic judgements on faith, disease categories must finally reflect both the experience of the disease by the physician and the patient, even though the contribution of the latter is often harder to detect in the discourses of organised medicine (Pietzman, 1992). The doctor-patient relation is also the primary site (despite the rise of online medical services) for the articulation of demand, need or desire for healthcare and medicine, including consumerist behaviour when it occurs.

In modern, scientific medicine knowledge and technology are closely bound together and constructed both by each other and by the socio-cultural environment in which they are developed and deployed. These processes of shaping need to be studied in order to understand how medicine functions in its social role. Thus informed, the constructionist model of medicine as a social practice, itself moulded by discourses of control, meliorism and economics, can properly analyse the phenomenon of biomedical enhancement and the specific case of human Growth Hormone.

Conclusion

The use of hGH by doctors, patients, manufacturers and others represents a site where not only individuals and institutions, but also different discourses and ideologies about identity, health, value and

society interact and coalesce around the notion of the physical, human body. Growth hormone as a chemical substance is detected in the human body through biochemical techniques and understood as a component of a 'hormonal model' of the body (Oudshoorn, 1994). The hormone is extracted from glands excised from the body or synthesised by biotechnological means to produce a chemical resembling the 'natural' substance. It then becomes a medical technology, a drug that can be applied to (other) bodies where it is intended to produce an effect understood in accordance with its role in the hormonal model of the body. Pharmaceutical medicines like growth hormone are 'vehicles of ideology': that is, they are not just material entities but embody ideas about the kind of bodies that they are interacting with, about the type of individual taking the medicine, about the disease or illness being targeted, about individual and social responsibility and entitlement, and about what is normal and desirable (Nichter & Vuckovitch, 1994). Pharmaceuticals form a link between ways of understanding the body and its diseases formed through scientific medicine and the actions of individuals who view their own bodies and illness in those terms. Growth hormone and the various diagnostic techniques which accompany it specify a particular way in which short stature (or ageing) is understood as a medical problem, and a problem that is amenable to redress through injecting the hormone into those affected bodies. This is the link between the different 'identities' of growth hormone; internal chemical secretion of the body, industrially produced medical technology, and

therapy. Thus the proper object of study is neither human growth hormone nor the medical understanding of short stature or ageing, but the interaction and mutual constitution of drug and disease(s).

In keeping with an STS approach, and in particular drawing on the critical drug histories of Goodman & Walsh (2001), Lowy (1996), Marks (2001) and Oudshoorn (1994), the project aims to trace a socio-historical account of the development of Human Growth hormone as a drug in order to produce a more informed description of its current applications. The chronicle of scientific medicine from the nineteenth century set out in this chapter also coincides with the period when the discipline of endocrinology- the study and medical employment of hormones- emerged, and when the statistical practices for assessment of children's growth, still in use today, were first set out. This is relevant to the project because, following the STS model, medical technologies do not simply appear fully formed to present ethical dilemmas about their use, but are shaped over the history of their creation, regulation and deployment into use. Hormone drugs are shaped by medical knowledge about how they act within the body (the 'hormonal model' of the body) and by networks of production, ideology and distribution which allow their deployment as therapies. Although growth hormone was not isolated and used until the middle of the twentieth century, the development of endocrinology involved the deployment of other successful hormone drugs- most notably insulin and the oestrogens. Part of this

investigation will deal with historical aspects pertinent to the development of growth hormone, beginning with the foundations of endocrinology where the expectations and conceptual ideas about hormones as drugs and the diseases they were intended to treat could act as exemplars- providing a model for the development of hormone therapies, including GH, that were to follow. This applies not only to concepts of disease but also to the networks of research, production and clinical application that were developed in the process of deploying those first successful hormone drugs. The understanding of the changing character of medicine over this period created through social theory will inform the discussion of data in both the relevant chapters and form a crucial part of this body of work.

The remainder of the project will address the development of growth hormone itself and its co-construction as therapy for the illnesses of short stature and, more recently, ageing. Analysis will consider the impact of changing networks of production and distribution, professional (disciplinary) interests, social and cultural values, and the material constraints imposed by the nature of GH itself. Recounting the drug's history and the expansion of its use (both in terms of overall patient population the number of different conditions for which it is a therapy) provides an opportunity to test the applicability of the accounts of medicalisation and consumerism described in this chapter- is there evidence of schismogenesis and/or

resistance to commercial imperatives? Taking a cue from Lowy (1996) the project will also incorporate the perspectives of contemporary endocrinologists on the applications of growth hormone. Investigation will focus on the construction of the rationale for therapy and patient need (the problem-solution model). Key questions include to what extent the therapy is portrayed as normalising or individualising, and how notions of risk[15], benefit and need are presented, utilised to make claims and disputed. The analysis will also address the effect of the historical development of growth hormone on current ideas about its appropriate use and the way in which past events are portrayed and interpreted by contemporary practitioners.

As the major indication for growth hormone, the therapy for various diagnostic categories of short stature will comprise the greater part of this study (forming the main topic of Chapters 5 and 6). The material presented in these chapters will attempt to reconstruct the use of hGH as an 'enhancement' to increase the height of 'normal' short children in terms of medicine and health viewed as socio-cultural phenomena which act through the co-construction of techno-knowledge to frame ideas about the human body and its ailments and act on them in these terms. Since treatment of short stature is a controversial topic within endocrinology the study also provides an opportunity to study not only how disease categories and medical need are constructed but how they are disputed by other physicians-

i.e. how medical justifications and limitations are construed. As well as providing a counterpart to the study of growth hormone as a treatment for short stature, the anti-ageing cause also offers a contrasting insight into the construction of diseases: the medical model of the hormonal body permits intervention but other values and considerations prevent ageing as yet from being viewed as a legitimate target for medical intervention. Through the application of the STS/social theory-informed model determined in this chapter, these case studies will elaborate specific instances of medical judgements being made as to what is appropriate practice and what is not, which are after all crucial to the distinction between 'enhancement' and 'therapy'. The subsequent chapter will describe how this theoretical model translates into a practical research approach and how the specifics of the case studies selected structure the investigative field. This chapter will also address the methodological implications of adopting a social constructionist with regards to interpreting and making claims from collected data.

Notes

[7] Although Hospitals had existed before this, Foucault maintained that they were not institutions of medicine but essentially places where the poor and destitute went to die (Foucault [1974], 2004).

[8] The normal curve was originally developed by Laplace and Gauss to describe errors of astronomical observations (Tanner, 1981).

[9] Indeed Gruman (1966) asserts that during the nineteenth century belief in progress was so commonplace that it was virtually taken to be a self-evident principle.

[10] An example of this stance in bioethics can be detected in a 1977 interview with Hastings Centre founder Dan Callahan who stated: 'Doctors want…to make all the choices. Well we're saying to them, no. There are some public interests at stake here and some general principles you have to abide by' (cited in Rothman, 1991 p209).

[11] Although there was recognition that in some instances, such as alcoholism, the main driving force for a medical definition of the problem was not doctors or other

medical personnel, but lay organisations formed to provide support for individuals experiencing social problems (in this case alcoholics). This produced a somewhat more nuanced account of medicalisation which could not simply adopt Illich's charge of medical imperialism as constituting the entirety of the problem (Conrad, 1992).

[12] Technologies after all generally claim to serve a social purpose, although the obvious practical effectiveness of technologies is often held as proof of the privileged irrefutable status of the scientific knowledge which drives them (Bijker & Pinch, 1987).

[13] Fee-based systems such as the US tend to employ more economic rationing methods, through private or social health insurance schemes and the market (Brown & Webster, 2004).

[14] Nettleton (1997) has argued that a similar manoeuvre is employed in public health promotion which uses epidemiology to provide an apolitical 'veneer of scientific legitimacy' (p215) to pronouncements of lifestyle choices as 'risky' or 'healthy'.

[15] Statistical, epidemiological and personal.

CHAPTER 3: Methodology

Introduction

The formative aim of this project was to explore the issue of human enhancement by focusing on a single drug, human growth hormone, as a case study of the phenomenon. The intent of this approach was to avoid taking 'enhancement' or essentially synonymous terms such as 'usage going beyond therapy' as *a priori* descriptive categories, as some previous social studies have done (e.g. Conrad, 2005) but rather to produce an in-depth and critical account of how such uses emerged and were understood outside of bioethics. The focus on *understanding* suggested that a qualitative approach would be best suited to this line of research. A number of other overarching methodological requirements arose from the orientation of the project around biomedical enhancement and the theoretical interpretation of that subject laid out in Chapter 2. These affect both the scope and structure of the research methods and the status of the data gathered and the conclusions that can be reached from it.

Dealing with the structural elements first, among the selection criterion for growth hormone as a case study, were that it offered the opportunity to compare the situation in the UK with that in the US on specific issues and that it was implicated in not one but two separate 'enhancement' uses; treatment of idiopathic or 'normal' short stature and as an anti-ageing therapy. In terms of national differences,

growth hormone in the treatment of idiopathic short stature has received regulatory approval in the US (since 2003) but not in the UK or Europe, while anti-ageing clinics are primarily an American phenomenon although there has been some interest in the practice in the UK. The issue of anti-ageing is presented as a conflict between orthodox medicine and fringe or pseudo-scientific practice, while the proper use of GH in short stature is mainly viewed as a debate on the appropriate limitations for an otherwise established and accepted therapy. It was believed that both of these components would be important in understanding the phenomenon of biomedical enhancement. The case study approach was thus intended to allow comparison of the influences of both different national systems of healthcare provision, regulation and the mechanisms by which 'good science' is delineated from poor practice among practitioners. Facilitating this comparative approach was thus a requirement of whatever methods of data collection were to be adopted.

The theoretical approach to enhancement as detailed in Chapter 2 also commits the project to a broadly social constructionist stance, utilising the techniques of science and technology studies[16] to investigate the development of GH as a medical technology. An important source of reference and inspiration in this respect came from recent critical drug histories such as Oudshoorn (1994), Lowy (1996), Goodman & Walsh (2001) and Marks (2001) which employed socio-historical accounts of development combined with the

interpretative framework provided by STS to explore the construction of contemporary positions and understandings about a range of selected pharmaceuticals. Considered broadly, this approach offered a promising technique for investigating the case of human growth hormone. It does, however carry important consequences for the status of the data collected during the research and the type of claims that can be made on the basis of it. The implications of a constructionist approach will be addressed in the final section of this chapter.

In view of the essentially intertwined relationship between the topical and conceptual commitments of the project and its methodology, theoretical and ethical concerns will be discussed alongside the account of the practical processes of conducting research, rather than as separate sections. The first section of this chapter will recount the mechanics of the project's design beginning with the initial mapping of the domain of enquiry and identification of relevant groups of social actors. The subsequent section deals with the processes of data collection. Following the project's approach of investigating both the socio-historical development of growth hormone and the contemporary perceptions of its application, this includes both the gathering of existing textual material and interviews with current medical professionals. The formulation of a suitable data collection instrument and the practical details of selecting and contacting interviewees and carrying out interviews will also be dealt

with in this section. The final segment will address the data analysis; both the techniques applied to interpret archive and interview material and the way in which the theoretical and practical approaches selected affects type of account that can be produced. This discussion of the status of the data- that is the extent and restrictions on what can be inferred from the data will also consider the general limitations of this research.

Project Design

i) Relevant Parties: Mapping the Domain of Growth Hormone

Initial investigation and mapping of field of human Growth Hormone and its application revealed a complicated network involving a range of different social actors, all of whom have a view on how the hormone ought to be used in line with their peculiar interests. Growth hormone for short stature is primarily administered by practitioners belonging to the medical sub-speciality of paediatric endocrinology. The hormone product currently used, recombinant DNA derived hGH, is produced and promoted[17] by several major pharmaceutical and biotechnology companies including Genentech, Eli Lilly, Pfizer, Serono and Novo Nordisk. A number of these companies have a close association with (mainly) US-based patient groups for parents and families of short-statured children such as the Human Growth Foundation and the MAGIC foundation, and also with many leading paediatric endocrinologists who consult for the industry, patient groups or both. National and international regulatory agencies, in this

case the US Food and Drug Administration (FDA), European Medicines Agency (EMEA) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA), are also involved in defining and approving the uses to which growth hormone is put. Beyond this there existed what I considered to be a second sphere of more peripherally interested groups: bioethicists (and some activists like Jeremy Rifkin) concerned with issues of enhancement, psychologists interested in exploring the supposed psychosocial disadvantages of childhood short stature and measuring the psychological benefits of GH therapy, and groups concerned with the economic impact of growth hormone use such as the UK's National Institute for Health and Clinical Excellence (NICE) or private insurance companies with specific policies on GH.

The mapping was made more complex because of the decision to look at both the use of GH to treat childhood short stature (its most prominent application) and the illicit off-label use as an anti-ageing agent. A similar network of interested social groups can be detected for anti-ageing applications. Adult endocrinologists are responsible for administering growth hormone to adult patients regarded as GH deficient and are also the main source of orthodox medical opinion on the potential applications of the hormone as a treatment for declining hormone levels in old age. Actual administration of GH for anti-ageing occurs mainly in private clinics run by practitioners who are almost exclusively not registered endocrine specialists (although

they are for the most part certified physicians). Again a further ‘outer sphere’ of interest exists: Other medical disciplines, primarily geriatrics and gerontology have an existing interest in treating elderly patients and have also produced opinions on the potential use of hormones like GH and testosterone in this group. Within the biotechnology sector certain companies have invested very heavily in promoting alternative technological interventions for the biological problems of ageing, collectively described as regenerative medicine, and consequently there is very little industrial interest or enthusiasm for promoting novel hormone therapy for ageing. Additionally there exists a veritable netherworld of internet sites offering growth hormone or growth hormone substitutes along with a wide variety of other anti-ageing products apparently for sale without prescription.

ii) Matching Cases and Methods

The next step was to decide which group of actors to focus on and which data sources to utilise. A number of considerations both practical and theoretical marked endocrinologists (paediatric and adult) as the most appropriate group to concentrate on. The major source of data about growth hormone naturally comes from academic papers published on the subject. As Weiner (1988) observes, the work of scientific research (including medical science) in the twentieth century often leaves ‘an impressive paper trail’ (p548) making documentary research the mainstay of reconstructing these activities. Endocrinologists, as the practitioners with the

greatest professional interest in, and authority concerning, growth hormone produce the majority of papers on the subject, although, as noted, other disciplines such as psychology and geriatrics have a minor interest in selected aspects of hormone therapy. Endocrinologists are also the only group central to both paediatric and adult uses of the hormone who are present and accessible in both the US and UK.

A preliminary examination of the medical literature on growth hormone revealed that the contemporary uses, especially those considered by bioethics as enhancement, do not exist in isolation but are discussed and compared to other existing therapies. Growth hormone given to short but otherwise healthy children with the diagnosis of idiopathic short stature was generally viewed as an expansion of the medical application of the hormone for other forms of childhood short stature, most of which are not considered enhancement. Similarly, the use of GH in ageing was often discussed in relation to the treatment of growth hormone deficient adults[18]. It became clear that separate applications of growth hormone could not be appropriately analysed as individual phenomena but must be understood as part of the changing, expanding use of growth hormone as a technology, and even in relation to other hormone drugs. A thorough account required a deeper investigation of the socio-historical development of growth hormone itself, including the influence of previous hormone

technologies, rather than simply a brief recounting of the origins of the more recent, controversial applications. The desire to follow this line of enquiry committed the project to a substantive historical component.

In keeping with this aim of exploring the influence of the past on the present status and understanding of growth hormone it was appropriate to supplement a historical document-based enquiry with data on contemporary perspectives. A large scale questionnaire approach to one or more relevant groups such as endocrinologists in the UK or US was one possible option, but a number of similar surveys have already been carried out, some very recently, suggesting some duplication of data would be likely (Cuttler et al, 1996; Finkelstein et al, 1998; Juul et al, 2002; Hardin, Woo, Butsch & Huett, 2007). In addition the type of data collected by these surveys, dwelling mainly on numbers of patients treated in different categories and types of diagnostic criteria favoured, is not well suited to the qualitatively-orientated goal of exploring how growth hormone therapy is understood by those involved in its use. Instead it was decided to select a smaller subset of endocrinologists in both the UK and US and carry out in-depth interviews in order to elicit more appropriate data. Having selected this dual methodological path the next step was to refine it.

The importance of symmetry in social research has been highlighted; in STS studies this manifests itself as a commitment to giving as much attention to failed technologies as to successful ones, in the sociology of knowledge it means giving equal weight to theories or models that are rejected compared to those that become accepted, and in studies of historical events it advocates studying the views of all parties rather than merely the dominant side (Bijker & Pinch, 1987; Weiner, 1988). Does the concept of symmetry then cause problems for the proposed approach? In regards to the historical analysis, the records and perspectives of endocrinologists must from necessity take precedence but some balance can be achieved by collecting and including texts including journal papers, books, web sites and online documents, press releases and newspaper articles produced by other relevant groups such as patient groups, anti-ageing proponents, or regulatory agencies.

These sources can supplement the main medical papers although there are discrepancies that, given the scope of this particular project, prevent such sources from playing a greater role; for example the US Food and Drug Administration makes minutes of its open meetings on growth hormone licensing publicly accessible while very little comparable documentation is available from the UK or European regulatory bodies. Similarly, in the UK, NICE documents provide nationally applicable evaluations for the cost of yearly treatment and even cost-benefit analysis for different diagnostic

groups treated with growth hormone while in the US cost and coverage data is only available from a very few of the many private insurance schemes (although again some surveying activity has been carried out [Finkelstein et al, 1998]. The point is that these data are a matter of ongoing research, not an available figure for consideration). The effort required to obtain better data on regulation or insurance would require putting regulatory or economic considerations at the heart of the project which would distort its original purpose.

Although the extensive literature on most medical and scientific subjects, including growth hormone, means that the most prominent body of work is already accorded to the orthodox perspective of endocrinologists, there is merit in carrying out additional interviews with this same group:

> [E]ven elite interviews can be very useful in eliciting otherwise unrecorded information and new perspectives […] knowledge of the functioning elites is as important to critiques of dominant power relations as knowledge of the disenfranchised (De Chadarevian, 1997 p53).

During the early years of growth hormone therapy the study and clinical application of GH had been almost exclusively the preserve of academic endocrinologists, the elite and *de facto* research arm of their profession. In the modern (recombinant) era of growth hormone academic practitioners are still the driving force behind much of the

official literature including guidelines on appropriate usage of the hormone (Neely & Rosenfeld, 1994). Academic endocrinologists thus provided a visible, relevant, and useful subgroup of medical professionals to target for interviews. It was also possible to select relevant members of this group through their authorship of academic papers uncovered whilst mapping out the domain of enquiry and collecting documents for the socio-historical aspect of the project.

In the interests of symmetry it would, at least theoretically, have been possible to investigate the perspective of patients receiving growth hormone. However there are only a small number of patient organisations for short stature in either the US or UK and they generally have a limited full time staff making the potential sampling frame rather small. There are no equivalent movements organised around hormone therapy for anti-ageing since it is essentially an illicit and privately funded treatment[19]. Interviewing actual recipients of GH therapy would be possible but would be logistically and ethically complex. Almost all current short-statured patients are children and potentially unable to give individual informed consent, while it would be very difficult even to identify patients attending private anti-ageing clinics in the US. Only a few studies have followed the route of investigating the motivations or experiences of patients (and sometimes families) having received hormone therapy for stature-related conditions leaving a limited pool of literature for comparison (Finkelstein et al, 1999; Pyett et al, 2005). To carry out such an

endeavour in addition to the interviews with endocrinologists was clearly beyond the scope of this project given the constraints of time and funding. In a choice between interviewing either endocrinologists or patients the former group presented a more coherent overall data set when combined with the historical material. Additionally, I was primarily interested in the understanding and arguments for and against controversial applications of growth hormone presented by medical practitioners since they are the main source of knowledge, and thus authority, on the drug. Through comparison with the bioethical description of certain uses of GH as enhancement this already provided a form of symmetry in comparing different (and potentially contrasting) professional accounts.

Through this process of exploration and deliberation the specific research methodology was arrived at. The investigation would take a dual approach: a socio-historical account of the development of human growth hormone as a medical technology based on documentary analysis of relevant medical papers covering the time-span of GH usage complemented by a series of qualitative interviews with leading academic endocrinologists in the UK and US who had a particular interest in growth hormone as identified from their output of publications. The process of investigation and the process of determining and assessing what was relevant are essentially mutually linked and ongoing processes so the boundaries of data collection remained flexible during the early stages of the research.

For example, during the investigation of GH as an anti-ageing therapy it became clear that there were important precedents for hormonal intervention in ageing dating back before the first utilisation of growth hormone. The investigation of this process eventually led to the expansion of the frame of historical enquiry back to the early years of endocrinology in the late nineteenth century, a development that was not anticipated at the outset of the project. The particulars of the data collection process are the focus of the next section.

Data Collection

As the document collection was essentially an extension and deepening of the initial domain mapping for growth hormone, and because an underlying skeleton outline of the history of GH was needed to inform the rest of the project, this part of the data collection was the first to commence.

i) Document Collection

The data collection for the socio-historical aspect of the study began using online bibliographic databases, primarily PubMed (URL<http://www.ncbi.nlm.nih.gov/sites/entrez>) and ISI Web of Knowledge (URL<http://wok.mimas.ac.uk>) to map out the domain of papers on growth hormone. The literature on growth hormone is extensive; using the search term ‘human growth hormone’ on either database will bring up results in excess of ten thousand papers. In the early stages the search was concentrated on growth hormone

therapy for short stature and narrowed by simple parameters such as time periods and searches for specific article types such as research reviews or historical papers. The aim of the search at this stage was to glean sufficient information to produce a rough outline of the major events in the history of growth hormone. As the research progressed the findings were employed to further structure and order the search process, for example by dividing material into pituitary era studies and articles or biosynthetic era papers, by searching for papers dealing with particular medical conditions such as GH deficiency or Turner syndrome, or by specific areas of study such as psychosocial aspects of short stature or methods of diagnosing hormone deficiency. Papers were obtained from the University of Nottingham library or through interlibrary loans. Much supplementary material was sourced online, for example from the websites of short stature support organisations, pharmaceutical manufacturers of growth hormone and state agencies such as the FDA or NICE.

When the programme expanded to include material on the use of growth hormone as an anti-ageing agent initial online searches revealed the extent of its illicit promotion (or at least promotions using the term ‘hGH’ regardless of the providence of actual product being advertised). A search for ‘human growth hormone’ using a popular search engine like Google will return over seven million hits. The majority featured on the first three pages (i.e. the first thirty results) tend to be links to websites promoting some form of anti ageing

services[20]. While testifying to the growth of hormone-based anti-ageing ideas and practice little of this material gave much insight into the scientific debate on the issue. Searches for medical papers produced articles and studies in endocrinology journals on the potential and pitfalls of growth hormone treatment for the elderly and also revealed the interests of other disciplines such as gerontology. Investigation in the origins of the association between the pituitary gland and growth or ageing uncovered the historical aspect to the study covered in Chapter 4. Reading material collected as part of this line of enquiry also suggested further research avenues and components of the emerging timeline of GH such as the medical study of growth or the importance of medical specialisation in shaping the discipline of paediatric endocrinology. In this way the process of document collection and historical investigation can be seen to be an organic, multidirectional process rather than a simple linear 'excavation' of data. With this work underway attention could then be given to setting up the interview programme.

ii) The Interview Schedule

It was decided that the interviews with endocrinologists should be semi-structured in order to strike a balance between eliciting interviewees' own responses - important for capturing *understandings* - but keeping the interviews thematic and attendant to the broad areas of GH therapy that were the main focus of the project. Sociologists and historians of science and medicine have

stressed the value of directed interviews, where the interviewer has familiarised themselves with an appropriate background knowledge of the subjects under discussion, for investigating particular issues within science[21] (Murphy & Dingwall, 2003; Thompson, 1991; Weiner, 1988). The specific structure of the interview schedule was informed by the developing historical overview of growth hormone and the influence of the idea of medicalisation through expanding use of the drug.

After a number of iterations the question schedule was designed around a series of open ended questions beginning with a request for a brief overview of the interviewee's work on growth hormone and then moving through the rationale for each of a series of applications for growth hormone. A single question schedule was devised for use with paediatric and adult endocrinologists, with the intention that, after the first autobiographical question, paediatric endocrinologists would be asked to discuss the expanding use of growth hormone beginning with the original or 'base line' application in severely hormone deficient short children and then moving through to idiopathic short stature (Questions 2-6). Adult endocrinologists would be invited to discuss the use of GH in hormone deficient adults and the possible use in elderly patients, in this case following the potential rather than actual expansion in use (Questions 7-9). All interviewees were asked about potential ethical or social implications posed by any or all of the applications discussed and were offered an

opportunity to comment on any areas of relevance or interest that they felt had not been covered in the interview up to that point. In keeping with the semi-structured approach most questions had a series of sub-questions which could act as prompts or reminders for the interviewer or spurs to stimulate further response on a topic of little response was forthcoming to an initial approach. A copy of the final interview schedule is provided in Appendix 1.

A list of potential contacts among adult and paediatric endocrinologists was drawn up. Names were collected from prominent papers written on growth hormone and also through bibliographic database functions such as the Web of Knowledge "results analysis" option to rank authors by the number of publications in a given subject area (i.e. growth hormone). Most of the contact details listed on papers provided mail or email addresses and institutional affiliations. It was thus possible to search for and build a background profile of many potential interviewees before contact was initiated. Once authors who had retired or whose interest in growth hormone was too distant from the project topic (for example experimental application of hGH in AIDS patients or GH doping in sport) were excluded from consideration a key list of some eighteen academic endocrinologists in North America and twelve in the UK were identified as core interview targets.

The lists were slightly weighted in favour of paediatric endocrinologists since this is the major arena where growth hormone is clinically applied and only these practitioners had any likelihood of having experience with pituitary growth hormone[22]. It will be noted that the location category 'North America' is used instead of 'US'. This is because a small number of practitioners on the list were based in Canada at the time of compiling the list. Additionally, a limited pool of persons outside the field of endocrinology, but belonging to other interest groups identified during mapping, were noted as being useful potential interviewees for the provision of supplementary information and perspectives.

A standard contact email was prepared and modified slightly to suit the precise occupation of each individual recipient (although the main division was into adult or paediatric endocrinologists, there were a few practitioners who had expertise in both areas and obviously I was interested to discuss the full range of their experience with hGH in these cases). This initial contact was followed up with further correspondence where required to answer any preliminary questions about the project and to arrange dates and times for interviews to take place. In total fourteen confirmations were received comprising six UK endocrinologists, six North American endocrinologists and two supplementary interviews, both based in North America. This amounted to a successful response rate of approximately 41% which, when considered alongside the socio-historical investigation,

was sufficient to produce a useful level of data for the purposes of this project.

iii) The Interview Process: Practical, Ethical and Reflexive Considerations

Interviews were carried out between May and December 2006. The majority of interviews were carried out face to face including a number carried out in North America. These interviews were conducted in a variety of settings, primarily in informants' offices located on university properties. A further set of interviews were arranged by telephone where arranging to meet informants in person was not feasible due to time or other commitments. In general each interview was around one hour in length although one interview was considerably longer, lasting around two and a half hours. Since most telephone interviews were conducted near the end of the process I believe that additional familiarity with the process and more refined interview technique probably compensated for the loss of rapport compared to meeting face to face with interviewees (Fielding & Thomas, 2008).

Formal ethical approval from a local or multicentre Research Ethics Committee was not required for the interviews carried out as part of this project. All participants were being interviewed in a capacity as academics (apart from one interview with an individual working in an organisational capacity for a patient group). While some UK

interviewees were also engaged in working for the National Health Service, no part of the interview schedule called for or discussed information about the treatment of individual patients or about the specific workings of the NHS itself and none of the interviews were carried out on NHS property. The purpose of these interviews was to explore how scientific medical understanding of the hormonal model of the body, primarily produced by academic endocrinologists, translates into a rationale for intervention and treatment expressed in guidelines and 'official' positions on GH. While links may be drawn between differences in national healthcare systems and variations in UK or US opinions on best practice in endocrinology as part of this project's overall remit, it was not a subject being directly addressed in these interviews.

All interviewees volunteered to participate in the interview process, although this in itself did not remove the need to develop a protocol for the appropriate treatment of interviews and interview material. Although written consent was not felt to be required, at the beginning of each interview the purpose and format of the interview and the project was discussed with each interviewee, and only when they were satisfied to proceed was the recording device turned on. While no confidential information was being requested from participants, the very nature of growth hormone being a controversial drug, combined with the fact that many elite endocrinologists have close ties with pharmaceutical manufacturers and patient groups (about

whom I *would* be asking questions) meant that potentially sensitive issues were involved:

> Speaking about their institutional and disciplinary affiliations, scientists have to position themselves carefully. Evaluations of colleagues or employers, especially negative ones, are frequently made only off record (De Chadarevian, 1997 p57).

In recognition of this, and in the hopes of producing a more open dialogue, all participants were assured that neither personal nor institutional information about interviewees would be included in the thesis or any published work derived from it. Instead participants are assigned a code based on their location e.g. 'NAM 3' to signify 'North American interviewee number 3' allowing quotations from particular interviews to be consistently tagged and referenced throughout this work. A table is presented at the end of this chapter listing all of the codes and giving relevant professional descriptions e.g. 'US-based professor of paediatric endocrinology with experience of working with pituitary and biosynthetic growth hormone' to provide some context for the interpretation of quoted material employed in chapters 4-7.

In the event, the only times when the digital voice recorder needed to be switched off during interviews was when a phone call interrupted the discussion. In terms of the dynamic of the interviews themselves, I was often asked about my background. Being able to explain that my undergraduate training was in biology provided reassurance to

the informants that I would be able to understand the majority of medical terminology which infused their normal working discourse and meant that their replies did not need to be simplified to the extent that would be the case with a correspondent entirely unfamiliar with natural sciences. In addition these were ‘elite’ interviewees; the majority of respondents were high status academics, well respected in their fields and used to imparting information to junior colleagues and students (i.e. persons of a similar status and comparative age to myself) in the course of their duties. These factors, combined with the familiarity with the general issues surrounding growth hormone I acquired from the (ongoing) historical side of the project and the fact that I made a point of profiling and familiarising myself with the specific academic output of each interviewee before the interview helped improve the flow and hopefully facilitated disclosure during the interviews as well. In addition, and again highlighting the intertwined nature of data collection and analysis, the discussions of individual careers and previous developments (especially concerning pituitary growth hormone) also provided novel material for the historical analysis aspect of the project. Some interviewees also took the opportunity to provide me with copies of papers in their possession which I had not yet uncovered or which had been difficult to find.

Data Analysis

'Telling stories is telling lies' – B.S. Johnson

'If stories are the form in which people account for past events, we cannot escape their structure' De Chadarevian, 1997 p58

Before a coherent account of the practical analysis of the research data can be given it is first necessary to address certain concerns pertaining to the status of the data; that is, what kind of claims can be made from an analysis, and conversely, what it cannot reveal. This project has adopted an explicitly social constructionist stance, drawing on both STS and a Foucauldian sociology of the body to describe the context and framing view of the social world, within which and through which the phenomenon of enhancement is to be investigated. The constructionist position, broadly stated, argues that categories and definitions, texts, practices[23] and ideas- in short the discourses- produced by professional disciplines such as the natural sciences and medicine cannot simply be taken as literal descriptions of an objective, observer-independent reality but are rather influenced by values, cultural assumptions and social/ organisational factors influencing the production (and the producers) of these discourses. Two problems in particular are associated with such a constructionist outlook: relativism and reflexivity (Bijker, 1993;

Murphy & Dingwall. 2003). These will be dealt with in turn, beginning with the relativist issue.

The relativist position, albeit summarised and simplified[24], holds that if all discourse is the product of subjective social and cultural processes then, extending the principle of symmetry, any one account of proceedings is as valid to the impartial investigator as any other since there no non-subjective criteria by which to judge 'validity'.[25] Taking a narrow view of discourse as texts and talk, discourse analysts have argued that natural scientists' (and others') discourse should be used not as a window to explanation but as the subject of research itself (Gilbert & Mulkay, 1984a, 1984b; McKinlay & Potter, 1987; Potter & Mulkay, 1985). Scientific papers and scientists' talk in interviews, at conferences etc has been characterised as utilising different, variable framings of content which are used to present scientists' own arguments, choice of theories, or accounts of developments within their field, as logical processes of investigation and deduction while suggesting that accounts in opposition to their own are due to uncertainty or external influences biasing the process of investigation. The very variability of this discourse, it is argued, prevents it being used as any form of description of 'real' events and thus analysis cannot go beyond reflecting upon the 'patterned character' of the discourse itself (McKinlay & Potter, 1987; Shapin, 1984). Indeed Gilbert & Mulkay (1984a) base much of their analysis of scientists' discourse on

material collected from biochemists talk and writing about a disputed area of biochemical knowledge concerning a phenomenon known as oxidative phosphorylation, but do not propose that their work can reveal anything about either oxidative phosphorylation itself or the scientific work being carried out on it[26].

An important criticism of relativism is that, through concentrating entirely on the discursive and cultural aspects of the social world, relativists ignore the materiality of that world (Murphy & Dingwall, 2003). Specifically the relativist insistence that all accounts are equally valid ignores the effects that physical, material properties of objects exert which limit the types of descriptions that can (meaningfully) be applied to them. It is a mistaken belief that to describe something as socially constructed necessitates the implication that it is either inherently false or it has no 'true' existence. As MacKenzie & Wajcman (1999) observe, technological artefacts are marked by their physical nature and are 'in no way reducible to the ensemble of beliefs around them' adding that:

> [E]mphasis on the social shaping of technology is wholly compatible with a thoroughly realist, even a materialist, viewpoint …indeed the very materiality of machines is crucial to their social role (MacKenzie and Wajcman, 1999 p18).

Foucauldian scholarship dealing with the body and illness has been viewed as introducing new 'relativising currents' into the constructionist approach to medical knowledge, eroding the notion of

an underlying biophysical body upon which medicine acts (Williams, 2001). Again, while this is certainly true of some analyses using the approach it is not necessarily inherent in a Foucauldian treatment. Although writing in critique of such a Foucauldian sociology of the body, Fox (1998) observes that there is sufficient contradiction and ambiguity in the Foucauldian corpus to envisage several different 'bodies' including a 'real' natural body overlaid with cultural values. This, in essence, is the metaphysical position adopted in this project, approximating to the position described as 'subtle realism'[27]: bodies and the medical technologies that interact with them have a material existence independent of observers, and this restricts the descriptions that can be made about these entities[28]. Different accounts and interpretations can be made about these phenomena but all accounts are not equally valid. Claims being made can thus be tested on the basis of the evidence supporting them and the validity of the arguments being made (Murphy & Dingwall, 2003).

In terms of the data sources employed in this project this means that primary or secondary texts (e.g. medical papers, orthodox histories) or informants' accounts given at interview cannot be read unproblematically either as objective, literal accounts or as wholly subjective views valid purely for their own sake. Rather, data must be critically evaluated with regards to the context of their production and the form of their presentation as well as their content. Interview data in particular require careful handling as the accounts presented in

interviews are subject to multiple contingent influences. Firstly, accounts in interviews often rely on the informants' recollection of events from memory which can not only be unreliable but also involve active processing and selecting of information. Memories are recalled in such a way (consciously or otherwise) that they reconcile the past with requirements of the present (De Chadarevian, 1997; Thompson, 1991). One of these requirements is to find a way of talking meaningfully about past events[29] by providing answers to the interviewer's questions. In this way interviewers are directly involved in the social interaction that results in production (or co-production) of accounts collected through interviews (De Chadarevian, 1997). The responses given by informants during interviews can also be affected by variable characteristics of the interviewer such as gender, social class, age, profession, and demeanour (Murphy & Dingwall, 2003). As Shapin (1984) observes:

> Talk is not just an account of behaviour and belief: it is itself behaviour that varies according to audience and purpose (p126).

During interviews (and other accounts of behaviour) individuals will strive to present themselves (to the interviewer) as competent, moral, beings by providing explanations for their behaviour, actions, beliefs etc that appear appropriate and rational (Murphy & Dingwall, 2003).

> Much of what interviewees tell is autobiographical and therefore embedded in accounts which make sense and do justice to their own lives and aspirations (De Chadarevian, 1997 p57).

For natural scientists this can include accounts of scientific practice and cognitive decisions (for example choosing to support a particular theoretical viewpoint) that are in accord with the norms of the profession as well as their personal standpoints. Scientific procedures such as experiments are recalled to fit a rational order that justifies the informant's current position (science is after all the business of producing order) (De Chadarevian, 1997; Gilbert & Mulkay, 1984b). If these contingencies and partialities are accepted as an inevitable part of oral discourse the question then becomes what *can* be inferred from interviews in lieu of being able to reconstruct a viable account of 'what really happened'?

In this respect a constructionist approach to interview data has much in common with the techniques of the discourse analysts:

> Analyses should start from the question of what informants *can be seen to be doing* with their interview talk (Murphy & Dingwall, 2003 p97, emphasis added).

Gilbert and Mulkay (1984a) described two distinct framing patterns or *repertoires* in scientists' accounts of work in their field that acted to present events in ways that justified the speaker's current position with regards to these events. The first of these, the empiricist repertoire, is described as a particular pattern of discourse where accounts are 'presented as deriving neutrally from the facts in such a way that the author's personal involvement becomes less visible' (McKinlay & Potter, 1987 p445). In empiricist accounting decisions

derive from experimental data that appear to obviate a particular interpretation, presenting the findings as inherently logical, rational and properly scientific in accordance with the orthodox model of scientific practice (Potter & Mulkay, 1985). By contrast the contingent repertoire invokes external personal or social forces which may have inappropriately influenced results or casts experimental results as 'uncertain accomplishments, with variable theoretical implications, the interpretation of which may often or always be influenced by a range of noncognitive factors' (Potter & Mulkay, 1985 p262). These two repertoires are employed to different ends; the empiricist repertoire generally lends itself to justifying a speaker's own interpretations, choices of theory and actions as scientific and flowing from the evidence. The contingent repertoire casts doubt on opposing perspectives to the speakers own and is used to explain alternative interpretations of data as incorrect because they have been inappropriately influenced by external (unscientific) factors, and to explain how scientific arguments can persist. 'Good' scientific data is described in empiricist terms while 'bad' scientific knowledge is described in contingent terms (Kerr, Cunningham-Burley &Amos, 1997). The concept of repertoires then provides a useful and relevant technique with which to interpret the interview talk of practitioners of scientific medicine.

How then, if accounts are partial, constructed and variable can research transcend the limitations placed by what Shapin (1984) has

termed the ‘restrictive programme’ of discourse analysis where social researchers must only concern themselves with analysis of scientists’ discursive practices because of the futility of trying to construct a definitive account of scientific practice? This issue also connects with the second problem mentioned, that of reflexivity:

> [M]odern students of science deconstruct the special character of scientific knowledge. To do so they need to maintain a privileged stance for the knowledge that their own studies produce, and hence they refute their basic claim. They saw off the branch on which they sit, and they saw it off between their seat and the tree (Bijker, 1993 p116).

Specifically, can constructionists, eschewing relativism and taking truth as the measure of the validity of research claims, then argue that their analyses, based as they are on the contingent discourses of natural science are more true, more real, than the accounts of the scientists they are studying? This risks a form of ‘sociological imperialism’, the ‘slippage from the having of something important to say, to the having of everything important to say on the matter’ (Williams, 2001 p150). Instead of a confrontational approach where scientists’ discourse is ‘ironically inverted, deconstructed, shown to be fragmented, confused, ill founded and so on’ (Potter & McKinlay, 1989 p140), it is possible to contest the claim that science produces value-neutral, objective knowledge about the ‘real’ world without concluding that science(social and natural) itself is impossible (David, 2008; Murphy & Dingwall, 2003).

It is here that the careful analysis and framework approach prescribed by a subtle realist approach to qualitative data analysis must be invoked. David (2008) suggests that reflexivity should instead act at the level of epistemology, producing a recognition that:

> [C]omplexity and contingency require more than just one level of explanation. Reflexive epistemological diversity means neither that anything goes, nor that all insights stack neatly in a complementary whole' (p347).

The aim of social research need not be to produce a 'definitive account' that trumps all others but to produce an account that is adequate for the purpose it is intended to serve (Shapin, 1984).

When applied in practice to the data in this project, the texts such as medical papers and online documents were examined through an interpretative framework provided by STS- looking for details of institutions, affiliations, ideas and technologies being described and used to make claims and assist in the co-construction of growth hormone and the diseases of hormone deficiency. The results of this process are presented in Chapters 4 and 5. The interview recordings were transformed into data by the process of transcription and the discourse analysed for evidence of repertoires; both Gilbert & Mulkay's empiricist and contingent repertoires and additional patterns of presentation peculiar to this data set. The transcription was all

carried out personally as a useful way of familiarising myself with the data set, and was limited to transcribing spoken material without pauses, hesitations or other minutiae of the performance of speech associated with conversation analysis as this was not required for this project. Assessment of this data was carried out with the application of the NVIVO software package, allowing data from multiple interviews to be grouped together under particular collective headings and moved around as the analysis developed. This process, in common with much qualitative work, was both inductive and deductive since interview data had already been given some structure through the thematic nature of the interview schedule and by a prior commitment to look for certain types of patterned speech in the data set, while remaining open to evidence of novel patterns, framings etc. The results of this part of the analysis are presented in Chapters 6 and 7.

Whilst the interview data clearly cannot be taken as reports of the reality of practice or as accurate accounts of belief they can reveal the norms of practice that the speakers take to be self-evident and the ways in which speakers construct their identity or that of a particular (professional) group to which they belong (De Chadarevian, 1997; Murphy & Dingwall, 1997). It is also possible, going beyond what the more relativist DA approach would allow, to make connections between external social, economic, political and historical factors and the interview data provided care is taken not to

infer that the data represent literal beliefs about these matters. Much of the interview data in this project also involved accounts of the history of growth hormone in the twentieth century. Some of these accounts have been used to inform the socio-historical account of GH developed in Chapter 5 (and also with regards to anti-ageing in Chapter 7). Their employment requires the consideration that these are accounts constructed in the present of prior events subject to the selectivity of memory and other attendant contingencies of oral data. However taken in the context of other sources of information,[30] and bearing in mind that at a basic level while informants' accounts are selective, 'it is unlikely that the factors to which they refer have no basis in external reality' (Murphy & Dingwall, 2003 p98).

Interview data can make some useful contribution to the reconstruction of the development of growth hormone by giving evidence of network elements such as the involvement of patient groups in transporting pituitary glands around the US or the requirement that endocrinologists apply to a central committee to request access to the limited supply of pituitary growth hormone. When inferred from a number of sources it is probable that these phenomena did occur even if not in the way described by any one source (Thompson, 1991). This strong historical element is also the reason why the sources used in this chapter derive as much from the theory of oral history as they do to other qualitative data analysis methods.

A final issue concerns the ethical dimensions of reflexive consideration. Who can be said to 'own' accounts of science? The aim of scholarship is to show that science is a social and historical process shaped by and shaping social factors (De Chadarevian, 1997). At the same time, scientists own accounts must fit the orthodox narrative of scientific progress, which generally denies or downplays these very elements as constitutive of good science. There is thus an inherent tension between natural science and the (external) study of natural science, especially in regards to the obtaining and appropriate use of interview material. Social researchers need to meet their own disciplinary standards and conventions in presenting and interpreting scientists' discourse while at the same time having a duty to their informants not to misrepresent or detrimentally affect them.

There is no ready solution to this tension, although one possible resolution may lie in the recognition of limitations of constructionism and other social explanations urged by Williams (2001) and David (2008). The aim of this project is not to confront the accounts of scientific medicine in order to debunk them but to append them. The claims being made here argue not that scientific medicine does not provide the correct or 'true' picture but, more pragmatically, that it does not provide the whole account; that neither natural science, nor sociology nor history or other disciplines can claim to 'have everything to say' about the complexities of reality. Multiple accounts

of phenomena from different disciplinary and epistemological positions can exist and even contradict one another without invalidating each other[31]. Given this, informants' interview data may be helpfully viewed as a gift; voluntarily given but never wholly disinterested (Mauss, 1967; Tittmus, 1970). The responsibility which receiving a gift carries may in this case be viewed as an indebtedness to an individual or group of individuals which nonetheless may be best discharged not by reciprocal action but through an obligation to a broader society to utilise the data to produce useful, constructive information.

Conclusion

This research is an attempt to investigate the phenomenon of biomedical enhancement through the specific case study of human growth hormone. This chapter has described how, from this initial standpoint, a series of strategic decisions were made to select and refine the particular focus and techniques of the research. Certain structural elements derive from the particular nature of growth hormone as a case study: the UK/US comparison and the study of GH both in short stature and in anti-ageing. Other decisions were influenced by theoretical and practical concerns: investigating the socio-historical development of GH as a medical technology and treating endocrinologists as the main source of information about this process. Beyond this much of the content of the project was developed through the intertwined process of data collection and

data analysis. Documentary analysis informed the structure of the interview schedule and highlighted issues of importance to be raised with informants, interview data provided insights to additional aspects of the socio-historical development of GH and even on occasion provided new documents to be analysed.

Of course, these choices and selections, whilst entirely necessary to facilitate the completion of this project on a manageable time-scale, also produce many of its limitations. It has been necessary to address only certain aspects of the history and development of human growth hormone. A number of perspectives have not been fully represented: patients, regulators and anti-ageing entrepreneurs among them. Only the most relevant aspects of even the orthodox history have been analysed (for example there is a whole adjacent stream of medical research and practice dealing with other hormones involved in the growth process such as Insulin-like Growth Factor-1 that there was no space to recount here). In particular there is a limit on what generalisations can be made about the situation in other countries outside the UK or US, since even a cursory inspection reveals conditions to have been considerably different in nations such as France, Japan or Australia (N. Pfeffer, personal communication, Feb 15 2008; Tanaka, 1999).

The chapter also addressed the ethical and methodological issues invoked by this particular line of research. Especial importance was

given to the implications of the theoretical underpinnings of the project. The arguments presented here are not intended to provide any definitive resolution to these problems but rather to present a case-specific situation of this project's stance within the context of a larger and ongoing debate within the social sciences. Nonetheless it was felt important to give a coherent account of the ontological and epistemological stance of the project and the ways in which this affected both the choice of interpretative techniques and the analysis of the data, as this forms the practical link between the conceptual framing of the research with the outputs presented in the following chapters. The ethical issues of data collection, specifically the linked issues of informed consent and fair representation of informants' oral accounts have also been discussed. While no complete solution is available some reflections on the tension inherent in such research and a potentially useful framing of the issues have been presented. These elements of the research have been discussed in conjunction with the practical elements of the work (and indeed in conjunction with each other) as they are integral and interrelated parts of the research rather than separate issues.

Finally then, this chapter has set out the means of investigation by which the core issues of this project are to be examined and processed. The remainder of the project deals with the historical and contemporary applications and understandings of human growth hormones and the emergence of so-called 'enhancement' uses. The

next chapter begins the socio-historical portion of the account with the birth of endocrinology at the close of the nineteenth century and the formation of the earliest scientific models of hormone action.

Notes

[16] Or more properly, following the original iteration "science, technology and society" studies (Bijker, 1993).
[17] To physicians. Growth Hormone is not generally advertised direct to consumers even in the US. FDA regulations expressly prohibit promotion of hGH for certain applications such as idiopathic short stature.
[18] And also in gerontological discourse by comparison with the hormone replacement therapy using oestrogen and progesterone offered to menopausal women.
[19] Although some ethnographic work has been done in the area of anti-ageing clinics and related activity- see Mykytyn 2006a; 2006b.
[20] Beyond this however the organised face of hormonal anti-ageing medicine is the American Academy for Anti-Ageing Medicine (URL<http://www.a4m.com>).
[21] As opposed to a more passive 'blank slate' approach to interviewing that may be used in eliciting less directed 'life history' stories from respondents.
[22] During the pituitary era (1958-1985) growth hormone was restricted to paediatric use. It was only after 1985 that increased supplies of biosynthetic GH allowed exploration of a clinical role for adults to take place (see Chapter 5 for details).
[23] Including technological practices.
[24] For example I do not propose to deal with distinctions between 'idealist' and 'anti-realist' positions or other similar divisions (see Potter & McKinlay, 1989 p 137-8).
[25] For further explanation of the relativist position and the difficulties it presents to social research see Chapter 1 (pp7-19) in Murphy & Dingwall, 2003.
[26] See also Halfpenny, 1988 and Potter & McKinlay, 1989 for discussion on this aspect of Gilbert & Mulkay's work.
[27] The term originates with Hammersley (1992) (Murphy & Dingwall, 2003).
[28] Against the charge of essentialism, it can be argued that the 'essence' of the natural body at least can be determined to exist phenomenologically, through experience or common sense (Fox, 1998).
[29] And since this project aims to trace the development of growth hormone up to the present, the majority of data, in interviews and otherwise, concerns events in the past, albeit often the recent past.
[30] In any case it is worth remembering that other more 'respectable' sources of data such as scientific papers are also prone to personal bias, inaccuracy, and above all selectivity in reporting of events. All data sources thus need careful interpretation and handling (De Chadarevian, 1997).
[31] At least in general terms. It is of course possible for evidence produced in one discipline to invalidate a specific claim made by another discipline as regards a particular issue.

Guide to Interview Respondents

In the interests of clarity, direct quotes from interviews are identified by a short code of the form 'UK X' or 'NAM X'. The first part of the code identifies the interviewee as working in either the UK or North America and the 'X' represents an identifying number given to each interview transcript. Descriptive details of each respondent are provided below along with the appropriate code.

MAIN RESPONDENTS	
CODE	**RESPONDENT DESCRIPTION**
UK 1	UK-based Professor of Paediatric Endocrinology with experience of working with pituitary and recombinant growth hormone formerly involved with the Dept of Health GH Committee.
UK 2	UK-based Emeritus Professor of Clinical Endocrinology with research and clinical experience of GH in adult patients.
UK 3	UK-based Reader in Paediatric Endocrinology involved with research on GH Therapy and physiology. Some experience of pituitary GH, mainly worked in recombinant era.
UK 4	UK-based Professor of Paediatric Endocrinology with extensive experience of pituitary as well as biosynthetic GH and the UK Medical Research Council / Dept. of Health committees.

CODE	RESPONDENT DESCRIPTION
UK 5	UK-based Clinical Senior Lecturer in Child Health with experience of current therapeutic practice using recombinant GH.
UK 6	UK-based Professor of Endocrinology with clinical and research experience of GH in adults and elderly patients.
NAM 1	US-based Professor of Internal Medicine and Neurosurgery with research and clinical experience of GH in adult patients.
NAM 2	US-based Professor of Paediatrics with experience of pituitary and recombinant GH.
NAM 3	US-based Professor of Paediatrics with extensive experience of pituitary GH and the National Pituitary Association as well as recombinant GH. Also involved in early investigations of GH in ageing.
NAM 4	US-based Professor of Paediatrics, Pharmacology and Therapeutics, with clinical experience of growth hormone in children and adults and research interests on GH use in ageing.

CODE	RESPONDENT DESCRIPTION
NAM 5	US-based senior figure with university medical school affiliated charitable foundation for children's health. Some experience of pituitary GH, mainly worked in recombinant era in both treatment and extensive research on molecular basis of growth pathology.
NAM 8	Canada-based Professor and Chair of Paediatrics, experience of Canadian pituitary hormone era and recombinant hormone.

ADDITIONAL MATERIAL	
CODE	**RESPONDENT DESCRIPTION**
NAM 6	US-based Associate Professor in Child Behavioural Health with extensive experience in psychosocial aspects of short stature.
NAM 7	US-based Executive Director of large patient support organisation for short statured children and GH-deficient individuals.

CHAPTER 4: The Historical Beginnings of Endocrinology

Introduction

> ‘ Scientists are, of course, in constant, intimate, dialogue with the real, material world, but they are active participants in that dialogue, bringing to it conceptual schema, experimental traditions, intellectual investments, ways of understanding the world, models and metaphors – some drawn from the wider society – and so on’ (MacKenzie and Wajcman, 1999 p6-7).

The first report of an effective demonstration of growth-promoting effects produced by the systematic application of human Growth Hormone (hGH) was published in 1958 (Raben, 1958), marking the emergence of a new therapeutic tool in the armamentarium of endocrinologists and growth specialists. This arrival comes at a relatively advanced stage in the history of endocrinology, with over half a century separating it from the inaugural use of the term ‘hormone’ to describe the body’s naturally occurring internal chemical messengers (Henderson, 2005). The purpose of this chapter is to explore the prior history of the discovery and application of hormones with the aim of highlighting important trends in practice and attitudes that would influence the development of Growth Hormone as a medical technology.

This investigation begins with the origins of endocrinology itself, in the nineteenth century phenomenon of ‘internal secretions’, and charts the often difficult and controversial emergence of endocrinology as a scientific discipline. Key events in this early history of endocrinology, most notably the actions of the French-Anglo-American physiologist Charles-Edouard Brown-Séquard, stimulated widespread popular interest in the seemingly miraculous properties of glands and the chemicals they produced, through practices that became known as organotherapy. Early interest centred on the reputed properties of the testis and ovaries, producing lasting associations between the therapeutic application of glandular chemicals and ideas of sexual character and rejuvenation (Borell, 1978). Much within the practices of organotherapy was unacceptable for a medical orthodoxy engaged in a struggle for professional legitimacy built around scientifically derived knowledge, but the new category of drugs proved popular with many ordinary doctors outside the elite of medical practice. Nevertheless, it was the very transformative potential of hormones that spurred uncritical therapeutic application, which also attracted the attention of elite academic researchers and ethical pharmaceutical companies. Research on endocrinology, along with bacteriology, was among the earliest areas where scientific practice could be seen to yield a direct improvement in clinical practices, as evidenced by the use of thyroid extracts to treat myxoedema (a form of hypothyroidism) in 1891 (Rasmussen, 2002). The tension between ‘opportunistic’ clinical

application of hormone products and laboratory scientists determined to claim the study of internal secretions as a new branch of physiology, was to dominate the field from the 1890s right up until the 1940s. Indeed the story of endocrinology's emergence and development can be profitably viewed as a microcosm of the wider struggle surrounding the professionalization of medicine around a scientific basis for practice.

Two aspects of this period are particularly relevant for the future conceptualisation of hormone therapies within the scientific paradigm of medicine which would come to dominate the twentieth century: the novel alliances formed between university-based researchers and pharmaceutical companies for the purposes of discovering new organ extracts and producing them on a large scale, and the methods of laboratory investigation which would shape the way hormone therapy was viewed by medical practitioners (Oudshoorn, 1994). In the early part of the twentieth century the academic-industry model of endocrine research produced some notable successes- insulin for the treatment of diabetes, oestrogens for a variety of female disorders, and to a lesser extent, testosterone and cortisone. The utility and prestige of these discoveries greatly assisted in elevating endocrinology from its dubious beginnings:

> [N]otwithstanding efforts by early geneticists to promote the gene, present fashion must not make us forget that in the first half of the twentieth century, hormones took pride of place as

> life's master molecules, and the endocrinologist took precedence over the geneticist as the scientist offering the means to control life (Rasmussen, 2002 p299).

While there are many informative similarities, the narratives of insulin and the sex hormones also provide examples of distinct, subtly but significantly different, models for the rationale behind hormone treatments. Insulin offered the relatively straightforward paradigm of a well-recognised disease, the symptoms of which could be alleviated by application of a hormone whose absence, diminished or inactive nature, was an explanatory feature in the aetiology of the condition. The development of oestrogens and testosterone however, was coloured by contemporary cultural assumptions about male or female 'nature' and masculinity/ femininity. Some pertinent aspects of the early clinical use of these hormones will be discussed as a means of highlighting the ways in which endocrine therapies were subject to shaping by social and cultural influences.

The final sections of this chapter will deal with two relevant, though at the time separate, aspects of medical study of growth: the laboratory-based research into the pituitary gland searching for a hormone factor responsible for stimulating growth, and an increasing public health interest in the issue of child growth as an indicator of proper development and well-being. The latter element, though not connected to endocrinology, is germane because it produced the statistical methodology for dividing childhood growth into 'normal' and

‘abnormal’ patterns and bringing the cases of abnormal growth to medical attention that would later be used to select patients for human Growth Hormone therapy after that first successful trial in 1958. The specific evolution of hGH and the effect of these factors on it, will be the focus of the successive data chapters, but the first task of this chapter is to briefly recount some of those ‘conceptual schema, experimental traditions, intellectual investments, ways of understanding the world, models and metaphors’ which characterised and prefigured the world out of which endocrinology would arise.

SECTION 1: THE NEW PHYSIOLOGY; SEX, AGEING AND THE GLANDS

‘Internal Secretions’: The Emergence of Endocrinology

The earliest physical manifestations of hormonal activity to be observed were most likely the effects of castration and the oestrus cycle, even if they were not specifically understood as such at the time. There is evidence that the effects of castration in men and animals has been known since ancient times as evidenced by the practice of employing eunuchs as servants, and in practices of animal husbandry involving removal of the gonads (Corner, 1965; Davis et al, 2005). Other symptoms, caused by the routine action of sex hormones were also known; Aristotle having documented observations on the menstrual cycle and menopause[32] (climacteric) (Davis et al, 2005). Banks (2002) recounts various examples from

ancient Egyptian, Babylonian, Chinese and Greco-Roman cultures of practices in which a perceived weakness in an organ was treated by the sufferer ingesting extracts of that organ from another source. Notably, the treatment mentioned often involves eating some component of the male organs of an animal to treat impotence. Ancient and classical cultures were also aware of other effects which are now associated with the action or absence of hormones such as diabetes (Tattersall, 1995) and of course human growth and development, but these were not yet associated with particular organs of the body.

The first suggestions that the body might internally produce chemical substances that affected its physiology came in the eighteenth century and again concerned the gonads. In 1775, Parisian physician Theophile de Bordeau, having observed the behaviour and characteristics of eunuchs and castrated animals, envisioned, with some perspicacity, that a substance secreted by the testis or ovaries into the blood stream might be responsible for the development of secondary sexual characteristics (Davis et al, 2005). Bordeau himself was content with the theoretical proposition and it was left to others to carry out experimental investigation of his work (ibid.). By the nineteenth century physiology had claimed its disciplinary independence from the much older traditions of medicine and anatomy and it was from this nascent discipline that the pioneering turn-of-the-century endocrinologists would largely arise, although

only some would be lionised for their achievements by the succeeding generations of practitioners, while others would receive derision or infamy for their efforts (Borell, 1985).

Another Frenchman, physiologist Claude Bernard is generally credited with inventing the term ‘internal secretions’ in 1855, in the course of his work on a different endocrine phenomenon, diabetes (Davis et al, 2005; Henderson, 2005). While Bernard was using the phrase to describe the secretion of sugar, not a hormone, from the liver, which he thought, was the site of the diabetic dysfunction, it appears the expression was commandeered into general use to describe ‘the passage of any molecule (including carbon dioxide) from tissues into blood’ (Henderson, 2005 p5). In 1869 in an address to the Medical Faculty of Paris, Charles-Edouard Brown-Séquard, a contemporary of and later successor to Bernard, posited that the glands ‘supply to the blood substances which are useful or essential and the lack of which may produce physiological signs’ (Biedl, 1913 cited in Tattersall, 1996 p236). In England, neurosurgeon Sir Victor Horsley was attempting to produce animal models of human disease, removing the thyroid gland of a monkey to induce a condition similar to myxoedema and also reported removing the pituitary glands of experimental dogs, although he did not detect any detrimental effects (Tattersall, 1995, 1996). Whilst it can be seen that a body of work amongst investigative physiologists was making some headway into uncovering the role of hormones as chemical messengers or ‘internal

secretions', the predominant model of bodily control was that of the non-chemical nervous system. By the turn of the century this would change through a series of dramatic events that would propel the idea of internal secretions and the role of the glands to widespread public and professional awareness.

Brown-Séquard's Organotherapy

In 1889 Brown-Séquard, now aged 72[33] and suffering from fatigue, loss of strength and insomnia, announced during a series of papers given at the Societé de Biologie in Paris, that he had been mentally and physically reinvigorated by a 3-week course of injections with an extract derived from the testicles of dogs and guinea-pigs (Corner, 1965; Kahn, 2005; Sengoopta, 2003). Brown-Séquard 's claims were largely, but not entirely, met with scepticism from the medical establishment of the day and with a mixture of derision and fascination from the lay press, which would come to typify the public reaction to various anti-ageing therapies from the nineteenth century to the present. Accounts of the exact nature of the criticism are varied; Borell (1985, p8) notes 'I have found no criticism of Brown-Séquard's experiments on the basis of physiological theory. It was the social implications of his claims that aroused particular antagonism within the medical community, especially in Britain.' Henderson (2005 p5) describes an article about Brown-Séquard appearing in the British Medical Journal at the time entitled 'The Pentacle of Rejuvenescence', the reference to the occult symbol of

the pentacle clearly inviting a similar view of the merits of testicular extracts. Given that Brown-Séquard 's statement led to a flourishing trade in testis extracts (Corner, 1965) it is likely that the most hostile reactions came from those adherents of scientific medicine, while more practically-minded physicians, pharmaceutical manufacturers and popular elements of the press, wholeheartedly endorsed the announcement.

Brown-Séquard made a second announcement in 1889 in which he proposed that the extracts of animal ovaries could have a similar effect on women as his testicular extract did for men (Corner, 1965) and a further claim in 1891 arguing that all tissues give something special to the blood;

> [E]ither an active principle or principles which might be extracted and used by physicians to treat a variety of intractable diseases (Borell, 1978 p284).

Despite the critical reception in some quarters of Brown-Séquard's ideas, therapy with glandular extracts, which soon gained the name 'organotherapy',[34] was popular with many physicians who were often quite happy to prescribe organ extracts when conventional treatments of the time did not appear to produce the desired results (Borell, 1985). The fact that Brown-Séquard was a physiologist of international standing, renowned for his work on spinal and vasomotor nerves, helped spread the interest and enthusiasm for using organ extracts (Tattersall, 1996). Schwartz observes 'after this

testimonial by one of the century's leading physiologists, the floodgates of organotherapy opened wide' (1999 p703).

The first products to appear were extracts of animal testicles or ovaries (often mixed with other organs). Haber (2004) reports that in August 26, 1889, *The Medical News* carried an announcement that a firm of druggists had isolated the 'active principal of testicular fluid' and were able to supply their compound, known as 'Spermine' to the public for reproducing the stimulant effects observed by Dr Brown-Séquard. Following Brown-Séquard's announcement it is reported that some 12,000 physicians had administered versions of the serum (Kahn, 2005) and 'organotherapy' grew into a 'fin-de-siècle panacea for virtually every conceivable disorder' (Sengoopta, 2003 p122). Brown-Séquard's 'elixir of life' was popular not only in Europe but also in the US (Cole, 1992; Banks, 2002). It is worth noting that for most of the nineteenth century the production and sale of medicines was essentially an unregulated activity, and proprietary medicines whose ingredients were not disclosed were widely sold (Anderson, 2006). Most remedies were prepared from plant extracts by pharmacists, apothecaries or doctors themselves, although pharmaceutical firms employing similar practices on a larger scale had been in existence for some time.

Brown-Séquard's announcement and the publicity it spawned led to extracts being produced from not just the testis or ovaries but from

virtually all tissues of the body (Hoberman, 2005). 'Spermine' type compounds may have lost some of their appeal over time, especially following the death of Brown-Séquard in 1894 (Achenbaum, 1978), but organotherapy products persisted. In 1896 the Burroughs Wellcome company had noted the professional demand for organ-derived products and were offering 'thyroid gland, thymus, orchitic substance, pituitary body, cerebrinin, ovarian substance, pineal gland, bone medulla, suprarenal capsules and splenic substance' in their patented 'tabloid' tablets (Tattersall, 1995). Kahn (2005) notes an advert appearing in the *Strand* magazine in 1912 for a Spermine-type elixir known as 'Sequarine' promising to treat 'nervousness', kidney disease, diabetes, anaemia, rheumatism, liver complaints, indigestion and paralysis among other ailments. Tattersall (1996) records that in 1913 the British Organotherapy Company offered a compound made from various organs including testes, spinal cord and brain, intended to treat 'conditions having as their origin degeneration, metabolic disorder, imperfect functioning, autointoxication, fatigue and exhaustion' (p239). Ovarian compounds were particularly durable as Corner (1965) and Banks (2002) report animal ovarian products still being commercially available into the 1930s and even the 1950s.

Schäfer, Starling, and the Rise of Scientific Endocrinology

As a challenge to the nervous theory of control, and given its source, the issue of internal secretions was firmly within the remit of

physiology. It is also of likely relevance that physiology had achieved independence as a discipline and had a number of figures keen to establish its scientific credentials. The contrast with the approach of clinicians can perhaps best be seen as one of methodology. The principle of organotherapy, based on Brown-Séquard's experiments, is that the glands of the body produce chemical substances which can be obtained through organ extracts (in the form of liquids, tablets or occasionally raw tissue) and applied as drugs to treat illness. Brown-Séquard had specifically envisioned his orchitic (testicular) extract as replacing the gonadal function lost to aging. Oudshoorn (1994) suggests that Brown-Séquard's theory harmonised with ideas of the testis as the seat of male sexuality that persisted in folk wisdom as well as with Victorian sexual theory that loss of testicular fluids led to loss of energy and debilitation whether through age or sexual indulgence. It is also likely that his ideas had some resonance with the replacement idea central to ancient practises (outlined above) of eating animal organs to treat perceived weakness in the corresponding part of the human body.

In the nineteenth century knowledge of functional anatomy and metabolism was limited; for example it was only in the 1840s that Claude Bernard had shown that sugar was normally present in the blood of animals and was not destroyed in circulation, while the functions of the pancreas, thyroid, pituitary and other organs was still

unknown or a subject of dispute (Tattersall, 1995). As a result much organotherapy involved speculative therapy based on perceived weakness of an organ in an illness, where kidney extract might be prescribed for any disease of the kidneys in the hope that a therapeutic replacement effect would occur. Pluriglandular mixtures, combining extracts of several organs were also used, on the basis that the body could extract those elements that it needed and whatever was superfluous would simply be ignored. These principles of organotherapy were explicitly laid down by organotherapy entrepreneur Henry Harrower in his 1914 book *Practical Endocrinology* (Schwartz, 1999), but it can be seen from the adverts and products on offer that the ideas were in use well before that date. Victorian sexual theory also infused much usage of the testicular and ovarian extracts. Ovarian extracts were applied not only to menstrual disorders but also to the broad range of 'women's problems' including hysteria and inappropriate sexual activity which came under the remit of gynaecology, while versions of Brown-Séquard's orchitic extract 'appeared to alleviate, if not cure, most known ailments' in the 1890s (Tattersall, 1995 p297).

Academic physiologists, as devotees of the scientific method, were committed to laboratory experiments to provide evidence of internal secretions. The cautious, methodological approach of the experimental physiologists was in contrast with the often enthusiastic use of largely uncharacterised organ extracts by physicians, as well

as the ‘home remedy’ organ preparations and elixirs produced by opportunistic hucksters. This generated a tension between the lab and clinical arenas caused by the gap between the expectations for organ extracts and technical expertise to measure the purported effects (Borell, 1985). These conflicts in endocrinology can be seen in the context of the times as:

> [P]art of a more general struggle between laboratory scientists and clinicians, which can be seen as characteristic of this period in medical history. The early decades of the twentieth century were marked by growing professionalization of the sciences, a process in which laboratory scientists presented themselves as the dominant professionals among those, including clinicians, who were concerned with natural phenomena (Oudshoorn, 1994 p45).

This conflict was also in many ways a clash between academic researchers, who ‘were convinced that they were “real scientists” and…more or less despised the average clinician’ (Sinding, 2002 p62) and practising clinicians, who resented the academics as out-of-touch and elitist (Schwartz, 1999; Sinding, 2002). The central issue was (instrumental) measurement rather than observation as the basis of proof.

Physiologists were not immediately attracted to the study of the internal secretions of the gonads, partly because they had very little

knowledge of the physiological role of these organs and also because claims made by Brown-Séquard about rejuvenation and restoring sexual function in the elderly seemed disreputable and damaging to scientific credibility (Borell, 1985). Instead the study of gonadal function was left to gynaecologists (discussed in more detail below) and the first evidence of a reliable therapeutic application for organ extracts would come from the study of other glands where there was a history of physiological investigation. In 1891 Victor Horsley and George R. Murray, building on Horsley's earlier animal model, showed that myxoedema (hypothyroid) patients could be treated with extracts of the sheep's thyroid to show clear remission of their symptoms. Further confirmation of the therapeutic activity of glandular extracts came in 1896 when William Osler reported successful treatment of Addison's disease with extract of the adrenal glands (Fisher, 2004).

A major event in developing British endocrinology came in 1893 when Edward Schäfer, professor of physiology at University College London, was directed to the apparent effect of adrenal gland extract on blood pressure following observations made by George Oliver (Henderson, 2005). Schafer was sufficiently impressed with the evidence that he was prepared to accept the principle that some glands could produce internal secretions capable of affecting the body's secretions and determined to study them. Schäfer was to play a crucial role in shaping what he described as the 'new

physiology' incorporating chemical as well as nervous control of the body (Borell, 1978 p283). Henderson describes Schäfer as

> [P]erhaps the first serious laboratory scientist to involve himself with the endocrine system… [He] was sceptical about clinical observation as a basis for the science of endocrinology, and had little time for Brown-Séquard's fantasies (2005, p7).

A significant part of the difficulty facing Schäfer and his fellow academic physiologists was the lack of existing reliable assays for chemical effects on physiology. Since biochemistry was barely advanced at the time, internal secretions could not readily be isolated and identified in the laboratory and instead physiologists like Schäfer insisted on rigorous laboratory experiments to verify the physical effects of organ extracts. As well as the traditional physiological approach of taking mechanical measurements, for example in muscle contraction or blood pressure, they now embraced the methodology of organ removal (extirpation), transplantation and extract injection as evidence of a chemical secretion affecting the body (Borell, 1985).

> The concept of hormones triggered a new experimental approach in laboratory science. At the turn of the twentieth century scientists began to search actively for the chemical substances in the sex glands using the techniques of castration and transplantation (Oudshoorn, 1994 p21).

The physiological approach had some early success in verifying the action and utility of some internal secretions. In 1895 Schäfer addressed the British Medical Association giving an overview of the state of contemporary knowledge on the internal secretions of the thyroid, pituitary and adrenal glands which had all been shown to produce measurable changes in the blood pressure, but notably omitting the gonads, the secretory potential of which he remained sceptical about (Borell, 1985; Sinding, 2002). The blood-pressure raising factor of the adrenal gland could be successfully isolated and was marketed by Parke-Davis Company under the brand name 'Adrenaline' (Rasmussen, 2002). Schäfer's successor at UCL, Ernest Starling, was co-discoverer (with William Bayliss) of another internal secretion, produced by the intestines, which they named 'secretin' (Henriksen & Schaffalitzky de Muckadell, 2000). In 1905; addressing the Royal College, Starling coined the term 'hormone'[35] for this new type of chemical messenger secreted by the glands and tissues (Henderson, 2005).

SECTION 2: THE NEW MASTER MOLECULES

Hormones in the Twentieth Century 1: From Gynaecology to Monkey Glands

In contrast to laboratory physiologists, nineteenth century gynaecologists were already aware of the physiological changes induced in women by removal of the ovaries because of the popularity of this operation as a treatment for various 'female nervous

disorders' in the later part of that century. As early as 1896 Viennese gynaecologist Emil Knauer experimented with transplanting excised ovarian tissue into oophorectomised rabbits in the laboratory, observing that restoration of gonadal tissue to animals in which it had been surgically removed would restore and could even accelerate sexual maturation (Davis et al, 2005). The incorporation of Victorian cultural and moral ideology into medical theory on sexual behaviour and in particular the nature of the ovaries as the 'seat of femininity' continued with the characterisation of the sex hormones. It was assumed that there were only two sex hormones, one produced by the testis and responsible for producing male characteristics, the other produced by the ovaries and responsible for the development of female characteristics (Banks, 2002; Oudshoorn, 1994). These characteristics were understood to incorporate the physical, mental and behavioural aspects of gender and personality traits, which in line with contemporary views on gender roles, were not just different but diametrically opposed.

In Vienna Eugene Steinach, director of the Physiological Section of the Institute for Experimental Biology, observed, like Knauer before him, that castrated laboratory animals, rats in this case, did not reach normal sexual maturity, unless given gonadal implants, which would restore to them normal adult sexual characteristics. The process of vasectomy was known to destroy sperm-producing cells and lead to increased proliferation of other interstitial cells in the testis.

Performed in elderly male rats, the operation appeared to produce increased levels of energy, sexual activity, weight gain and glossier fur (Sengoopta, 2003). Steinach believed that amongst these non-sperm-producing cells lay a 'pubertal gland', which was responsible for male hormone secretion. Applying the theory to human males, Steinach reasoned that by killing off sperm-producing cells through vasectomy he could induce proliferation of hormone secreting cells and thus increase the body's hormone levels. If performed in ageing men this would restore their hormone levels to their youthful levels and effectively rejuvenate them like Steinach's experimental rats (Kahn, 2005; Sengoopta, 2003).

Throughout the 1920s Steinach promoted his operation (essentially a simple vasectomy) as a means to rejuvenation and attained a certain celebrity status (Haber, 2004; Hoberman, 2005). Steinach operations were performed all over the world and had a number of celebrity recipients including the poet W.B. Yeats and Sigmund Freud. American novelist Gertrude Atherton[36] also underwent a female rejuvenation process based on the Steinach principle, which involved irradiation of the ovaries (Kahn, 2005). The popular press of the time were filled with 'gossipy accounts of Steinach operations performed on ageing millionaires' (Sengoopta, 2003 p123). Steinach was not the only physician to translate the methods of animal experimentation into a clinical technique intended for the rejuvenation and reinvigoration of human patients. French-Russian surgeon Serge

Voronoff directly adapted the grafting techniques used to demonstrate the chemical potency of testis and ovaries in laboratory animals by grafting testicular tissue from apes and chimpanzees ('monkey glands') on to ageing men in a bid to restore their potency (Kahn, 2005, Sengoopta, 2003). He travelled the world exhibiting his star patient Edward Liadet, a 76 year old Londoner who claimed monkey gland transplants helped him feel and look as if were 45 again (Haber, 2004).

Despite criticism from the French Surgical Congress and Academy of Medicine who refused to support his research, Voronoff received significant, if not always deferential coverage in the lay press and, like Steinach achieved a certain celebrity[37]. The medical establishment of the day appear to have been more openly critical of Voronoff's more sensationalist practices than of the Steinach operation. Sengoopta reports that

> The medical press of the time was full of well-informed and spirited debates on Steinach's work, especially the operation for men. These discussions were uniformly respectful, but rarely uncritical or adulatory. One frequent and obvious charge was that the Steinach operation produced its effects solely by suggestion (Sengoopta, 2003 p125).

In comparison Voronoff's techniques met with a more sceptical response ranging 'from polite hearings to direct attacks' where 'many

authorities directly challenged the idea of transplanting animal glands onto humans' (Haber, 2004 p517).

Voronoff was by no means the only physician of the time practising testicular transplants. L.L. Stanley, a physician at San Quentin prison in California, is reported to have performed testicular transplants on over 600 inmates and other subjects between 1919 and 1922 involving both human and animal donors (Haber, 2004; Kahn, 2005). Despite increasing doubts among medical professionals about the efficacy of the method, Voronoff and other glanders 'continued to perform both animal and human operations to popular acclaim' (Haber, 2004, p518). If Serge Voronoff achieved a certain notoriety as the most well-known 'monkey-gland' proponent to arise from the ranks of medicine, perhaps the most infamous, disreputable and blatantly fraudulent gland transplanter was "Doctor" John Brinkley, the "goat gland doctor". Operating in Milford, Kansas, Brinkley combined radio evangelism and preaching with running his own hospital offering goat and human testicular transplants to treat everything from impotence to insanity, whilst offering the hope of unlimited lifespan (Hamilton, 1986). Through his glanding activities Brinkley became a millionaire and later ran unsuccessfully for governor of Kansas. In 1930 the Kansas Board of Medical Registration and Examination revoked his license to practice, his credentials were publicly challenged and bankruptcy threatened,

forcing Brinkley to move to Mexico and restart his operation there (Haber, 2004; Hamilton, 1986).

Hormones in the Twentieth Century 2: Industry and Insulin

While Voronoff and Steinach were touring the world with their rejuvenation cures, those researchers who had stayed in the laboratory were also making progress. The first textbook of endocrinology, *Innere Sekretion* was published in 1910 (initially in German) with the first English textbook *Internal secretion and the ductless glands* following in 1912, written by Swale Vincent a former student of Edward Schäfer (Borell, 1978). Physiologists had by this stage established an accepted protocol for the investigation of glandular properties:

> Typically, a deficiency condition was created in an experimental animal (ideally, a condition with clear similarities to a human disease) by surgical removal of an endocrine organ, and then chemical extracts of the organ were prepared from slaughterhouse waste or other abundant sources and tested for their capacity to remedy the experimental animal's condition (Rasmussen, 2002 p301).

These experimental animal models also provided a means of measuring the activity of different extract preparations, for example the rate of comb formation in cockerels used to test testicular extracts or the growth rate of the tails of rats injected with pituitary extracts.

While the early history of endocrinology was primarily a European and British affair, the laboratory investigation of hormones in the twentieth century became increasingly dominated by North American research teams. In Britain the elite of endocrinology consisted mainly of qualified physiologists such as Schafer, Starling, Bayliss and Vincent[38] who tended to gravitate towards a few centres of excellence mainly in London or Edinburgh and were, in the early decades of the twentieth century, divided over the proper relationship between laboratory investigation and practical medicine. By contrast, in North America the Flexner report of 1910 had stimulated reform of medical education, there had been an active endocrine society since 1917[39] and clinicians and chemists were 'less discouraged to take an open interest in the new field than was the case in Britain' (Medvei, 1993 p276). The lack of biochemical knowledge which had so hindered earlier investigations of the body's glands was being addressed with the rise of biochemistry as a distinct laboratory-based discipline and by the 1920s most major US medical schools had a biochemistry department (Rothman & Rothman, 2003).

By the beginning of the 1920s the importance and therapeutic potential of the endocrine glands was sufficiently known to generate a 'critical mass' of endocrinology research but it was still a field troubled by a confusion of information and opportunistic practitioners (Tattersall, 1996; Sengoopta, 2003). Medvei (1993) attributes much

of the freedom of US clinicians to get involved in endocrinology to the strenuous advocacy and teaching of Harvard-based endocrinologist Fuller Albright, who promoted the dual path of laboratory research and clinical experimentation with patients as the best practice for academic medicine. US experts were also more likely to leave established centres and establish successful new departments elsewhere. This latter tendency is perhaps best exemplified by the career of Herbert Evans who trained at Johns Hopkins but moved to Berkeley (comparatively unknown at that time) in 1915, setting-up one of the first 'super-labs' with modern equipment and a team of experienced investigators from different backgrounds, several of whom, including Evans were instrumental in researching the hormones of the pituitary gland (Medvei, 1993).

The importance of the US contribution to endocrine research is highlighted by two significant discoveries made in the early decades of the twentieth century.

The study of hormones was a high priority for biochemists, not least because it provided a means through which ambitious practitioners could elevate the status of their discipline, which was often regarded by clinicians and others as essentially a technical or service role (Rasmussen, 2002). One such biochemist was Edward C. Kendall, head of biochemistry at the Mayo Clinic, who in 1915 successfully isolated and crystallised the thyroid hormone, which he named 'thyroxine'. In its pure form this chemical could replace the use of

crude thyroid gland extracts to treat myxoedema pioneered some years earlier by Horsley and Murray. At least as important as Kendall's discovery is the fact that he took out a patent on his method of producing the drug with the University of Minnesota which then licensed manufacturing rights to Squibb Pharmaceuticals in return for a share in the profits from Thyroxin sales (Rasmussen, 2002). Pharmaceutical firms had been attracted to the commercial potential of organotherapy since Brown-Séquard's announcement but now they, especially those firms who wanted to secure a reputation as 'ethical' pharmaceutical companies, were becoming attracted to the potential of laboratory-derived products bearing the scientific seal of approval. Thyroxin set an important precedent for possible academic-industry collaborations but it was another endocrine discovery that would truly highlight the potential, clinical and commercial, of the field.

Diabetes Mellitus had already been identified as a disorder of the metabolism linked to the pancreas in the nineteenth century through the work of investigators like Claude Bernard and Oskar Minkowski. In the intervening time a number of researchers had attempted to derive a pancreatic extract that would ameliorate the symptoms of diabetes in various animal models but with limited success (Tattersall, 1995). Side effects caused by the impure nature of the extracts had all but halted any progress in this area until Frederick Banting, part of a team working on the problem at the University of

Toronto, Canada, suggested a new surgical technique, which might produce a better extract (Sinding, 2002). In 1922 Banting, together with his colleagues, medical student Charles Best, biochemist James Collip and head of the department of physiology J.J.R Macleod produced and successfully tested an alcohol-based extract of bovine pancreas on a number of patients (Bliss, 1983). As with Thyroxin, the discovering researchers took out a patent on their method of production through the University and licensed production of their discovery to a commercial manufacturer, this time US-based company Eli Lilly[40] (Bliss, 1983; Sinding, 2002).

There were a number of advantages to all parties in these agreements. Laboratory researchers faced restrictions on the amount of raw material- usually in the form of glands removed from animal carcases- they could practically obtain and process and would also have faced significant expense in attempting large scale preparation of hormone extracts (Davis et al, 2005; Oudshoorn, 1994). By licensing their discoveries to industrial manufacturers they were able to relieve themselves of this burden and gain financial recompense for their discoveries which often took the form of increased research funds paid through the patent-holding Universities (Rasmussen, 2002). In return Eli Lilly gained preferential access to a new scientifically-validated drug with a large, medically recognised but poorly controlled patient population- in other words a ready-made market. Eli Lilly was already an established pharmaceutical company

in 1922 and had publicly declared itself an ‘ethical’ company dedicated to scientific standards of research and standardisation as a means of distinguishing itself from patent medicines made of secret (undisclosed) ingredients and the general suspicion of charlatanry accompanying many pharmaceutical enterprises at the time. Insulin was seen as a ‘respectable’ drug because it was aimed at a well-defined disease (Oudshoorn, 1994).

By the 1920s states were also beginning to take a greater interest in the regulation of pharmaceuticals:

> In the early 1920s drug legislation was very similar in the United States, Canada, and the Britain. The Canadian Food and Drug Act was enacted in 1920, and its American counterpart had been enacted in 1906; these acts made the adulteration and misbranding of drugs illegal, but did not oblige pharmaceutical manufacturers to disclose the content of their preparations (Sinding, 2002 p253).

Scientific luminaries of the time including such as renowned neurosurgeon Harvey Cushing and Leonard Rowntree, president of the Mayo Clinic were increasingly vociferous in their criticism of the less scrupulous clinical and commercial adherents of organotherapy (Hoberman, 2005; Schwartz, 1999). In this atmosphere pharmaceutical companies interested in fostering a credible reputation with physicians, found it could be best achieved by aligning themselves with the increasingly dominant scientific

character of the mainstream medical profession and the prestige of association with universities and indirectly with state governments who funded the universities (Oudshoorn, 1994; Sinding, 2002). The popular acclaim which greeted insulin was also a significant boost to all involved with the enterprise of endocrinology- it was treated as a new 'miracle drug' and in 1923 Banting and Macleod were awarded the Nobel Prize for their discovery, which they shared with their two co-workers (Bliss, 1983).

The Commercial Model

Although much of the impetus of scientific discovery of hormones had passed from the UK to the USA, the UK was to play an important role in the standardisation process. The 1911 National Health Insurance Act made the British government a major purchaser of pharmaceuticals and this promoted a greater interest in regulating drug quality and efficacy, notably through the involvement of the Medical Research Council (Sinding, 2002). By the end of 1922 the UK MRC had sent a delegation headed by Sir Henry Dale to liaise with the Macleod's team and Eli Lilly, and also set up its own committee of physicians to oversee the clinical experimentation with insulin in the UK. Two international conferences on insulin standardisation, both chaired by Dale, were held; the first in Edinburgh in 1923, the second in 1925, at which agreement on international units of measurement of insulin activity and the standard assays were agreed among the scientific community. A dry

powdered sample of insulin to act as an international reference standard was prepared at the National Institute for Medical Research in London (NIMR) (Sinding, 2002).

Government health officials were not the only parties interested in the new wonder drug. The Scandinavian pharmaceutical company Novo Nordisk was founded following a visit to Toronto and insulin was the first product of the Dutch firm Organon founded in 1923 (Bliss, 1983; Oudshoorn, 1994). The story of Organon exemplifies the new academic- industrial partnerships which were coming to characterise the scientific development of hormones: Ernst Laqueur, head of the leading Dutch research group in endocrinology, the Pharmaco-Therapeutic Laboratory of the University of Amsterdam, founded the company as part of a solution to the problem of getting access to raw materials for the Laboratory's endocrine research program. Laqueur signed a contract with Zwanenberg slaughterhouses in Amsterdam making Laqueur scientific consultant for the preparation of medical organ products in return for sufficient animal organs for his academic work, marking the founding of the pharmaceutical company Organon (Oudshoorn, 1994). Like Eli Lilly, Organon styled itself as a pharmaceutical company with a firmly scientific approach as reflected in its early full title: 'Organon limited company for the manufacture of organ preparations on a scientific basis'.

> By emphasising its scientific character, Organon tried to clear the clouds of illegitimacy and quackery hanging over previous

> organ preparations, and sought to convince the medical profession of the superior quality of its products (Oudshoorn, 1994 p84.)

Although Organon's first commercial product was insulin the company would go on to specialise in Laqueur's main interest, sex hormone preparations.

In 1926 the presence of oestrogenic hormones was detected in urine, providing a new and much cheaper source of raw material from which to obtain hormonally active substances and which pharmaceutical companies were better placed to collect on a large scale than academics (Davis et al, 2005; Oudshoorn, 1994). By 1929 three separate research teams, in the US, Germany and the Netherlands, had isolated a crystallised pure chemical substance from human urine which was named Theelin by the US investigators and oestrin (now oestrone) elsewhere (Davis et al, 2005). This was the first purified chemically discrete oestrogen[41]. Importantly all three teams of scientists were working in conjunction with pharmaceutical companies: Edward Doisy working in the US collaborated with Parke, Davis and Company, Adolf Butenandt in Germany worked with Schering-Kalhbaum Company and the third team was headed by Ernst Laqueur at the University of Amsterdam and Organon (Oudshoorn, 1994). Biochemist James Collip, who had worked with Banting, Best and McLeod on the discovery of insulin, isolated another oestrin-like hormone for Ayerst Laboratories in 1930 that was

marketed for clinical use under the brand name Emmenin (Davis et al, 2005).

The 1930s were marked by further ‘races’ to discover new hormone drugs as academic researchers and their pharmaceutical industry backers competed for the prestige and profits. Laboratory and clinical tests had suggested that adrenaline was not the only hormone produced by the adrenal glands. Edward Kendall at the Mayo Clinic worked with Parke-Davis to try and isolate the new hormone or hormones while his main rival Tadeus Reichstein of Switzerland was supported by Organon (Rasmussen, 2002). Following the success of the oestrogens (and later progesterone) the discovery of testosterone in the mid 1930s was also fuelled by competition between three rival research teams, all supported by different pharmaceutical company backers[42] (Freeman, Bloom & McGuire, 2001). In 1930 the UK Medical Research Council set up a Committee on Sex Hormones chaired by Francis Marshall (Schafer’s co-worker at Edinburgh and author of *The Physiology of Reproduction*). Its main purpose was to deal with an increase in funding applications for work on the newly discovered sex hormones and also ‘to confer respectability on what had been regarded as a rather shady subject’ (Borell, 1985 p27).

The first Conference of the Standardisation of Sex Hormones was held in 1932, with a second in 1935, at which the international standard assays were determined for detecting oestrogens and

testosterone respectively (Oudshoorn, 1994). The availability of genuine, scientifically verified hormone preparations spelt the end of the market for organ extracts, of which gonadal preparations had always been amongst the most popular and by the 1930s the sales of glandular products were in irreversible decline (Hoberman, 2005). Henry Harrower, one of the last popular organotherapy enthusiasts, died in 1934 (Schwartz, 1999) while the techniques of Voronoff and Steinach could not produce lasting results and were gradually dropped from clinical use (Kahn, 2005). In their place was a new network of drug production driven by scientific research and characterised by international standardisation and industrial-scale production.

Renegades or Pioneers? The Scientific Basis of Rejuvenation Therapies

From a contemporary perspective, especially one drawing on normative, retrospective historical accounts, the anti-aging activities of Charles-Edouard Brown-Séquard, Eugen Steinach, Serge Voronoff and their contemporaries may appear at best naïve, eccentric or as simple medical quackery. Certainly there were those such as “Dr” Brinkley whose medical qualifications were entirely suspect[43] and whose central purpose seems to have been a mixture of self-promotion and profit. A large part of the significance of Brown-Séquard’s observations can be linked to the attention they drew to the issue of internal secretions and the resultant stimulation of

research into the glands leading to the emergence of endocrinology. In many ways the activities of Steinach and Voronoff can be seen as extensions of Brown-Séquard's work, in particular taking the association between ageing, loss of function and activity of the testis or ovaries. While they may have earned controversy in the medical community for their practices it should be noted that they were all part of that community and made significant scientific and medical contributions outside their anti-ageing work.

Brown-Séquard was already a famous neurophysiologist, renowned for his work on spinal and vasomotor nerves (Tattersall, 1996) and his study of the effects of adrenal gland removal (Freeman, Bloom & McGuire, 2001) when he made his 1889 announcement about the rejuvenating properties of testicular extract. Steinach was nominated for the Nobel Prize in physiology six times between 1921 and 1938, although he was never awarded it (Sengoopta, 2003). Voronoff too made contributions to the practice of graft and transplantation in clinical practice, although his choice of graft material never achieved truly legitimate status (Kahn, 2005). Steinach and Brown-Séquard were certainly cautious in reporting their results and eager to seek confirmation of their results from other practitioners. Indeed in an effort to counter the more unscrupulous vendors of copycat elixirs, Brown-Séquard and his assistant Arsene d'Arsonval distributed their own compound free of charge to physicians willing to administer it

and record the results on their patients (ibid.) in a move that could be considered an early form of clinical trial.

Brown-Séquard, Steinach and Voronoff all drew their therapeutic rationales from prior experiments and observations in animal experiments and had a specific theory of how their interventions would work. With regards to gland grafting, it was commonly assumed in the nineteenth century that tissue could be unproblematically grafted from animals to humans or between unrelated humans and it was only after a body of experimental work in the 1920s and 1930s, in particular on skin grafts, that the problem of rejection was understood (Hamilton, 1986). Hamilton contends that it was only later, when the monkey gland transplants and private clinics like Paul Niehans' became more embarrassing to orthodox medicine, that the medical histories were written or rewritten to make it appear that there had never been any mainstream enthusiasm for rejuvenation – hence the reputations of Claude Bernard or Edward Schäfer remain in high esteem among modern practitioners while Brown-Séquard's does not.

A significant part of the criticism and disreputable air attracted by the work of these individuals can be attributed to the topic rather than the means of their research. The idea of reversing aging carried obvious connections to medieval alchemists searching for an elixir of life or the apocryphal fountain of youth (an association alluded to by Harvey

Cushing when he branded Brown-Séquard ‘the Ponce de Leon of our predecessors’ in 1921 (Schwartz, 1999 p705). It appears that it was especially the focus on the sexual aspect of rejuvenation that troubled many commentators at the time (Borell, 1985). At the time of his announcement the *Boston Medical and Surgical Journal* responded with an editorial stating ‘we hope that we may soon hear the last of Brown-Séquard’s disgusting advice to old men’ (Unsigned editorial, 1889 cited by Cole, 1992 p180). Although Victorian ideas about the inevitable immorality and health risks of any and all sexual behaviour died along with the theory of nervous energy, the prospect of reawakened libidos still gave rise to concern over the Steinach operation in the twentieth century (Sengoopta, 2003).

While concerns over male sexuality may have rendered any therapeutic intervention unacceptable for many commentators, the same did not apply to women. Ever since de Gardanne codified the menopause as a specific medical condition at the beginning of the nineteenth century the characteristics of the menopause and post menopausal state came to be seen in an increasingly negative light by gynaecologists. The ovaries were viewed as ‘organs of crisis’ responsible for both preserving a feminine essence when functioning correctly and for producing a wide range of physical and mental or nervous disorders when failing (Banks, 2002; Hoberman, 2005; Oudshoorn, 1994). Oestrogens were investigated in virtually the whole spectrum of contemporary ‘female disorders’: in 1927

Organon's ovarian extract Menformon, was being tested in psychiatric disorders- schizophrenia, melancholia, psychoses and depression and further indications for joint and skin diseases (although in the context of being related to some ovarian dysfunction at root cause) were added two years later (Oudshoorn, 1994). They found particular focus in treating the menopause, that 'crisis' of female health:

> With the discovery of hormones, emphasis shifted from the ovary to oestrogen as the source of femininity. In the 1930s many diseases common in older women came to be attributed to the low levels of sex hormones following menopause. In this way, menopause (and ageing in women) became increasingly characterised as an oestrogen deficiency disease, with replacement of oestrogen as the logical treatment (Banks, 2002 p7).

In contrast although a male climacteric (hormone decline with ageing) was proposed in 1939, mass testosterone therapy was championed in the 1940s by popular science writer Paul de Kruif, and pharmaceutical companies like Schering AG tried to promote the use of their testosterone products for treating aging males, testosterone therapy never achieved a significant market (Hoberman, 2005, Oudshoorn, 1994).

Enthusiasm for glandular therapy was selective and imbued with cultural concerns: homosexuals and 'sexually frigid' women were

treated with testosterone to cure their errant tendencies while oestrogen injections were tested as a means of stimulating breast enlargement, but male physicians of the 1940s had little interest in salvaging the sex lives of their middle aged or elderly patients and there was no direct-to-consumer advertising to stimulate grass roots demand (Hoberman, 2005). Additionally, Oudshoorn suggests another element:

> Although there existed a potential audience for male sex hormones, it was not embedded in any organised market or resource network. The marketing of male sex hormones lacked an institutional context for both production and promotion of male sex hormones, as it was not connected to any medical profession comparable with gynaecology (Oudshoorn, 1994 p109).

Urological clinics were too limited in medical remit and patient population to serve a similar function to their gynaecological counterparts. The issue of testosterone in ageing and whether there is any medical benefit in addressing it remains a point of debate in the present time (Blackman et al, 2002; Tenover, 1998; Vance, 2003; Vainionpää & Topo, 2005; Vermeulen, 1993). However, testosterone did not disappear and instead found acceptance in several non-sex related clinical applications such as treating testosterone deficiencies (hypogonadism) which could cause stunted growth and sexual immaturity in adolescence (Rothman & Rothman, 2003). It was also

tested as a growth-promoting agent in infants and small children and in other cases of dwarfism (Hoberman, 2005).

SECTION 3: GROWTH AND THE PITUITARY

The Pituitary in the Laboratory

The earliest clinical association between the pituitary gland and the phenomenon of human growth is generally credited to Pierre Marie, Chief Assistant to Jean-Martin Charcot at the Salpêtrière during the closing decades of the nineteenth century (Medvei, 1993; Tattersall, 1996). It was not dwarfism that prompted Marie's observations but cases of acromegaly (excessive growth) which he deduced to be caused by tumours of the pituitary gland. However, the field of pituitary exploration was still in a state of relative confusion; following Marie's association of enlarged pituitary size with acromegaly, the physician Fröhlich described the syndrome that would bear his name, in a teenage male patient displaying sexual infantilism, female patterns of fat distribution and a pituitary tumour (Tattersall, 1996). How could the pituitary apparently cause acromegaly in some patients, dwarfism in others and sexual infantilism in Fröhlich's patient? The scientific investigation of the pituitary, as with other hormone secreting glands, was to be directed not from the clinic, but from the laboratory.

Between 1908 and 1912 the pituitary gland came under the special attention of renowned US neurosurgeon Harvey Cushing, working at

Johns Hopkins Hospital, after he encountered a patient with Fröhlich's syndrome (Fulton, 1946). Cushing's surgical technique allowed him to successfully produce an animal model of pituitary damage in dogs, finding that full removal of the pituitary (hypophysectomy) was inevitably fatal but a model of diminished pituitary function could be produced by partial removal or lesion of the gland. In 1912 Cushing published a monograph entitled *The Pituitary Body and its Disorders* setting out a number of advances in the study of that gland (ibid.). The pituitary he announced, was split into two main lobes: posterior and anterior, which secreted separate 'principles' to different locations, challenging the prior assumption that each organ only produced one type of active extract or hormone (Tattersall, 1996). In *The Pituitary Body* Cushing refers at least twice to 'the hormone of growth' although such a principle had not been isolated or even fully demonstrated experimentally. Once a viable animal model of hypopituitarism had been produced the way was open for trials of pituitary feeding and injecting.

At Herbert McLean Evans 'super-lab' at the University of California in Berkeley, animal experiments showed that injected extracts of bovine anterior pituitary lobe could reverse the effects of pituitary removal in tadpoles and rats and could also produce growth considerably above the normal level in normal rats so treated (Medvei, 1993). For the production of these 'gigantic rats' Evans was awarded the Gold Medal of the American Medical Association in 1923, although the

event was somewhat overshadowed by that year's Nobel Prize awarded to Banting and Mcleod for the discovery of insulin (Tattersall, 1996). This series of experiments demonstrated that there was a growth-promoting factor present in the extracts of the pituitary but there was still much uncertainty as to which hormone or hormones might be responsible (Hughes, 1977; Sawin, 2001).

During the 1930s, no doubt stimulated by the clinical and commercial successes of other scientifically derived hormone drugs, laboratory research on the pituitary intensified with attempts centring on the biochemical separation of the different active components from dried animal pituitaries (Ibid.). Nonetheless the sheer unprecedented number of pituitary hormones[44] meant that the investigational process was particularly complex. A letter published in the British Medical Journal in 1939 provides good overview of the physiological work at the time:

> The complete cessation of growth after hypophysectomy, the demonstration by Evans and Long of giant rats produced by extraction of pituitary extracts, and the similar production of acromegalic symptoms in dogs described by Putnam, Benedict, and Teel, confirmed by Evans, leave little doubt of the major part played by the pituitary gland in the control of normal growth. There has been, however, much discussion, at times quite acrimonious, about the identity of the hormone responsible for these effects. Whereas Evans and his

> colleagues maintain that they are due to the action of a specific growth hormone, Riddle and Bates suggest that the growth effects of pituitary extracts are the result of "a balanced combination" of prolactin, thyrotrophic, or perhaps adrenotrophic hormones (Anon, 1939 p653).

Evans' team continued to search for a specific growth hormone and in 1944 Evans' former student turned collaborator Cho Hao Li successfully isolated and purified growth hormone from animal pituitaries (Hughes, 1977; Medvei, 1993). Even as the era of growth hormone research was beginning, interests outside the field of endocrinology were emerging which would also have a significant impact on its application.

Child Health, Paediatrics and Auxology

A concern for the health of children emerged as a specific interest of the public health movement during the nineteenth century. Infectious diseases were a major cause of child mortality[45] during this era, prompting the growth of child care as an area of medical specialisation in Europe and the US. In Britain, public health concern over the welfare of children manifested itself in other ways. Tanner records:

> In the early part of the nineteenth century a new tradition of growth studies appeared, born of the reaction of humanitarians to the appalling conditions of the poor and of their children. It developed amongst the conglomerate of Factory Legislation, Poor Law Commissions, and Sanitation and Housing Acts

> which embodied the new and powerful practice of public health (Tanner, 1981 p142).

The first British factory report, published in 1833, drew upon the public health work of Villermé and Quetelet[46] comparing the height of factory-employed children to the statistical average height for their age groups as an indicator of overall health status (Tanner, 1981). Further factory reforms (1872-3) put the issue of children's growth firmly under medical supervision as a combination of height, weight, chest circumference and weight-for-height was employed to prevent children too sickly or too young from being employed by unscrupulous factory owners.

In the early decades of the twentieth century the issue of child health took a significant place in the public health mission of nation states, through an increasing range of institutions and programmes of surveillance:

> The significance of the child was that it underwent growth and development: there was therefore a constant threat that the proper stages might not be negotiated that in turn justified close medical observation. The establishment and wide provision of antenatal care, birth notification, baby clinics, milk depots, infant welfare clinics, day nurseries, health visiting and nursery schools ensured that the early years of child development could be closely monitored (Armstrong, 1995 p396).

Growth, as a major component of child health was also monitored through the spread of school-based height surveys in Europe and

America (Tanner, 1981). A new wave of academic, multi-disciplinary, mainly US-based growth studies were able to adopt and build on the work of the anthropologists and statisticians of the nineteenth century, including the observations that different individuals develop and physiologically mature at different rates and that the development of bones ('bone age') can often be a better measure of an individuals physiological advancement than chronological age. X-rays were now available to take measurements of the bones in the hand and wrist and the first atlases of skeletal maturation were produced by Todd in 1937 and Greulich and Pyle in 1950 (Tanner, 1981). Studies were made of the times of bone development (including epiphyseal appearance and fusion), growth tempo, skin thickness, pubertal development; psychological and social functioning and new charts were created for predicting an individual's adult height from skeletal age measurements.

In 1948 the Ministry of Health decided to set up a large-scale UK-based growth study based at the National Children's Home in the town of Harpenden near London (Tanner, 1981). James M. Tanner, a medical graduate lecturing on growth and anatomy at Oxford was approached to run the study and travelled to the US in 1948 to tour all the major longitudinal studies of growth being carried out there and learn their methodology. The UK and, through international collaboration, European growth studies thus adopted the statistical and anthropometric approach to the study of growth distilled from the US studies, producing national standards for childhood growth and

development which could be readily applied by easily distributable charts.

The Endocrinology of Growth

By the third and fourth decades of the twentieth century the medical techniques existed to bring physical height into focus as a specific object of medical surveillance. Of course extremes of human stature had been recognised for centuries as dwarves or giants, but the instrumental measurement of standing or sitting height, bone age, and fat distribution provided the necessary 'objective' indicators of the body's developmental status to categorise children as having normal or abnormal growth patterns (Hall, 2006). This was not, however, of much immediate significance for endocrinologists. There is evidence of some organotherapy for growth disorders using crude pituitary extracts, as Harvey Cushing in a 1921 address to the Association for the Study of Internal Secretions entitled *'Disorders of the pituitary gland. Retrospective and Prophetic'* was moved to give the following sarcastic appraisal of such practices:

> [C]hildren are either too short or too tall, too fat or too lean… the Lewis Carroll of today would have Alice nibble from a pituitary mushroom in her left hand and a lutein one in her right and, presto! She is any height desired (Cushing, 1921 cited in Tattersall, 1996 p 239).

Tattersall (1996) also records that fashionable London endocrinologist Langdon Brown was in the habit of recommending pituitary and thyroid

extract for defective growth, while second-generation gland grafters like Paul Niehans and new York surgeon H.L. Hunt offered transplants of animal pituitary glands as a therapy for dwarfism even into the 1930s (Hamilton, 1986). More generally though, the use of crude pituitary organ extracts was shunned by practitioners wishing to present a modern, respectable and scientific character.

With infectious diseases on the wane in the 1920s and 1930s due to the availability of new vaccines, anti-toxins (especially diphtheria anti-toxin), paediatric academic centres and increased funding, especially in the US, a number of academic paediatricians moved into biochemical and metabolic clinical investigations of childhood ailments such as dehydration, hypoglycaemia, diabetes, and rickets (Fisher, 2004; Medvei, 1993). In 1935 the first clinic dedicated specifically to studying and providing training in the endocrine disorders of childhood began operating at Johns Hopkins Hospital, with the second at Massachusetts General Hospital (MGH) in 1942 (Fisher, 2004). In 1938 Henry H. Turner had published a report in *Endocrinology* describing the characteristic symptoms of reduced growth, sexual infantilism and developmental abnormalities which became known as Turner's syndrome (Medvei, 1993). In 1937 Fuller Albright described a syndrome of hormone-related precocious sexual development in females which also resulted in reduced stature (Albright's Syndrome) and in 1942 characterised Klinefelter's Syndrome, which causes excessive height in boys.

The increasing understanding of the endocrine underpinnings of growth and development, as well as an interesting characterisation of the two as-yet mainly separate medical professions involved can be seen in this extract from a 1947 paper entitled 'Some endocrinologic aspects of retarded growth and dwarfism' published in *Medical Clinics of North America*:

> Dwarfism, to many a practitioner, is a mere curiosity; an enigma to the ever patient paediatrician as he predicts an unpredictable spurt of growth, and a challenge to the over-zealous endocrinologist as he attempts to link alterations in skeletal growth with some childhood or adolescent endocrine disorder (Greenblatt & Nieburgs, 1947 p712).

In the paper Greenblatt and Nieburgs comment on the limitations of previous classificatory systems for human dwarfism in paying too little attention to endocrine causes and instead propose a two-step classification of either genetic or hormonal causes for short stature. The hormonal causes of dwarfism recognised are short stature due to deficiencies of the thyroid and pituitary glands, the gonads and the pancreas (growth failure caused by untreated diabetes). All other causes of short stature are deemed genetic- either disproportionate achondroplasia or true 'primordial' dwarfism. Tattersall, (1996) comments that primordial dwarfism was a "dustbin" category used to cover all the numerous unexplainable causes of retarded stature. In this way the classification system can be seen as separating out the

causes of dwarfism where some symptom could be measured, used to attribute the cause of growth failure and offer some prognosis, from the unknowns. This is expressed in the author's treatment recommendations that '[t]herapy of dwarfism should be directed towards the correction of the underlying cause', recommending thyroxin for thyroid deficiency and oestrogen for 'ovarian failure' and testosterone for the corresponding male condition (Greenblatt & Nieburgs, 1947 p728).

These therapeutic recommendations show that paediatricians, endocrinologists and those few emergent paediatric endocrine specialists were becoming accustomed to using hormones to treat the abnormalities of growth, which were themselves made more visible by the various programmes monitoring childhood growth and development. Oestrogen and testosterone were trialled extensively in infant and childhood growth in the years after World War II (Hoberman, 2005; Lee & Howell, 2006). Growth hormone was also expected to follow the same developmental path as these other hormones. Unlike the sex hormones, thyroid hormone etc there was no laboratory test for measuring growth hormone levels in the human body and instead pituitary abnormalities were inferred from the general pathology of the patients (Raben, 1962). At this point growth hormone had been isolated from cows (by Li and Evans in 1944) and pigs (by Raben and Westermeyer at Tufts in 1951) and was soon experimentally administered to human subjects, mainly children with retarded growth.

The Armour Company, a Chicago-based meat packing firm with a pharmaceutical division, had set up a large-scale program of collecting and extracting GH from animal pituitaries in the early ‘50s, anticipating the commercial potential of a new hormone drug (Frasier, 1997; Tattersall, 1996).

Although the animal GH extracts had been proved effective in rats and other laboratory animals, when it came to human application there was very little observable effect. Greenblatt & Nieburgs reported:

> The pituitary growth hormone on the whole has given very unsatisfactory results. Its frequent administration and possible antihormone formation make its application at this time undesirable. Although a pituitary growth preparation may in some cases produce slight growth, it will, when administered alone, never restore a dwarf to anything near to normal height (Greenblatt & Nieburgs, 1947 p728).

In the absence of the preferred treatment, children with pituitary disorders had the option of treatment with gender-aligned sex steroids to promote development but with the risk of inducing an early cessation of bone development and compounding the short stature. In the face of this lack of clinical efficacy, growth hormone remained a subject for laboratory investigation (Tattersall, 1996). By the time of the First International Symposium on Growth Hormone held in Detroit Michigan in 1954 it was generally agreed that bovine, porcine and other animal growth hormones were inactive in man, and

the search had moved on to try and isolate human and primate growth hormone (Frasier, 1997; Tattersall, 1996). In 1956 a team led by C.H. Li at Berkley succeeded in isolating human growth hormone, followed by Raben in 1957 (Frasier, 1997). In 1958 the first trial of human growth hormone to successfully induce an unequivocal increase in height in a human adolescent was reported, ushering in the first era of human growth hormone (Raben, 1958).

Conclusion

The emergence of hormone drugs from the late nineteenth century to the opening decades of the twentieth century can be seen as a struggle between alternative visions of a new technology as two competing regimes of healthcare attempted to entrench the new drugs in their respective networks. Organotherapy remedies utilised traditional practices of small-scale manufacturing of medicines using simple technological procedures, supplied through local providers such as pharmacists, individual doctors or apothecaries and enjoyed early popular success. By contrast scientific medicine, as necessitated by its own doctrines, required intensive laboratory research, production of standardised chemicals often requiring the processing of material on a large-scale, and delivery by elite practitioners with specialist knowledge to validate its therapeutic claims. The eventual dominance of the latter model of endocrine therapy must be understood in the context of the ultimate success of the scientific model of medicine in the western world. An integral part

of the process of the professionalisation of medicine was the standardisation of medical training and knowledge. Education in the scientific principles of medicine became a way of separating authorised practitioners from the 'irregulars' and of placing scientific practice at the heart of orthodox medicine. Where this was successful, for example following the 1910 Flexner report in the US, it facilitated the spread of scientific practice and made it easier to marginalise unapproved practices like organotherapy.

The importance of healthcare provision to the biopolitical interests of states created a need for regulation and control of medicines through new legislation and new institutions. The scientific approach promises a rational, objective means of drug evaluation and so appeals to state interests (Bodewitz, Buurma & Devries, 1987). This in turn gave an advantage to those pharmaceutical companies who overtly aligned themselves with the scientific medical establishment. Bell (1986) has used the case of the first synthetic oestrogen drug, DES, to illustrate this: In 1941 some ninety-six pharmaceutical companies had considered the possibility of marketing DES but only twelve of the leading ethical companies, including Abbott, Lilly, Squibb, and Upjohn were serious about the process. Only they had the resources to comply with the regulatory requirements to present appropriate experimental human and animal safety data (as required by the 1938 Federal Food, Drug, and Cosmetic Act in the US) because they had recruited scientific staff and had a working

relationship with academic medical departments, while their competitors did not. Thus the emerging and expanding networks of scientific medicine provided a niche in which to embed scientifically validated hormone drugs while excluding alternative models such as organotherapy preparations.

During the process of establishing the dominance of the scientific medicine particular therapeutic goals and practices were categorised as acceptable or unacceptable to orthodox medicine including the techniques of organotherapy and gland grafting and the goal of prolongevity or rejuvenation. The process is not a simple one but involves a complex process of shaping by different cultural values, disciplinary interests and organisational structures. Rejuvenation and explicitly anti-ageing treatments were generally unacceptable partly because they echoed early goals of a now-discredited alchemy and partly because of an association with undesirable male sexuality. However aspects of female sexuality and ageing were successfully brought under hormonal control under the rhetoric of reproductive control and treating the ‘pathology’ of the menopause, where gynaecologists had an established disciplinary interest. The dominant network for producing hormone drugs that had emerged by the 1940s thus incorporated alliances between academic laboratory-based researchers, university-affiliated medical schools, pharmaceutical companies, state regulatory agencies and specialist

medical practitioners such as gynaecologists or paediatric endocrinologists.

In orthodox accounts the rise of scientific endocrinology is usually presented as a narrative of progress with scientific practitioners gradually elucidating the true nature of the endocrine system and the diseases affecting it, banishing alternative conceptions as mistakes or falsehoods. From a constructionist perspective the story can be conceived as the triumph of a hormonal model of the body described by scientific means. Following Oudshoorn (1994), medical knowledge renders the body transparent but also understood and open to intervention in new ways. The hormonal model links physical and behavioural symptoms and signs to levels of chemical substances within the body. In particular undesirable symptoms are associated with a deficiency (or less commonly an excess) of hormones in the body which can be remedied by replacement with exogenous hormone. The idea of replacement conflates the idea of the normal (i.e. statistically average or most common) level of hormones with the natural (and therefore healthy or desired) state of the body. This model acts as an exemplar ‘problem-solution’ for therapeutic practice. As knowledge of hormone drugs spread through networks of scientific medicine (including the state and industrial sectors) so too this particular model of the body was disseminated. Indeed a scientific hormone drug and the hormonal model of the body are mutually constitutive and form an artefact of ‘techno-knowledge’.

Though the hormonal model of the body may create new disease categories and patient identities it is still subject to interpretation and translation across different medical settings. While insulin may be the archetypal clearly defined deficiency disease treated by hormone replacement it was actually somewhat atypical in its narrow specificity of use. Oestrogen achieved a particularly varied range of applications, but Thyroxin too, was a popular drug in the inter-war years, not only for the treatment of hypothyroidism but also as a 'stimulus' for the body's metabolism, believed to alleviate a range of conditions like constipation, the near-obligatory menstrual disorders and even as an aid to weight loss (Rasmussen, 2002). Similarly corticosterone and later cortisone, the hormones of the adrenal cortex, were used to treat Addison's disease, which resulted from failure to produce these hormones but were also utilised in patients with functioning adrenal glands who had Addison's-like symptoms such as fatigue, muscular weakness, impaired sexual function, insomnia or low spirits (Ibid.). The main argument was that marginal but undetected hormone insufficiencies must underlie these more common but related complaints as it was assumed that normal individuals would not respond to hormone therapy so a response indicated a deficit (Rothman & Rothman, 2003). In this way the deficit-replacement model of therapy could be invoked to justify therapeutic decisions as well as to produce them.

The study of the pituitary had never been as popular with gland-grafters or organotherapy practitioners as gonad-based therapies and so fell primarily under the auspices of laboratory research. By the 1940s a hormone had been identified and associated with the process of linear growth. That growth hormone was expected to follow the established developmental path set out by insulin, oestrogen and other successful hormone drugs, is evidenced by the fact that companies like Armour were preparing extracts of animal pituitaries and collaborating with academic research teams at different medical schools. An account of how growth hormone was developed as a therapeutic drug and how this was influenced by the existing networks and intellectual resources associated with hormones discussed in this chapter, as well as certain unique circumstances pertaining to growth hormone itself, is the subject of the next chapter.

Notes

[32] However modern medical attention did not become focused on the phenomenon until 1816 when the French physician C.P.L. de Gardanne conceptualised the climacteric as a syndrome, 'la ménespausie' (shortened to menopause in 1821) the first time these various symptoms had been collectively labelled as having a common cause and as being a medical condition (Banks, 2002; Davis et al, 2005).
[33] Having succeeded Claude Bernard as Chair of Medicine at the College de France in 1878 (Tattersall, 1996).
[34] Banks (2002) reports that ancient practices of organ consumption were known as 'organotherapy' and Brown-Séquard's extract was referred to as 'the method of Brown-Séquard'. Cole (1992 p179) also makes reference to 'Brown-Séquard's Elixir of Life'. However the general enthusiasm for preparing and testing extracts of all virtually animal tissues, which followed Brown-Séquard's announcement, does appear to have received the popular title of organotherapy in both supportive and hostile accounts of the time (Corner, 1965; Henderson, 2005; Schwartz, 1999).
[35] From a classical Greek word meaning 'I excite or set in motion'. The term is reported to have been suggested by biologist Sir William Hardy of Caius College, Cambridge and his classical colleague W.T. Vesey (Hadden, 2005).

[36] Atherton incorporated ideas about rejuvenation through ovarian irradiation into her novel *Black Oxen* which was published in 1923 and adapted into a silent movie the following year (Kahn, 2005).
[37] In Mikhail Bulgakov's satirical 1925 novel *'The heart of a dog'* the Russian surgeon P.P. Preobrazhensky transplants the testes and pituitary gland of a human into an ageing stray dog intending to restore its vitality only to find that 'transplantation of the pituitary induces not rejuvenation but total humanisation' whereupon chaos ensues as the humanised dog escapes into Soviet-era society (Bulgakov, [1925] 2005 p63-4). It has been suggested that Serge Voronoff was the model for the surgeon Preobrazhensky (Hamilton, 1986).
[38] There were of course exceptions such as Francis Marshall, the zoologist who worked with Schafer and increasingly biochemists like Frank Young who studied the diabetogenic effect of pituitary extracts in the 1930s (Sawin, 2001).
[39] Unlike the UK where the reputation of endocrinology was even more suspect and no successful professional body for endocrinologists would emerge until after World War II.
[40] Production of insulin was initially handed over to Connaught Laboratories in Toronto a small industrial plant set up in 1914 in the hygiene dept of the University of Toronto. However there were difficulties producing even limited amounts of insulin on a regular basis at Connaught and main production was soon outsourced to Eli Lilly. In the terms of the original license agreement, Connaught received 12% of Lilly-produced insulin for Canadian distribution (Sinding, 2002).
[41] The name 'oestrogen' is a broad term for a group of chemically and functionally related hormones. The name comes from Greek oistros (literally 'gadfly') meaning 'frenzy or mad desire 'and gennein meaning 'to beget or procreate' (Banks 2002).
[42] Butenandt and Hanish, funded by Schering, Laqueur and his team at Organon and Ruzicka and Wettstein in Switzerland (Freeman, Bloom & McGuire, 2001).
[43] Brinkley studied for three months at the Eclectic Medical University of Kansas, receiving a medical diploma that he used to obtain a practitioner's license in the states of Kansas and Arkansas (Haber, 2004).
[44] Considering all components of the gland, nine separate hormones are currently recognised as being pituitary in origin (Bogin, 1999- see p354 for illustration).
[45] Infectious diseases such as tetanus, summer diarrhoea and diphtheria were a major, even epidemic cause of mortality amongst children and fewer than one in five new-borns survived to reach their fifth birthday (Haggerty, 1997).
[46] See Chapter 2 p55.

CHAPTER 5: The History of Human Growth Hormone

Introduction

The previous chapter described emergence of endocrinology at the end of the nineteenth century and the resultant tension between the academic, laboratory investigation of glandular extracts and their practical application by physicians. Two hormones in particular were highlighted, in their development from objects of physiological study to industrially manufactured drugs, as models, or visions, of how their production, both literal and figurative, could unfold. Insulin was sought specifically as a therapy for diabetes, a socially and institutionally recognised condition that became understood as a manifestation of a deficiency of that hormone. The application of sex hormones, (estrogens and testosterone) carried stronger social and cultural assumptions (in this case about gender) and had a broader and more nebulous range of applications, though these too were often characterised as replacement for some form of deficit. Elements of both these models of development can be detected in the history of growth hormone recounted in this chapter.

The structure of the chapter comprises two sections based around two distinct eras in the history of human growth hormone. From its initial deployment at the end of the 1950s until the mid-1980s growth hormone was extracted from human pituitary glands collected at

autopsy. The hormone was in short supply and its use was restricted mainly to academic paediatric endocrinologists, the elite of their profession. In the 1980s a link was discovered between pituitary-derived growth hormone and transmission of the fatal neuro-degenerative disease Creutzfeld-Jacob Disease (CJD) causing the use of this form of growth hormone to be abandoned. At this time a synthetic version of the hormone, produced through recombinant DNA technology and free from potential contamination with CJD was in the late stages of development. Recombinant human growth hormone was launched in 1985 bringing with it both an effectively unlimited supply of hormone and the involvement of pharmaceutical and biotechnology companies like Genentech and Eli Lilly. The pituitary and recombinant eras of growth hormone are characterised by different networks of production and distribution, different interests and actors, and different applications and understandings of growth hormone and short stature, and hence are addressed in separate sections.

The first section concerns the period following the initial isolation of human growth hormone in 1957-8. Unlike the previous hormone drugs, growth hormone derived from the glands of animals such as cows or dogs had no discernible effect in humans and an active preparation could only be obtained from pituitary glands of human origin. This meant that the established model for developing a hormone drug, where the results of laboratory investigation would be

licensed to industrial partners to be mass-produced from animal material, was not viable in this instance. The novel networks of supply and distribution which grew up around pituitary-derived human growth hormone in the absence of major industrial involvement frame the discussion of this first era. This part of the analysis will focus on describing the key institutional and social factors shaping the development of growth hormone in North America and the UK. As discussed in the previous chapter, some statural abnormalities had been treated with hormones (mainly oestrogen and testosterone) since the 1940s. However, the availability of the hormone believed to be most closely involved in controlling human growth prompted much greater attempts to incorporate the phenomena of human growth into a medical, hormonal model of the body. The development of new technologies of measurement and categorisations of disease that accompanied the deployment of hGH during the pituitary era can be considered a crucial part of the co-construction of hormonal disease and therapy in short stature. The remainder of the first section of this chapter will examine how the influence of particular measuring technologies, professional interests and cultural and social perceptions about stature combined to shape the understanding of growth hormone as a therapeutic drug and the production of growth hormone-deficient short stature as its main indication.

The second section of the chapter recounts the upheavals of the recombinant growth hormone era, which encompasses the period from 1985 to the present. The new technology of synthetic growth hormone was intended as an ‘update’ of the existing technology that would colonise and embed itself in the niche of the existing networks of (pituitary) hormone delivery. The involvement of new actors such as commercial pharmaceutical companies and regulatory agencies reconfigured and disrupted the existing networks, creating new interactions and reshaping the role of existing organisations such as paediatric endocrinologists and patient support groups. The increased supply and promotion of growth hormone promised to facilitate maximal treatment of previously under-treated or untreated populations of short-statured children but also threatened to destabilise the existing diagnostic procedures and disease categorisations by challenging the validity of the measurements on which they were founded. It was during this somewhat turbulent process of network realignment and scientific uncertainty that the application of growth hormone for short stature emerged as an economically and ethically contentious treatment and characterisations (and accusations) of human enhancement were first made. As this section will show, the claims being made, the interests and influences involved and the understandings being disputed are thoroughly informed by the prior socio-historical development of pituitary growth hormone in particular and of hormones and endocrinology in general. It is thus the goal of this

chapter to demonstrate the pertinent influence of the past on the current development of growth hormone as a technology. To this end, where appropriate, extracts from interviews with paediatric endocrinologists and others carried out as part of this project have been used to illustrate contemporary understandings of key events discussed in the subsequent sections of this chapter. The socio-historical account of human growth hormone presented in this chapter is also intended to inform and complement the investigation of paediatric endocrinologists' discourse on contemporary uses of hGH.

SECTION 1: THE PITUITARY ERA

New Networks in the Creation of a New Therapeutic

The first era of clinical human growth hormone research and therapy began in 1958. In a letter published in the *Journal of Clinical Endocrinology and Metabolism* Dr M.S. Raben announced:

> Human growth hormone, prepared by the glacial acetic-acid extraction method from pituitaries obtained at autopsy, was found to be continuously effective and well tolerated when administered by intramuscular injection to a 17-year-old male pituitary dwarf for a period of ten months [ ] The total increase in height during the ten months of growth hormone therapy was 2.1 inches, representing a growth rate slightly higher than that of a normal child of the same height' (Raben, 1958 p901).

The availability of biologically active growth hormone finally allowed growth hormone research to move on to the path of dual clinical and laboratory investigation, and the most significant development was the clinical application of pituitary GH in human patients. Since only growth hormone from primate pituitaries would produce an effect in human patients, the most readily available source was to extract human pituitary glands from corpses being autopsied. Endocrinologists, hoping to treat patients with suspected pituitary-deficient short stature, began to organise the collection of pituitary glands from hospital pathologists who had access to human cadavers. One senior US paediatric endocrinologist who was involved with the formative years of GH therapy recollected:

> [S]o there were individual pituitary collection programs set up and the endocrinologist, myself for example, would collect the pituitaries from certain pathologists and the parents [of patients] would help out a lot, they would knock on the pathologists door etcetera (NAM 3).

The procedures for extracting GH from human pituitaries were complex so endocrinologists, in general, did not attempt to process the pituitaries themselves, but instead sent them to the laboratories of the original biochemical researchers who first isolated hGH:

> [T]he endocrinologist would send Roy [Raben] the pituitaries he collected, some of us worked with Wilhelmi, we'd send him the

> pituitaries, some of the endocrinologists worked with C.H. Li and [ ] then they would purify the pituitaries, take out the growth hormone, take out half of it for their investigations whether they were animal, chemical or human, and send the other half back to us (NAM 3).

As the above extracts illustrate, informal networks soon arose connecting the source of human pituitary glands- hospital pathologists, with the processors (the laboratory-based extractors) and the end users- endocrinologists, paediatricians and patients. Almost all of the early papers published on growth hormone in the pituitary era contain a plea for more pathologists to get involved and to increase the supply of pituitaries indicating both clinical interest in the new hormone and a sense of the ad hoc nature of the burgeoning production operation.

The limited supply of pituitary glands was a new and crucial factor, not encountered with previous hormones like insulin, oestrogen, or thyroxin which had been available from relatively plentiful animal sources, and, with the exception of insulin, were now available in synthetic form. As the previous quotes reveal, the supply of pituitaries had to be split between clinical and laboratory investigations, further reducing the amount available directly to physicians. This new type of network that was emerging is also notable for incorporating an active, sourcing role for the parents and families of patients, where previously university laboratories and later

pharmaceutical companies had been responsible for supply, leaving patients as passive recipients. This novel approach was not without consequences:

> [C]ompetition to obtain GH had also developed among these workers. Into the middle of this was injected the determination of the parents of hypopituitary children who had both the desire and the financial resources to get the GH their children needed. The situation was ripe for the development of a black market in GH (Frasier, 1997 pS1-2).

Dr Robert Blizzard, Lawson Wilkins' successor in paediatric endocrinology at Johns Hopkins took a keen interest in the new growth hormone. Recognising the undesirability of an illicit trade in pituitary glands developing, and seeing a need to co-ordinate the distribution of a scarce resource, Dr Blizzard and extractor Dr Alfred Wilhelmi formed the National Pituitary Agency (NPA) in 1961 (Frasier, 1997). The NPA can be seen as an attempt to give a formal structure to the informal networks that had arisen around growth hormone. In the act of its founding the agency brought together the principal extractors (Li, Wilhelmi and Raben), representatives from the College of American Pathologists to ensure the co-operation of their members and the National Institute for Arthritis and Metabolic Diseases[47] (NIAMD) to provide state-associated legitimacy and, after 1963, funding. The stated aims of the NPA were to 'co-ordinate the collection of pituitaries and the distribution of hormone in a logical and sensible manner' (Anon, 1963 p 284).

In practice this meant that US researchers interested in clinical or other work with growth hormone had to submit a research protocol outlining their intended experiment(s) to the NPA for approval before the extractors would be authorised to supply the program with growth hormone. It was not only the restricted availability of pituitaries that led to this experimental approach. The National Institutes of Health mandate extends only to providing support for research and is explicitly prohibited from acting in a way that would constitute state sponsorship of healthcare (Snyder, 1994; Stevens, 1998). With no other viable long-term source of funding, the experimental grant-based approach was prescribed. US endocrinologists with experience of operating under this system recollected its operation:

> [I]n order to get growth hormone [before 1985], you can only get it through the National Hormone and Pituitary Program, [ ] previously called the National Pituitary Agency, and you had to have a research protocol even though it didn't have to be a very sophisticated research protocol (NAM 4).

> [W]e had to report what we were going to do- we're we going to study dosage phenomena, were we going to [look at] biochemistry, biochemical changes, female versus male difference in growth rates, so forth and so on (NAM 3).

The authority of the NPA was assured by securing the services of the very few laboratories capable of processing pituitaries to get GH in

return for which the lab workers were entitled to retain half of the hormone they produced for their own work, mainly in animal models:

> [W]hat they did was two separate things. Part of the investigation was still done in animals because the people who derived the hormone, who extracted the hormone, kept fifty percent and gave fifty percent to the NIH (NAM 2).
>
> [S]ince Wilhelmi and Li and Raben were essentially the only extractors they wouldn't violate taking pituitaries from somebody else [ ] so the participants who had set up the NPA or agreed to work with the NPA were the policing force (NAM 3).

There were other effects of this structural arrangement: for the patients and their families, the arrangement meant that the costs of collecting pituitaries and extracting and distributing the hormone was borne by the NIH (i.e. by the state) making growth hormone treatment an entirely non-commercial venture. In return all NPA-supported patients were entered in a clinical trial with an NPA-approved protocol for a minimum of at least part of their first year of treatment (Frasier, 1997). This put growth hormone on a rather different trajectory from previous hormones; insulin, for example, had undergone a limited one-year clinical testing period when Eli Lilly had provided free supplies to investigators and research teams involved in attempting to produce an international standard for insulin activity but then moved to a wholly commercial supply (Sinding, 2002).

In the UK the institutional response at least followed the pattern set out by the introduction of insulin almost forty years earlier. Aware of the reports from the US, the UK Medical Research Council once again became involved, creating a Pituitary Hormone Committee with a Working Party briefed to design, set up, and run a clinical trial investigating the potential of human growth hormone as a growth promoting agent for short children in the UK (Milner, 1979; Tattersall, 1996). The MRC Working Party followed a consultation model with patients referred by their physicians to a panel of the hormone committee and assessed for inclusion in the trial, which in its initial stages was almost entirely based on the Hospital for Sick Children, Great Ormond Street in London (Tanner, Whitehouse, Hughes and Vince 1971; Tanner, 1981). As with the NPA, the UK group was headed by a paediatric endocrinologist, Professor R.D.G. Milner, and was if anything more dominated by paediatricians than US or, later, Canadian studies. Pituitaries were collected by NHS pathologists from autopsies and sent to Dr A.S. Hartree in the Dept of Biochemistry at the University of Cambridge who was the UK's main, and indeed practically only extractor of pituitary growth hormone during the entire era 1959-1985 (Milner, 1979).

Although there had been therapies for some forms of dwarfism such as thyroid deficiency or hypogonadism, the discovery of growth hormone appears to have increased the profile of short stature both in medical circles and to the public. In the US the formation of the

NPA did not reverse the early involvement of patient's families. Instead, their involvement was also institutionalised in a series of charitable ventures. Human Growth Incorporated (better known by its current appellation the Human Growth Foundation) was a nation-wide organisation of parents of short-statured children who assisted in gathering pituitaries with the approval of the NPA (American Academy of Pediatrics Committee on Drugs, 1969). A senior US paediatric endocrinologist explained:

> [T]he Human Growth Foundation was set up, you know not to be a growth hormone deficient agency, it was set up for all forms of growth disturbance [ ] of course what we could do, effectively could do most for was growth hormone deficiency so there was a lot of emphasis on that (NAM 3).

The transport of pituitaries was facilitated by associated programs like the TWA airlines 'clipped wings' program, as one US patient support group worker recalled:

> [I]t was five families and one [paediatric endocrinologist] who started this foundation and they would have somebody like a doctor, or somebody like me, a volunteer, who would go to the hospital pick up the growth hormone from the cadaver, drive to the airport and TWA would ship to you who was waiting in Florida to give it to little Johnny down the block (NAM 7).

As these comments suggest, the limited availability of pituitaries and the need for a non-commercial national network of supply and

transportation gave patient families a role to play which may have served as a focal point around which to galvanise activities of charitable fund raising, and establishing a more general patient-support network for short stature.

In the UK the centralised nature of the MRC trial and the availability of the NHS network of pathologists precluded any similar development but the profile of growth disorders was raised in other ways. In 1963, James Tanner, who had moved the Harpenden Growth study to the Institute of Child Health in London in 1956, set up the London Growth Disorder Clinic at the Hospital for Sick Children (to which the ICH is attached) (Tanner, 1981). The clinic became the main assessment centre for children referred to the MRC's Pituitary Hormone Committee and importantly this meant the application of auxological as well as clinical and biochemical tests (Tanner, Whitehouse, Hughes and Vince, 1971; Tanner, 1981). As the UK trial progressed and its remit expanded, a network of specialist growth clinics, totalling nineteen by 1977, were set up across the UK to cover the whole population (Milner et al, 1979; Milner, 1979). These clinics 'soon revealed a great reservoir of children suffering from short stature for a variety of reasons' (Tanner, 1981 p371). Continuing the trend, in 1968 the Canadian Medical Research Council, citing the confusion of prior experimental data, set up an official committee to organise the collection of pituitary glands from hospitals and run a Canadian national trial of GH therapy in hypopituitary children (Guyda et al,

1975).

As will be clear from this section, the development of pituitary growth hormone followed a very different path from previous hormone drugs, which had been significantly commercial ventures. Commercial companies such as Armour therapeutics had been anticipating a market for growth hormone and had even supplied bovine and other animal pituitary extracts during the 1950s (Tattersall, 1996). The unexpected species specificity of growth hormone meant that the standard model for hormonal drug development by industrial-scale production from relatively cheap animal glands could not be followed. Where pharmaceutical companies like Lilly or Organon had the advantage over laboratory workers in being able to contract and process large amounts of animal material from slaughterhouses, doctors and academic laboratory workers had preferential access to the hospital pathology departments that were the primary source of human pituitary glands. The development of collection and supply networks in North America and the UK essentially limited the entry of commercial companies into the market, although this was not the case in Europe where Novo Nordisk, KABI and Serono all established commercial ventures of pituitary collection and extraction.

Making Growth Hormone Deficient Short Stature: New Technologies of Measurement and Old Ones Rediscovered

The study of endocrine control of growth did not begin with the isolation of human growth hormone. As described in the previous chapter, deficiencies of thyroid hormone, oestrogen and testosterone had been associated with stunted growth and other developmental abnormalities and treated as instances of hormone replacement therapy since the 1940s. Other syndromes of abnormal development, increasingly recognised as being genetic in origin, such as Turner syndrome in girls and Klinefelter's syndrome in boys, often included a statural abnormality and could be treated with hormone regimes. Turner girls, for example, were often treated with estrogens to stimulate their otherwise delayed or absent sexual maturation, sometimes coupled with low doses of steroids like oxandrolone to try and boost their height (Conte & Grumbach,1978; Levine, 1978). There was thus already a population of patients with statural and developmental abnormalities of varying and often uncertain diagnoses known to paediatric endocrinologists when human growth hormone became available in 1958.

A general enthusiasm for the potential of the new hormone can be detected in an early review of progress by Raben:

> It [GH] has been successfully used in pituitary dwarfism and promises to be helpful in some cases of short stature without hypopituitarism, but its potential use in other conditions that

> may be helped by an anabolic agent has only begun to be investigated (1962, p82).

The paper goes on to report successful therapy with growth hormone in three pituitary dwarves as well as five other children 'who were judged to be normal apart from their height' (ibid. p85) and noted an increase in growth rate in all cases. In this paper Raben also speculates on possible applications of GH in adults with pituitary deficiencies, and patients where tissue degeneration has occurred such as burns victims or the elderly. Similar cautiously optimistic sentiments are expressed in an article by Dr Blizzard entitled 'The past, present and future of pituitary growth hormone' appearing in the *American Journal of Diseases in Childhood* the following year:

> The effect of growth hormone on other types of dwarfism is still under scrutiny. While the results have been variable, there is reason to believe that the short stature of Turner syndrome may be amenable to therapy. The use of growth hormone in genetic short stature has been supported by at least one published series but the results are as yet inconclusive. Certainly on a theoretical basis, pharmacological doses should be effective in most children before epiphyseal fusion. Two conditions in which beneficial effects appear unlikely are achondroplasic and primordial dwarfism (Blizzard, 1963 p439).

In the UK too, it was considered important to investigate different types of short stature under the auspices of the Medical Research Council trial. Among the first hundred patients included in the trial

were those with diagnoses of multiple pituitary deficiencies (due to tumours etc), suspected hypopituitarism, patients with a variety of syndromes of growth retardation linked with chromosomal or other genetic abnormalities including Turner syndrome and Prader-Willi syndrome, children with poor growth associated with low birth-weight and other patients with uncertain (idiopathic) growth failure (Tanner and Whitehouse, 1967; Tanner, Whitehouse, Hughes and Vince, 1971). One senior North American endocrinologist later recalled 'Tanner included everything only the kitchen sink' (NAM 8). The first criterion for therapeutic consideration with pituitary growth hormone was thus abnormal short stature of known or unknown aetiology.

In 1963 a new technology capable of measuring the levels of growth hormone in a blood sample taken from a human patient was deployed: the radio-immune assay (RIA) (Najjar and Blizzard, 1966; Tattersall, 1996). This meant that patients with a variety of growth disorders could be evaluated for levels of growth hormone and compared to adults and children of normal height; in other words the hormonal model of the body could be correlated with the statistical model of height. Insulin injections were used to stimulate the pituitary to release its (presumed) store of growth hormone into the blood, which could then be sampled and tested with the RIA. The combination of these procedures, known as the insulin tolerance test (ITT) were used to investigate normal and presumed hypopituitary children, allowing new sets of classifications to be made. Patients

with known pituitary damage did indeed produce a significantly lower response to the ITT than healthy subjects and also produced a measurable increase in growth upon administration of pituitary hGH (Najjar & Blizzard, 1966). Accordingly they could now be categorised as hypopituitary (growth hormone deficient) dwarfs, fitting comfortably into the existing deficit-replacement model of hormone therapy.

In a number of other cases including Turner girls, achondroplasia, premature infants, malnutrition (kwashiorkor and marasmus) and assorted cases of uncertain diagnosis or primordial dwarfism, growth hormone therapy did not appear to produce a measurable increase in growth rate (Chiumello, Vaccari and Sereni, 1965; Najjar and Blizzard, 1966; Hadden and Rutishauser, 1967). The results with Turner syndrome girls were mixed, with some evidence that larger doses than given to hypopituitary patients might produce an acceleration in growth rate but that in general their response to the ITT test and RIA showed GH levels similar to normal childhood levels (Najjar and Blizzard, 1966; Tzagournis, 1969). These conditions could now be categorised as non-growth hormone deficient forms of short stature. Although RIA measurements were not made in many of these studies (it was still a new technology and was not fully embedded in clinical practice until some years after its initial deployment) the failure to respond to hGH administration correlated with the assumption that hormones administered to non-

deficient individuals would have no effect (Rasmussen, 2002). While some existing causes of short stature were becoming labelled as 'non-growth hormone deficient' the RIA was also allowing the creation of entirely new categories of growth failure.

In the first report from the MRC study, Tanner and Whitehouse (1967) reported that of a number of patients admitted with 'idiopathic dwarfism' (i.e. of unknown cause) some were now suspected of being growth hormone deficient without the accompanying loss of any other pituitary hormones, while others might be evidence of a new class of non-responding dwarfism. By 1971 these new categories had been accepted (at least within the UK context) and codified respectively as isolated growth hormone deficiency and growth hormone insensitivity, commonly known as Laron dwarfism (Tanner, Whitehouse, Hughes and Vince, 1971; Laron, 2004). Further new categories appeared through the combination of blood growth hormone level testing and other diagnostic approaches - patients with low GH levels on the ITT who did not seem to respond to growth hormone injections but demonstrated catch-up growth when removed from their home environment could now be diagnosed as suffering from growth failure brought on by emotional deprivation (Frasier and Ralliston, 1972). By the 1970s the elaboration of new categories was prompting some to call for the discontinuation of the old 'wastebasket' category of primordial dwarfism in favour of more descriptive, 'scientific' categories such as growth delay, low-

birthweight short stature, and later, intrauterine growth retardation (Tanner, Whitehouse, Hughes and Vince, 1971; Tanner, 1981).

The first results coming out of the UK MRC study also added measurement criteria of a different kind. The central involvement of James Tanner and his team from the Institute of Child Health meant that the methods of statistical study of growth from the ongoing Harpenden Growth Study were brought to the MRC study. While American studies did utilise the standard bone and height prediction charts, the MRC team had access to newer Harpenden bone-age standards tailored specifically to British children. Recognising that growth rates vary seasonally, UK patients receiving growth hormone were treated for at least one year at a time, unlike the six month schedule in the Canadian MRC trial, or the stop-start schedules of many American studies. The UK trial data also included measurements of skin-fold thickness, showing that the response to GH involved a reduction in subcutaneous fat deposits, detailed growth charts displaying percentile values for age, height bone age and other measurements (Tanner and Whitehouse, 1967; Tanner, Whitehouse, Hughes and Vince, 1971). Much of this anthropometric detail was uncommon in North American studies at the time.

Tanner (1981) attributes the lack of awareness of auxological data arising from the North American longitudinal growth studies among paediatric endocrinologists to Lawson Wilkins' relative disinterest in

the subject of growth being transmitted to the subsequent generation of such practitioners. However given that a number of paediatric endocrinologists, including National Pituitary Association founder Dr Robert Blizzard, and a significant number of others who trained at either Wilkins' Johns Hopkins clinic or at Massachusetts General Hospital in the 1950s, went on to make important contributions in the field of growth hormone therapy this explanation maybe oversimplified (Fisher, 2004 p720 provides a list of notable graduates from both programs). Rather, it appears likely that the institutional basis to facilitate an exchange of ideas and information between those preventative paediatricians, school doctors and others interested in growth as an index of health, and more biochemical or endocrinologically-minded therapeutic investigators was largely absent in the US context. In contrast to the diffuse American field of paediatrics, in the UK the small, centralised pool of experts, the late development of paediatrics, and the emphasis placed on auxology at the ICH by its then-director Alan Moncrieff, created a unique situation. There were relatively few people for the MRC to call on to set up its working party and it was logical to include someone like Tanner who was not an endocrinologist but was one of a limited number of experts on growth in the UK, resulting in a close association between statistical study of human growth and the attempt to measure and evaluate the effects of human growth hormone. In this way the new standards for normal growth being developed at Harpenden were simultaneously driving new

measurements and standards of abnormal growth in the MRC trial and, through the publication of its results and new instruments, the wider paediatric endocrine community.

Rationalising and Rationing Growth Hormone Therapy

As the first decade of investigative therapy with pituitary growth hormone drew to a close, it became clear growth hormone was not going to be a simple panacea for all deficits of human growth. It was believed, in the UK context at least, that given the poor response of many apparently non-hormone deficient forms of short stature, GH deficiency was necessary in order to produce any kind of beneficial response to the hormone (Milner et al, 1979).The issues of how growth hormone worked, under what circumstances and how to properly measure and record these effects appeared more complicated that had perhaps been hoped in the initial burst of optimism following the hormone's isolation. In addition supply of pituitaries continued to be severely limited: in 1969 the American Academy of Paediatrics Committee on Drugs estimated that only 10% of the required demand for pituitary growth hormone was being met by existing supplies (AAP Committee on Drugs, 1969). A new focus on both rationalising and rationing the use of growth hormone began to dominate the academic agenda. After assessing the data on the initial cohort of one hundred patients, the UK team announced that the primary concern of the therapeutic investigation of human growth hormone was:

> [W]ith treating patients who respond to a clinically useful degree

(Tanner, Whitehouse, Hughes and Vince, 1971 p752).

This was to be achieved by concentrating exclusively on the treatment of patients with confirmed growth hormone deficient short stature.

GH deficient patients were the logical choice, given the predominant deficit-replacement model of hormone therapy, and the fairest on rationing grounds as these patients had been shown to demonstrate the most unequivocal increases in growth rate in response to treatment. Of course limiting the treatment to growth hormone deficient patients meant establishing, even if only by proxy, the definition of deficiency. While the American Academy of Pediatrics Committee on Drugs announced that 'the increasing availability of growth hormone immunoassay has made it possible to diagnose growth hormone deficiency relatively easily', this opinion was not shared by everyone (1969, p766). A number of investigators in the UK felt that the RIA was not sufficiently reliable to stand alone as a diagnostic tool and instead primacy was given to detailed auxological and statistical assessment of growth retardation and response to treatment (Hubble, 1966; Milner et al, 1979; Tanner, Whitehouse, Hughes and Vince, 1971). One UK paediatric endocrinologist involved in the trial described the admission criteria:

> [I]t was a tight system [ ] Strict auxology, attention to, you know, height, height standard deviation score, height velocity, bone age et cetera and then the endocrine profile of growth

> hormone deficiency with or without other pituitary deficiencies (UK 1).

While a North American paediatric endocrinologist with experience of the Canadian trial recollected:

> We thought we had real hypopits [ ] and so from the very beginning we said that any kid who had the major investment of growth hormone for a significant period of time, at least one year [ ] they were all re-tested [with the RIA] So we thought we had a pretty pure program (NAM 8).

It is interesting to note that the emphasis in these responses reflects, to an extent, different priorities given to auxological and biochemical measurements in the different trials. In the Canadian trial patients were only considered 'real hypopits' if they got a sufficiently low score on two repeated RIA/ITT tests and were retested at the end of each treatment phase as well, although strict height and growth rate limits were also applied (Guyda et al, 1975).

In the US, Dr Robert Blizzard of the NPA and paediatrician Dr Thomas Aceto conceived the National Collaborative Growth Hormone Treatment Project (NCGHTP) in response to the lack of standardisation in treatment[48] and published its first report in 1972 (Aceto et al, 1972; Frasier, 1997). The collaborative study took a similar line to the UK and Canadian national studies in only dealing with hypopituitary patients with clear evidence of low GH levels in the blood and reduced bone age, height and/or growth rate. In addition

GH dosages were now being cited in international units and patients were treated for at least 18 months continuously allowing seasonal changes to be taken into account, although the NCGHTP papers still lack the detailed percentile growth charts of the UK MRC trial publications. Despite the restrictions on therapy imposed by NIH sponsorship and the limited supply of pituitaries the NCGHTP had something of a service approach in that patients who were eligible for the study were allowed to continue therapy once they had completed the research protocol, although poor responders were removed from the trial (Frasier, 1997). The national study was supported by the Human Growth Foundation and the TWA 'clipped wings' transport program.

The UK and Canadian trials ended and institutionally moved to functions of national service provision for growth hormone deficient children in the period 1977-1980 (Frasier,1997; Milner, 1979) In the US the more fragmented auspices of the NPA meant that although the National Collaborative Study was looking only at children with confirmed growth hormone deficiency during the 1970s, there were many other smaller studies receiving NPA approval and these were not unilaterally restricted to growth hormone deficient cases. The following interview excerpts from US paediatric endocrinologists active at the time describe how the system is remembered:

> [P]ractically speaking, you wrote protocols that related to growth hormone, you know the classical growth hormone deficient

> children [ ] But I even way back then considered, but we never followed through, giving it to children with cystinosis which caused renal failure as a genetic disease, because my colleague in the lab next to me had a whole cadre of children coming from all over the country and elsewhere [ ] for research on cystinosis (NAM 4)

> The 50% that came from the NIH was for children with growth hormone deficiency [ ] but in addition there was a small amount put aside for the study of other conditions. Dr Blizzard for instance is the person who took a small for gestational age group of kids, that weren't growth hormone deficient and said "growth hormone's not going to work on you guys" ,gave them a ton of growth hormone, and it worked. Of course there was never enough to treat them (NAM 2).

These accounts illustrate how the NIH-driven requirement for all applications of growth hormone to be research driven, combined with the desire of academic physicians to both ameliorate and explore novel aspects of illness, could stimulate continued exploratory studies beyond standard GH deficiency. Another notable example was the work of Dr Daniel Rudman and his team at Emory University. Exploring the application of growth hormone in categories of short stature that had been declared 'non growth-hormone deficient' Rudman proposed the existence of sub-categories of 'sub-responders' who could show potential height gains if given increased dosage or duration of treatment (Rudman et al, 1971; 1974;1974;1978;1981). Other NPA-

approved studies of non-GHD conditions had also suggested that a measure of response to growth hormone in non-GHD conditions such as Turner Syndrome (Tzagournis, 1969), Intrauterine Growth Retardation (Foley et al, 1974), and small-for gestational-age babies (NAM 2) was detectable and could be used in future to ameliorate these conditions.

Importantly the diagnosis of growth hormone deficiency, with the emphasis from all quarters on the strictness of the criteria, was not intended to separate deficient children from non-GH deficient short children; rather it was intended to select only *most* deficient children; the greatest deficit conferring the greatest entitlement to therapy (Johanson and Blizzard, 1990). It was a response both to the shortage of growth hormone and to the very uncertainty that still surrounded the hormonal model of growth. A senior UK paediatric endocrinologist who was involved with the MRC trial and subsequent distribution of pituitary growth hormone explained:

> [I]n the days when pituitary growth hormone was available, roughly speaking the criteria for the diagnosis of growth hormone deficiency were tailored so that the supply of growth hormone more or less met the number of children candidates coming forward for growth hormone treatment (UK 4).

Although the treatment of growth hormone deficient patients was characterised and understood as replacement therapy, the desired outcome of therapy was always to increase the growth rate of the

affected individuals and increase the final adult stature that they would achieve. The ultimate benefit of increased stature is rarely discussed in academic papers published during the pituitary era.

Some parallels can be drawn from other hormone treatments being prescribed during the era of pituitary growth hormone. The treatment of Turner syndrome girls with oestrogen to induce delayed or absent sexual maturity was indicated to promote their 'feminine identity [and] is recommended for the psychological well-being of the girl with Turner syndrome' (Levene, 1978 p1097). Rothman & Rothman (2003) note that many early reports of testosterone therapy for hypogonadism (which, untreated, produces not only short stature but failure to reach sexual maturity) related not only to the physiological changes involved but also the psychological restoration of patients who were formerly 'broken men'. Another statural treatment that was popular during this period was the use of estrogens to reduce the growth of children, primarily girls, with normal but tall predicted adult heights (Lee & Howell, 2006). Constitutional tall stature is defined statistically as height two standard deviations or more above the average population height, adjusted for height and gender[49] (Frasier, 1968). The primary reasons for treatment were psychosocial concerns- either expressed by the children themselves or, commonly, their parents. A 1975 editorial on the subject in the British Medical Journal explained:

> Tall slender girls are favoured in our society, but excessive height

> is a source of considerable embarrassment and misery. Parents whose daughters' tower above their contemporaries have often experienced the difficulties of being tall themselves and are anxious that growth should be slowed or arrested (Anon, 1975 p648).

Lee & Howell (2006), in reviewing this body of literature, note the preponderance of negative associations between social success and tall stature for women. Potential difficulties for the tall woman included: poor prospects for future employment and marital success, potential psychological problems as a child such as shyness or disruptive behaviour, and potential social isolation, although 'the single most commonly cited social reason for reducing the height of tall girls was social attractiveness' (Lee & Howell, 2006 p1036). The definition of excessive height can be clearly linked to ideas of the appropriate social role for a woman at the time. In particular, to be 'too tall' for a woman was to be taller than the average male in western society. A corresponding height reduction treatment for boys using testosterone was available but there were very few studies with very small patient numbers[50] and much higher height cut-offs for eligibility were employed because 'tallness in boys is generally considered to be an advantage' (Zachman et al, 1976 p116).

There is some evidence of gendered norms at work in the application of growth hormone therapy. The shortage of pituitaries and the need to conserve hormone meant that the UK and Canadian trials and the

National Collaborative Growth Hormone Treatment Project in the US were led to impose height bars above which patients were no longer eligible for treatment as they had reached a minimally acceptable height. Typically the height bars were set higher for boys than for girls. Frasier (1997) reports that the NCGHP limits were to168cm (5'6") for boys and 163cm (5'4") for girls. The UK trial had similar gender-adjusted height limits and in the absence of sufficient hormone to treat individuals until they finished growing the best aim of therapy was:

> [T]o treat all patients until they are of a socially acceptable height, even if this is not the maximum they might obtain (Milner et al, 1979 p36).

The nature of what precisely defines a 'socially acceptable' height is not elaborated. The implication, however, is clear; these short children, the majority of whom were boys, required and needed growth therapy in order to play a normal role in society and achieve the psychological well being that would accompany normal development.

Armstrong, Lilford, Ogden & Wessely (2007) have noted that the 1960s and 1970s saw the increasing professional recognition of a psychological and social element to disease in the form of the 'Quality of Life' (QoL) concept. Patient questionnaires developed during this period promoted the idea that the psychosocial effects of certain diseases could be captured through standardised instruments and used in rationing and care allocation decisions, although the concept seems in general to have pervaded medical practice in a less defined

way. A Hastings Centre project on surgically shaping children which investigated surgeries to 'correct' abnormalities of genitalia (intersex conditions), limb-lengthening surgery for achondroplasic dwarfs and reconstruction of cleft lips and palates found that in many cases physical abnormality was automatically considered to put patients at risk of psychological damage and justify intervention on quality of life grounds without any clear measurement or assessment of either concept (Parens, 2006). Endocrinologists and surgeons would often prescribe a programme of hormonal and surgical treatment to assign children with ambiguous genitalia to a particular gender category as a matter of course, and it is only more recently that the possibility of non-intervention has been discussed (Morris, 2006). It certainly seems likely that similar assumptions are intertwined with the treatment of short stature during this period and in the present. The latter assumption will be investigated in the subsequent chapter through analysis of paediatric endocrinologists' views on contemporary rationales for growth hormone therapy.

SECTION 2: THE RECOMBINANT ERA

The Origins of Biosynthetic Growth Hormone and the CJD Crisis

By 1980 most hormones were available in synthetic form and of the major products only insulin and growth hormone were still derived from harvested glands. Of course, the potential of a synthetic growth hormone to resolve the shortage of pituitary-derived hormone had

been recognised for some time. As early as 1963 Dr Blizzard of the NPA commented;

> [W]idespread use [of GH] must await synthesis or conversion of animal growth hormones, which are inactive in humans into active hormones (Blizzard, 1963 p51).

Laboratory research into these possibilities had been pursued since pituitary GH first became available and following Sanger's pioneering determination of the amino acid sequence of insulin in 1955, C.H. Li succeeded in decoding the considerably larger sequence of human growth hormone in 1966 (Anon, 1971). By the 1970s Li's team managed to synthesise a protein with the amino acid structure of human growth hormone but the process was complex, low yielding and extremely expensive (Ibid.). Although the synthetic protein had similar chemical properties to naturally occurring hGH it was neither sufficiently active nor sufficiently pure to be used in human patients.

Ultimately it was not conventional synthetic chemistry that produced the first man-made growth hormone but the new technology of recombinant genetic engineering. Genentech, founded in 1976, was one of the earliest biotechnology companies, and its business model was based around the idea that transferring a human gene for a valuable protein molecule into a bacterial cell would enable the cell to produce the protein, which, when the process was scaled-up, would allow industrial scale production of commercial protein products (Cronin, 1997). Genentech selected growth hormone for their first

attempt at proving the new technology was commercially viable because the sequence of the GH protein was known and the new product would essentially be replacing an existing one with a pre-existing market and a defined patient population: it was targeted at an existing network and thus had a greater chance of becoming successfully adopted and embedded than an entirely innovative product (ibid.). The small existing patient population also made Genentech's new product eligible for orphan drug status which would guarantee seven years of market exclusivity in the US (Rohde, 2000).The process of recombinant DNA manufacturing began in 1979 and the first samples were available for phase one clinical trials in growth hormone deficient patients by 1981 (Dean & Friesen, 1986; Kaplan et al, 1986).

During this process Genentech worked closely with the US academic paediatric endocrine community, forging links with physicians at twelve US growth centres selected for the early trials, while KABI were also carrying out clinical trials of recombinant hGH in Europe (Kaplan et al, 1986). Thus the potential of the biosynthetic product was known and anticipated among the international paediatric endocrine community well before it was available. In the UK, a fall in the supply of collected pituitary glands meant that as far as practitioners were concerned:

> [T]he introduction of biosynthetic human growth hormone, derived from recombinant DNA technology, will not come a moment too soon (Preece, 1981 p1145).

For a variety of reasons, recombinant insulin, not growth hormone, manufactured in collaboration with Eli Lilly, was the world's first recombinant DNA-derived biosynthetic protein to be approved for clinical use in 1982. In 1985 reports appeared in the medical literature that three adult patients in the US and one in the UK who had received pituitary derived growth hormone as children had died of the rare neurological condition Creutzfeldt Jacob Disease (CJD) (Koch, Berg, De Armond & Gravina, 1985; Powell-Jackson et al, 1985). CJD was known to be transmissible through contact with contaminated neural matter and the connection with all four cases having received growth hormone was too high to discount. Amid fears of a potential epidemic of CJD, treatment with pituitary growth hormone was unilaterally retracted midway through 1985 and by the end of that year biosynthetic GH had been approved in the US, UK and elsewhere to replace the withdrawn medicine (Tattersall, 1996).

The New Networks of Biosynthetic Growth Hormone

The sudden, crisis-driven switch from pituitary growth hormone to the recombinant product meant that there was no phased introduction of the new product, but rather the old networks were usurped and new sets of relations imposed in the space of a few short months. The old nationally-orientated networks, administered by physicians based at

a small number of specialist (usually academically affiliated) centres that provided hormone essentially free-at-the-point-of-care to a small patient population, were replaced by an entirely commercial operation. The national pituitary collection schemes and the bodies overseeing them were now redundant. In the US the NPA (renamed the National Hormone and Pituitary Program in the 1970s) was discontinued. The UK's Health Services Human Growth Hormone Committee (HSHGHC) was also dissolved but the network of specialist growth assessment centres, with their auxologically-trained personnel, remained (Milner, 1985). Other national authorities such as the Canadian Growth Hormone Advisory Group continued into the biosynthetic era, maintaining an advisory and safety-monitoring role to national healthcare systems although they no longer needed to co-ordinate the collection of pituitary glands. With the demise of national pituitary collection and processing schemes, the supply and financing of growth hormone reverted to the standard provision pattern for drugs peculiar to each country's healthcare system. In the UK this meant that recombinant GH was available through the National Health Service, while in the US financial coverage was dependant entirely on various private health insurance or state Medicaid programs (Finkelstein et al 1998; Tanaka, 1999). In Canada, Australia and many European countries government reimbursement or state insurance programmes met some or all costs of GH therapy with any remainder coming from private insurance or funds (Tanaka, 1999).

The licensing of the drug also meant that any appropriately qualified paediatrician or paediatric endocrinologist could prescribe it, which effectively moved the day-to-day therapeutic application of the hormone outside the exclusive remit of the limited group of academic specialists (Milner, 1985; Wyatt, Mark & Slyper, 1995). Nationally and internationally the community of paediatric endocrinologists was growing in size. Membership of the Lawson Wilkins Paediatric Endocrine Society (LWPES), the major professional organisation of paediatric endocrinologists in North America had grown from around 160 members in 1972 to over 500 members by 1995 and reached more than 800 active endocrinologists by 2002 (Cuttler et al, 1996; Fisher, 2004). One senior US paediatric endocrinologist characterised the differences with the pituitary era:

> [I]t was more of an elite group because it was only the people writing protocols [ ] back then in the United States, essentially with few exceptions, everybody who was a paediatric endocrinologist, practising paediatric endocrinology, was in academic life- that's evolved (NAM 4).

With Genentech's authorised US distributors Caremark supplying their recombinant GH product *Protropin* directly to board-certified endocrinologists there was no longer the NIH-imposed need to be able to write research protocols before getting access to growth hormone. Accordingly, availability of growth hormone expanded from being prescribed at only 50 specialist centres in the US before 1985

to being provided at hundreds of hospitals and medical centres across the country by 1990 (New York Times, 1990).

In Canada, Eli Lilly offered to conduct clinical trials of its own recombinant GH products in conjunction with the existing national program, although Genentech's Protropin was also commercially available (Dean & Friesen, 1986). This helped sustain the central role of the Canadian Growth Hormone Advisory Group and (temporarily) kept Canadian healthcare costs down, while providing Lilly with a pre-selected patient population for its trials and a possible advantage in the Canadian market. Lilly's Canadian testing, combined with some controversial regulatory manoeuvring eventually allowed them to gain orphan drug status for their own GH product *Humatrope*, allowing them to effectively split the North American market with Genentech until the mid-1990s (Rohde, 2000). In the new era of commercial hormone supply, the differences in national socio-economic systems of healthcare provision and the considerably expanded basis for provision would significantly affect the way in which growth hormone was utilised. However, there was a third current of change that would have, perhaps, the greatest impact on the application and profile of the drug.

And Growth for all?

One of the most frequently cited descriptions of biosynthetic hGH is that it offers an 'unlimited' or 'potentially unlimited' supply of the hormone. As described above, even before recombinant GH was approved, paediatric endocrinologists recognised that it had the potential to alleviate the central problem which had affected the era of pituitary hormone therapy- that of limited supply (Dean, 1985; Gertner et al, 1984; Preece, 1981; Conrad & Potter, 2004). Unlike the pituitary era treatment, commercially produced hGH had to receive regulatory approval for a specific, recognised disease and so the original approval was for the pituitary-era definition of growth hormone-deficient short stature. The first change offered by the unrestricted supply was the opportunity to provide full treatment to all those existing GH deficient patients, removing the height bars and dosing limits imposed by the paucity of supply of pituitary glands. This was not the only possibility, as one joint study group at the Stanford and Yale University Schools of Medicine noted with some understatement:

> The prospective availability of large supplies of human growth hormone produced in bacteria by recombinant DNA techniques has rekindled interest in the potential usefulness of this agent in short children who are not growth hormone deficient (Gertner et al, 1984 p172).

A measure of the interest in this area can be seen from the amount of activity preceding the approval of recombinant growth hormone.

Anticipating this ‘new era’ the US National Hormone and Pituitary Program and the UK’s Health Service committee supported trials of pituitary GH in short children who did not meet the biochemical criteria for GH deficiency but who, following Rudman’s work in the 1970s, it was believed might still show a diminished but beneficial response to GH therapy (Hindmarsh & Brook, 1987). Genentech were unsurprisingly also interested in the potentially larger markets for their new hormone, and their connections with the US paediatric endocrine community soon bore fruit. One academic paediatric endocrinologist working at a US centre involved in Protropin trials recalls:

> [A]fter the initial study of recombinant growth hormone in growth hormone deficient children was completed, Genentech asked our advice in terms of what directions they might consider going in, in the future [ ] and we recommended the area of Turner syndrome and idiopathic short stature and Genentech became interested in both (NAM 5).

The first trial of biosynthetic GH in Turner syndrome was initiated in 1983, while the investigation of GH in normal variant or idiopathic short children was taken up by Genentech-sponsored studies after the pituitary GH studies were cancelled in the aftermath of the CJD issue (Johanson & Blizzard, 1990; Hopwood et al, 1993). The UK normal variant short stature trial was replaced by a larger investigative trial using biosynthetic hormone but was still run by

paediatric endocrine researchers at academic medical schools (Preece, 1986). Even as the new era of biosynthetic growth hormone was offering the ability to finally treat a range of short-statured conditions the diagnostic boundaries that defined the current classification system were being undermined and blurring into the grey-area of poorly or undefined short stature.

Growing Markets, Shrinking Consensus

'[T]he more GH we have, the less we agree about who should receive it' (Allen & Frost, 1990 p16).

As described previously, the entire distribution and diagnostic system for pituitary growth hormone was based on a concept of rationing the limited supply of hormone to the most needy and most responsive cases. For endocrinologists using pituitary hormone the limitations of supply were not just an operational difficulty; they actively defined the majority of practices and decisions made during that era. The networks and practices set up during this era, including their financial arrangements, 'worked efficiently and fairly so long as growth hormone was in short supply and there was only one route of distribution' (Milner 1985, p1593). Authorities tailored the definition of deficiency to meet the supply of hormone, raising both the minimum height for treated children and the cut-off point on biochemical tests of blood GH levels which defined 'deficiency' itself, as the number of

pituitary glands being collected rose during the 1970s (Allen & Frost, 1990).

Interest in the new 'unlimited' resource of biosynthetic GH was beginning to expose the limitations of the diagnostic methodology inherited from the previous system. If, as became evermore apparent from the growing body of experimental work, short children who did not have growth hormone deficiency *could* show an acceleration in growth rate in response to treatment with recombinant growth hormone, were they not also eligible for treatment? The definition of growth hormone deficiency relied on the biochemical cut-off points to distinguish what was increasingly being referred to as 'classic' or 'severe' GHD from other auxologically-defined short statured conditions. Increasingly it appeared that secretion of GH did not fall easily into two levels- the deficient and non-deficient, rather there appeared to exist a continuum between the most severe deficiency and the levels seen in normal, healthy children, with poor correlation between height or growth rate and hormone level. Without the limiting factor of supply to consider, what made these cut-off points anything other than arbitrary? (Neely & Rosenfeld, 1994).

The issue was made more contentious by the variety of different stimulation methods[51] replacing or competing with the insulin tolerance test, and the introduction of commercial laboratory testing which employed a variety of unstandardised assay techniques that

could give very different results from a single sample of blood (Guyda, 2000; Ayling, 2004). Overnight or 24-hour sampling of growth hormone levels without stimulation by insulin or other agents was possible with improved assay techniques and was proposed as a method to detect subtle imbalances in natural secretion (Rose, 1995). However this physiologic testing was expensive, technically difficult, and showed a large overlap in values between normal-statured, normally growing children and short children, including some with documented GHD (Johanson & Blizzard, 1990; Rose, 1995).Some commentators interpreted the poor correlation between auxological measurements and overnight and stimulated GH testing as evidence that both biochemical methods were inherently unsound (Allen & Frost, 1990).

While paediatric endocrinologists were debating the limitations of growth hormone deficiency, the market and patient population for growth hormone especially in the US, were rapidly expanding, producing a belated reminder that this was no longer the sole preserve of academics. There were a number of reasons for this expansion: distribution, and with it pharmaceutical company marketing was extended to all paediatric endocrinologists and increased availability meant that all short children with GH deficiency or partial GH deficiency could now be treated fully. Height bars were removed, dosage and dose frequency (which had previously been determined by availability) increased, in some cases to a daily

regime of injections and double dosing (Wyatt, Mark & Slyper, 1995). Promotion of growth hormone by pharmaceutical companies was not limited to endocrinologists- both Genentech and Eli Lilly formed a close association, including provision of financial support, with US patient groups like the Human Growth Foundation (HGF) and the more recently founded MAGIC foundation whose mission now included raising awareness of short stature (Conrad & Potter, 2004).

In addition to marketing campaigns, the HGF and Genentech in particular were involved in sponsoring and organising school-based height surveys in a number of states, in which children were assessed for height and those with short stature often recommended to seek specialist appraisal (Weiss, 1994). These efforts appear to have been effective as one academic paper commented in 1990:

> An increasing awareness of the social and psychological implications of short stature is resulting in increasing referrals for evaluation of short children (Johanson & Blizzard 1990 p61).

Published data from the National Co-operative Growth Study (NCGS), Genentech's post-marketing surveillance program for Protropin show that in the period 1985-1987 already some twenty-percent of patients in the registry were receiving hormone for a variety of non-GHD conditions including Turner syndrome, intrauterine growth retardation, normal variant short stature and sundry miscellaneous diagnoses (Kemp, 2005).The size of the patient population rose from an estimated 3,000 in 1985 to around

20,000 by the mid 1990s and with it grew the profits to be made from selling recombinant growth hormone- Genentech made an estimated $217 million from sales of Protropin in 1993 while Lilly's Humatrope earned around $200 million in the same period (Neely & Rosenfeld, 1994; Fisher, 1995).

The new era of commercial and therapeutic success for human growth hormone was attracting interest beyond the medical realm. One of the primary issues raised was the predicted financial burden if growth hormone use was to be approved for short children without growth hormone deficiency (Grumbach, 1988; Allen & Frost, 1990). For bioethicists there was a second concern, that:

> [T]he modification of height, which is possible through administration of biochemical GH, raises the same questions about therapeutic versus enhancement uses of genetics (Tauer, 1995 p18).

Central to both concerns was the issue of how to demarcate acceptable therapy from unwarranted use of growth hormone. While these concerns were mainly articulated within the confines of academic articles, other individuals and groups were making the issue of growth hormone more public. Activist Jeremy Rifkin began a campaign against the use of growth hormone in short normal children, decrying it as human enhancement and 'cosmetic endocrinology' and mounting a legal challenge to halt NIH-sponsored trials of recombinant GH in children with idiopathic short stature

(Lehrman, 1993; Weiss, 1994). After an article in the New York Times in 1991 entitled 'How short is too short?' questioned Genentech's marketing practices the FDA began an investigation of the company (Nordenberg, 1999). In 1994 a series of congressional hearings called by the House Committee on Small Business heard evidence that Genentech and Eli Lilly had both been involved in illegally promoting their growth hormone products for off-label use, and that kickbacks and other illegal payments to physicians had been made to boost prescription rates (Conrad & Potter, 2004). Allegations were also made that Genentech's sponsored school studies were being improperly and coercively used to increase recruitment of short patients for treatment as part of a scheme to help the company maintain a market advantage over Lilly, given that both their drugs had the same wholesale price[52] (Kolata, 1994). As a result short stature became not only a scientific, financial and ethical controversy, it became a public one too.

The Contemporary Uses of Human Growth Hormone

In the absence of clear diagnostic categories many paediatric endocrinologists, for whom it should be noted growth disorders were not the major component of their practice, fell back on auxological characteristics as an implicit basis for making treatment decisions (Neely and Rosenfeld, 1994; Cuttler et al, 1996). Two large scale surveys of US paediatric endocrinologists in the mid-1990s reported that the majority continued to use the standard biochemical tests in

evaluating children with short stature for growth hormone deficiency but the main guiding factors in making an assessment of growth impairment were auxological, the key factor being growth rate (Wyatt, Mark and Slyper, 1995; Cuttler et al, 1996). Additionally a majority of respondents reported that they were prepared to use GH in children without 'classical' growth hormone deficiency, mainly in children with a poor growth rate or Turner syndrome (Ibid.). In the latter case an unofficial consensus appears to have been reached that growth hormone in TS was acceptable as over 90% of respondents in both surveys approved of this use.

The first regulatory approval of hGH outside the 'classic' deficiency indication was the FDA approval of Genentech's updated synthetic hormone Nutropin in 1993 for the relatively minor indication of improving the growth of children with renal insufficiency[53]. Turner syndrome followed in 1996 by which time the orphan drug protection had expired on Protropin and Humatrope allowing other pharmaceutical companies with growth hormone products to enter the US market including Pharmacia and Upjohn[54], Serono and Novo Nordisk (Rohde, 2000). The Lawson Wilkins Paediatric Endocrine Society and the American Academy of Paediatrics separately issued guidelines in 1995 and 1997 respectively, endorsing the use of growth hormone in GHD, Turner syndrome and renal insufficiency and recommending a conservative approach to prescribing and that other causes of short stature be investigated through controlled

clinical trials alone (Furlanetto/ The Drug and Therapeutics Committee of the Lawson Wilkins Paediatric Endocrine Society, 1995; Berlin et al, 1997). It is evidence of the impact of the controversy surrounding pharmaceutical company promotion of GH that the AAP guidelines felt compelled to warn physicians that:

> [S]pecial care must be taken to avoid financial relationships that either compromise or appear to compromise the physician's commitment to serving the patient's best interests (Berlin et al, 1997 p126).

In general European regulatory approvals followed the pattern of those in the US, although clinical trials were carried out by pharmaceutical companies on an international scale and generally combined data from North American and European studies. Further approvals followed for adult growth hormone deficiency (1997), Prader-Willi syndrome (a genetic syndrome causing short stature among other developmental problems) (2000) and children born small for gestational age (2001) (Hintz, 2004). Despite regulatory approval for each of these indications being granted by the FDA and EMEA, considerable debate about the proper application of growth hormone still remains among paediatric endocrinologists, healthcare policy makers and ethicists. While national guidelines exist in many countries there is still no universal definition of short stature or growth hormone deficiency (Tanaka, 1999; Guyda, 2000). Ayling (2004) notes that despite more than 6000 academic papers on the subject of

biochemical testing for growth hormone levels in the blood there is still no agreed standard. In 2003 the most recent and also the most controversial extension of regulatory approval for GH occurred when the FDA approved Lilly's Humatrope for children with a diagnosis of idiopathic short stature defined purely on auxological criteria as the shortest 1.2% of the population (FDA, 2003).

With no diagnostic consensus much of the regulation of growth hormone usage at national and local levels is shaped by institutional and economic factors. In the UK the 2002 National Institute for Clinical Excellence (NICE) guidelines recommended GH for use in children with growth hormone deficiency, Turner and Prader-Willi syndromes and chronic renal insufficiency only (Bridges, 2005). Estimates suggest that the incidence of GHD in the UK is around one tenth that of the US, making it comparable to other European countries such as France and Germany (Guyda, 1999). Surveys in parts of Europe and the UK have shown, however, that there is considerable variation in both the clinical and laboratory assessment of short stature, and interview data has confirmed that many UK centres use their own local or 'in-house' diagnostic criteria when making the assessment (Ayling, 2004; Juul et al, 2002). Canada has one of the stricter requirements in terms of patients demonstrating a measurable response to GH in order to remain on treatment and has one of the lowest frequencies of GHD per general population (Tanaka, 1999). By contrast the US had the largest patient

population, one of the highest frequencies of diagnoses of GHD in the general population and the highest standard dosage of any country surveyed (Tanaka, 1999). Whilst the majority of US insurance payers were willing to cover therapy for a diagnosis of GHD, less than two thirds on average[55] also offered coverage for non-GHD approved indications like Turner syndrome and renal failure (Finkelstein et al, 1998). As Ranke observes in a commentary on Tanaka's findings, the different patterns of national GH usage may also reflect 'the respective societies' willingness to spend money on improving the quality of life of a group of individuals rather than on their physical health and survival' (Tanaka,1999 p80).

Conclusion

As this chapter has demonstrated, the use of growth hormone is intrinsically intertwined with conceptions of the short stature it is intended to treat. Indeed the very naming of the (then putative) 'hormone of growth' identified it as the master molecule responsible for controlling human growth and development. To an ordering, normalising medicine this naturally represented and was welcomed as a new tool to rectify those patterns of growth and development marked as abnormal, disordered and aberrant. The measurement of growth stands out as a special case even among modern disease entities, because it so clearly relies on specialised techniques of measurement on a variety of indexes- biochemical, physical, radiographic and statistical, to make visible both the target and effect

of therapy itself. In dwarfism, or short stature, the condition for which growth hormone was, and is, mainly applied the most important symptoms literally are measurements. It can in some ways be considered a *disease of measurement*. The technologies of measurement, used to make short stature visible, come with their own cognitive baggage- the hormonal model of the body with its exemplar model of deficit and replacement, and the statistical approach which places the average and expected as the ideal. But the co-construction of disease and therapy is also shaped by the other resources available to the networks across which it takes place. This is most clearly illustrated in the case of growth hormone by the effect of the change in hormone supply from the pituitary to the recombinant eras (indeed it is so significant it presented an obvious device around which to structure the account in this chapter).

The introduction of biosynthetic growth hormone and the subsequent expansion of the patient population can be viewed as a classic case of schismogenesis: pharmaceutical industry marketing raises awareness and grows its own market by fostering a sense of need for the new product (Nichter & Vuckovitch, 1994). As this chapter has shown, the initial impetus to treat short stature came from, and remained within the medical profession. The goals of growth hormone therapy gained their structure as the elite of paediatric endocrinology claimed disciplinary authority over the new hormone by building networks of practice and ideas around growth hormone.

Treatment became centred on the dual deficits of hormone deficiency and low current and predicted adult height partly because these forms of measurement were available to the nascent networks: through their own endocrine training or transmitted by the involvement of auxologists like James Tanner. This cognitive framing was stabilised by the utility of both forms of measurement in providing a justification for the rationing of growth hormone during the pituitary era. The disruption of the network by new actors with new technology, new interests and importantly new resources, challenged and ultimately destabilised this disease/measurement concept. This occurs because the hormonal pathology of the body and the statistical approach do not actually refer to the same object and are not interchangeable. Uncertainty and confusion arise because the plurality of biomedical models of the body is revealed (Mol & Berg, 1994; Waldby, 2000). Pharmaceutical marketing, and especially Genentech's early school promotions certainly amount to an attempt to promote the desire, understood as need, to avoid short stature by recourse to hormone therapy but this cannot be taken as the whole story.

Decoupling the treatment of short stature from the idea of replacement therapy also exposed the previously uncodified, socially normative aspects of the treatment. Normalising expectations about 'socially appropriate height' can be detected in the different height bars for male or female patients used to ration hormone access, and

the parallel oestrogen treatment of ‘overly’ tall girls to produce a more acceptable stature. The construction of pathological, abnormal short stature thus incorporates cultural values about height which reflect pre-scientific ideas about masculinity and femininity, many of which have been later reiterated as justifications for therapy. A challenge to its scientific basis, and thus objectivity, left the treatment of short stature open to accusations of human enhancement and industrial ‘disease mongering’ by outside interests such as journalists and bioethicists.

Ultimately the use of growth hormone has been at least partially stabilised by the other actors in the networks of the commercial, biosynthetic era. Economic constraints, shaped by the differing national systems of healthcare provision and pharmaceutical regulation have imposed limits on who is entitled to hormone therapy and on what grounds. This is reflected in the significantly different proportions (relative to population size) of patients recognised as growth hormone-deficient in the UK, US, Australia or Japan, and indeed in the different practical criteria for what abnormal short stature actually is, in different states. As Mol & Berg (1994) observe, many scientific controversies are not resolved with any clear winner or loser but rather fade from view with a mutual loss of interest on all sides. The issue of growth hormone, however, remains contentious as long as a future but potentially imminent European regulatory decision on idiopathic short stature hangs over the topic. The impact

of this history on the practices and the framing of practices of treating short stature among leading paediatric endocrinologists will be examined in the next chapter. Among the issues for investigation are understandings of the benefit of height as an outcome of medical therapy and reasons why the psychosocial disadvantages associated with short stature were difficult to formalise, despite the existence of quality of life instruments and an increasing awareness of the significance of this component of the treatment rationale among medical professionals.

Notes

[47] A branch of the US National Institutes of Health (NIH).

[48] The extent of this problem can be seen in the data of Henneman (1968) who collected data from eleven teams of investigators across North America in order to present data on a total of fifty hypopituitary patients. Even focusing exclusively on this sample from the most promising group of patients, Henneman was faced with trying to evaluate at least six different preparations of hGH used in seven different treatment programs with patients ranging in age from 2 to 17 years old, treated from between 6 and 60 months with dosages range from 10 to 45mg (dry weight) of hormone per month.

[49] Just as short stature is correspondingly height two standard deviations or more below this average.

[50] Ruvalcaba, Tattoni & Kelley (1975) reported the treatment of a single case of height reduction using testosterone treatment, in a boy whose predicted adult height was close to 7ft (over 200cm) and noted they were aware of only one other case of such therapy being reported.

[51] Ayling notes that by 2004 there were over 34 methods to stimulate blood GH levels described, the most common being insulin, argenine, clonidine, glucagon and growth hormone releasing hormone, although there is no agreed 'gold standard test' (Ayling, 2004).

[52] In 1999 criminal charges were eventually brought against Genentech, which admitted 'it aggressively marketed the drug Protropin [ ] for uses other than the one approved by the FDA' and accepted a $50 million fine as part of a plea agreement (Nordenberg, 1999 p33).

[53] Cuttler et al (1996) estimated that patients with renal insufficiency constituted only 2% of the treatment population, making it relatively uncontroversial in the atmosphere of ethical and financial concern over increasing application of GH.

[54] Pharmacia and Upjohn had bought over Swedish growth hormone manufacturer KABI and were now responsible for producing and distributing their biosynthetic GH product Genotropin. Pharmacia is now incorporated into Pfizer who continue to market Genotropin.

[55] While on average, 94% of insurance providers, including state Medicaid programmes would cover GH deficiency only 52% would pay for Turner syndrome

patients, 58% for renal insufficiency and barely 10% would cover idiopathic short stature (Finkelstein et al, 1998).

CHAPTER 6: Endocrinologists' Contemporary Discourse on Growth Hormone

Introduction

This chapter is concerned, primarily, with current perspectives on the therapeutic employment of GH and follows on from the previous account of the socio-historical development of human growth hormone. The development and social shaping of growth hormone as a medical technology has so far been investigated in terms of the influence of networks of supply and production, the interests of different social groups, and the deployment of technologies of measurement that brought disease and therapy into visibility. The purpose of this chapter, then, is to examine the contemporary discourse of paediatric endocrinologists, as the group whose professional domain incorporates assessing short statured children and administering human growth hormone, concerning the rationale for treating short statured children. The primary data comes from a series of qualitative interviews conducted with leading academic paediatric endocrinologists in North America and the UK, as detailed in Chapter 3. The aim is neither to attempt to reconstruct a 'definitive' account of the practical and specific interactions that occur in a growth assessment or endocrine clinic, nor the beliefs or mental states of physicians involved, but rather to investigate the construction of legitimacy and illegitimacy in their discourse on the

employment of growth hormone as a treatment for short stature . Charting the impact of the historical development of the drug, as recounted in the previous two chapters, on the current professional discourse is of particular importance, given the contention in this project that current controversies over enhancement uses of pharmaceuticals cannot be dissociated from the prior development of these medicines.

In line with the objective of investigating the framing and content of the interview data, a discourse analysis (DA) approach is adopted, drawing broadly on Gilbert & Mulkay's (1984a; 1984b) concept of discursive repertoires. As described in Chapter 3, repertoires in DA examine discourse not for its representations of the external world but for the way in which it is ordered and the particular effects this achieves in the context of its production. A body of work has interpreted the spoken and written discourse of natural scientists in a variety of settings in terms of two distinct repertoires, the empiricist and the contingent (Potter & Mulkay, 1985). In the empiricist repertoire findings, opinions and choices (for example between competing scientific theories) are based on experimentally verified evidence and appear objective, rational and self-evident. Interpretations following the 'orthodox' model of science appear authoritative because the act of interpretation itself is hidden and presented as a process of observer-independent, disinterested logic. The contingent repertoire, by contrast, presents experimental data

and other scientific evidence as ultimately uncertain and open to interpretation, especially where the possible influence of external factors is concerned. These repertoires act to frame discussions in particular ways which often support particular justifications and offer opportunity to refute contrasting positions; specifically the empiricist can describe and support ‘good’ science in approved-of decisions while refuting contradictory positions and opinions as based on contingent ‘bad science’ (Kerr, Cunningham-Burley & Amos, 1997).

These repertoires are useful tools for interpreting scientific discourse and will be employed where relevant in this chapter. This approach has also been adapted by others to investigate medical discourse as well as that of ‘pure’ natural scientists. Kerr, Cunningham-Burley & Amos (1997) have used the concept of empiricist and contingent repertoires to interpret the discourse of professional geneticists with regard to the way that they separate ‘science’ from ‘non-science’ in interview talk. Other investigators have envisioned repertoires beyond the empirical/contingent template to describe salient features of discourse around a particular issue, for example psychiatrists use of electroconvulsive therapy (Stevens and Harper, 2007) or GPs’ descriptions of ME patients (Horton-Salway, 2002). These examples highlight an important aspect of discourse analysis: that it allows an examination of how authority is constructed, especially in contested situations such as justifying or rejecting a controversial therapeutic procedure like ECT, separating patients as ‘genuine’ ME sufferers or

not, or apportioning responsibility for genetic knowledge between scientists and the public (Horton-Salway, 2002; Kerr, Cunningham-Burley & Amos, 1997; Stevens and Harper, 2007). Interviews, after all, are well characterised as instances when informants attempt to persuade the interviewer of their own competence and the morality of their situation (De Chadarevian, 1997; Murphy & Dingwall, 2003). This provides a useful opportunity to reveal the concepts or beliefs that are taken to be 'self-evident' by informants, the norms of particular professional practice, which underpin explanatory discourse. In the case of human growth hormone, the professional norms of paediatric endocrinology are being examined to reveal how some height-boosting treatments are legitimised as therapy while others are discounted or framed as uncertain and suspect.

During the interviews, respondents were asked about the use of human growth hormone in children with short stature across the range of diagnostic categories taken from the academic medical literature – severe and partial growth hormone deficiency, and non-hormone deficient categories including Turner syndrome, children with renal failure and idiopathic short stature. This line of questioning afforded a ready-made structure; following the historical development of growth hormone from the narrow indication for use in the pituitary era through to the wider range of applications made possible following the introduction of biosynthetic hormone in 1985, whilst simultaneously addressing the expansion of the scale and scope of

medical treatment for short stature. A common feature of the responses, both between interviews and across indications for growth hormone, was to employ a range of diagnostic criteria to describe the patients being treated with growth hormone and the outcomes of the therapy. In particular, informants' accounts focused on the nature of the deficit requiring treatment and the way(s) that this can be measured or made visible. Stevens and Harper (2007) have described a 'biomedical-medical' repertoire employed by psychiatrists when discussing electroconvulsive therapy, which is characterised by the use of 'diagnostic medical language' (p1479). While there are obviously similarities in the type of language being recounted, some of the significance for that report lies in the fact that there are potentially other repertoires of description available to psychiatrists, such as psychological or even emotional models of behaviour and actions. In this case the use of medical terminology would be expected from endocrinologists and is hardly a finding in itself.

Rather, the specific employment of indices of measurement and the categorisations they support in paediatric endocrinologist informants' talk about patients and decisions about the medical treatment they receive has been styled here as a 'diagnostic repertoire'. Another strongly recurring theme to the discourse was the rhetorical appeal to a sense of appropriate performance of paediatric endocrinology - that physicians orientate their actions and goals around an idea of the

proper authority and competence due to their position. This can be displayed through mentioning experience, exercise of professional judgement and capabilities to make assessments, common sense, and duty to patients, and lessons from medical practice beyond the application of growth hormone. If pure scientists present their own findings and interpretations in an empiricist repertoire to grant them the authority of natural, logical scientific endeavour, the informants in this chapter appeal to an idea of medical authority of which competent scientific interpretation of experimental data is a part, but that also extends to notions of a broader competence and authority, a duty to patients and even financial responsibilities. The aim of this chapter ultimately is to explore the professional norms and appeals to particular kinds of authority that are employed by paediatric endocrinologists, especially through their (flexible) use of the diagnostic repertoire, and interpret them in the light of the history of human hormone therapy set out in the previous chapters.

The Diagnostic Repertoire: Dual Scales of Deficit in GH-deficient Children

The use of the diagnostic repertoire could be clearly observed when respondents were asked to explain the rationale for therapy in what has become known as ‘classical’ growth hormone deficiency. This category is used to describe the most severely affected hormone-deficient children and is based on criteria determined during the pituitary era of GH use. For the majority of practitioners interviewed

this indication would have formed the major, often the only, approved use of growth hormone during the earlier stages of their career, giving an historical perspective to the dialogue, as in the following two extracts from a UK and a US paediatric endocrinologist respectively:

> So the prevailing rationale for the administration of growth hormone was low growth hormone and low growth rate (UK 4)

> I came in at a time when it was pretty easy. We knew who was growth hormone deficient, they had the growth curve: failure to grow, the phenotype: short pudgy little kid, and when we did the tests, their biochemical tests were in the netherworlds (NAM 2).

In both responses the rationale is approached in terms of diagnostic tools - the measurements that physicians can make to separate out illness and abnormality from health. In the case of growth hormone deficiency the two most prominent areas of measurement are the physical and the biochemical. Both of these are prominent in these two extracts – 'low growth hormone'/ 'tests in the netherworlds' referring to the biochemical measurement of hormone levels in the blood and 'low growth rate'/ the 'failure to grow' on a growth curve being the physical measurement. One effect of this approach is to channel a potentially open issue of why endocrinologists opt to treat children with short stature at all, into a question of how to select the most appropriate patients for therapy on the basis of empirical criteria. The focus on measurable factors makes the assessment of patients appear objective and therefore scientific. Another outcome

of the diagnostic terminology is to highlight as evident and obvious the symptoms, which characterise the patient's abnormal status. In the extract from NAM 2 this certainty, the 'pretty easy' diagnosis, is facilitated both by the specialised measuring instruments of the blood test and growth chart but also the simple physical appearance of the patient - the 'short pudgy little kid'.

In the following extract, a North American paediatric endocrinologist described the approach to treatment in Canada in the early pituitary era when biochemical tests were not yet available:

> Well [ ] there were two drivers. One: there were some kids, and these kids got very quickly and were treated all year round, were kids that had very severe [ ] hypoglycaemia [ ] they had hypoglycaemic micropenis, the whole ball of wax including congenital hepatitis which was well described being growth hormone related and so on, so that was one, and then the next was auxology, the Tanner stages for growth failure (NAM 8).

As well as listing the prominent diagnostic symptoms of the most severely affected children, this extract also describes a progression from general symptoms of abnormality, evident and recognisable to the broader medical community (hypoglycaemia, hepatitis etc), to more disease specific items requiring more subtle measurement techniques - the auxological assessment of growth stages. Concentrating on the diagnostic measurement also foregrounds the professional expertise of the paediatric endocrinologist in both

recognising and executing the correct measurement. These descriptions mirror the general process of identifying growth hormone deficient children. Initial assessment and referral would often be based on visual assessment of physical characteristics - ‘short stature’, ‘the phenotype’, whether by parents or family doctors, and then subsequent assessment would involve detailed auxological assessment of bone x-rays, growth rate etc and laboratory analysis of the patient’s blood. Height measurement and blood hormone levels require the use of specialised measuring devices in the growth and bone-age charts, and the laboratory assays for GH, which fall within the professional domain of the paediatric endocrinologist. The cumulative effect is to render the diagnosis, and thus the condition, as something at once obvious, requiring attention, and yet obscured, needing specialist observation to reveal it. More recently, genetic and molecular level screening in patients with previously unknown causes of short stature has taken the search for abnormalities still deeper, adding a further level to the separation of healthy and afflicted children.

In the ongoing disputes and controversy surrounding the appropriate use of growth hormone played out in the academic literature, severe hormone deficiency is the one disease category that is still considered unequivocal and indisputable. Neely and Rosenfeld state that:

> The justification for hGH treatment and its efficacy in patients with GHD have not been challenged (Neely & Rosenfeld, 1994 p410).

The case for treating GH deficient children is 'clear and uncontroversial' (Voss, 1999) and 'no one would argue with the use of GH in these [completely deficient] children' (Rose, 1995). Discussions of the patient populations treated with pituitary hormone reflect this diagnostic certainty. One North American paediatric endocrinologist remarked of the early patients 'nobody would argue that they had growth hormone deficiency' (NAM 2). Another, discussing the Canadian Medical Research Council trial of pituitary hormone, explained '[w]e tried to be purists, thought we had real hypopits[56]' (NAM 8). In describing the patient selection for the equivalent UK MRC scheme, a British paediatric endocrinologist stated 'they had to have severe and definite growth hormone deficiency to qualify for treatment' (UK 1). The two scales of measurement underpinning this 'real', 'definite' and incontestable diagnosis in effect describe the rationale for therapy itself.

There is a biochemical deficit explicitly contained within the category label 'growth hormone deficiency'. The therapy for GHD is often described both in the literature (e.g. Najjar and Blizzard, 1966; Rudman, 1973; Johanson and Blizzard, 1990; Furlanetto/ The Drug and Therapeutics Committee of the Lawson Wilkins paediatric Endocrine Society, 1995) and during interviews as a replacement

therapy. The apparent conflation of diagnostic validity – that the patients were 'really deficient' – with the *rationale* for treating any cause of short stature reveals an intrinsic assumption being made. Another respondent who was, tellingly, not an endocrinologist, but a US-based psychologist with experience in evaluating children with short stature for psychosocial adjustment, explained:

> I mean there is a sort of general acceptance that, you're missing something and it has some biological function then you replace it, [ ] in the American colloquialism 'it's a no-brainer' (NAM 6).

In this sense, part of the rationale for treatment is evident from the diagnosis; to a physician, growth hormone deficiency logically requires and obviates growth hormone replacement. Chapter 4 outlined how the concept of replacing a deficiency in a particular bodily substance was integral to early practices of organotherapy and the hormonal model of the body that followed it. That replacement seems so natural and automatic as a response and as a justification in hormone therapy surely owes something to the great weight of historical precedent that accompanies it, as well as its own internal logic. A similar rationale of replacement operates in hormone therapy for deficiencies of thyroid hormone, insulin and sex hormones (in hypogonadism), all of which can cause stunting of growth during childhood (as well as other distinct and often more life-threatening symptoms).

This embedded biochemical conception of hormone action and the purpose of hormone therapy is clearly discernible in the following quote from a senior UK paediatric endocrinologist:

> [M]y view is that the use of growth hormone really comes back to the use of all the other hormones which is that they are there for the replacement of hormone deficiency [ ] I mean we don't use thyroxin for anything but thyroxin deficiency, we don't use insulin for anything other than insulin deficiency or sometimes insulin resistance, but we don't use insulin just for fun and we shouldn't use growth hormone [lightly] in my view (UK4).

Replacement therefore forms an intrinsic norm of endocrinologists' training and practice, a natural and appropriate form of intervention.

The other scale of measurement is the more immediately visible one, the phenotypic symptom that almost always brings the condition to medical attention in the first place - short stature. Short stature was constructed as a deficit in a number of ways by the respondents. One US paediatric endocrinologist explained that the purpose of treating short hormone deficient children was 'they've fallen behind and we want them to catch up' (NAM 3). The deficit on this index is in height and growth rate. The benefits are more clearly elaborated in the following account:

> I think the basic endpoint has been growth enhancement for those kids who have severe or significant short stature with the proviso that some of them have significant [hypoglycaemia] but

> the majority were growth enhancement, to get them in a more normal height range for their genetic potential... that always was the target (NAM 8).

Notably the redress of therapy brings not increased height, but a more normal height, as defined through the instrument of measurement, the growth chart. Thus the therapy is positioned as corrective, despite the term enhancement being employed, and normalising. The extract also makes reference to another restoration - that of a height closer to the patient's genetic potential.

The idea of 'genetic potential' for height relates to the method of devising a target for final (adult) height that a particular child is expected to reach, by recording the heights of both parents and calculating the average (Allen, Blizzard and Rosenfeld, 1995; Wright and Cheetam, 1999). This value, known as the mid-parental height (MPH), was introduced in the early 1970s by Tanner and associates working at the Institute for Child Health in London (Tanner, 1981; Wright and Cheetam, 1999). The MPH, when plotted on a growth chart, is used as a crude measure of whether the child is growing appropriately to attain the height they should achieve, assuming height potential is based primarily on genetic influences inherited equally from each parent. It should be noted that the assumption that height is genetically determined does not derive directly from genetic research, where only a few genes are known to have a

restricted influence on stature, but rather seems to have achieved the status of being something ‘everyone knows’:

> This concept is so well entrenched in the field of human growth research that it is almost always used without definition or justification from research (that is, without reference to the literature) in scientific and popular articles (Bogin, 1999 p333).

Nonetheless, the use of ‘genetic potential’ creates a sense of an appropriate or proper height to which a person is entitled based on an ‘internal’ genetic standard. This has a similar effect to, but is distinct from, the idea of normal height, which sets a population-based ‘external’ standard for normality against which a child’s height can be compared. In either case the technique produces a standard of height, allowing an evaluation of ‘what is’ in the light of the ‘what ought to be’ of normal or mid-parental height, revealing (producing) any deficit or abnormality accordingly.

In the final report of the UK MRC Working Party on pituitary growth hormone, Milner et al (1979) express a sentiment comparable to the informant quoted above, that:

> The principal aim of hGH therapy is to allow the patient to grow to his genetic potential (Milner at al, 1979 p35)

However, discussions of ‘genetic potential’ are relatively scarce in pituitary-era literature, perhaps because the term and accompanying calculations were still in the process of filtering into common usage

amongst paediatric endocrinologists. Additionally, given the limitations of pituitary supply most national treatment programs were forced to impose height bars, which, once attained, meant patients were no longer eligible for therapy even though they may not have finished growing and could potentially have achieved a taller final adult height (Frasier, 1997). Concerning the necessity of this restriction Milner et al (1979) reflect that:

> [I]t seems more sensible to treat all patients until they are of a socially acceptable height, even if this is not the maximum they might obtain. In general an adult height of 10-25th centile would seem a satisfactory compromise until such times as supplies are not constrained (Milner et al, 1979 p36).

The specific nature of what constitutes a 'socially acceptable' height is not discussed at any length. However, the setting of a target height range, below average height (the 50th centile) but deemed sufficiently close to normal to be worthwhile, gives some idea of the value attached to the (social) norm of height in this therapeutic endeavour. Thus, as described above, the goal of therapy is to restore both normal hormone levels in the blood and a stature closer to a standard set either by the population mean or the parental height. The goal and purpose of the therapy can be seen in these extracts to be linked, albeit obliquely, to the social value of this statural outcome. While the term is not specifically employed, the goal, as suggested in Chapter 5, is essentially one of restoring or improving quality of life. One US endocrinologist offered an

explanation of the purpose of therapy for GH deficient children, which lies mainly within the social realm.

> The real issue is …in inches how much is 30 cm? All right... that's the difference between a growth hormone deficient kid not treated and fully treated. So they can drive a car, they can reach things on a shelf in the house, activities of daily living make a heck of a difference (NAM 2).

In this account the benefits of additional height are described in terms of physical abilities (as befits an inherently physical characteristic) but firmly embedded in a social and psychological setting. Increased height confers increased performance in routine social functions (driving a car, reaching a shelf) and this in turn, it is implied, leads to increased satisfaction with the individual's life. In this description the acceptability gained is the patient's own attainment of an acceptable quality of life through standards of social interactions.

While elaboration on the disadvantages of short stature and the benefits of increased or more normal height is relatively scarce concerning therapy for severe growth hormone deficiency, they are more evident for other categories of GH application. There are a number of reasons for this that are best considered after an analysis of those expanded categories of use. It is also worth noting that the apparent appropriateness of replacement therapy for a severe hormone deficiency may have hidden, and may continue to hide,

implicit assumptions among physicians and patients about the undesirable nature of short stature at the time growth hormone therapy was being pioneered.

The Impact of Biosynthetic Growth Hormone: Maximising Opportunities for Therapy and Research

As described in the previous chapter, the diagnosis of severe growth hormone deficiency arose from the need to ration limited hormone supplies to the most needy children: those at the bottom end of both the physical and biochemical indices of measurement. The introduction of biosynthetic hormone meant these restrictions no longer needed to apply, at least for the purposes of rationing. When discussing the impact of the increased supply of growth hormone after 1985, informants generally characterised their own response, and that of the wider paediatric endocrine community, in positive terms: 'it was a big mountain that had been climbed (NAM 3). The impact was described as 'enormous' (NAM 2), 'a huge effect' (UK4), 'amazing, major [ ] it changed it immensely, what could happen' (NAM 4). Their response can be understood in the context that it allowed fulfilment of two important aspects of their role. The first of these is the treatment of that patient population that was already entitled to therapy, but whose treatment was rationed by height bars and sub optimal treatment schedules:

> [T]here was just with the present indication [GHD], nothing else, joy among us. We knew we could make a difference (NAM 2).

> [I]n the early days it dramatically changed everything because we could provide it at a reasonable dose, continuously around the year and have more realistic height attainment goals for kids with GHD [ ] so it made a profound difference (NAM8).

The supply of biosynthetic hormone can be seen as allowing physicians to fulfil their roles, not just technically by providing an adequate therapy according to what they judged to be necessary - 'reasonable doses' producing 'realistic height attainment goals' - but also in a broader context of helping their patients. Another respondent added:

> We all, as children's doctors, endocrinologists, wanted growth hormone to help kids (NAM 3).

The second function that increased supply of GH facilitated was clinical research. In the mid-1980s the majority of practitioners in the field of paediatric endocrinology also held academic research posts, and, especially in the US, had continued to investigate the potential application of GH in patients outside the 'classic' GHD indication throughout the pituitary era.

> [W]e now had the ability to design a study, which we could always do, but guess what, we could carry the damn study out (NAM 2).

> I think that once it was demonstrated that recombinant growth hormone was safe and active then there was considerable

> interest in the possibility that it might be useful in other forms of growth failure (NAM 5).

The possibility of using growth hormone in a broader patient population arose, and two main groups suggested themselves: those patients who had short stature but whose biochemical measurement for hormone deficiency was not extreme enough to qualify for treatment in the pituitary era, and those patients who were short for reasons other than hormone deficiency. Although experimentation in both patient populations began even before biosynthetic hormone received regulatory approval and developed simultaneously, the expansion of the partially hormone deficient pool will be considered first.

Expanded Uses of Growth Hormone: Contingent Accounts and the Prioritisation of Height

A common theme in respondents' accounts was to invoke uncertainty in biochemical measurement in this broader patient population. The empiricist approach to describing severe or 'classical' growth hormone deficiency, where diagnostic decisions appear to flow from the appropriate measurements, is lost. In these accounts the measuring process is now described as contingent and open to question. The diagnosis of severe growth hormone deficiency is retained as a readily quantifiable entity, but it is now positioned at the lower end of a continuous scale where:

> [A]part from the person who's got zero growth hormone, that's fairly easy, the fact it probably is just this continuum into the normal range. (UK 3)

> [T]here's a spectrum there and then you have these arbitrary numbers that you used [ ] but I just think it's all a continuum from people who don't have pituitaries or people [who] have genetic diseases (NAM 4)

It is the upper boundary, crucially the limit between deficient and healthy individuals, where the element of contingency appears; the numbers are 'arbitrary', and the cut-off point is open to interpretation. Part of this is attributed to the 'imperfect' nature of the tests, as illustrated below:

> [E]ven if one wanted to limit the use of growth hormone to children with growth hormone deficiency, we were confronted with the problem that we really didn't know how to diagnose it that well (NAM 5).

Children who have short stature but growth hormone levels that do not meet 'severe,' i.e. pituitary era, criterion for hormone deficiency occupy a diagnostic space opened up by this lack of correlation between the two principle indices of measurement on which diagnosis is based.

The interpretation of this space comes under the professional authority of paediatric endocrinologists. One option is to introduce new diagnostic categories as in the following account:

> I use pathological growth retardation; so they're going along with growing poorly and so some of the criteria fit classical growth hormone deficiency only on provocative testing they made growth hormone so I would be willing to treat them (NAM4).

In this example the space arising from conflicting measurements allows creation of a new intermediate category, 'growth retardation,' which lies between hormone deficiency and normal health and is also deemed worthy of treatment. Other intermediate categories suggested in the literature include partial growth hormone deficiency, neurosecretory dysfunction and normal variant short stature (Blizzard, 1985; Hindmarsh & Brook, 1987; Neely & Rosenfeld, 1994; Preece, 1981; Rose, 1995). These categories serve to reinterpret the continuum of biochemical values as discrete ranges, thereby returning this index of evaluation to a scientific, evidence based system. However, these categories are far from universally accepted - they remain in the area of uncertainty and professional judgement. An alternative to introducing new diagnostic categories is to reconfigure the boundaries of the existing definition of hormone deficiency.

Describing how practice had changed since the introduction of synthetic hormone, one respondent offered the following model:

> [O]riginally we selected the children at the bottom of that curve [relating symptoms to hormone levels] so we got maximum effect from minimum treatment, what we've done now is simply to move up the curve and we are administering larger amounts of growth hormone to more normally growing children including children who are growing perfectly normally and then arriving... hopefully at an increase in adult stature (UK 4).

The next extract follows an endocrinologist's explanation of how a cut-off point between deficiency and sufficiency might be established on the biochemical scale of measurement:

> I suppose if you were saying "well look I'm only going to go and treat people who I'm, 80, 90, 95 percent certain have got a condition" well ok you might well put it [the cut-off] in fairly steep and accept that you might miss the odd person here and there, and I guess what people have done, although not consciously maybe, is they've traded it off against "ok it's probably not that harmful so getting a few where we treat them and they didn't need it well, does that actually matter?" (UK 3).

Although the empiricist certainty of the diagnosis of severe GHD is lost, the physicians' professional authority is retained and exerted through the ability to make judgements based on efficacy (in the account of UK 4) or risk/benefit profiles (in the account of UK 3) to

justify setting the upper boundary of ‘growth hormone deficiency’ as a condition. All of these options, employing intermediate diagnostic categories and/or adjusting category boundaries, allow the paediatric endocrinologist to legitimise treatment for children they deem to be sufficiently short or slow growing. However professional authority is exercised, the decision to treat children who cannot be classified as having severe growth hormone deficiency ultimately involves a choice to prioritise which form of measurement determines normality or abnormality, and thus entitlement to therapy: the biochemical or the physical, hormone levels or height.

Beyond Biochemical Deficit: Growth Hormone in Non-GH Deficient Short Children

As well as expanding the patient population and the diagnostic boundaries of growth hormone deficient children, the increased availability of recombinant GH also meant that children diagnosed with other forms of non-hormone deficient short stature could be treated with growth hormone. This process began as experimental therapy but over the two decades since the introduction of biosynthetic hormone a number of these applications have received regulatory approval. Differences exist between international regulatory regimes but there are four main paediatric indications, in addition to growth hormone deficiency, for which recombinant hormone has received regulatory approval in the US, European Union and UK. These are; children with renal failure, Turner

syndrome (TS), Prader-Willi syndrome (PWS) and poor growth for gestational age (Hintz, 2004). In 2003 the US Food and Drug Administration approved growth hormone for the treatment of idiopathic short stature (ISS), although to date this decision has not been mirrored by other regulatory agencies worldwide. As with treating less hormone deficient or partially hormone deficient children, the decision to investigate, and later treat, other forms of short stature involves a prioritisation of height as the factor which indicates a deficit and which requires amelioration. Reduced stature and the desire or need to increase physical height is the factor that connects patients with Turner syndrome, low birth-weight and the other categories with GHD patients:

> So the rationale was pretty easy, they were equally short and did have a growth response (NAM2).

> The children who need treatment are the children, who are growing very slowly, or they're going to be very short adults, they definitely need treatment. And if they can be helped with growth hormone, well that's fine (UK1).

These patients all fall within the broader uniting category of 'abnormally short' children, which now carries the entitlement to treatment without an accompanying biochemical deficit in GH. While avoiding the difficulties associated with imposing a scientifically justifiable cut-off point on the apparent continuum of values on the biochemical index, the decision to treat non-hormone deficient

patients then shifts the issue of how and where to place the boundaries of normal and abnormal on the scale of height.

One US-based informant observed that, while there was a wide variety of opinion about where to draw the line between short individuals requiring treatment and a degree of short stature that is insufficiently problematic to warrant intervention, some professional assessment can be made regardless of diagnostic criteria:

> My own sense is that there is some point of short stature where any endocrinologist will think that this is sufficiently disabling that if there's a therapy that offers a chance of benefit they want to be able to do it. (NAM5).

Another UK paediatric endocrinologist echoed this view:

> [E]ven though they may not fall within the licensed indications, if they're exceptionally short, we will give a trial of growth hormone (UK 5).

Regardless of how and where the boundaries are drawn between diagnostic categories and even which categories are employed, the option of off-label prescribing, as described above open to physicians (in both the UK and US contexts) offers additional therapeutic routes. Here, the use of the drug is at the professional authority of the physician rather than a regulatory authority, and thus does not require a precise definition of the boundaries or nature of the condition being treated. There is evidence in the published literature

(see Chapter 5) that many paediatric endocrinologists were treating or prepared to treat children who were 'sufficiently short' in all of these, and other indications, before formal regulatory approval was granted. This suggests that the prioritisation of height as the basis for therapy was already being widely made at the level of individual practitioners before official decisions were made. Practice in this case appears to have driven regulatory change rather then the reverse.

In the absence of a measurable deficit of growth hormone to allow the treatment to be characterised as a biochemical replacement therapy, the abnormality of the growth itself in other conditions is often asserted. The non-GH deficient short statured conditions have been considered by some as 'growth hormone resistant' states and the effect of therapy is often seen as giving a boost to correct the patients' abnormal growth:

> You're pushing the system, the child, to grow faster by giving higher, supraphysiological levels of growth hormone. That's the principle in every non-growth hormone deficient condition - Turner's syndrome, SGA, Noonan's, whatever (UK1).

The conditions for which growth hormone was first approved as a treatment for non-hormone deficient short stature – renal insufficiency (1993), Turner's syndrome (1996) and Prader-Willi syndrome (1997) – are all conditions diagnosable without recourse to either biochemical assessment of hormone levels or measurement of physical stature alone. The latter two conditions are genetic

syndromes detectable through standard and uncontroversial chromosomal analysis, while in the case of renal failure the purpose of therapy has been linked with other benefits such as boosting the child's growth to accommodate a larger transplanted kidney or compensate for physiological problems caused by the faulty kidney before its removal. Small-for-gestational-age (SGA) patients are mainly diagnosed through measurement of physical size, but treatment of infants who are unexpectedly small from birth has a long history stretching back to the use of sex hormones to try to stimulate growth in premature babies in the 1930s and 1940s and thus already has some legitimacy as a therapeutic area amongst endocrinologists. Importantly, the diagnostic mechanisms that assign these patients to categories of abnormality are not themselves in dispute or regarded as contingent by physicians. The short stature that accompanies these conditions is then readily viewed as a symptom of an empirically detectable abnormality and amenable to redress and restoration as part of the therapy. This characterisation of 'growth failure' incorporates a sense of lost or missed growth in a similar way to the biochemical deficit of hormone deficiency in GH deficient patients and carries a similar sense of entitlement to therapy as restoration of something 'lost' due to illness. This also forms a rhetorical link with the treatment of the original (and undisputed) GHD patient population.

Idiopathic Short Stature

The most recent and most controversial category to receive regulatory approval (in the US only) is idiopathic short stature (ISS). Although the condition has its origins in classifications like Daniel Rudman's normal variant short stature (Rudman, 1979; 1981) it was only after biosynthetic hormone became available that wider research began into both defining and treating the condition. The label idiopathic short stature essentially means 'short stature for which there is no known cause'. The indication as approved by the US Food and Drug Administration in 2003 is defined as those children who are at least 2.25 standard deviations below the average (population) height for age and gender (FDA, 2003). Opting to treat ISS children can thus be considered the ultimate diagnostic prioritisation of height as an indicator of abnormality. Height is no longer the physical manifestation of an embedded bodily disorder, whether hormone deficiency, the chromosomal abnormality of Turners girls, or renal failure; height itself now becomes the entirety of the pathology. This point is highlighted by the fact that ISS is the only indication for GH therapy whose regulatory approval stipulates a height restriction for treatment (FDA, 2003). It was this suggestion, that being short without additional underlying disorder could be considered sufficiently abnormal to warrant treatment, which first prompted concerns over human enhancement from bioethicists and accusations of excessive marketing of growth hormone from authorities and watchdogs in the 1990s.

When discussing idiopathic short stature as an indication for GH therapy, US-based paediatric endocrinologists tended to view the treatment of ISS children with more merit than UK-based physicians, which may well reflect their being situated in regimes of practice and regulation that support those respective positions. However, where therapy for idiopathic short stature was described with approval it was not presented as an unequivocal endorsement of the practice. The role of therapy in idiopathic short stature was described as 'minor' and restricted to certain situations where 'it is absolutely required for some kids and their families' (NAM2). The most common treatment of the topic of ISS from both North American and British informants was to characterise it, drawing on the diagnostic repertoire, as a problematic and imperfect diagnostic category:

> It's not a diagnosis, it just describes a collection of small children, who may have, some of them may be normal small children, others may have specific abnormalities (UK1).

> I think it is clearly a heterogeneous group of patients and it is going to encompass children who are normal and are just at one end of the bell shaped curve, and it's going include children [ ] who are part of the normal Gaussian distribution , it's going to include children who have significant pathology (NAM 5).

The discourse in these extracts responds to the 'problem' of ISS, specifically that it is essentially only a measurement of height and does not incorporate any additional measurement of abnormality,

unlike all the previously discussed diagnostic categories for which GH is used to alleviate short stature. ISS is a 'diagnosis of exclusion' (Wit & Rekers-Mombarg, 2002 p604), similar in many ways to previous 'wastebasket' categories such as primordial dwarfism, which are used to describe individuals who exhibit a symptom, in this case short stature , but whose pathology (if any) cannot be determined; essentially a failure of measurement. In the extracts above, there is recognition that ISS can potentially include children with a variety of as yet undetected conditions as well as those who perhaps have none and are essentially 'normal'. A 'diagnosis', or more appropriately a height measurement, indicating short stature or growth rate outside the normal (population) range is only a starting point for the endocrinologist and further action requires the exercise of professional authority to make a judgement:

> They're such a mixed group idiopathic short stature that it's difficult. You know you can't consider them as a single group, you have to look within that general category at the child who may really respond very well and if you look hard you can find them [ ] I think it doesn't help particularly treating children of short parents. I mean there are some short children who are abnormally short for their family, particularly if they have low levels of IGF-1In the circulation, they might benefit from growth hormone (NAM 1).

> I do not exclude the possibility that there's some very short kids who may be in the familial/ idiopathic category who may benefit

> from growth hormone, the problem is we can't identify those kids easily and all these manipulations of looking at growth hormone receptor and GHRH[57] have not panned out yet. It may well be that there is a subset of kids who have a defined genetic abnormality who may benefit from either growth hormone or anabolic peptide of some sort (NAM 8).

The imprecision of ISS as a diagnosis in itself means that paediatric endocrinologists must turn to additional, empirical measurements in order to identify potential patients within the group who may be entitled to therapy. This stance is echoed in the literature, where the main contenders for novel measurement are further biochemical entities (IGF-1, GNRH) or genetic and molecular sources of abnormality (Blair & Savage, 2002; Wit & Rekers-Mombarg, 2002; Rosenfeld, 2005). None of these additional indices of measurement are yet fully accepted within the profession but, in keeping with the aim of diagnostic repertoire, they create the suggestion that novel measuring techniques will yet yield objective means of dividing normality from abnormality. Further clinical and molecular investigation, it is hoped, will:

> [C]hip away at the monolith of ISS and, by identifying new pathogenic mechanisms, to gradually reduce the number of children who currently fall into this rather unsatisfactory category (Blair & Savage, 2002 p329).

This acts to refute the accusation that treating ISS is treating short stature alone and so making shortness a disease, while at the same

time justifying continuing investigation and therapy of that pool of children whose diagnosis is contested but who are 'sufficiently short' to warrant treatment.

Empiricist and Contingent Repertoires in Evaluating Treatment

Through the diagnostic repertoire, treatment of short stature across diagnostic categories is presented as restoration to standards of normality and replacement for quantifiable deficits, which suggest and indeed invite intervention. The merits of this intervention are also assessed in quantifiable terms. The primary indices of evaluation are: efficacy of treatment counted in increase in growth rate or height gained[58]; the safety of therapy, logged as instances of adverse effects per number of patients treated; and the cost, or rather cost/benefit ratios for therapy in different short statured conditions. In the academic endocrine literature, arguments for and against treatment in particular categories or over the placing of boundaries to particular categories employ these three, linked indices of measurement and are often couched in familiar empiricist and contingent terms. Informants wishing to support their endorsement of a particular treatment regime can emphasise the evidence in favour of their position:

> The thing is you titrate to a behavioural endpoint [ ] it's definitely going to work [ ] If you are watching out for your IGF-1 levels and make sure that the IGF-1 is not in the toxic range I truly

> don't care how many milligrams it is [ ] so I think that's a very, very silly point of view to worry about the milligrams (NAM2).

In this case, if the correct measurements are made (here of IGF-1, another blood-borne hormone), safety of treatment is assured, and concerns about individual dosing levels are contingently 'very very silly' – the professional judgement of opponents is lacking. The treatment is characterised as rational and safety assessment flows clearly from the appropriate empirical data. However, the weight of evidence is also invoked by opponents of particular treatment regimes:

> There is a substantial body of opinion which believes that children
> who are born light for dates, particularly if they have catch-up in the first year of life are prime candidates for hypertension and coronary artery disease and the whole kibosh in adult life if you add to that large doses of growth hormone then I think you are asking for trouble and I suspect that trouble will come (UK 4).

The 'substantial' and presumably scientific opinion supporting this view is endorsed as a matter of professional judgement, in much the same way as the case is made above. Proponents of therapy in particular instances argue that adverse effect data demonstrates that GH is safe to use while opponents claim that there is insufficient data to make long-term risk assessments and caution should be employed.

Disputes over the financial and economic evaluation of therapy, however, engage more directly with differing ideas of the proper role of a physician, which rest on matters of professional judgement lying beyond the remit of empirical assessment of data. Consider two points of view at opposite ends of the spectrum:

> What I object to in the literature for the last 20 years is the fact that it's a 'limitless' or 'unlimited' supply of growth hormone. That's not true; someone has to pay for it (NAM 8)

> I don't deal with the economics I make decisions based on trying to be the best doctor I can for that child, that family and so obviously I have a limited practice (NAM 5)

In the first quote from a paediatric endocrinologist in the Canadian health system, the informant invokes the need to consider the evaluations of efficacy and safety in light of the third factor - the cost of hormone therapy to healthcare providers. In the second, a US paediatric endocrinologist places the financial consideration firmly outside his remit of calculation, although not directly discounting its importance. In different ways, both of these standpoints can be argued for by invoking the weight and importance of economic evaluations:

> I think one can't ignore the ethics and the economic arguments so because it is an expensive product (NAM 8)

> I do take money out of the equation, because if you just concentrate on how much it costs per inch or centimetre it

> doesn't sound as good, but if you're trying to look at the whole picture. So [ ] my bias is to treat (NAM 5)

In the first case, not to consider the financial burden of providing hormone therapy is portrayed as inappropriate practice because of the magnitude of the effect of cost - it is not trivial and therefore must be considered. By contrast, in the second extract the paediatric endocrinologist justifies ignoring the financial impact of providing therapy precisely because it has a distorting influence on the calculations of benefit for therapy. This is couched as being the correct thing to do in order to 'be the best doctor I can'. Indeed both approaches present themselves as being the appropriate, responsible thing for a practitioner to do. The costs or risks, of course, must themselves be considered relative to the benefit, usually the efficacy, of the treatment, which is itself disputed for most indications except classical GHD.

Beyond the Diagnostic Repertoire: Quality of Life and the Burden of Short Stature

Although the major expansion of therapy beyond severe GHD only occurred after 1985, it seems clear that at least the instinct to treat the physical index of short stature as the key marker of abnormality and entitlement to treatment regardless of other considerations predates the introduction of biosynthetic hormone. Before biochemical tests for growth hormone were available, all patients were selected primarily on the basis of height and a wide range of

short-statured conditions (beyond those now having regulatory approval) were investigated using pituitary hormone (see Chapters 4 and 5). The UK MRC trial also continued to favour the use of deviation from normal height as plotted on Tanner's growth charts as the primary indication of eligibility for treatment even after biochemical tests became available. The characterisation of replacement therapy being for the dual purpose of increasing height and boosting the broader metabolic wellbeing of the body, as is now claimed for GH deficient and Prader-Willi patients, is a recent one. It has not historically been part of the rationale for therapy, as one informant explained 'in the old days we thought growth hormone was only for growth' (NAM 4). Another added 'yes, their body compositions changed a lot but we never talked about that' (NAM 2).

During the era of pituitary growth hormone the logic of replacement and the relatively experimental nature of the treatment may have obscured any requirement to elaborate what the specific benefits of more normal height may be. Some indication of intent is obtained through the use of phrases like 'achieving socially acceptable height' and 'restoring genetic potential'. The significant expansion of the patient population and the accompanying rise in economic cost of therapy occasioned by the transition from nationalised physician-led pituitary hormone programmes to a commercial market for synthetic hormone brought the issue of the intended benefit of height to much greater prominence. As Neely and Rosenfeld (1994) explain:

> The transition from pituitary to recombinant hormone shifted the limiting factor in treatment away from the supply of drug to the practitioner-assessed boundaries of efficacy and *treatment justification* (p408 emphasis added).

If height was to be prioritised as the indicator of entitlement to therapy, then the issue of exactly how a lack of height was detrimental, beyond the idea of a measurable deficit in itself, could no longer be ignored. During the first era of growth hormone therapy the idea of quality of life (QoL) as a social component of disease and therapy was emerging, primarily in psychology and related disciplines, but was not yet a widespread part of medical practice (Armstrong, Lilford, Ogden & Wessely, 2007). However, since the 1990s the idea of QoL has taken off and now plays a significantly more prominent role in the overall scheme of medical practice, such that a contemporary textbook of pharmacology can declare in its opening pages:

> Overall, the major benefits of modern drugs are quality of life (measured with difficulty) and exceed those on quantity of life (measured with ease) (Desmond, 1997, p3).

Quality of life, the social and psychological aspect of therapy, has come to play an increasingly important role in the scientific and the broader debates about the use of growth hormone. This is especially conspicuous as the discussion moves away from the old, unchallenged certainties of severe GH deficient patients to the expanded uses where a greater amount of physicians' authority is

(seen to be) required to interpret the contingent measurements in deciding who is entitled to therapy. Discussions of the social component to short stature move beyond the instrumental measurements of the diagnostic repertoire and reveal other facets of the judgement on which paediatric endocrinologists' authority to dispense growth hormone rests.

Physicians' Understanding of the Social and Psychological Deficits of Being Short.

During the interviews paediatric endocrinologists articulated a variety of ways in which social difficulties associated with short stature could be conceived:

> [I]f you're asking what is the rationale for treating short stature by itself... well I think there is a perception, you know rightly or wrongly and that's something that can be debated all day long, that children and adults who are significantly short are disadvantaged, that they are handicapped, that, you know, whether it has to do with social performance, or academic performance or marital opportunities or employment opportunities and you know you can find literature on both sides of the fence on that issue, none of the data are perfect or are very good, but certainly there's a perception in families that a small child is disadvantaged (NAM 5).

In this relatively short speech a range of different types of deficit are posited. Social performance here refers not only to functional abilities

but also to emotional development, interpersonal skills and educational, personal and financial achievements. All of these possible deficits are acknowledged, but with the understanding that there is only equivocal data in support of any particular argument. Other respondents recognised ‘a certain social pressure on children who are not very tall [ ] to be taller’ (UK 1) or ‘a social bias’ (NAM 4) against shorter individuals. Intervention is recommended when this shortness becomes ‘sufficiently disabling‘ (NAM 5) or ‘a handicap to normal living’ (UK 5) but this idea of the handicap can extend beyond physical functioning to encompass all or part of the whole constellation of potential difficulties iterated in the extract above.

Many of these difficulties are posited in terms of social coping and social attainment - emotional and maturational difficulties fall under the auspices of psychosocial wellbeing, while life-attainment goals like educational performance, lifetime income and ability to sustain relationships are classed by psychologists and health professionals as markers of an individuals’ Quality of Life[59]. There is a significant area of overlap between the two categories and they are not considered mutually exclusive. Studies to discover the problems of coping with short stature are not a recent phenomenon. Psychological and psychiatric evaluations were being carried out in growth hormone deficient children as early as 1959 and continued throughout the pituitary era (Abbott, Rotnem, Genel & Cohen, 1982). While there was a general agreement that the children in this

population were predisposed to emotional and maturational difficulties, there was considerable disagreement about the extent and gravity of the problems. Part of the problem at that stage was the small patient population and the fact that they were not being fully treated, making it difficult to evaluate what, if any, effect GH therapy was producing on their psychological state. In any case there is very little evidence in the literature that paediatric endocrinologists were particularly aware of, or concerned about, the psychological findings, and cross citation of work from that field is almost entirely absent in the endocrine literature before 1985.

This situation has changed since the introduction of recombinant hormone, with the psychological studies playing a greater role in the debates over growth hormone therapy (Johansen & Blizzard, 1990; Hull & Harvey, 2003; Ulph, Betts, Mulligan & Stretford, 2004), but even beyond this, as Stephen Hall has noted:

> [t]he notion of shortness as a psychological disadvantage – indeed, disability, - runs deep and persistently through a huge scientific literature on human physical stature (2006, p16).

Evidence in the form of (usually unspecified) studies is often evoked to support the view that height is socially detrimental backed up with anecdotal evidence, as in the following example:

> you take simple things like usually the taller man wins the presidency of the United States, there're very few short people

> in that position [ ] and it's been stated in the past that they [earn] more (NAM 4).

In particular, the story about the taller US presidential candidate winning the election is a recurring theme in economics literature[60] discussing the effects of physical and social characteristics on financial success (Wilson, 1995; Judge and Cable, 2004; Persico, Postlewaite & Silverman, 2004) and appears to have found its way into the general discourse on the social status of short stature. Staples of this literature, which spans much of the twentieth century, are assertions that short or below-average height individuals, primarily men, earn lower wages and are less likely to achieve positions of authority in society or succeed in other markers of socio-economic status (SES).

> Numerous studies, from a diversity of disciplines, find that the taller, non-obese man or woman is given preference in many areas linked with SES, such as the perception of intelligence, academic performance, and social skills, as well as initial job hiring and perception of both current and future job performance (Bogin, 1999 p325).

Other popular accounts of the negative effects of short stature, that have migrated into general discourse from scholarly work, focus on the psychological and emotional dysfunction of especially short individuals, as exemplified by the 'Napoleon complex'. The idea of the Napoleon complex, where short individuals feel inferior by virtue of their small stature and overcompensate, often aggressively, to

compensate for this, was promoted by US psychoanalyst Alfred Adler in 1908 and continues to be referenced to the present day (Hall, 2006; Judge and Cable, 2004). Supplementing this, anecdotal accounts of distress, juvenilisation, bullying and teasing of short children also appear in patient group literature, news reports, and pharmaceutical literature, especially on idiopathic short stature[61]. Biosynthetic era paediatricians are well aware of this background of negative characterisation of short stature. In an article in *Pediatrics* in 1990, Allen and Frost reviewed a range of studies suggesting that short stature can be detrimental to an individual's development, psychological wellbeing, social and financial success and concluded that :' discrimination based on height- "heightism"- pervades American life' (Allen & Frost, 1990 p17). Others, however, such as Sandberg & Colsman (2005), have criticised the research literature as being replete with 'negative stereotypes' (p276) supported by questionable experimental methodology.

Informants' Evaluations of Psychological Testing for Short Patients

While endocrinologists recognise that there can be detrimental effects from being short statured in childhood or adult life, it is rarely explained in any detail how exactly they operate - what the 'certain pressures' or 'many ways' might be - nor how their severity should be measured and ranked in order to justify treatment. Paediatric endocrine informants' evaluations of the utility of psychological

metrics were equivocal at best. In part, this was attributed to difficulties in applying the concept of QoL to a paediatric population:

> [Q]uality of life for an adult is being able to have a regular job, to hold down a job, to be able to cope with the normal responsibilities which adults have; you know children don't have these responsibilities (UK 1).

Another informant agreed that it was 'more challenging' to try and apply QoL to children and also added that:

> [T]hat that was necessary in adults [ ] because they don't have the ability to objectively measure growth response, I mean a paediatrician dealing with a child can say look this child was growing one inch a year before treatment and now he's growing four inches per year so I feel comfortable convincing myself that that child is having a positive response [ ] you can't do that in an adult population you know, you have to assess those things you can assess (NAM 5).

QoL is seen as an additional measurement, required for adults with hormone deficiency, where it is a mandatory part of the assessment in deciding eligibility for treatment, but not required or applicable in children. The traditional metric of efficacy in GH therapy - increase in physical height - is preferred because it is instrumental, seemingly more objective and more closely allied to the professional skills base of endocrinologists.

The psychologists' focus on the issue of childhood short stature has been primarily on psychosocial studies of short children's emotional and psychological adaptation, rather than the broader concept of 'quality of life'. Informants' discourse about psychosocial tests mainly concerned the shortcomings of data obtained from studies carried out to date:

> T]he Canadian psychosocial arm has been a disaster, we have not been able to have clean data there, and the psychosocial for the ISS NIH study was zero, they didn't show any gain, they didn't show any loss, they also didn't show there was anything wrong with them when they started, so.. .Duh (NAM 8).

The idea that short stature can cause psychological problems is especially important to idiopathic short stature where it forms the *de facto* primary rationale for treatment in the absence of any measurable biological pathology. The Wessex Growth Study in the UK and an Eli Lilly-sponsored psychosocial component to the clinical trials of their growth hormone Humatrope in ISS are among some of the notable large-scale studies to address the issue of the psychosocial effects of stature in short but otherwise healthy children. This sense that this type of measurement may not be of much diagnostic use to paediatric endocrinologists is compounded by the fact that, as mentioned above, several studies have not shown any measurable psychological deficit in short ISS-type children either before, or after, GH therapy:

> Because people would bring their children and say they're suffering because they're short, we devised a trial to see whether we could improve the adverse psychological factors that we could identify in short children, well when we got hold of a bunch of short children we couldn't find anything to test. So we abandoned the trial (UK 4).

As with quality of life, there are difficulties in determining what particular psychosocial difficulties for children might be; in other words to 'find something to test'. Psychologists studying the psychosocial effects of short stature have their own measurement disputes, the most controversial being over which is the correct population of short children to look for psychological stress in - those referred to clinics or short children in the general population. Paediatric endocrinologists are aware of this, as one US-based practitioner observed 'if you look at the data, there are two sets of data' (NAM 2) and another noted that proponents of each approach 'reject each other's studies' (NAM 8). For paediatric endocrinologists this is a theoretical dispute outside their direct domain of expertise and thus not amenable to resolution by them. This means there is conflicting evidence from outside their professional competence upon which to draw when formulating their opinions and this may lead to a sense of uncertainty about using the specific criteria of psychosocial wellbeing.

Formal psychological testing also encroaches upon an area in which paediatric endocrinologists had already claimed as part of their professional competence. As described in Chapter Five, there is evidence that it was common for paediatric endocrinologists to recommend corrective hormone treatments aimed at 'normalising' patients with a variety of conditions, including girls with tall stature and children with intersex conditions, based on assumptions that this would be psychologically beneficial. Literature from the 1960s and 1970s, when oestrogen therapy for girls with a tall predicted adult height was at its most popular, highlights a focus on social functioning and emotional distress which is shared with much of the current discourse on the effects of short stature (Lee & Howell, 2006). The 'negative psychosocial effects of excessively tall stature, which included depression [and] social withdrawal' (Ibid. p1036) that characterised the deficit / burden of tall girls, were matters for detection and assessment by the paediatric endocrinologist alone. The literature from the time gives some evidence as to the nature of this assessment. Crawford (1978) notes that girls were not accepted into the program on the basis of height alone but that:

> [T]hey have been accepted if they were able to impress us that they (not just their parents) had a reasonable argument for subjecting themselves to some real risks and, certainly, to some considerable expense to achieve a lesser stature than predicted' (p1191).

This indicates an unquantitative form of psychological examination where assessment is made through discussion during the physician's encounter with the patient. The advice given by Prader & Zachmann (1978) to their fellow paediatric endocrinologists confirms this impression:

> For the psychosocial evaluation, it is helpful to note the physique, gait and posture of the adolescent. Weak muscles and poor posture often accompany a psychosocial indication for treatment (p1209).

This suggests that the assessment was, and is, considered a matter of professional authority and competence for paediatric endocrinologists. The treatment of tall stature with sex hormones offers a useful proxy for exploring the approaches taken in treating short stature. The exclusively psychosocial nature of the rationale for treatment meant that the nature of the assessments being made is discussed more visibly in the literature on the subject, unlike GH therapy, where the early discourse is almost exclusively concerned with technical matters of physical and biochemical measurement. It is likely that some social value judgements about short stature were being made in the pituitary era and continue to be made with today's treatment, as one informant noted:

> [I]t doesn't matter if we're clinicians or the average man or woman on the street, being short is presumed to be, you know, a bummer (NAM 6).

This preference for prioritising the measurement and treatment of the physical deficit rather than the social keeps the primary assessment of childhood short statured patients within the remit of paediatric endocrinologists rather than psychologists, or others, and avoids this difficult issue of defining and standardising the nature of the social deficit of short stature.

Physicians' Strategies for Patient Assessment

Confronted with the uncertainty over psychological data on the effects of short stature, respondents tended to react in one of two broadly characterised ways. Some described a process of patient analysis carried out by themselves as physicians, very similar to that described above for tall statured girls:

> I think every patient [ ] has to be individualised and so before I would say yes or no to any patient I, and I think every paediatric endocrinologist should do this, every doctor ought to sit down and learn about the child, does that child have confidence or is that a child who is very shy and retreats. Is the child bothered enough by being short that it's really affecting the mental development and I'd want to know what the parents think, but I want to know the child thinks about it when the parents aren't around (NAM 3).

This encompasses a number of recurring elements - an emphasis on individualisation in making the assessment and looking for signs and reports of emotional distress or social difficulties from both child

patients and their parents. Other US-based respondents echoed this approach, noting that when making assessments ‘each endocrinologist has to pick and individualise it from child to child’ (NAM 5), ‘you have to look at the individual’ (NAM 6) and ‘why the hell should we treat a disease, we should treat a child’ (NAM2). The doctor-patient interactions being recounted in these accounts concern those children referred to see a growth specialist because of prior concern on the part of their families or family doctor. In line with the approach of some psychologists, this can be taken as a first sign of potential need for therapy:

> They’re coming to me for that, there’s enough concern on the basis that the child and the parents, and I do recognise that there are some serious investigators showing that short kids often end up ok and when you do prospective studies... I understand that, on the other hand I see the kids while they’re undergoing the problem, if they’re closer to their peers, as a child it may make things better for them [ ] my goal is the same as the parents’ goal, they are the most important people for that child, they want their child to grow into being a secure adult (NAM 4).

The individualised, paediatric endocrinologist-led patient evaluation also draws on the authority and competence of the practitioner to make judgements without deferring to the (contested) evidence from psychological studies, and treatment decisions can be legitimated through rhetoric of duty to the patient and their family. Informants

were able to demonstrate their competence to make these evaluations of patients' emotional and psychological wellbeing by citing awareness of the appropriate boundaries and displaying recognition of inappropriate scenarios such as undue parental influence: '[j]ust if it was a parent who was pushing, I wouldn't go along with it' (NAM 3), or illegitimate or unfounded desires for increased height:

> I got a call from someone [ ] "of course my son is this, he's a great tennis player and he's going to be, he's 5'8" he's going to be 5'10" but his tennis coach says he'll have a better chance of getting a college scholarship if he's 6'2". And I want to know if you'll treat him with growth hormone?" [ ] I said "what message are you trying to send to this kid?" and that's the whole point... that is cosmetic endocrinology, and if this kid is destined to be 5'10" it is extraordinarily unlikely that we will make him more than 5'10" unless we used a ton and the only difference is he might reach his 5'10" [ ] a little bit sooner (NAM 2).

The alternative is to advocate a more sceptical view of psychological claims as an entitlement to therapy:

> I really do subscribe to the view that nobody has really suffered significantly from being short (UK 4).

This can be especially reinforced in cases where the likely gain in physical stature is limited, as is common in conditions outside classical growth hormone deficiency and Turners syndrome:

> In the main whatever the kid's psychological hang-ups are, if you make him two inches taller he's the same brat, he's only two inches bigger. This is not the cure for psychological ills, I don't care if "they call me shorty, they call me this, they do that" (NAM 2).

This scepticism can also extend to questioning the origin of worries over the (supposed) burden of short stature and the diagnostic origins of many non-GHD short stature patients reaching the clinic:

> Whose problem is it? Is it the child or is it the parents? And so you know I think most of the time we're creating a short panic (NAM 8).

> [A] lot of parents, they come there in front of the children, they say 'oh well she's too short, it's unacceptable, she's going to be bullied', and they might not even be bullied, and 'I was short and I had a miserable life' and they're so negative about everything, and if we had the resources to just get parents to change their attitude and think in a different way then we wouldn't need to have a licence for idiopathic short stature (UK 5).

These positions are also justified by recourse to the physicians' competence in performing their role through their authority to recognise the futility of treatment or rather of patients'/parents' hoped-for treatment goals in inappropriate cases. This approach is still founded on a paediatric endocrinologist's ability to assess the

presence of psychosocial distress in patients independently of formal psychological testing, but in this case the outcome is to reject the validity of such claims in a broader number of patients or diagnostic categories. In general, informants displaying a pronounced scepticism towards claims of psychological distress or social stigma as a basis for assessing entitlement to therapy preferred to rely on the physical and biochemical indices of measurement for making diagnostic decisions and judging the effectiveness of treatment.

Conclusions

The importance of the diagnostic repertoire lies in the way that it represents the instrumental rationality that underpins scientific medicine and the capacity it offers for framing short stature, especially growth hormone deficient short stature as a disease category. Although some diagnostic categories of abnormal short stature, such as Turners syndrome, were recognised before human growth hormone was isolated, the empirical, objective presentation of severe growth hormone deficiency existing at the bottom end of the dual scales of physical and biochemical measurement provides a crucial discursive anchor for the rest of the therapeutic enterprise of treating short stature. The diagnostic repertoire describes the phenomena of hypopituitary growth failure as an observer-independent measurable deficit, an abnormality in the form of a loss, which requires (additive) treatment to restore normality to afflicted individuals. This connects with the idea of replacement therapy that

lies at the heart of the conception of hormone therapy and allows the promotion of growth and increase in the final adult height of this group of short children to be viewed not as enhancement (at least in its pejorative connotation) but rather as restoration, a therapy. Here the impact of the socio-historical development of GH can be seen; the shortage of pituitary glands and the selection of measuring technologies available in the 1960s and 1970s were strong driving factors in the formulation of the diagnostic boundaries of severe growth hormone deficiency. Without this set of conditions it is very unlikely that the same diagnostic consensus would have been reached during this time.

The development of biosynthetic hormone constitutes another major shaping event in the history of growth hormone. This is generally regarded as a favourable event by informants; it allowed fulfilment of two central functions of their professional role as academic clinicians: treatment of the sick and clinical research. It should be remembered that while physicians' authority lies in their expertise and their ability to discern the underlying causes of pathology that are invisible to the lay public, their position also requires a duty and responsibility to help, by alleviating suffering, those patients over whom they exercise authority. This is sometimes forgotten or denied in more negative sociological characterisations of modern medicine. The definition of growth hormone deficiency through both physical and biochemical indices then necessitates that other forms of short stature are

described by comparison: partial GH deficiency and non-hormone deficient short stature cannot exist as diagnostic categories without GHD as a baseline. This discursive turn draws attention to the prioritisation of height as the main marker of abnormality in these conditions, i.e. they are *by definition* less biochemically deficient than the baseline condition. The resulting inadmissibility of hormone replacement as a justification and entitlement for therapy outside GHD forced a greater scrutiny of the broader benefits of height in terms of psychological status or quality of life. Idiopathic short stature is the ultimate prioritisation of height as the indicator of abnormality and need, and primarily for this reason it is the most controversial paediatric indication for GH.

Informants often referred to a general sense that short stature could be a social disadvantage in some way - in adult life or childhood - as a result of reduced social opportunity or as a result of psychological difficulties or any combination of these. At the same time paediatric endocrinologists remain sceptical about the value of psychological or QoL tests to quantify this disadvantage into a measurable index of social deficit that could be used to assess need and entitlement to GH therapy. One potential reason for this is suggested; as with the psychosocial assessment of excessively tall girls or intersex patients, paediatric endocrinologists already consider the evaluation of the social and familial circumstances of individual patients within their authority and competence and therefore are not inclined to cede

responsibility to an outside discipline such as psychology. Nonetheless, psychological testing has been involved in a number of clinical trials of ISS patients, as the social disadvantage of short stature is one of the main parts of the rationale for treatment. The results of the psychosocial arms of these trials have been extremely equivocal, reinforcing the scepticism of those endocrinologists who prefer to stick to more 'reliable' and objective instrumental technologies of measurement.

This allows much of the discussion on the merits of different treatments to be carried out as a debate over the empirical evidence in favour of each particular claim. Discourse here was patterned in empiricist claims and contingent refutations of counter claims about the data on efficacy (height gained), safety and cost/benefit ratios for different diagnostic categories and treatment regimes. Differences in healthcare systems play an important role in this discourse. While the responses in this chapter are individual and cannot be said to typify the positions of the respective national paediatric endocrine communities, informants operating in nationalised healthcare systems were more likely to attach a higher importance to financial considerations as a limiting factor in deciding where to place treatment boundaries and to present awareness of economic factors as a positive trait compared with those in the US. One UK-based paediatric endocrinologist felt that 'most of us are relatively conservative [ ] about using growth hormone' (UK 1) and another

noted that the level of patients being treated for growth hormone deficiency on the NHS had remained ‘remarkably static’ (UK 3). This type of stance can be understood in relation to the role that physicians in the NHS or other nationalised systems of healthcare provision are required to take.

> Prescribing doctors, who have a duty to the community as well as to individual patients, cannot escape involvement with economics (Desmond, 1997 p25).

The financial costs of a particular therapy must be brought into consideration when assessing its merits if made available as a standard treatment on the NHS, although the specific calculations are rarely done by practitioners themselves.

In contrast, US physicians are faced with a much more heterogeneous network of costs and remuneration. Their patients will be paid for through a variety of private health insurance schemes, state sponsored equivalents like Medicare and Medicaid and often some portion of the costs will be borne by private individuals or families as well as the insurance contribution. Informants were more likely to describe a ‘service approach’, even if reluctantly, where the emphasis was on treating the individual patient (and family) without the requirement to consider the economic implications of treating the entire patient population meeting that individual’s diagnostic criterion.

> I’m not looking at the population when I’m practising medicine; I’m looking at the family that’s coming to me for advice (NAM4).

The use of the diagnostic repertoire, describing the condition of short stature in terms of diagnostic measurements, masks the rhetorical shift from the individualisation of patients in the doctor-patient encounter to the consideration of treating patient populations (as part of a social medicine). Like is often not compared with like, but rather the merits of an individual's need and entitlement to therapy, which include the informal measures of assessment as well as instrumental measurement, are argued against clinical trial-based claims concerning the treatment of entire patient populations based on diagnostic categories. Informants (and, it would seem, the broader paediatric endocrine community) even in the UK are likely to offer GH therapy to individual cases whom they deem to be 'sufficiently short', regardless of indication, but the implications of scaling this up to patient populations are different in the context of different national regulatory and health economic regimes.

The contingent, heterogeneous discourse around endocrinologists' authority to interpret indices of measurement, physicians' duties to the patient in the context of differing national regulatory and healthcare economic regimes, the formal and informal merits of assessing the psychosocial impact of short stature and individual versus population needs creates a space where idiopathic short stature can exist as a possible diagnostic category, but one that at the same time exists in a permanent state of uncertainty or controversy. The suggestion at the end of the previous chapter that

local regulatory and economic factors have achieved some stabilisation in GH usage implies that this must be the result of informal compromises rather than formal agreement on the boundaries of particular diagnostic categories. Such an agreement is certainly not evident in the discourse on idiopathic short stature, or indeed in a number of other aspects of GH therapy.

The next chapter will consider the application of growth hormone in adults, and, in particular, its second controversial application as an anti-ageing treatment.

Notes

[56] In dialogue endocrinologists often referred to cases of hypopituitarism, where some or all pituitary hormones are deficient, by the abbreviated form 'hypopits'. Cases of pituitary damage due, for example, to tumours that could cause this type of loss of function had been recognised by endocrinologists even before growth hormone was isolated as described in the final section of Chapter 4.

[57] Growth Hormone Releasing Hormone - a protein involved in the physiological regulation of growth hormone secretion.

[58] Either as compared with the mean population heights (adjusted for gender) or as an advance over the patients' predicted adult height if left untreated. This in itself is an area of some dispute as to the best method.

[59] There are a number of models of Quality of Life including health-related QoL, which measures physical, psychological and social functioning and the presence/absence of pain and is generally used to make cost/benefit assessments. Other variants include the individualistic model, which emphasises the patients' personal circumstances, and needs-based QoL, which evaluates the extent to which patients' needs are fulfilled through social functions such as employment, leisure etc (Hull & Harvey, 2003). In general these distinctions are confined to the psychological literature.

[60] The story appears in different versions, some claiming that the taller candidate has always won, since World War 2 or since televised coverage of presidential elections began, while Judge & Cable (2004) backdate the story to 1896. More recent articles make note of the exception that in the 2004 presidential campaign the incumbent, George W. Bush, defeated his opponent John Kerry although Kerry was the taller of the two men.

[61] For example Eli Lilly's brochure 'Understanding Idiopathic Short Stature' (available from http://www.humatrope.com/pdf/understanding_iis.pdf) notes that 'some children who are significantly short may experience challenges, such as teasing, bullying or exclusion from activities, while other children may suffer no such problems'.

CHAPTER 7: Historical and Contemporary Accounts of Growth Hormone in Anti-Ageing

Introduction

The final data presentation chapter in this thesis deals with the application of human growth hormone as an adult enhancement drug used in attempts to retard or reverse the process of ageing in human beings. In contrast to the treatment of short stature there is no accepted diagnostic base of treatment, such as severe growth hormone deficiency, upon which other more controversial applications are based. The closest medical analogues are the use of GH in adults categorised as having growth hormone deficiency and the use of oestrogen and progesterone to treat the menopause and post-menopausal symptoms in women. Use of GH as an anti-ageing therapy mainly takes place in private clinics administered off-label by practitioners who are not endocrinologists. Orthodox adult endocrinologists, and others concerned with the study of ageing such as gerontologists, generally refute this private practice as unscientific, yet the potential application of growth hormone (usually along with testosterone) remains a minor but persistent interest within mainstream endocrinology. Given the expansion of hGH therapy in short statured children it is of interest that adult application, excepting the strictly limited indication for adult hormone deficiency, has moved outside mainstream medicine in this way,

despite having being the subject of both medical and industrial attention.

In order to interpret contemporary discourse on the use of growth hormone in anti-ageing it is necessary to return to the socio-historical study of hormones as medical technologies. The early association between hormones and rejuvenation in the practices of organotherapy, the Steinach operation, and gland-grafting was discussed in Chapter 4. The first section of this chapter will begin by returning to that era to explore how changing social and cultural conditions influenced and connected with medical theories about old age. The rise of organotherapy and testes transplants coincided with a broader medical and social attitude that old age was dangerous, detrimental and in need of amelioration, just as their fall was occasioned not only by the pre-eminence of scientific medicine, but by a changing cultural view that old age could be rendered tolerable and even pleasant through socio-political initiatives promoting the welfare of the elderly. Changing concerns about old age and population levels continue to affect professional and public perception of medical interventions in ageing in the present. The closing decade of the twentieth century has seen a re-emergence of anti-ageing medicine, both from the off-label application of hormones to retard the ageing process and also from biotechnology industry-backed biogerontologists promoting new genetic, molecular and cellular therapies in the form of regenerative medicine.

It is also important to explain how the seemingly incongruous association between a hormone drug used to boost the growth of short children and the bodily changes of old age came to be made, and how the idea of GH as a means to intervene in the ageing process, fits in with the hormonal model of the body. Perhaps unsurprisingly, the advent of biosynthetic growth hormone and its seemingly limitless supply facilitated the research effort into the potential uses of GH in an adult population, although both the idea of adult GH deficiency and growth hormone as an age retardant can trace their origins to the pituitary era. In order to examine how some adult uses of GH came to be accepted as legitimate treatments while anti-ageing remained a suspect prospect, the development of the indication for adult growth hormone deficiency will be considered alongside the early experiments with growth hormone in elderly volunteers. From an STS perspective, important social and institutional factors can be detected in the shaping of technological options that have contributed to the acceptance of GH as therapy for adult GHD within the network of orthodox endocrinology, and the rejection of growth hormone as an anti-ageing treatment. There are notable parallels with the competing paradigms of hormone technology that accompanied the birth of endocrinology in the nineteenth century, although the picture is complicated by the involvement of novel non-hormone based technologies for anti-ageing in the form of regenerative medicine.

The second section of this chapter will then consider the discourse of contemporary endocrinologists on the subject of the appropriate use of growth hormone in adults. As with Chapter 6, this section involves the analysis of material collected at interview from prominent academic endocrinologists in the UK and US. Informants included not only adult endocrinologists, whose professional domain includes the administration of growth hormone to adult patients diagnosed as hormone deficient, but also, because of the unique history of GH, paediatric endocrinologists who have a research interest in the use of the hormone outside growth promotion. In keeping with the prior chapter, this section takes a discourse analysis approach, interpreting informants discourse in terms of patterned speech, primarily the empiricist, contingent and diagnostic repertoires previously described. There is less of a comparative approach because, unlike idiopathic short stature, rejuvenation is not a legitimate therapeutic indication either in the US or in Britain, although the majority of off-label anti-ageing activity takes place in North America. The focus here is mainly on the discursive co-construction of the diseases of adult growth hormone deficiency and hormone decline in old age with the idea of growth hormone as therapeutic remedy. In particular, attention will be given to the ways in which informants legitimise their own scientific interest in growth hormone as a potential medical intervention in elderly patients while renouncing and discrediting the actual application of GH being

practiced in life extension clinics. Informants also offered a variety of rationalisations why the exploration of GH as a scientifically legitimate treatment had not succeeded, drawing on a range of institutional and social factors to explain this state of affairs, and this part of the discourse will be considered in the final component of this section. Taken together, the two sections of this chapter aim to offer useful insight into the contrasting successful and unsuccessful development pathways of growth hormone as a medical technology and the role of the framing of disease by medical practitioners in this process.

SECTION 1: THE MAKING OF GROWTH HORMONE AS AN ANTI-AGEING DRUG

The Cultural History of Anti-Ageing Enterprises

Gruman (1966) identifies two fundamental strands of thought in the history of ideas on ageing; the meliorist school of prolongevity[62], regarding senescence and death as problems to be overcome, and the apologist tendency which views attempts to increase the human life span as 'neither possible nor desirable' (p6). Both traditions have long histories although within the discourses of religion, science and philosophy it has tended to be opposition to the prospect of extending life that has been the most deeply embedded position (Gruman, 1966; Morley, 2004a). In medieval Europe, alchemy, which had at its core the aim of developing an elixir to increase lifespan, gave rise to the Iatrochemical School of practice generally

recognised as laying the foundations for modern chemistry and biochemistry (Gruman, 1966; Tanner, 1981). However as the new science of chemistry sought respectability its practitioners 'did not hesitate to resort to sarcasm and ridicule' (Gruman, 1966 p50) in their attempts to separate themselves from the increasingly anachronistic-seeming origins of their profession[63]. Remnants of this scorn and the aesthetic disdain for prolongevity ideas stemming from apologist thought can be found in the criticism which greeted Charles-Edouard Brown-Séquard's 1889 announcement of the rejuvenating properties of testicular extracts, and the later efforts of animal gland transplanters like Serge Voronoff, to reverse the symptoms of ageing (see Chapter 4). However, organotherapy and the glanding operations of the 1920s were popular and widely practiced. They occurred at a time when there was both scientific and cultural support for treating old age as a debilitating pathology, the remedy of which through modern medical science would be a benefit to all mankind.

Work first carried out in the elite hospitals of Paris was key to this way of thinking; scientific study of the body led to the realisation that the pathologies of old age could be linked with specific damage to the tissues and even the cells of the human body (Haber, 2004). Jean-Martin Charcot's work characterising the medical symptoms associated with old age inspired his contemporary, renowned immunologist Elie Metchnikoff to propose a theory of bacterially-

induced senility, reasoning that all the negative symptoms of old age could be accounted for by the accumulated action of hostile bacteria in the gut (Achenbaum, 1978). Metchnikoff coined the term "gerontology" to describe the scientific study of ageing in 1903 (Gruman, 1966; Morley, 2004a). He was not alone in going further than Charcot and describing ageing itself as a degenerative disease. In the US, Charles A. Stephens preached the doctrine of lasting youth by preserving the body's cells through proper nutrition and hygiene while New York physician George Millar Beard popularised the idea that ageing was caused by a slow decline in the organic matter of the brain, in essence a disease of the cerebral tissue (Cole, 1992; Haber, 2004).

> By the early twentieth century, to most authorities, aging was a disease that destroyed both the body and the mind (Haber, 2004 p516).

But this medical consensus did not develop and flourish in a cultural vacuum.

While the impact of the industrial age brought fears that such work was harmful to the health of children, the concern for the elderly was that the majority would be unable to adapt to the physical demands and new skills required for factory work and thus would be redundant - 'to be old was to be poor; modernization, for the old, meant dependence rather than respect' (Haber, 2004 p518). For those not independently wealthy, old age meant being supported by family or ending up in the

poorhouse (Morley, 2004a). Both Metchnikoff and Beard were concerned about the social and economic impacts of old age. Beard famously calculated that seventy percent of the world's work was carried out by those under forty-five and speculated that the loss of fertility in later life was a natural device to prevent the world being populated with 'those whose powers had fallen from their maximum' (Beard, 1874, cited in Cole, 1992 p165). Metchnikoff cited the financial burden which the elderly placed upon the state as a compelling motive for medical attempts to affect the decrepitude of old age (Cole, 1992; Haber, 2004). Western societies at the turn of the century, according to many commentators were facing a 'crisis of ageing' (Haber, 2004 p518). This is not to suggest that there was a single all-pervasive view of old age during this period, but to note a number of discourses emerging around the same time which emphasised the negative aspects of old age and which thus had an impact of prevalent attitudes and debate. It was into this social and cultural milieu that organotherapy arrived, with its promise of reinvigoration and rejuvenation. Kahn (2005) has observed that 'ability to work' is a key phrase in the history of rejuvenation research.

Perceptions of old age would, if anything, worsen in the early years of the twentieth century.

> Americans between World War I and World War II believed that new theories in the biological and social sciences as well as data gathered by economists, demographers, government officials,

> and social workers verified negative ideas about the elderly that had emerged during the last third of the nineteenth century. The most recent and authoritative evidence indicated that old age brought pronounced physical decay, mental decline, unpleasant and sometimes deviant psychological and behavioural traits, economic uselessness, personal isolation and social segregation (Achenbaum, 1978 p109).

Considering this context, it is not so surprising that there was a resurgence in anti-aging therapies propounded by physicians during the 1920s despite the prior opprobrium generated amongst the scientific community by Brown-Séquard's elixir. However the decade from 1920-1930 was to prove the zenith of gland grafting's popularity. In the 1930s the isolation and eventual synthesis of the hormones oestrogen and testosterone and the efforts of scientists like Starling and Cushing to gain respectability for endocrinology through an emphasis on rigorous laboratory investigation diminished the appeal of organotherapy compounds. Controlled experiments on humans and animals provided increasing evidence that grafting did not work and that testosterone did not in any case have a rejuvenating effect beyond some improvement in muscle mass (Hamilton, 1986; Rothman & Rothman, 2003). By the 1940s both the overwhelmingly negative medical view of old age and social conditions were changing.

Geriatric care, although established by Nascher in the US, was developed primarily in the UK during the 1930s and 40s introducing the

concepts of rehabilitation, motivational programmes, home visits for aged patients and, in 1946, the decision to make specific provision for the elderly in the nascent National Health Service (Morley, 2004a). British and American professional societies for geriatric practitioners were established with a new focus on separating the pathological conditions associated with old age from normal healthy old age (Haber, 2004; Morley, 2004a). At the same time increased provision of social security (such as the Social Security Act of 1935 in the US), healthcare (the British NHS and a move from almshouses and poor hospitals to nursing homes in both the UK and US) and private pensions ameliorated the fear of economic danger (ibid.). The promises of the anti-ageing practitioners could not live up to the ultimate failure of their methods to produce definite long-term results. As the cultural and financial climate changed:

> Authorities who had once emphasized the incapacity of the old now spoke of the last stage of life as a time of independence and autonomy Haber, 2004 p520).

The medical study and management of old age became formally separated from the practice of endocrinology and these disciplines now developed largely in isolation. The movements to establish endocrinology, gerontology and geriatrics as legitimate and respected domains of science and medicine involved a certain necessary rejection of the practices of the turn-of-the century period and perhaps a downplaying of genuine contributions to medical development made during this era.

Ideas of prolongevity and rejuvenation did not, of course, disappear entirely, they merely moved further away from the current of mainstream medicine and courted a more select clientele. Paul Niehans, a former gland transplanter, reinvented his treatment as 'cell therapy[64]' supplied exclusively through his private Swiss clinic and achieved both fortune and fame when he was summoned to treat Pope Pius XII in 1953 (Hamilton, 1986). In Romania, Ana Aslan used money made from the sale of the procaine-based serum known as Gerovital H3, which was reported to fight the ageing process, to found the Institute of Geriatrics in Bucharest in 1952 (Morley, 2004a). Gerontology, especially biogerontology the science of the biological mechanisms of ageing (across all species) seems to have suffered from the negative image of anti-ageing medicine more than either of the medical specialities of endocrinology or geriatrics. US gerontologists' frustration with their lack of funding led to a political campaign to have a separate National Institutes of Ageing (NIA). The proposition attracted considerable criticism from the scientific hierarchy and 'themes suggesting the marginal status of biogerontology persistently emerged' during the hearings (Binstock, 2004 p525). The only area in which the association between hormones and rejuvenation was retained was the application of oestrogen for treatment of the menopause and post-menopausal women with the promotion of the 'feminine forever' concept beginning in the 1950s (Rothman & Rothman, 2003; Morley, 2004b).

However, even as orthodox endocrinology, in line with the rest of mainstream medical opinion, moved away from the idea of treating age itself, a new association between the hormonal model of the body and the changes associated with age arose from an unlikely source.

The Origins of Growth Hormone Treatment in Adults and the Aged

Because of the species-specific structure of its proteins and the subsequent failure of the animal-derived model for hormonal drug production, human growth hormone was not isolated or available for clinical investigation until well after endocrinology, geriatrics and gerontology has been separated out into their modern forms and associations with glandular rejuvenation had been abandoned. At the 1954 international symposium on *The Hypophyseal Growth Hormone, Nature and Actions* the research under discussion was almost entirely drawn from experiments with animal models and conducted with animal growth hormone preparations as human GH had not yet been isolated. Indeed, the evidence for growth hormone action in man was so 'meagre and inconclusive' (Shorr et al, 1955 p522) that the presentations on growth hormone in humans were restricted to sharing one of the five symposium sessions with data on the action of GH on mammary glands in animal models. Nonetheless, within the animal data efforts had been made to characterise the actions of growth hormone on a wide range of physiological indices beyond simple

growth promotion: its interaction with other glands and tissues, with insulin and regulation of carbohydrate storage, on nitrogen retention and amino acid balance, on lactation, and other cellular functions (Smith, Gaebler & Long, 1955). Perhaps it was the uncertainty and frustration with metabolic data from (animal) GH administrations in adult human subjects, moving some investigators to wonder if a single growth promoting hormone even existed in humans (Kinsell, 1955), that drew clinical investigators to concentrate on pituitary-deficient patients in the hope of eliciting a response to the hormone:

> The ideal subject would seem to be one who is normal in all respects except for a deficiency in growth and without a genetic factor limiting the capacity of tissues to respond to a growth stimulus (Shorr et al, 1955 p523).

In any case, when Raben first tested his preparation of pituitary-derived human growth hormone in 1957-8 he chose to administer it to a teenaged patient with hypopituitary short stature (Raben, 1958). The success of this intervention meant that treating GH deficient patients became the first accepted clinical use for human growth hormone, and the scarcity of supply meant that until recombinant-DNA-derived growth hormone arrived in 1985 it remained essentially the only such application for hGH.

In a follow-up paper in 1962 Raben reported the successful treatment of more hypopituitary short children but also speculated that, since patients with gigantism/acromegaly demonstrated that adult tissues

remained responsive to GH even after bone growth had ceased, GH might have further uses in adult conditions that 'may be helped by an anabolic agent' (Raben, 1962, p82) including burns patients, renal failure and hypoglycaemia. He was even led to speculate:

> [W]hether an additional amount of hormone could advantageously prevent the catabolic changes of old age (Raben, 1962 p82).

Also in the same paper was a report that Raben had treated a female, adult patient suffering from multiple pituitary deficiencies using a thrice-weekly dose of pituitary growth hormone and found that she 'noted increased vigour, ambition and sense of well-being' (Raben, 1962 p85).

The paediatric indication took priority and among paediatric endocrinologists it appears that producing a growth response in short statured children quickly became the main clinical focus, as evidenced by the assertations that 'we thought growth hormone was only for growth' (NAM 4) while the metabolic changes induced by GH were acknowledged, but often ignored[65]. In this context of limited pituitary supplies and paediatric specialists dominating clinical investigation of the hormone, the clinical option of adult investigation appears to have been quickly closed off. One US-based adult endocrinologist recalled this sense of impracticability:

> [I]t was always a limited supply of growth hormone so there was no question of giving it to adults. There was also [ ] the original

> impetus for growth hormone was to promote linear growth in children, that's why it's called growth hormone [ ] the issue of adult was not even an issue- it was a non-issue (NAM 1).

Despite the restrictions, investigational work on the metabolic effects of growth hormone continued, albeit in a limited, low-key and small-scale fashion. The capacity of growth hormone to build up muscle and other tissue had suggested an application in treating burns patients as early as the 1954 conference (Tattersall, 1996) and was followed up in the pituitary era in experiments which showed some positive but hardly overwhelming responses (Soroff et al, 1967; Wilmore et al, 1974). Metabolic profiling of the effects of GH in adults even extended to some consideration of elderly patients but the emphasis was on investigating physiology or determining life-long patterns of growth hormone secretion rather than achieving any anti-ageing effects (Root & Oski, 1969; Finkelstein et al, 1972).

Ironically, however, it was observations from paediatric practice which spurred the first steps towards experimental investigation of growth hormone as an anti-ageing agent in the late 1970s. One US paediatric endocrinologist who was involved in this early research recounted:

> [W]hat prompted me to consider [anti-ageing] was that the [ ] untreated growth hormone deficient patients, age prematurely and because of that I asked the question whether growth hormone could turn around the ageing process (NAM 3).

This clinical observation had been well documented from the days when neither human growth hormone nor biochemical assays of GH levels were available and hypopituitary patients were recognised by indirect metabolic tests and physical symptoms including progeria (or premature ageing) as in this description of a ‘”classic” pituitary dwarf:

> At a relatively early age in adolescence, the skin becomes dry and wrinkled giving the individual a wizened owlish appearance. Sometimes they present definitive senile features (Greenblatt & Niebergs, 1947 p715).

Metabolic studies of GH secretion in adults were also beginning to show that growth hormone secretion levels decrease with age in normal healthy adults (Rudman et al, 1981b; Tattersall, 1996). Spurred by these two observations, a small-scale trial was set up in 1982 to investigate whether ‘administration of GH will reverse or retard certain aspects of the ageing process’ (Blizzard et al, 1988). The trial comprised of 5 volunteers, mainly parents of growth-hormone deficient children taking daily injections of US National Pituitary Hormone Distribution Program-supplied pituitary growth hormone (NAM 3). The trial was cut short by the withdrawal of pituitary growth hormone due to the risk of CJD in 1985. The results were largely inconclusive and were not published until a few years later but they had already inspired other practitioners, most notably Dr Daniel Rudman who had been a reviewer on the earlier study (ibid).

Rudman had moved on from his previous work in paediatrics and, in a late career change, began to work in the field of geriatric medicine, bringing with him an interest and expertise in endocrinology including growth hormone (Duthie, 1994). As with the initial clinical investigation, the emphasis in Rudman's experiments was on testing the idea that the decline in GH secretion with age was linked, by way of the hormones metabolic effects outside growth, to detrimental changes in body composition; loss of muscle mass and increase in fat deposits (Blizzard et al, 1988; Rudman, 1981b). The inference was that GH could be employed to reverse these changes; literally 'building up' the decaying ageing body, following a similar logic of anabolic action to the burns therapy experiments and Raben's original observations. The withdrawal of pituitary GH and the subsequent introduction of recombinant hormone prematurely ended these early small-scale trials but opened up the possibility for much broader investigation and development of growth hormone use in adults.

The Biosynthetic Explosion

As with the use of GH in children, the most immediate effect of biosynthetic hormone on adult-orientated research came from its increased availability. By the early 1990s trials of recombinant growth hormone were underway in adult patients with a variety of catabolic conditions including malnourished cancer patients, gastro-intestinal surgery patients, obese patients receiving reduced calorie diets and

HIV infection (Mulligan et al, 1993). The availability of synthetic, prion -free GH also allowed Rudman's work in GH in elderly patients to recommence. In Europe, Kabi Pharmacia[66], manufacturers of the "Genotropin" brand of recombinant GH, began sounding out adult endocrine researchers in Scandinavia and the UK about a different potential application for the hormone in adults. One member of the UK team recalls:

> The reason why Kabi came to talk to me was because of my background with growth hormone, they wanted to do some trials with growth hormone replacement in adults with growth hormone deficiency and we were the first group that they came to in the UK (UK 6).

Two papers, one from the UK group and the other from the Scandinavian researchers announcing the beneficial physiological and psychological effects of GH therapy in adult hypopituitary patients appeared in high-profile medical journals (the New England Journal of Medicine and the Lancet respectively) in 1989 (Jorgensen et al, 1989; Salomon, Cuneo, Hesp & Sonksen, 1989).

The US endocrinology establishment was slow to accept the idea of an adult GHD syndrome as a clinical reality. A UK-based adult endocrinologist explained the situation thus:

> I think the reality is that all of the initial work came from Europe, from northern Europe and from the UK and precious little came out of the United States. The United States has actually in a

> sense come into this much later, and has repeated a lot of the work that was done previously in Europe (UK 2).

US-based informants generally concurred with this assessment of the situation, as in the following example:

> [W]e in the United States were pretty slow to move into believing that adults who had had growth hormone deficiency needed it as adults and thanks to the Europeans, they really took the lead [ ] and it took a while to convince us but certainly, we were convinced (NAM 3).

A less charitable interpretation of the situation highlights the potential hegemonic dominance of the US scientific community:

> [B]ecause it was discovered in Europe the Americans didn't like it, and didn't accept it, and poured as much cold water over it as they possibly could (UK 6).

There are also a number of other factors that may have influenced the situation.

Almost concurrently with the first data on hypopituitary adults, the first report from Rudman's group, about the experimental application of recombinant growth hormone to elderly patients was published in the NEJM. In this experiment 12 men aged 61 to 81 with low levels of blood-hormone had received weekly administration of synthetic GH (supplied by Eli Lilly who part-funded the research) over a period of six months and were found to have increased lean body mass, bone

density, skin thickness and decreased adipose (fat) tissue compared to nine untreated control subjects (Rudman et al, 1990). The authors' appraisal was that

> The effect of six months of human growth hormone on lean body mass and adipose-tissue mass were *equivalent in magnitude to the changes incurred during 10-20 years of ageing*' (Rudman et al, 1990 p5, emphasis added).

Unsurprisingly for such a sensationalist presentation, the publication of the Rudman group's findings garnered significant media interest. The New York Times ran the story with the headline "Human growth hormone reverses effects of ageing" (Angier, 1990) while the Associated Press announced "Hormone injections can reverse some of the damage of ageing and give people back the firmer flesh of their younger years" (AP press release cited in Rothman & Rothman, 2003 p201). The fact that these potential new indications for growth hormone in adults (both of which were positioned as replacement therapies) appeared in concert meant that to an extent they were considered together by the US endocrine community. A critical article accompanying the Rudman publication in the NEJM entitled 'Growth hormone in the elderly?' reviewed both Rudman's data and the results of the European studies of GH in adults with hormone deficiency and concluded:

> Because there are so many unanswered questions about the use of growth hormone in the elderly and in adults with growth hormone deficiency, its general use now or in the immediate

> future is not justified. A better use of scientific and financial resources would be to determine whether growth hormone is beneficial in patients with severe catabolic illnesses (Vance, 1990 p53).

In the early 1990s the announcements that growth hormone had potential use in thermal injury, renal failure, AIDS, adult hormone deficient patients and the elderly, as well as a growing awareness that it was being used illicitly in bodybuilding and athletics, coincided with bioethical and media concern about the significantly increased paediatric use of hGH. These additional adult uses fed into media and public disquiet about the seemingly unstoppable spread of GH use and the fear that this was fuelled by corporate desire rather than patient need. It is also possible that some professional disquiet was raised among medical professionals by the enthusiastically anti-ageing tone of Rudman's findings. Ultimately supporters of therapy for both adult GHD and age-related GH decline continued to investigate these lines of therapy during the 1990s. However the association of growth hormone with ageing and its increased availability post-1985 were also to have effects beyond the realms of mainstream endocrinology or geriatrics.

Growth Hormone and the Rise of the New Anti-Ageing Movement

The last decade of the twentieth century saw a resurgence of prolongevitist biomedical activity and thinking (Binstock, 2004; Mykytyn, 2006a). Operating mainly in the US, anti-ageing practitioners began to set up 'rejuvenation clinics' such as the Palm Springs Life Extension Institute and Ceregenics of Las Vegas whose treatment approach was founded on a regime of growth hormone and testosterone augmentation backed up by a plethora of vitamins and nutritional supplements, controlled diets and exercise[67] (Rothman &Rothman, 2003; Binstock, 2004). The 1990 publication of Rudman's NEJM paper on hGH in the elderly and the publicity surrounding it provided the crucial spur for a new hormonal anti-ageing movement. Many of the anti-ageing proponents cited, and continue to cite, results from Rudman's work[68] and the ongoing studies of growth hormone in GH-deficient adults as proof of the scientific legitimacy of their enterprise (Drazen, 2003; Perls, 2004). In 1993 the foundation of the American Academy of Anti-Age Medicine (A4M) institutionalised the idea of hormone-based prolongevity and acted as a statement of intent on the part of the movement (Haber, 2004). The A4M's president Ronald Klatz and chairman Robert Goldman, who had published books on drug and training regimes intended to enhance athletic performance during the 1980s, turned their proselytizing to growth hormone and other 'anti-

ageing secrets' of hormone therapy (Binstock, 2004). It is claimed that following their hormone treatment regimes will help recipients:

> [L]ose fat, gain muscle, enhance your sex life, decrease wrinkles, prevent disease, and reverse the ageing process (Klatz & Kahn, 1998 cited in Haber, 2004 p515).

These claims have been repeated and expanded upon by a proliferation of web sites claiming to offer human growth hormone or GH-stimulating agents along with a wide variety of dietary supplements (Perls, 2004). Many of the anti-ageing clinics and A4M members are licensed physicians, although rarely from the specialisms of endocrinology or geriatrics, using their ability to prescribe off-label to provide access to hormone treatments. The A4M and other anti-ageing organisations also produce a number of peer-reviewed and non-reviewed journals, books and provide certification of anti-ageing physicians as part of their drive to present their activities as institutionally and scientifically grounded.

The most vociferous criticism of the resurgent anti-ageing movement has come, not from endocrinologists, but from the academic biogerontology community, which has increasingly engaged in a 'war of words' with anti-ageing proponents, especially the A4M (Binstock, 2004; Mykytyn, 2006a). The most prominent statement to date is a 2002 article in *Scientific American* entitled 'No truth to the fountain of youth' which was linked to a widely disseminated online statement signed by fifty-one leading biogerontologists decrying and

condemning the ‘phoney’ anti-ageing industry (Olshansky, Hayflick & Barnes, 2002). In this statement and article the authors evoke the archetypes of prolongevity’s disreputable mythology; Ponce de Leon’s misguided search for the magical fountain of youth, cabalistic medieval alchemists and anti-ageing elixirs of dubious providence, with implicit invitation to place the claims of the modern hormone-promoting faction in the same calibre of enterprises, without diluting the futuristic promise of regenerative medicine. Even in its fallow, under-funded years, advances in the scientific study of ageing had moved away from endocrine models and focused primarily on cellular and molecular mechanisms described in animal models. In the 1990s developments in molecular biology and genetics fed into biogerontological work on ageing to produce the paradigm known as regenerative medicine. The enterprise was not limited to academic research but also spawned a new wave of biotechnology companies, beginning with the founding of Geron, the first explicitly ‘ageing orientated’ biotech start-up, in 1992 (Hall, 2003b). Others soon followed, notably Advanced Cell Technologies (ACT), Osiris Therapeutics and StemCells, all following a regenerative medicine approach. The perceived need for boundary work stems from US biogerontology’s long struggle for legitimacy and the many evident, if superficial, similarities in the goals of both groups. Both biogerontologists and anti-ageing physicians essentially advocate a classic prolongevitist stance treating human ageing, if not as a disease *per se*, then as a biological process in which intervention is

both possible and desirable. Both groups also position old age as an undesirable, painful time of life with few redeeming features and posit the ageing of the 'baby boomer' generation (Americans born 1946-1964) as a potential 'crisis of ageing' which can only be averted by the development and employment of their technologies (Hall, 2003b, Perls, 2004, Vincent, 2006). The struggle for legitimacy, as biogerontologists know too well, is the struggle for funding and the endemic calls for extra financing of ageing research rely on generating support for the viability of their particular technological predictions of future benefit[69].

While these events were unfolding, the clinical investigation of growth hormone in adults continued in the endocrine community and, to a lesser extent, among geriatricians. In spite of the lukewarm reception of adult GH deficiency as a concept in the US, multi-centre controlled trials went ahead, with pharmaceutical company involvement, in both Europe and North America (UK 2; NAM 1). While supporters of adult GH deficiency were convinced that they had described a new syndrome, not everyone was so ready to accept these conclusions, not least because the lack of an obvious goal of therapy like linear growth, means the adult indication relies on detecting less substantial improvements in symptoms like body mass, muscle strength, bone composition and psychosocial wellbeing that many practitioners felt were too non-specific and subjective (Cummings & Merriam, 2003; Hoffman, 2005). Not only, practitioners, but state authorities and

healthcare providers too, appear to have had reservations about the perceived 'vagueness' of the new condition, as US-based informant observed:

> In Europe, the governments wouldn't pay for [adult GHD], unless they provided [ ] …its not a question about growing anymore, you have to show me data, and just kind of some little changes in carbohydrate metabolism, you know…at what cost? In the UK National Health Service you've got a constrained budget, unlike here, you know the sky's the limit, so you have to pile on more evidence that this is really valuable (NAM 6).

After extensive investigation; as of 2003 there were at least one hundred reported clinical trials of hGH for adult replacement therapy, growth hormone was ultimately approved for use in adult GHD (AGHD) in 1996 in the UK and received FDA approval the following year (Cummings & Merriam 2003). It is perhaps indicative of US reticence that the FDA approved Serono's 'Serostim' recombinant growth hormone for AIDS-related wasting on a much smaller evidence base before they granted approval for the adult hormone deficiency indication (Ibid.). The acceptance of AGHD has not been without caveats- a few countries have adopted a universal approach of providing GH replacement to all adult hypopituitary patients, others have resisted the indication entirely but most have opted for a policy of patient selection, which in the UK and many European states is made on the basis of Quality of Life and/or bone mineral density evaluations (Drake, Howell, Monson & Shalet, 2001).

Investigation of the effects of GH in the elderly was also continued following Rudman's findings, although the emphasis has been increasingly on treating specific pathological entities such as sarcopenia ('loss of muscle mass and diminishment of muscle function that occurs with ageing' Morley, Perry & Miller, 2002 p699) rather than on 'reversing the ageing process'. A number of follow-up clinical trials of GH, sometimes accompanied by testosterone in elderly individuals, including more data from the Rudman group, have been conducted although compared to the investigation of adult GHD they have been relatively few in number and small in scale (Cummings & Merriam, 2003). The second section of this chapter will examine the discourse of adult endocrinologists concerning the application of GH in adults, and in light of this history, emphasis will be given to examining the differences between the now-accepted adult deficiency indication and the still controversial anti-ageing option.

SECTION 2: PRODUCING THE SCIENTIFIC AND UNSCIENTIFIC IN ENDOCRINOLOGISTS DISCOURSE

'Classic Endocrinology': Treating Adults with Growth Hormone Deficiency

Despite the initial scepticism about an adult form of growth hormone deficiency as a viable medical diagnosis the condition was eventually recognised as a legitimate indication for treatment (Gibney et al,

1999; Cummings & Merriam, 2003). A UK-based endocrinologist who was involved with the early work on the adult indication described the decision to investigate the use of GH in hypopituitary adults:

> From our point of view it was a genuine scientific question [ ] we had suspicions that people with growth hormone deficiency had an altered body composition and altered metabolism but it wasn't known (UK 6).

Here the idea of investigating the application in adults is legitimised as a proper area for scientific investigation, the purpose of which is to resolve uncertainty and produce new knowledge. Other accounts of the discovery of adult GH deficiency syndrome also emphasise the performance of correct science underlying the recognition of the condition:

> I think the important milestone was first describing the deficiency syndrome in adults and then doing the careful studies- double blind placebo control- to show what the effects were of replacing the hormone; so classical endocrinology (NAM 1).

This discourse is empiricist in nature; diligent scientific practice- "double blind placebo control" clinical trials- objectively reveals the evidence that adult growth hormone deficiency 'exists'. The existence of the condition is manifested in the biochemical deficit it involves: As with the diagnosis of 'classic' hormone deficiency in childhood, biochemical testing for levels of GH secretion in the blood remains

the 'gold standard[70]' for measuring, and thus defining, severe GH deficiency in adults (UK 2). The illness and its therapeutic redress are also portrayed in an empiricist vein as a scientific *fait accompli* where measurement of the appropriate indices objectively demonstrates the efficacy of successful therapy:

> And remember that we all take for granted now that growth hormone is useful for decreasing cholesterol and decreasing central fat mass but those issues needed to be demonstrated in placebo controlled trials (UK 2).

There are also recurring aspects of the diagnostic repertoire familiar to paediatric accounts of hormone deficient patients. As with endocrinologists' descriptions of short-statured patients, the adult patients are described in terms of a biochemical deficit, inherent in the label 'growth hormone deficient' and also, of accompanying disturbances in the physical aspect of the body. In adult GHD patients these characteristic imbalances are in bodily fat distribution and muscle mass as well as further biochemical abnormalities and performance deficits including insulin resistance and reduced muscle strength.

The treatment of adult GHD patients is described, like the childhood indication, by informants and in the academic medical as replacement therapy:

> I see it only as a replacement therapy, and it's identical to giving someone back thyroid hormone or cortisol, these are hormones

> that are necessary for life and their production is dependant on the pituitary (NAM 1).
>
> I think if you give it on a replacement basis it's associated with normal life, if you don't give it you get shortened life. [ ] Growth hormone is important for normal living in adults (UK 6).

Replacement of GH for adults is given additional justification by categorising it along with other accepted hormone treatments such as thyroid hormone replacement or by emphasising that it is needed by patients for 'normal living'. There is some contrast with paediatric accounts, where replacement was often presented as a fully functioning, self-evident rationale in itself. This response may reflect the struggle to gain acceptance for adult GH deficiency as a syndrome given that both the physical and psychological deficits associated with it were less visible and historically considered negligible compared to the needs of short hormone deficient children.

Indeed, although Raben had mentioned a possible elevation of mood resulting from his treatment of a single adult hypopituitary patient, the observation was largely overlooked until the first UK clinical trial of GH in adults (Raben, 1962; Sonksen & McGauley, 2005). Even then the idea of looking for a psychological aspect to the adult syndrome was only added to the research protocol at a late stage, after some preliminary data on the Quality of Life (QoL) of hormone-deficient adults was passed to the UK team by the Kabi pharmaceutical

company sponsoring the trial. In a paper reflecting on the experience, two members of the original UK study commented:

> As endocrinologists we were quite ignorant on such matters. By great fortune we had a young psychiatrist-in-training [ ] working in the department (on a research project on anorexia nervosa) and we set her the task of deciding how to do it (Sonksen & McGauley, 2005 p174).

This extract suggests that the original concept of adult GH deficiency as an illness (or potential illness at this stage) envisioned an entity described mainly by biochemical and physical measurements. The other early (1980s) trial conducted by Scandinavian researchers did not include a psychological study and the UK trial added such a component, in the form of health questionnaires, almost as an afterthought. This impression is reinforced by informants' recollections:

> The trials did also examine quality of life but [ ] because I think none of the people designing the trials had any notion that the quality of life issue would be as major as [it] subsequently became, they weren't heavily powered in that direction [ ] quality of life wasn't as much on people's radar as a therapeutic endpoint in the late 80's as it is now. People were much more likely to define hard physical endpoints (UK 2).

A US-based paediatric endocrinologist, agreeing that adult GH deficiency was now shown to be a 'legitimate therapy' nonetheless

described the quality of life improvements as ‘a pretty squishy endpoint’ (NAM 2) compared to the increase in physical height measurable in short-statured children given GH.

This rhetoric of ‘hard’ and ‘soft’ endpoints ties in with the finding from Chapter 6 that endocrinologists, as practitioners of scientific medicine with the corporeal body as their focus, preferred to utilise ‘hard’ physical or biochemical measurements as indicators of both deficit and the redressing effect of hormone therapy in patients. ‘Hard’ measurements are seen as inherently more objective and so more scientifically valid than ‘soft’ more subjective data, such as symptoms reported by patients. It was left to practitioners from an external discipline; that of psychology/ psychiatry, to introduce formal testing for ‘soft’ psychological elements to these hormone-related conditions. In paediatric practice this has been restricted to a parallel program of assessment, never formally involved with the process of diagnosis, partly because of the lower status of soft data as scientific evidence and partly because, as discussed in the previous chapter, paediatric practitioners had historically asserted their own prior claim to the professional authority to assess patients’ state of mind with respect to the suitability of treatment. It appears that while psychosocial assumptions may strongly contribute to paediatric endocrinologists’ understanding of the (patients’) need for therapy, they are surplus to requirements when measuring either the deficit of the illness or the benefits of therapy.

In contrast to the paediatric practice, while the early investigators of GH deficiency in adults 'did not have any pre-conceived ideas that GH would have any effect' on psychological factors, the Quality of Life aspect has become a major component of the adult diagnosis (Sonksen & McGauley, 2005 p174). Two factors seem likely to have impacted this: In the face of resistance to the recognition of adult indications for GH described above, the measurable improvements detected in psychological wellbeing became an important piece of evidence in favour of the diagnosis. Secondly, faced with the possibility of adult patients requiring a life-long programme of expensive recombinant GH therapy (compared to the relatively short-term childhood applications) and the potential for a diagnosis which could incrementally expand up the continuous scale of biochemical deficit as paediatric indications were threatening to do, healthcare authorities seized upon QoL testing as a means to restrict the size of the patient population. Thus QoL questionnaires have become embedded in many regulatory authorities' definition of adult GHD as an additional, required measure of deficit accompanying the biochemical and physical indices. The psychosocial burden of growth hormone deficiency for adults has now become both part of the definition and part of the narrative of patient need, which also contributes to the justification for treatment. The introduction of formal measurement for psychosocial deficit and benefits to therapy appears to have acted to stabilise the diagnosis of growth hormone

deficiency in adults by contributing to the evidence-base in favour of there being a condition to treat and providing a narrative of patient need for practitioners, but also by providing the means to limit the definition of the condition for the purposes of healthcare provision[71].

The Production of Scientifically Valid Ideas About Growth hormone in the Elderly

Emerging into medical and public awareness at approximately the same time as the idea of an adult growth hormone deficiency syndrome, the suggestion that declining hormonal levels in old age produced detrimental changes in body composition comparable to the illness recognised in GH deficient children (and later adults) provided another potential avenue of application for the newly plentiful recombinant growth hormone (Rudman, 1990; Blackman et al, 2002; Giannoulis et al, 2006). However, unlike the adult GHD indication, there have been relatively few clinical trials of GH in elderly patients conducted since Rudman's 1990 article and no regulatory approval has been requested or granted for a use in this indication. In one sense, of course, the expansion in application has already occurred, through off-label use by the anti-ageing movement. While the position of most within the medical establishment is to condemn the practices of the longevity clinics and the A4M, the idea of using growth hormone (and testosterone) in elderly patients has not been completely rejected by endocrinologists. One US-based adult endocrinologist explained that:

> [F]rom the very beginning all of us who worked in the field recognized the potential for doing, for maybe reversing some of the changes associated with the elderly the loss of muscle mass, the frailty, the loss of bone density (NAM 1).

The contemporary focus of this discourse, in the literature and in interviews, deals mainly with treating specific symptoms associated with ageing, often consolidated under the label of 'frailty'. In the twenty-first century the concept of frailty as a specific medical syndrome associated with old age has emerged in geriatrics and gerontology (Bortz, 2002; Morley, 2004a). While not regarded as a pathological entity *per se*, most definitions of frailty incorporate symptoms such as loss of muscle mass (sarcopenia), changes in body mass, and bone fragility, all of which are regulated hormonally (Bortz, 2002; Morley, Perry & Miller, 2002). The risks involved incorporate linked sets of biomedical and social components; for example frail individuals are said to be at increased risk of falls, and the accompanying risk of hip fractures due to brittle bones, or musculo-skeletal deterioration leading to physical weakness and related psychosocial risks such as isolation because of an inability to leave the home (Bortz, 2002; Morley, Perry & Miller, 2002).

The focus on specific risk factors, and the ongoing debates about how best to define and measure them, has had the effect of bringing the issue and its potential remedies under an explicitly scientific and empiricist rhetoric of measurement, risk and benefit, which acts to

distance the topic from the anti-ageing discourse of longevity practitioners. There is still considerable discussion about what form treatment might take and what the precise goals should be:

> [A] lot of the research though has focused from [ ] the National Institute of Ageing point of view, on people who are already frail and so the cat's out of the bag there and I'm not opposed to helping [improve] quality of life there but what you're really talking about here are the people in their 40's and 50's and 60's who... can you do something to delay that frailty period? (NAM 4).

However, whatever age range the intervention is posited for, the orthodox emphasis is on ameliorating rather than reversing age-related conditions, or as another informant admitted 'you're not going to turn the wagon around, the question is whether you can slow the wagon down' (NAM 3). This puts the proposed research more in line with the traditional goals of medical care for the elderly established in the twentieth century, of palliative and preventative care rather than the direct intervention in the ageing process proposed by biogerontologists and anti-ageing practitioners.

The issue is also framed as a 'genuine scientific question', an area of uncertainty, much as the use of GH in adults was in the account above. Even those who are sceptical about the potential of GH or testosterone therapy view the situation as unresolved:

> So at the very best, what you could say is that there may be grounds for doing some clinical trial work in the elderly to see if they benefit from growth hormone replacement (UK 2).

> [T]here's merit to looking at that, that's all I can say. There's not much data supporting it [but] if you can figure out a way to keep somebody's quality of life higher for longer that is a gift (NAM 4).

The issue is framed as one of potential; potential redress of patient need, and potential contribution to scientific understanding and knowledge of the body, which justify and legitimise investigating the area. Contemporary discourse from mainstream medical practitioners highlights the empiricist requirement for more evidence before any legitimate appraisal as to the merits of treatment can be made.

> [J]ust because people are frail we do not have any solid scientific information that says giving these people growth hormone is beneficial [ ] you will find enthusiasts in endocrine community for raising growth hormone levels and "this is really going to make a difference" and I would theoretically say that is true which is why I would support these studies (NAM 1).

> I think the evidence that has accumulated already is sufficient to see that there is a very real potential role of growth hormone in preventing frailty and prolonging independent life at home (UK 6).

Indeed, this recourse to an objective evidence base has the rhetorical effect of producing the speaker as being within the scientific medical establishment. Professional support is given for the *concept* of hormone use in the elderly in the form of future investigation – theory testing- with the caveat that it must be objectively and scientifically carried out, rather than for the *activity* of therapy, the domain of anti-ageing practitioners, which is renounced as unsupported by evidence and thus unscientific. By citing age-related frailty rather than ageing as the condition under scrutiny and by invoking a discourse of objective investigation endocrinologists' validate their professional interest in the area and distinguish it from competing claims to authority to treat similar patients. This is in contrast to their description of anti-ageing practitioners.

'It's how you go about it': Anti-ageing Medicine as Beyond Science

In general endocrinologists descriptions of anti-ageing practitioners were disparaging, and employed contingent rhetorical devices to distance hormone based longevity practices from the accepted-as-legitimate activities of endocrinology. US-based endocrinologists were more likely to aim criticism at specific examples of anti-ageing practices such as the American Academy of Anti-Ageing Medicine (A4M) or well known longevity clinics, since they are more familiar with these mainly US-located enterprises. One US-based endocrinologist described the A4M as:

> [A] bunch of bogus entrepreneurs [ ] None of these are respectable endocrinologists (NAM 1).

Another commented:

> [W]ell first of all the idea to look at it as the fountain of youth is totally preposterous [ ] I went to one of the A4M meetings, it was ludicrous [ ] so I don't have respect for that organization (NAM 4).

Both the concept, or the perceived concept, of anti-ageing (the fountain of youth) and the practices of prolongevity advocates are critiqued. Neither the practice nor the practitioners are considered 'respectable', an assertion which was then qualified in a number of ways in further discourse. In particular, attention was drawn to the fact that while many of those involved were medical practitioners they were not endocrinologists and are therefore not (properly) trained in endocrinology:

> In the United States you have people who are already making a lot of money who don't depend on the insurance like plastic surgeons, emergency room doctors, all sorts of people are getting involved in it and interestingly enough too, probably hardly any are endocrinologists, internal medicine endocrinologists [ ] right now there're not enough [endocrinologists] practicing just to do classical endocrinology so they don't have to get into this, but this whole area of

> medicine you don't have to deal with insurance companies, you don't have to deal with bureaucracy (NAM 4).

A similar theme emerged during a discussion of one of the largest longevity clinics, based in Las Vegas:

> [T]he two founders, one is a radiologist and the other is an emergency room physician. In other words they have zero training in endocrinology but they were featured on one of our big news shows, that shows up every Sunday night called 60 minutes and one of the founders was driving a Rolls Royce, he makes 10 million dollars a year and they're giving growth hormone out like candy (NAM 1).

In these accounts the anti-ageing practitioners are placed outside the boundaries of professional authority granted by formal training and qualifications as 'internal medicine endocrinologists' , thus questioning their capability to carry out correct endocrine practice (e.g. as suggested by their prolifigate use of hormone). At the same time their motivation is characterised as suspect- they appear driven by financial gain and the desire to avoid bureaucratic procedures- which is implicitly in contrast with, and presumably at the expense of, the appropriate desire of physicians to help patients. Whilst it is much less widespread, some anti-ageing practice has spread to the UK where it elicits similar reactions from UK-based endocrinologists:

> I was actually approached by a number of newspapers [about the case] of a doctor who was proposing to use these therapies

> from his Harley Street practice. Not an endocrinologist, it was somebody who was in a sense, I think he was more of a cosmetic doctor but setting out to improve the way people look. All very fanciful stuff (UK 2).

Again, the concept of anti-ageing is derogatively portrayed as 'fanciful' and 'cosmetic' in presumed contrast to the proper 'classical endocrinology' of respectable practitioners.

These arguments were supplemented by various accounts in which anti-ageing practice, specifically giving growth hormone and testosterone to elderly (and not-so-elderly) individuals, was characterised as going beyond the remit of correctly-practiced scientific medicine. As one article on the possible merits of using testosterone therapeutically in elderly men noted:

> [T]he media and the public in general appear to have moved beyond science in this field (Asthana et al, 2004 p461).

In keeping with endocrinologists' accounts of the potential use of GH in ageing or age-related frailty as a scientific uncertainty requiring further study before an evaluation of its ultimate utility (as a risk/benefit calculation) can be made, the practice of employing it as a prolongevity treatment is characterised as failing to properly address these risks and the requirement for evidence-based objective decision making:

> [T]he problem is they're not following these people and we don't know, we have no way of knowing if something bad is going on in that population, because again by definition they're older, they're more prone to medical problems [ ] and more risk for cancer (NAM 1).

> [O]n the grounds that if you don't know what you're doing you shouldn't be doing it, I would say that treating the normal elderly person with growth hormone is currently a totally inappropriate thing to do (UK 2).

The risk, especially pertaining to cancer, and the uncertainty which accompanies it, frame treatment as inappropriate and irresponsible medical practice in view of the inadequate professional capabilities of non-endocrinologists who 'don't know what they're doing' and are 'not following' their patients to detect adverse effects. Anti-ageing medicine is also depicted as unscientific in the way its members use data produced by the mainstream endocrine community:

> [T]hey've taken the scientific studies, the properly done, randomized, placebo-controlled studies of growth hormone deficiency in adults and they've said "this is what happens in anti-ageing". Now, that is not valid, that's why I said they're bogus entrepreneurs, they extrapolate from one population to another and anyone who works in science or medicine and does studies, I mean that is totally egregious and totally incorrect (NAM 1).

The cumulative effect of this discourse is to legitimise the potential use of growth hormone (and other hormones) in selected elderly individuals as an area of scientific interest but to present the current practice of this treatment as being outside scientific legitimacy. The primary rhetorical tools which are used to support this distinction are an emphasis on the proper practice and technique of scientific medicine and the proper conduct of a physician. The discourse of endocrinologists supports their professional interest by being critical of the conduct of anti-ageing practitioners rather than condemning their therapeutic approach. One US-based endocrinologist explained:

> Had they legitimized themselves they could've taken off and done a great job but they... not that everything they say is wrong, you know, it's how you go about it, (NAM 4).

During their interviews two US-based informants recounted how they had entered debates with leading anti-ageing practitioners at mainstream endocrine meetings and one (quoted above) even attended an A4M meeting. Whilst their impressions of these encounters were not favourable, this sort of engagement would be unthinkable for the biogerontology faction which also campaigns against anti-ageing practitioners, and marks a boundary of professional interest between these two groups.

Institutional and Conceptual Obstacles to Hormonal Therapy for Ageing

Having established hormonal treatment for symptoms of frailty as a legitimate area of scientific investigation for endocrinologists, respondents cited mainly institutional and technical factors as being responsible for the fact that the appropriate research had not yet been carried out:

> The real problem, at least in the US, is that none of the pharmaceutical companies were willing to sponsor the large trial of sufficient duration (NAM 1).

Others have criticised a perceived lack of interest, or excessive caution, on the part of government institutions such as the National Institutes of Ageing (NIA) for failing to support the research. In particular, it is often stated that the trials which have been carried out to date of GH and testosterone in elderly individuals involved too few individuals for too short a duration to draw meaningful conclusions about the full impact of therapy (Blackman et al, 2002; Cummings & Merriam, 2003; Asthana et al, 2004). The difficulties of conducting the sort of study which would prove suitably scientifically rigorous were also a noted impediment:

> [The elderly population] would be difficult to work with and it would have to be a large study and it would be expensive (UK 6).

> [I]t's going to take a lot of time and that kind of study, -a lot of dollars- and that kind of study at least in the United States probably cannot be done (NAM 3).

Especially amongst US-based respondents, pharmaceutical manufacturers of recombinant growth hormone were seen as the most viable source of backing for the required trials. However, they were characterised as being deterred by the potential cost- in time, money and deployment of expertise required to conduct large-scale clinical trials, especially when they may already be benefiting from the market in anti-ageing:

> Nobody's ever applied for it for ageing [ ] the problem is that, at least in this country you can use a drug after it's been approved, for a purpose for which it hasn't been approved. Now you can get sued if you did that and something goes wrong but [ ]... it's done a lot as you know (NAM 3).

> [T]he pharmaceutical companies, they are not interested in that market but they let their drug be sold for that purpose (NAM 4).

The latter respondent also raised the likelihood that since regulatory authorities were specifically orientated towards pharmaceuticals intended to treat defined diseases there could be procedural difficulties in trying to get approval for a drug to intervene in a process, such as ageing, which is not considered a pathology.

In addition to these perceived obstacles, it is possible to consider a level of conceptual difficulties affecting the progress of hormonal therapy for the elderly and frail. Growth hormone therapy for deficient adults has been successfully conceived of and deployed as a replacement therapy, anchoring it to a body of historically accepted and institutionally validated hormone therapy including the childhood GHD indication, thyroid and cortisone therapy in hypopituitarism and insulin treatment for diabetes. In some accounts replacement can be seen to carry not only a historical logic and validity but also a sense of moral weight as an appropriate act of medicine:

> I think that it's important to tailor all this business of [ ] adult growth hormone treatment in adult practice to the concept that maybe what we have is enough and therefore that it's only deficiency that we really should be treating (UK 4).

> [I]f you're replacing growth hormone in someone who's deficient it's replaced to keep their IGF-1 levels in the range that is appropriate for that age; [ ] we're trying to emulate mother nature not change the course of mother nature (NAM 1).

Replacement is counteracting deficit, returning the patient to the 'course of mother nature' where 'what we have is enough'; it is normalising, where (biochemical) normality is positioned as determined by nature. Possessing an abnormal hormone level is therefore un-natural and pathologic- thus creating a link between the idea of replacement and the moral entitlement to therapy. In contrast

the approach of anti-ageing medicine was often located in the realm of ‘cosmetic’ or enhancement applications:

> [T]he utilization of medical resources to change how one looks or to change how long one lives, I mean they become, they’re not issues of medical judgment in the end, they are societal issues aren’t they? (UK 2).

> But the phenomenon is social, I mean why do people get plastic surgery to remove their wrinkles, or liposuction or, you know, all the things that people want to be young and beautiful, and if you can do it with a little injection, with a tiny little needle once a day, if you think you can do it, why not? That’s our mentality, I don’t know if that’s as pervasive in the UK or Europe (NAM 1).

These applications (although the informants did not necessarily use the term ‘enhancements’) are positioned as being ‘social issues’ which exist beyond the remit of medical authority alone. Cosmetic applications are positioned as a matter if individual or social choice rather than instances of disease or illness and thus they do not carry the same weight of entitlement. At present the idea of hormone therapy in elderly patients, even a subset defined as frail, who do not meet the criteria for adult growth hormone deficiency, appears to lie somewhere between the concepts of replacement and anti-ageing and thus cannot fully draw on the same weight of moral and historical legitimacy in the eyes of mainstream medicine.

Conclusion

The conception of ageing as a specifically medical problem reflects an increasing understanding of the body as a biological entity, whether cellular, hormonal or genetic models have been applied to provide the particular description. Whether or not old age itself has been considered a disease or not has been significantly influenced by a wide range of social factors especially social and economic concern about managing the elderly cohort within the population, and the interests of different medical specialities in refuting or supporting particular models of intervention. The connection between growth hormone and ageing first came through physical observation of the effects of deficiency on the original and most phenotypically visible group of patients, completely hypopituitary children. Investigators within the medical profession initially sought to link this observation to the phenomenon of human ageing through the by-then established concept of hormone deficiency. By comparing the hormone levels in the body in old age with those of middle aged or young adults, old age itself is produced as a category of the abnormal and pathological measured against the standard of middle age. This is not dissimilar in many ways to the initial comparison made by Brown-Séquard comparing the characteristics of (testosterone-deficient) eunuchs to ‘decrepit’ elderly men, and prescribing testicular organotherapy to restore the deficit of old age. Indeed testosterone therapy for the elderly has enjoyed something of a renaissance as part of the current wave of investigation both within and outside orthodox medicine.

Anti ageing promoters and longevity clinics are more likely to retain this characterisation of ageing as a time of hormonal decline focusing on the potential negative symptoms of declining appearance, sexual functioning and 'vitality' as the deficits to be avoided through hormone therapy (usually augmented with a large component of vitamin and nutritional supplements, and sometimes exercise regimes as well). This type of lifestyle benefits from hormone therapy, which are now decried by orthodox practitioners as frivolous and characterised as enhancement by bioethicists, bear a remarkable similarity to the mainstream medical promotion of HRT for women in the 1960s and 70s. By contrast, informants wishing to present the potential applications of growth hormone in elderly patients employ new pathological categorisations such as 'frailty' where the deficit needed to create entitlement and justification for treatment is linked to measurable (hard) physical characteristics such as muscle and bone strength, and through this to negative social consequences such as lack of mobility, social isolation etc which combine to form a model of medical need. Importantly concepts such as frailty separate out pathological old age from the process of normal ageing avoiding the charge of medicalising an entire stage of life that can be levelled at anti-ageing clinics. The case of adult growth hormone deficiency demonstrates the importance of establishing limiting boundaries as part of a novel diagnostic

category in stabilising the concept and allowing it to become accepted and entrenched in medical practice.

Informants justified their own interest in hormone use in the elderly and adult GHD as the investigation of an area of uncertainty- a legitimate foundation for a scientific enterprise medical or otherwise. In keeping with the diagnostic repertoire, which embodies instrumental rationality as one source of the physicians' authority, they employed techniques of legitimisation deriving from the orthodox view of scientific medical practice. Patients were selected on the grounds of appropriate diagnostic criteria; objective, measurable abnormalities in physical and biochemical characteristics which can, if necessary be linked to broader social needs, and the appropriate evaluation of therapy through the prescribed scientific procedure for evidence production, double-blind, placebo-controlled, clinical trials. In accord with the broader conception of medical authority discussed in Chapter 6, informants also emphasised their moral conduct in the treatment of patients by mentioning their commitment to placing patient wellbeing before financial concerns, having the appropriate professional competence to carry out procedures at an acceptable standard of safety, and belonging to an appropriate professional organisation as a guarantor of this conduct. By contrast, the work of anti-ageing practitioners was described as unscientific, and thus inappropriate, through a reversal of these characteristics. Informants described them as financially driven, unconcerned with patient

safety, fanciful and frivolous, and above all acting without a rational decision making body of experimental evidence to back up their claims. Particularly scathing criticism was reserved for the 'appropriation' of legitimate medical studies, particularly Rudman's first paper to create a 'false' sense of legitimacy. This same approach has, in essence, been used the since endocrinologists of the early twentieth century were trying to demonstrate the superiority and validity of their work over the practices of organotherapy.

From an STS perspective, the deployment of growth hormone as an anti-ageing technology has been shaped by resistance from different actors within the existing networks for the production of hormone drugs. Endocrine researchers attempting to legitimise the technology through clinical trials etc have been hampered by lack of funding from state or industrial sources due to competition from novel technological approaches and their supporters (regenerative medicine) or because of negative associations with previous failed attempts to produce anti-ageing technologies. There are also concerns that the existing regulatory system may not be structured to favourably assess a therapeutic aimed at treating ageing, although other hormonal technologies, notably the contraceptive pill, have successfully been approved as interventions in normal biological processes. The whole idea of restorative hormone therapy in the later stages of life is facing a serious challenge to its credibility after the widely-publicised findings of the women's health initiative (WHI)

and heart and oestrogen/ progesterone replacement study (HERS) trials (Krieger et al, 2005). In 2002 the WHI was curtailed three years before its intended completion date, on the grounds that the data collected so far demonstrated that the women receiving hormone therapy had a significantly raised risk of breast and ovarian cancer and heart disease compared to the group receiving the placebo treatment. These findings were widely reported in medical and lay press as a 'shocking' revelation about the cancer risk of hormone therapy and in their wake a sharp decrease in use of HRT therapy has been noted in the US, UK and elsewhere (Morley, 2004b; Krieger et al, 2005; Clarke & Glaser, 2007). Some authors have attributed a perceived lack of institutional support for further studies of testosterone or growth hormone in old age to the impact of the WHI data (Asthana et al). This risk perception most likely applies to both state and industrial actors making significant support on the necessary scale extremely unlikely for new investigations of growth hormone or testosterone therapy in the elderly.

Hormonal anti-ageing technologies have not disappeared entirely but instead have been deployed through a novel and unorthodox network of private clinics. This network is deemed controversial and condemned by institutions of orthodox medicine because it challenges their authority and control over the provision of healthcare. Nonetheless this network operates because of rules and regulations that act to the benefit of orthodox medicine in other

situations. The off-label prescribing of growth hormone that allows anti-ageing clinics to operate, remains common among paediatric endocrinologists treating children who they deem are 'sufficiently short' where ISS is not an approved indication or when dealing with other rarer groups of short statured conditions such as Noonan syndrome (a genetic syndrome, comparable to Turners syndrome, producing childhood short stature along with other more detrimental developmental abnormalities) that have not received specific regulatory approval. Rejuvenation clinics operate through off-label prescribing and the lack of regulation of dietary supplements, but they exist because people are willing to pay for the anti-ageing therapies they offer, either driven by renewed cultural anxieties about old age or following a logic of self-maintenance and self-care directed at the level of the bodily self. This suggests that processes of medicalisation or the desire for 'enhancement' drugs can exist and act not only with the backing of the medical establishment and the pharmaceutical industry, but also in the face of opposition or indifference from them.

Notes

[62] The term "prolongevity" was introduced by Gruman in 1955 to denote 'the belief that it is possible and desirable to extend significantly the length of life by human action' (Gruman, 1966 p3). For the purposes of this work it is suitable to employ this term as being synonymous with the enterprises of anti-ageing, since almost all prolongevitist thought aimed to increase the healthy duration of human life necessitating a reversal of the debilitating effects of growing old.

[63] Although as Gruman notes, the original iatrochemists whilst committed to developing a chemical understanding of the human body were not 'above speculating about an elixir of youth' (Gruman, 1966 p67).

[64] Niehan's therapy was based on the injection of foetal animal cells, mainly derived from sheep, in the hope that they being less developed would not be rejected and confer their youthful properties to the recipient. It is more likely that such cells would be destroyed by the host's immune system immediately on administration (Hamilton, 1986).

[65] There is also the issue that there were, and are, very few standards for 'normal' body composition in children and adolescent populations with which to make a meaningful comparison. A review of hGH therapy in children and adults in 2001 found that '[t]here are very few data concerning the impact of GH status on parameters other than growth, such as body composition, BMD [Bone Mineral Density], and lipids during childhood' (Drake, Howell, Monson & Shalet, 2001 p443) suggesting the situation has not changed much even with the advent of synthetic hormone.

[66] Formerly Kabi Vitrum, and as of 2003 part of Pfizer.

[67] Arguably the roots of this budding anti-ageing movement can be traced to the 1980s with the publication of popular but critically-denounced books like "Life Extension: A practical scientific approach" (Pearson & Shaw, 1982) which promoted large amounts of vitamins and other nutritional supplements to increase life span and boost health, and the growing underground culture of growth hormone and steroid use in sports (Barrett, 1983; Sonksen, 2001).

[68] The use of Rudman's data as the basis for anti-ageing therapy with growth hormone has become so widespread that in 2003 the New England Journal of Medicine issued an editorial warning about fraudulent promotions trading on the article and took the unusual step of providing all online viewers of the article with links to editorials discussing the interpretation of the data (Drazen, 2003, Perls, 2004). The editorial noted with concern that the online version of the Rudman article 'receives as many "hits" in a week as other 1990 articles do in a year' (Drazen, 2003 p777).

[69] Securing financing for further research is perhaps more important than ever, especially as the 'biotech bubble' around ageing has to some extent evaporated with Geron opting to concentrate on cancer research and other companies experiencing financial difficulties, not to mention the public controversy over embryonic stem cells and therapeutic cloning which has dominated the US purview of such science (Hall, 2003b).

[70] This remains accepted despite the uncertainty and controversy that surrounds the reliability of biochemical assays in the diagnosis of partial GH deficiency (Chapters 5 & 6).

[71] The 2000 position statement from the UK-based Society for Endocrinology on the use of GH in adult growth hormone deficient patients recommended that decreased QoL (in addition to a low blood GH test) was the main recommended indication for treatment, but that patients failing to show improved QoL after 6 months of therapy (after dose adjustment) should be withdrawn from treatment (Society for Endocrinology, 2000).

CHAPTER 8: Conclusions

Introduction

This concluding chapter returns to the central investigative aim of the project: what can a detailed exploration of the case of human growth hormone reveal about the issue of human biomedical enhancement? In Chapter 2 a Foucauldian, constructionist view of medicine and the body was used to describe how the phenomenon of enhancement technologies could be understood as part of an ongoing process of medicalisation. Following Foucault, the success of modern, scientific medicine was linked to its ability to categorise and regulate individual bodies and the way this could be employed to serve the biopolitical interests of states in governing their populations. As Rabinow & Rose (2006) have noted, this Foucauldian analysis of the eighteenth and nineteenth century take-off in medicine cannot simply be projected forward to explain twenty-first century phenomena, because in the intervening space 'significant mutations' have occurred in the forms of welfare, security, health and hygiene. In particular, they observe:

> [N]ew modes of individualisation and conceptions of autonomy with their associated rights to health, life, liberty and the pursuit of a form of happiness that is increasingly understood in corporeal and vital terms (Rabinow & Rose, 2006 p204).

The conceptual framing of this project reviewed recent sociological arguments that the contemporary biopolitical agenda is being shaped by an increasing commitment to a (neo-liberal) commercial,

consumerist model of medical service provision, and the growing cultural import of the idea of a biological basis for many aspects of behaviour. The use of medical technologies in 'lifestyle' or enhancing applications arises as individuals increasingly view their problems as biological and are encouraged to turn to the consumption of medicine in order to find solutions, giving rise to expanded use of drugs such as anti-depressants, Ritalin or human growth hormone to control socially undesirable aspects of embodiment. This argument was taken as a potential model to be investigated through this study of growth hormone rather than as an unproblematic explanation for the phenomenon of biomedical enhancement.

The enhancement / therapy dichotomy that forms the bioethical response to much of this expanded drug use is also inherently a normative issue: at the heart of the debate are attempts to define who should, and should not, be entitled to receive medical treatment. Enhancements are ethically suspect specifically *because* they involve treating people who are 'normal' and thus transgress the boundary of appropriate practice. In the debates over human growth hormone, concerns about its potential enhancement uses centre on the contention that idiopathic short stature or ageing constitute normal aspects of human embodiment and therefore not only should they not confer entitlement to medicine, but to apply medical technologies in these cases may itself be harmful to human dignity. The counter claims made by those in favour of such treatments

attempt to legitimise growth hormone use in ISS or in ageing as addressing an otherwise unmet clinical need and thus as something both suitable for, and worthy of, medical intervention.

These two core issues of medicalisation and entitlement were identified as key to understanding the phenomenon of enhancement technologies. The issues are not wholly separate: in order for any phenomenon to be successfully brought under medical authority a consensus must be reached that it is proper and deserved for people affected by that phenomenon to receive medical treatment. To investigate the mechanisms by which medicalisation might occur and entitlement might be constructed in the specific case of growth hormone, the analytical tools of STS were employed. From an STS perspective, the deployment of a new drug requires the accompanying definition of the disease that the drug is intended to treat. The study of how growth hormone has been deployed as a medical technology is thus also the study of how some aspects of stature and adult GH-related conditions have been constructed as medical conditions and how claims of entitlement to therapy have been made to legitimise these interventions. The aim of this technology-focused study are twofold: firstly, following the approach employed by recent critical drug histories such as Oudshoorn (1994), and Goodman & Walsh (2001), the investigation has dealt with the historical shaping of the indications for growth hormone by factors such as prescientific ideas about growth and age, networks of pharmaceutical production and delivery, and the changing landscape

of healthcare provision. The second goal has been to show how this historical development of the drug influences the contours and content of contemporary professional discourse about growth hormone - that is, to demonstrate the impact of the past on the present, especially in regards to the arguments being made for and against the legitimacy of particular, contested applications such as ISS.

The previous four chapters have set out the origins and social shaping of the major indications for growth hormone across three key eras; the beginnings of endocrinology in the late nineteenth century, the era of pituitary-derived growth hormone begun in 1958, and the current era of recombinant DNA derived synthetic growth hormone. This chapter will begin by reviewing the most significant groups, ideas, material resources and networks involved in shaping the development of human growth hormone. The purpose is to highlight the crucial elements that have supported those successful applications of growth hormone, such as the childhood and adult deficiency syndromes, and whose absence has undermined the viability of those indications currently contested as enhancements, primarily idiopathic short stature and anti-ageing.

The success or failure of indications can be linked to the context in which they operate and the functions diagnostic definitions must serve in presenting a sense of entitlement and facilitating the

medicalisation of phenomena as diseases. From this, some ideas about the current rejection by orthodox medicine of growth hormone as an anti-ageing medicine and the contrasting US/UK positions over idiopathic short stature will be proffered. Finally, these findings will be used to reflect on this project's conception of enhancement as medicalisation (in a given biopolitical environment) and on the use of human enhancement as a category for the regulation of pharmaceuticals.

Creating the Hormonal Model of the Body

The phenomenon of organotherapy marked the first deployment of hormones as a medical technology. Although growth hormone was not part of the first wave of hormone drugs, the early history of the technology had an important impact on the later development of GH because of the ideas, systems and practices established during this period. Novel technologies are often at their most malleable in the early stages of their development. Multiple and often competing versions of a particular technology can appear. This can be seen in the case of hormone drugs where endocrinology became embroiled in the wider struggle, between popular, or irregular, practitioners and advocates of scientific medicine, for professional control over the domain of healthcare provision. As different technological options compete they are shaped by the strategies adopted to differentiate one from another and by the resources available to the producers of each particular technology. If one version of the technology emerges

as the dominant form, the model of ‘problem and solution’ that it embodies and the systems of manufacture and distribution that support it become entrenched and act as a niche, shaping the future development of similar or related technologies (Koch & Stemmerding, 1994; MacKenzie & Wajcman, 1999).

Many organotherapy practitioners embraced the new technology as the potential solution to any and all medical complaints that were not amenable to existing therapies and often manufactured and dispensed their own organ extracts as small scale local enterprises. Organ extracts were recommended as much on the basis of perceived character of the organs and the chemicals they produced, as on any underlying notion of disease aetiology. Testicular extracts contained the essence of ‘male vitality’ and could thus be applied to restore vigour, strength and sexual ability diminished by age. Preparations containing extracts of multiple organ extracts could remedy virtually all the body’s ills from kidney diseases to ‘nervous disorders’ and enfeeblement, offering a general fortifying effect. In their construction, these therapeutic approaches drew upon (and reconstituted) cultural associations between particular organs of the body and human traits. This model gave the popular version of hormone drugs an early advantage in capturing the market.

Laboratory physiologists, on their way to becoming the first endocrinologists, needed to produce a scientific model of endocrine

disease and endocrine therapy in order to compete with the organotherapy preparations. To do this, they drew on the tried and tested techniques and resources available to nineteenth century laboratory physiology to produce experimental animal models of endocrine diseases. The animal models had a particular endocrine gland surgically removed to produce symptoms of pathology associated with the absence of the internal secretions produced by that gland. Organ extracts, or chemical fractions derived from them, could then be tested for their ability to restore normal activity in the experimental animals. Here the co-construction of endocrine disease and endocrine therapy can be seen, emerging from this intersection between the new knowledge of the body's chemical secretions and the existing instrumental practices of physiology. The first experimental (and therefore scientific) model for hormonal control of the body incorporated a strong association between illness (the basis of entitlement) and hormonal deficit (the literal absence of the entire gland), and between hormone replacement and the therapeutic restoration of normal functioning. The concept of replacement therapy, implicit in Brown-Séquard's original idea about testicular extracts restoring the vitality lost with age, was codified as part of the scientific rationale for hormone therapy and remained an important cognitive and intellectual resource for the construction of future diagnostic categories to describe endocrine pathologies.

With the establishment of this therapeutic model, academic endocrinologists were able to connect with ‘ethical’ industrial partners for the mass production and dissemination of hormonal drugs. Although the academic research needed to provide scientific legitimacy to hormone drugs was more resource intensive than irregular ‘home remedy’ style organotherapy preparations, the linkage of academic institutions to large pharmaceutical companies offered a much greater scale of manufacturing. This network produced notable successes in insulin, the estrogens and cortisone. The introduction of state interest, in the form of compulsory regulatory oversight for new drugs, reinforced the emergent scientific network of hormone drug research and production as smaller organotherapy companies could not meet the scientific standards required to gain regulatory approval and were ultimately forced out of the market (Bell, 1986).

Molecules of Character

The rise of scientific medicine lead to the rejection of the somewhat vague and generalised disease entities of organotherapy in favour of clearly defined, organ-specific diagnoses and detection of underlying biological pathologies. Notably ageing, itself the spark for much of the investigation of internal secretions, was one such overly generalised target for therapeutic intervention to be rejected by scientific medicine. Separate and specific pathologies of old age were separated from ‘normal’ ageing and the endocrine investigation

of ageing was largely abandoned, with one important exception. An anti-ageing aspect persisted in the use of oestrogen (and later progesterone) to treat menopausal and post-menopausal women. The restorative 'feminine forever' ideal was explicitly linked to the hormone deficit and replacement model and developed and nurtured away from mainstream endocrinology by the distinct professional interests of gynaecologists. However, cultural notions about particular characteristics such as masculinity, femininity and vitality were not wholly abandoned by the endocrinologists of the early twentieth century. Ideas about the proper social roles of men and women were incorporated into the study of the ovaries and testis and the hormones they produced (Banks, 2002; Oudshoorn, 1994). The exemplar of deficit and replacement became enshrined in the scientific model of the hormonal body but persistence of this idea of hormones as 'molecules of character' alongside the notion of therapy as replacement can also be seen even in the latter half of the twentieth century. Medical journal articles recommending oestrogen to alleviate the delayed or limited sexual maturation of girls with Turner syndrome could still rationalise the intervention on the grounds that it 'promotes their feminine identity' (Levine, 1978 p1097).

Growth may seem like a less obviously cultural entity compared to the idea of gender roles but the 'character' and social connotations of growth shaped the later development of growth hormone in particular

ways as much as ideas about femininity shaped the application of the estrogens. Over thirty years before it was isolated, Cushing speculated in *The Pituitary Body and Its Disorders* (1912) that the pituitary gland produced a 'hormone of growth' (Tattersall, 1996). Despite the broad characterisation of a wide range of metabolic attributes evident in the programme of the 1954 First International Symposium of Growth Hormone[72], 'growth hormone' is what the newly isolated pituitary chemical became, its function, indeed its purpose, (pre)indicated in its naming. The social aspect of growth, especially the cultural value of height (as the outcome of successful growth) remained oblique in the early literature on growth hormone but it nonetheless constituted, and continues to constitute, an important component in the therapeutic rationale for the major use of the hormone, as will be discussed below.

Deploying Growth Hormone as a New Technology: GH Deficiency in the 1960s

The isolation of human growth hormone in 1956-8 did not induce the medical surveillance of growth and stature (public health had already done this) but it did provide a considerable spur to the drive by paediatric endocrinologists to treat abnormal stature. As such, this first deployment of growth hormone is a crucial step in the medicalisation of stature because it represents the creation, within orthodox medicine, of a legitimate entitlement to the first truly viable

hormone therapy to promote growth and increase the height of short children.

The most significant factor shaping the development of growth hormone in this era was the limited supply of pituitary glands. Rationing was therefore the dominant characteristic of the pituitary era of human growth hormone.

This situation directly affected the development of growth hormone in a number of important ways. The limitations of supply affected the construction of diagnostic categories that accompanied the first therapeutic mobilisation of the drug. Equally significantly, the source of human pituitary glands drastically shifted pituitary GH from the developmental path set out with previous successful hormones such as insulin and oestrogen. Pituitary glands were collected from hospitals, not slaughterhouses, meaning that the supply of glands was less readily accessible to commercial interests.

Instead, at least in the UK and US, the harvesting and processing of glands and the distribution of the resulting hormone extract was entirely carried out by health professionals on a non-commercial basis. These networks of supply were essentially state-funded (either through the NHS or NIH) and since only nominal payments were made for the collection process (in the US pathologists were paid a token sum of around $2 per pituitary) growth hormone was a relatively low cost technology. Unlike commercially produced hormone drugs GH did not need to be sold at a profit to national or

local healthcare organisations. As an outcome of this arrangement, growth hormone was given as an experimental therapy. This meant that it was effectively being used off-label in a series of extended trials, a situation that continued for much of the 1960s and 1970s. Growth hormone was not the only height-altering therapy used in this way – oestrogen treatment to reduce the stature of tall girls was similarly conducted in this way, although that hormone still had to be bought at a cost from industrial manufacturers. As experimental therapy, GH treatment was not subject to regulatory oversight. This meant that academic endocrinologists were in sole charge of determining who was eligible for treatment, and that these criteria did not have to be fixed in accordance with a regulatory agency-approved definition of disease, but were flexible and could be adjusted to adapt to the fluctuating supplies of pituitary glands and the preferences of particular research groups.

The majority of endocrinologists appeared to have been unaware of the intricacies of the statistical model of growth or the work being carried out at that time in the European and UK longitudinal growth studies. Accordingly, they devised their own methods of measuring normality and abnormality in the spectrum that they were most familiar with - the biochemical body of endocrinology. The radio immune assay (RIA) and the insulin tolerance test (ITT) became the first set of standards for endocrine assessment of growth and the standard was, under pressure of limited resources, essentially a

binary one: patients either had growth hormone levels below the cut-off point upon testing and were GH deficient, or they tested above the cut-off and were not deficient. In the circumstances, the extreme shortage of pituitary glands favoured a more, not less, restrictive approach to defining illness and entitlement to therapy. The peculiar institutional environment in the UK led to the Medical Research Council appointing a non-endocrinologist, in Tanner, to its Growth Hormone Committee and the subsequent reintroduction and updating of statistical measures of growth.

The statistical assessment of growth provided a second index of measurement that could be used to identify the greatest need (i.e. those most biochemically *and* statistically below average) and was useful in the circumstances where there was so little GH that not even all children meeting the criteria for biochemical deficiency could be guaranteed treatment. The success of GH deficiency as a diagnostic entity lies in the successful combination, not only of two indices of measurement, but of two models of the body, two different logics of normality and abnormality. Entitlement to therapy is inherently linked to deficit from an expected norm: GH deficient children do not 'make enough' hormone, and very short children have not fulfilled their potential for growth compared to their peers or their expected parental inheritance of height. At the bottom of the biochemical and physical-statistical scales, the phenotypic symptom of failure to grow can be correlated with the absence of an agent that

promotes growth, giving considerable explanatory power to this diagnostic category. The diagnosis also provided a seemingly objective and value-neutral means to ration the use of pituitary hormone to a limited patient population, retaining scientific medical authority over its application. This diagnostic success in turn stabilised the technology of growth hormone in the emergent networks that were developed to deploy (and ration) the hormone.

Stable and Contested Indications in the Biosynthetic Era

The introduction of biosynthetic growth hormone radically reshaped the dynamics of growth hormone use. Propelled by the incidence of CJD and the necessity of abandoning pituitary-derived hormone, GH use shifted rapidly from a non-commercial, limited scale, physician-run project to being a commercial enterprise based around an expensive product capable of being produced in large amounts and subject to national and international standards of safety, efficacy and financial regulation. The advent of recombinant DNA-derived hormone did not affect the legitimacy of severe GHD as a diagnostic category but it did undermine the position of the diagnosis as the *de facto* boundary of GH use. The availability of biosynthetic GH opened up the possibility of exploring the broader uses of the hormone, as a growth-promoting agent and in adult applications, which had been envisaged but unfulfilled during the pituitary era. It is in this period after 1985 that the scale and scope of growth hormone use begin to expand, and it from this point where GH use becomes contested.

Examination of the construction of these new categories for deploying growth hormone can reveal the core requirements supporting successful indications and detect the weaknesses in contested applications.

Following the introduction of recombinant GH, the biochemical model of hormone deficit, as measured by the ITT and blood assay technique, formed the basis for two potential new diagnostic entities in adults: an adult syndrome of growth hormone deficiency and the hormonal decline in old age. The former condition, adult growth hormone deficiency, posited that adults, as well as children, could be deficient in growth hormone, whether as a result of damage to the pituitary gland or as the continuation of the childhood condition. Obviously, adults no longer undergo linear growth so the statistical measure of such symptoms no longer applies. In place of stature or growth rate, a series of physical abnormalities in body composition such as reduced muscle strength and increased abdominal fat deposits were presented as the phenotypical manifestations of the deficit. And yet, even though the adult GH deficiency classification was based on essentially the same biochemical criteria as the unchallenged diagnostic category of severe childhood GHD, it was considered a contentious prospect.

A number of contributory factors were suggested in Chapter 7, but of particular importance was the reticence of healthcare providers and

sceptics in the medical establishment to accept the necessity for treatment on this description alone. Hormone deficiency may carry an intrinsic logic of replacement, but it appears that this alone is not sufficient to constitute entitlement to therapy. The manifestations of illness must carry sufficient moral or cultural weight to warrant treatment. In the case of adult GHD appropriate 'weight' required a third measure of abnormality and deficit to stabilise the indication and this came from the other, subjective symptoms reported by patients in clinical encounters. The depression and lack of energy associated with adult GH deficiency, summarised as quality of life, and quantified by psychological QoL questionnaires, was the key to creating a workable diagnostic category. Once this category was established it could then be employed in clinical trials to generate the scientific evidence of safety and efficacy on which medical decisions are ostensibly made.

The comparable cultural 'negative' associated with short stature is not readily visible in the construction of growth hormone deficiency as a category of illness during the pituitary era, partly because quality of life aspects of therapy were not routinely included in the official, published rationales for therapy at this time, even if they were a factor in practice, and partly because the deleterious consequences of exceptional short stature may have been taken as self-evident both by physicians and patients (or their parents). The expansion of growth hormone use beyond the classic deficiency indication has, as

with the extension of GH use to adults, raised questions about entitlement and so made discussion of this social component of deficit more visible. In Chapter 6, many informants expressed the belief that there are distinct social and psychological disadvantages to being short statured, either during childhood or later in adult life, and that this is a major justification for GH therapy. Surveys have suggested that, at least amongst US paediatric endocrinologists, this view is commonplace (Cuttler et al, 1996). Such a perception is not limited to physicians, but also forms a key part of the perceived need for therapy among patient advocacy and support groups for families of short statured children, and by the parents of short-stature patients (Finkelstein et al, 1999; Visser-van Balen et al, 2005). Hall (2006) has described a distinct body of work across different disciplines from psychology to economics that suggests shortness is socially disadvantageous, especially to men and boys. Importantly this idea of psychosocial deficit associated with short stature applies not only to children meeting the diagnostic criteria for classic GH deficiency but also those with Turner syndrome, small-for-gestational age births and all the other categories of abnormal short stature including ISS.

As the availability of biosynthetic hormone allowed the expansion of GH use beyond the binary diagnostic limits of the pituitary era it was the expansion of treatment up the scale of biochemical deficit (i.e. away from the cut off points defining classical deficiency) and towards more biochemically normal children that was the most

controversial aspect. Expansion of the remit of growth therapy to non-hormone deficient conditions such as Turner and Prader-Willi syndromes or renal insufficiency did not require the creation or redefinition of any new diagnostic categories. Nor was the short stature and failure to grow associated with these conditions a previously unremarked-upon feature of the conditions. The physical symptoms of short stature and the associated psychosocial deficit that this carries were essentially transferable from the GHD indication. Although the move away from the logic of hormone replacement was the cause of some concern among the medical community, alternative underlying causal mechanisms- in the form of genetic abnormalities or renal disease were available for these conditions. In these already-stable categories the process of scientific assessment of GH therapy was then a matter of carrying out properly controlled trials and evaluating the results. Empiricist and contingent accounts were produced in the literature concerning the interpretation of particular trials, but the practical application of GH therapy in these conditions by paediatric endocrinologists was already underway before regulatory approval was granted. Approval in this case can be seen as a retrospective endorsement of existing practice.

By contrast the treatment of less hormone deficient children, taken to its logical extreme in the category of idiopathic short stature prioritises the treatment of the psychological and physical symptoms

(also transferable from GHD) while moving further away from any acknowledged biological cause; there is neither a biochemical nor a genetic deficit detectable in the condition. That this is problematic can be seen in informants description of ISS as a heterogeneous, non-scientific category, a failure of diagnosis, and explains the desire to find a new category of measurement - at the genetic or cellular level - which would allow the scientific separation of ISS children on new grounds of normality and abnormality. In the absence of any such development, ISS remains controversial and contested. This is both in addition to, and prior to, the often poorly regarded results for height gain in this group (Freemark, 2004; Wit & Rekers-Mombarg, 2002). This finding is echoed by sociological research on other contested medical conditions. Investigations of chronic fatigue syndrome (CFS), fibromyalgia, multiple chemical sensitivity (MUS) and Gulf War syndrome have found that illnesses that present as sets of symptoms, but where no clear underlying causal mechanism can be found are often treated with scepticism by medical professionals (Åsbring & Närvänen, 2003; Barker, 2005; Zavestoski et al, 2004). The absence of a biological aetiology for an illness undermines patient's claims to occupy the sick role and the entitlement to medical treatment that it entails. For Åsbring & Närvänen (2003) the subjectivity of reported symptoms and the uncertainty they raise clashed with the scientific medical ideal of assessment based on objective measurement, relegating these conditions to a lower status that established diseases. There is an

obvious connection between this lack of a mechanistic explanation and the claim that ISS is ‘not really a disease’ made by many of its critics.

In the case of hormonal anti-ageing, no single reason can be given for the failure of this technological option to become successfully entrenched in the practices of orthodox medicine. The prospective diagnostic category shared a biological logic, in the form of hormone deficiency and set of physical symptoms (muscle weakness etc) with adult GHD. There was also a narrative of patient need, in the prospect of physical decline and debility associated with ageing, leading to dependence or social isolation. However, unlike short stature there was no existing legitimised anti-ageing application within endocrinology to base an expansion upon. Even adult GHD could be related to the existing replacement therapy given to patients deficient in multiple pituitary hormones, although it is worth remembering that the latter indication was only stabilised by the introduction of formal quality of life assessment which anti-ageing lacks.

There is also the factor that growth hormone remains, in character, the master molecule for growth not age or metabolic balance. It is certainly more obvious to use GH as an agent to increase height than for other purpose, and, while resistance can be overcome by producing a convincing narrative of need in the form of physical and psychological deficits it probably requires a greater investment to do so (note the very

high number of clinical trials carried out for adult GHD). According to many endocrinologists, this support, whether from industry or state funding, was not forthcoming. One possible deterrent cited was the potential cost of carrying out the appropriate trials in an elderly population. Another factor is the increased concern about the risk/benefit balance of such interventions, stemming in particular from the Women's Health Initiative trial findings that hormone treatment in old age can induce cancer. Indeed there is some irony in the fact that the only age-associated hormone therapy to achieve widespread application, oestrogen and progesterone HRT for menopausal and post-menopausal women, may have ultimately provided one of the major disincentives for a resurgence of scientific interest in more general hormone use in the aged population.

As with GH in short stature, treatment outside the approved indications followed the initial research. Unlike the off-label use of GH in short children, however, this off-label use was carried out by non-endocrinologists and operated outside the standard protocols for experimental therapy. The proper conduct of scientific medicine was not seen to be followed and so this anti-ageing practice was categorised as pseudoscientific and illegitimate, even if its aims could, in theory, be reconciled with orthodox medicine. That anti-ageing exists as an 'outlaw' medical practice stems from the individualist, consumer-driven aspect of US medicine, the discretionary authority of physicians to prescribe drugs outside the bounds of regulatory approval, and the

cultural idea, prevalent in some quarters (for example, in transhumanism) that extension of healthy life by (bio)technological means is a desirable goal. The nascent category of frailty (as a syndrome rather than a general term) was not yet in use in the 1990s when the use of GH as an anti-ageing agent was first brought to public and medical attention, and its current development can be seen as an attempt to rescue some form of GH use in the elderly as a valid area of scientific investigation.

Key Components in the Success or Failure of Indications

The case of growth hormone illustrates that medicalisation is neither a simple nor an automatic process. In the conventional view of science and scientific medicine (the empiricist account) the success of a particular pharmaceutical is a matter of employing the correct scientific practice (the experiment, the randomised control trial) to produce objective evidence of efficacy and safety on which a rational assessment of its merit can be made. From an STS perspective however, a drug and its application, the disease for which it is intended as a treatment, are co-constructed. For a drug to 'succeed', to become established and entrenched in practice, the diagnostic category that defines the disease must be accepted *before* the assessment of clinical trial and experimental data can be completed. The analysis of the development of growth hormone in its different applications suggests that successful diagnostic categories must fulfil three crucial requirements in order to be accepted:

- A set of phenotypical symptoms that mark the physical presence of the illness
- Allocation of an underlying biological causal mechanism to explain the problem
- Recognition of a debilitating or negative psychosocial element to the condition

The importance and effect of these factors can be understood by considering the function of diagnostic categories. The utility of diagnostic categories, as the conceptual and instrumental definitions of disease entities, lies in making decisions about who is entitled to medical care and who is not. Medicine, after all, is a dividing practice and must separate out the sick from the healthy, those in need from those whose claims are insufficient, and those entitled to receive a share of limited medical resources from those who are not. This occurs in two related, but distinct, ways: physicians employ diagnostic tools to evaluate individual patients and make decisions about who requires treatment and what form that treatment should take. Diagnostic categories are also used across health networks to make decisions about regulation of medicines and allocation of healthcare resources at the level of populations and states. Consequently the stability and acceptance of diagnostic categories depends on their suitability to perform *both* the tasks of assessing individual patient need and rationing medical resources in an acceptable and objective-seeming manner.

Rationing and the Biological Basis of Disease

The importance of establishing a biological causal mechanism for endocrine disorders can be traced back to the beginning of scientific endocrinology itself. The attribution of an underlying pathology that can only be detected through careful instrumental measurement and interpretation by a trained clinician is the basis of the claims-making authority of scientific medicine. The specific linking of cause and symptoms was a major differentiating factor in separating scientific endocrine disease categories from the general 'cure-all' approach of organotherapy practitioners. This type of measurement, because of its seeming observer-independent neutrality and objectivity, is the basis of the rational, scientific allocation of medical resources, and of medicine as a dividing practice. The need to ration medicines is integral to the success of any diagnostic category. The success of severe growth hormone deficiency as a diagnostic category was that it offered a means to objectively ration the limited supplies of pituitary hormone by employing linked biochemical and physical indices of measurement. Its utility is evident in that it has become entrenched in paediatric endocrine practice and retains a virtually uncontested legitimacy as an indication through to the present.

Contemporary use of biosynthetic growth hormone is firmly ensconced in the wider networks of healthcare including regulation and financial oversight. The focus of rationing has shifted from the

allocation of scarce material resources to cost containment (Schwartz, Soumerai & Avorn, 1989). Categories of non-GH deficient short stature such as Turner and Prader-Willi syndromes are limited by their relatively low incidence in the population, and thus do not pose a significant (financial) burden on healthcare resources. By contrast, ISS with no biological basis to separate out the patients from the wider 'normal' population, places a whole segment of the population, defined by statistics alone, as having potential entitlement to therapy. Anti-ageing too, despite having an attributed underlying cause of hormone deficit places an entire stage of human experience as a disease state carrying entitlement to therapy. In this latter case, the posited biological mechanism fails to act to separate out a distinct patient population from the wider category of 'the elderly'. Treating all short children or all elderly people would be a massive and untenable commitment for any healthcare provision system, and this is one reason why these indications for GH use remain contested. Additionally, growth hormone, although considered a relatively low risk drug, is not without potentially iatrogenic side effects and any large scale, practically unconstrained treatment raises the prospect that unacceptable levels of adverse reactions will result. The fact that some treatment for anti-ageing and idiopathic short stature persists reveals that biological abnormalities alone do not create the sense of entitlement and rationale for therapy.

Physical and Psychosocial Components of Entitlement

Physical symptoms, such as short stature or the physical decline associated with ageing are often the initial cause of an individual's referral to medical professional. These, along with the psychosocial aspects of an illness provide the visible 'face' of an illness that can be understood by physicians, patients and members of the public alike. If short stature was not both physically self-evident and considered a socially undesirable trait there would be no basis upon which to initiate a doctor-patient encounter about height-altering hormone therapy. Where these symptoms are less evidently abnormal, as with the manifestations of adult growth hormone deficiency, it can lead to the condition being overlooked or ignored unless further investigation is undertaken. Informants' resistance, as reported in Chapter 6, to the idea of formal psychosocial or quality of life testing as part of the diagnostic definition in short statured conditions, suggests that this type of evaluation is not considered a suitable part of the objective, scientific measurement constituting formal diagnosis. Similarly, quality of life testing in adult growth hormone deficiency began essentially as afterthought for the original European researchers who preferred to concentrate on 'hard' physical and biochemical indices and only became incorporated into the final diagnostic terminology because of the demands of healthcare finance.

Nevertheless the (psycho)social aspect of treating short stature does form a significant part of the rationale for therapy even if it is not

included in the technical appraisal of the condition. Medical authority, as argued in Chapters 6 and 7, comprises more than the scientific, it also incorporates physicians' competence to make moral assessments of need and the duty to alleviate suffering where it is found. There is evidence that this type of cultural valuation is not unique to hormone therapies. Edwards (2006) argues that the supposed social consequences of physical or behavioural abnormalities form a significant part of the rationale for medical intervention in other fields. Discussing the practice of surgical intervention in cases of childhood facial defects and ambiguous genitalia, the restoration of normality is seen as a requirement for successful social and psychological development, for self-esteem and wellbeing, that justifies medical intervention:'[t]he need to reinforce self esteem or confidence is presented as a moral trump (Frank, 2006). As with GH therapy for childhood short stature, the psychosocial benefits of surgery for children with ambiguous genitalia or facial deformities tend to be assumed by physicians, whether surgeons or endocrinologists, rather than verified by psychological testing (Frank, 2006; Marsh, 2006).

The evaluation of the individual patient and his or her situation is carried out by physicians in a discretionary space where their *professional* authority is exercised (Hedgecoe, 2006). In this discretionary space paediatric endocrinologists can exercise their authority to assess which patients meet the informal criteria of

psychosocial need, which children within the different diagnostic categories appear to be at risk of developing a 'thwarted personality' (NAM 3) and are entitled to treatment and which are not (and where, perhaps, the need is parental rather than that of the child). Once again providing an insight to paediatric endocrinologists assessment of matters of stature, Prader & Zachman (1978) discussing the issue of tall stature in girls, observe that the statistical definition of abnormally tall stature as two standard deviations above average, means that in effect fully 2.5% of all normal girls are eligible for oestrogen therapy. They note that the instrumental definition of the condition is only part of the process of determining entitlement to therapy:

> [O]ne may wonder whether as many as 2.5% of all girls wish to be treated. This is obviously not so and, *certainly, nobody would consider such mass treatment* (Prader & Zachman, 1978 p1208 emphasis added).

Rather, the diagnostic criteria were to be supplemented by the practitioners' assessment of the individual patient's case in terms of the emotional and psychological impact of tall stature[73] (Conte & Grumbach, 1978; Prader & Zachman, 1978). The consequences of the heterogeneity of entitlement between the individualising doctor patient interaction and the purely instrumental diagnostic criteria operating at group level play out differently in different health systems, where the financial burden of therapy is allocated in different ways. This suggests an explanation for the differences in

regulatory evaluation of idiopathic short stature in the UK and US and proposes an alternative understanding of how 'enhancement' operates as a concept.

The Impact of Heterogeneous National Healthcare Systems in Producing Idiopathic Short Stature as a Contested Indication

In the US, the availability of healthcare resources is determined by the patients' medical insurance, whether private or a state programme, and is thus an individual more than a collective matter. The majority of insurance schemes will provide financial coverage only for a condition that has received regulatory approval from the FDA. Therefore, if physicians believe some patients with a particular set of symptoms, such as abnormal short stature, have an authentic need for treatment, they have to be assigned to an approved diagnostic category otherwise those patients and their families will be forced to pay for the treatment from personal finances, which is often prohibitively expensive. When a medical technology receives regulatory approval it does so for a specific illnesses, defined in diagnostic terms. The therapy-disease then becomes a standard practice, available to the entire patient population meeting the definition of the diagnostic category. However as demonstrated above with therapy for tall statured girls, physicians may not believe that all patients within the diagnostic set have sufficient need to warrant treatment, but if the condition is approved they cannot avoid the possibility of this 'mass treatment'. By contrast, in the UK

healthcare is free at the point of delivery, so physicians can continue to exercise discretion in selecting patients for off-label treatment without posing a financial burden to individuals and their families and without necessitating regulatory approval for an entire set of symptoms.

Informants from both countries felt that some children were sufficiently short that this aspect of embodiment by itself could be considered functionally or psychologically disabling and so constitute an entitlement to growth boosting therapy with human growth hormone. In the UK this therapy can be carried out off-label in the limited subset of short patients who do not fit a current diagnostic definition for which hGH is approved by the EMEA or NICE without the families of those children having to pay for the therapy and without necessitating the entitlement of all short children to similar treatment. In the US, before the approval of ISS in 2003, this option would not be possible. Physicians and families may agree on the course of GH therapy for a child but financial support was unlikely to come from medical insurance and so the burden would fall on the family. Thus the support of some US endocrinologists for ISS can be explained in that it facilitates their ability to make discretionary decisions about patient entitlement, even though they simultaneously recognise that not all the children falling to that descriptive category are likely to need GH therapy. Conversely, the reticence and opposition of many UK paediatric endocrinologists where formal

approval for ISS is concerned can be understood in the context that such an approval would not benefit their discretionary authority to treat needy patients and only offer the potential for demands for unnecessary use of growth hormone.

The approval of idiopathic short stature in the US has been criticised for 'making short stature a disease' but the regulatory decision should not be considered in isolation from the rest of the network of healthcare provision in which it is embedded. If the only affordable access to healthcare requires having a categorised and defined disease then any social problems that are to be addressed medically must therefore be forced into adopting the title of diseases. Lakoff's (2004) work on anti-depressant use in Argentina has highlighted how a different regulatory environment can produce a contrasting result. During Argentina's hyper recession of 1998-2001 the use of anti-depressants rose considerably. Despite this, the incidence of the diagnostic category of clinical depression did not rise in accordance with prescription rates for anti-depressants because the regulatory culture of Argentina at that time allowed prescription for explicitly 'social' purposes. An increased number of people were experiencing psychological distress because of the period of severe economic hardship and accompanying social instability, creating a problem which in the absence of other solutions, they attempted to address using medicine as a resource. The case of ISS illustrates how the process of regulatory approval currently favoured in Europe and

North America can actually act to further medicalisation. The calculation of entitlement to therapy, and thus what counts as a 'disease' is the result of the intricate and ongoing balancing between addressing need and rationing scarce resources across complex and heterogeneous networks of health.

The disconnect between the two measures of entitlement used in these networks, at the level of the individual doctor patient assessment and at the level of regulatory assessment of pharmaceuticals for specific patient populations, creates a space of uncertainty where the fear of enhancement, as improper practice, arises. It is the concern that parents will put the ideal of a successful 'perfect' child above the child's own wellbeing by forcing them into treatment they neither need nor want; that pharmaceutical companies will boost the use of their drugs by promoting the fear and stigmatisation of abnormality to those who would not otherwise have sought medical assistance; that doctors will prescribe to increase their own revenue or authority, and that medically unnecessary risks will be taken and health resources squandered frivolously. Thus enhancement, like medicalisation is produced within networks of health. To a significant extent the existence of enhancement as a label and a concept has emerged, through the external assessment of medical practice by bioethics, as a manifestation of the concerns raised by uncertainty over entitlement. However bioethical concern over enhancement is in many ways *a proxy* for the economic and

political problems of healthcare finance and resource allocation, and for medical concerns about weighing the risks and benefits of (expensive) therapies.

Reflections on Medicalisation and Enhancement

The traditional formulation of the medicalisation critique asserts that medicalisation occurs when medicine expands its authority to *inappropriately* bring ever more areas of social life under its remit. This suggestion that there is a 'proper' domain of medicine, separate from purely social problems or desires, is a normative position shared by the bioethical dichotomy of therapy and enhancement. The concept of biomedical enhancement raises two related, but distinct, issues: which medical interventions are permissible, and who should be entitled to occupy the sick role and claim medical care. These two questions are often subsumed into the general bioethical discussion as to what the limits of medicine ought to be, where the enhancement / therapy split can be understood as a device for moral rationing, which attempts to apply an external ethical schema, in order to determine the limits of 'neutral' medical technologies. However, while growth hormone, especially in its plentiful, biosynthetic form is a recent phenomenon and its applications are a very modern dilemma, the medicalisation of both growth and ageing as aspects of embodiment has considerably older origins.

Positive cultural associations of strength, morality, and health with tall

stature and corresponding negative evaluations of short stature as indicative of weakness or immorality can be traced back to Roman times, and can be detected as recurring cultural motifs through to the present day (Hall, 2006). Stature, as an aspect of bodily development, becomes a specific problem for the state in the eighteenth and nineteenth centuries, first as a marker of the fitness of military recruits and then through the issue of endemic poor health among child factory workers. Through these social developments, short stature in adults and children came under medical surveillance as a symptom of underlying ill health. Similarly, with the issue of ageing and old age, the conflict between the desire to delay or reverse the process of human ageing (by whatever means) and the sense that it should be accepted has a history dating back to antiquity (Gruman, 1966). In the nineteenth century ageing, on the scale of populations as opposed to a matter of individual circumstances, becomes a particular social problem framed by growing industrialisation and the fear that the elderly as a group would become redundant and a burden to society. The emergent scientific medicine, through the work of Charcot, Nascher and others, investigated the bodily symptoms of ageing, associating it with a process of decline and decay. These circumstances led some within the new medical orthodoxy to believe that the cumulative disorders of old age meant that old age itself was a pathological process, bringing it under medical authority.

Importantly, growth/ stature and ageing became particular social problems, arguably *before* they came under medical jurisdiction, and certainly at a time when their social framing would have had an important constitutive affect in the medical formulation of these phenomena. While these categories were conceived of in medical terms, as the appropriate resource for dealing with problems of the body, the drive to do so cannot be said to lie entirely within medicine. Both growth and ageing became understood as states of vulnerability and being 'at risk': growth because children's development was felt to be delicate and susceptible to disruption if not properly regulated, and old age because the elderly were seen as physically fragile, at risk of disease and unable to work to support themselves (Armstrong, 1995; Haber, 2004). At least part of the cause of 'vulnerability' in these states comes in the context of having to live and work in the urban, industrial world, i.e. being at risk of illness makes them *socially* vulnerable. Taken at the level of populations, these risky aspects of embodiment became biopolitical problems.

This refutes the suggestion there is (a priori) a 'proper' domain of medicine and that medicalisation only occurs when medicine attempts to transgress these boundaries. Rather, the findings of this project support the Foucauldian standpoint that all medical problems are inherently social problems. The medicalisation of a phenomenon can be viewed as a response to a perceived risk and this perception need not arise solely on the part of medical practitioners, but rather is part of

a biopolitical agenda. Medicine's social role is as a resource for both individuals and the state to deal with risks, primarily those with a bodily/embodied component. Medical surveillance formalises and gives visibility to risks in particular ways, while retaining, if sometimes obliquely, the socio-cultural aspects of the problem. Medicalisation then proceeds by co-constructing the problem, and its medical solution as disease and therapy.

This process of medicalisation is neither monolithic nor inflexible. As the biopolitical emphasis has shifted from state macro-management of groups within the population to the micro-management of individuals through self regulation, the framing of problems of embodiment has been reconfigured in line with this shift, as illustrated by the case of growth and stature. The contemporary risks associated with short stature in the developed world have less to do with protecting children from factory labour or ensuring the male population is fit for military service, than the potential emotional vulnerability of short children due to bullying and juvenilisation and the supposed reduction of life prospects for short men. The case of hormonal anti-ageing also demonstrates how medicalisation of an aspect of human embodiment is neither inevitable nor driven by any single interest. Although the pharmaceutical company promotion of biosynthetic growth hormone or the advocacy of anti-ageing groups such as the American Academy for Anti-Ageing Medicine fits, to an extent, the 'disease mongering' or schismogenesis model of medicalisation, the expansion of the markets

for new therapeutic indications is limited by what the systems of healthcare can support. The open-ended possibilities of growth hormone and testosterone therapies for anti-ageing mean these therapeutic options can only be practised off label. As such, they will never be covered by insurance and so access is restricted to those with sufficient personal wealth to pay for treatment. This makes rejuvenation therapy an economically self-limiting option.

This is true not only of the present era but also for the Steinach operations and gland-grafting of the early twentieth century, which were solely the preserve of the wealthy. Medical intervention in ageing has never been a valid prospect for a large-scale population level intervention and so, at the turn of the previous century, non-medical solutions had to be found. This involved the change from poor houses to care homes and the establishment of pension plans and other social security for the non-working elderly population by the early decades of the twentieth century. It is not inconceivable that if social solutions to the current problems of an ageing population are not forthcoming that renewed support will be given to medical solutions for age-related bodily difficulties such as infirmity. Recent interest has been directed at the paradigms of regenerative medicine but, if significant industrial and state support is given to greater medical investigations of ageing phenomena, then growth hormone therapy, very possibly for the indication of frailty, could find itself once again accorded a place within mainstream medicine. Medicalisation is dynamic and varies in

response to changing social conditions.

Like rejuvenation and anti-ageing, idiopathic short stature is contested as an indication because of its uncertain boundaries and the very real concerns about the potential unneeded expenditure of medical resources, unnecessary exposure to iatrogenic risk, and financial burdens that it raises. There is an inherent biopolitical tension between the promotion of health consumption and the need to contain healthcare costs. This is not only true in state-run health systems but also in heterogeneous, market driven networks of healthcare such as the US, where the task of economic restriction falls to HMO's and insurance companies. Bioethics, through the enhancement / therapy dichotomy, and the standard medicalisation critique both propose normative limits to the application of medicine based on external divisions between the medical and the social, or on the grounds of a perceived threat to a biologically embedded notion of human dignity. The concerns raised about enhancement uses of medical technologies through the normative issues of who is entitled to medical intervention and which interventions can be permitted, can be viewed as proxies, corresponding respectively to the need for financially regulation of access to medicine and the regulatory risk / benefit assessments of the ultimate worth of such interventions.

The ethical concerns about the morality of the desire to avoid old age or to be taller, in a given social context, are only indirectly related to the issue of what medical coverage a society is obliged to provide and it is a misreading of the situation to allow the former to stand in as a solution for the latter (Scully & Rehmann-Sutter, 2001). In doing so, although the concerns for which enhancement or medical practice 'beyond therapy' are a proxy are serious issues, this bioethical argument ignores the impact of the linkage between institutions and practices in the national and international networks of healthcare and the tacit competence and authority exercised by physicians in making moral evaluations of individual patient need. Any worthwhile attempt to consider the issue of 'human enhancement' in the context of formulating public policy must take the insights afforded by this current study of human growth hormone into account.

The case of idiopathic short stature can be seen to be as much a problem of the systems of medical evaluation and drug regulation as it is a problem of the appropriateness of the desire to be taller. Enhancement is not merely a matter of entitlement. The process of medicalisation, as regards bringing growth and ageing into the hormonal model of the body as potential targets for intervention with human growth hormone, has been illustrated in detail over the course of this project. Specific medical categories are constructed in such a way as to reinforce medical authority and ration access to healthcare.

They are produced within systems of healthcare and their stability depends on them reconciling the heterogeneous requirements of different elements within those systems. Such a network orientated stance is not apolitical: it does not invalidate, for example, the claim that medical framing of a problem can have negative social consequences such as diverting resources away from alternative (collective) methods of dealing with social problems. It does, however produce a more nuanced account and offers a greater range of sites of potential intervention from a public policy standpoint.

Although these observations derive from a very specific study of human growth hormone they are potentially relevant to a range of other cases of enhancement drugs including Ritalin, Viagra, Prozac, or Modafinil, which are all aimed at helping individuals cope with particular social demands on aspects of their embodiment. Indeed, this approach is relevant to the investigation of the wider realm of contested entitlement to medical intervention such as the recent moves towards greater medical intervention in the burgeoning sections of western populations described as obese and the attempts to add requirements such as diet plans and compulsory exercising as part of the criteria for entitlement to treatment.

Notes

[72] Presented in Smith, Gaebler & Long, 1955.
[73] This does not mean that formal psychological testing was ever a part of the process. Pyett et al (2005) comment that: 'Some of these 'indications' were little

more than assumptions about feminine norms and the importance of physical importance to a girl's future career and marriage prospects' (p 1638).

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ADDITIONAL ONLINE RESOURCES REFERRED TO IN THE PROJECT

American Academy of Anti-Ageing Medicine (A4M) Homepage: <URL: http://www.worldhealth.net/>

Eli Lily brochure “Understanding idiopathic short stature” available from <URL: http://www.humatrope.com/pdf/understanding_iis.pdf>

ISI Web of Knowledge <URL: http://wok.mimas.ac.uk/>

Pub Med Database <URL: http://www.ncbi.nlm.nih.gov/sites/entrez>

The source for the B.S. Johnson quote used on p114 is Coe, J. 2004, *Like a fiery elephant: The story of B.S. Johnson*, Picador, London.

APPENDIX ONE: Contact Letters and Interview Schedule

Interview Letter Version 1 (used in first phase of interviews)

Dear_____,

I am writing to ask for your help with a research project exploring the development of applications for human Growth Hormone in clinical practice. The project is funded by the UK Economic and Social Research Council (ESRC) and aims to gain an insight into endocrinologists' views on use of hGH to treat an increasing variety of causes of short stature in children as well as other applications.

I am conducting a series of interviews with academic endocrinologists in the United States of America and in the UK and I would appreciate the opportunity to interview you as part of this study. The data from this research will be used to produce a contemporary perspective on the use of biomedical therapies by expert practitioners as distinct from bioethicists or regulatory authorities and would be relevant for the UK's emerging policy debate on expanded use of biomedicine and enhancement.

The interview would last approximately 60 minutes and could be carried out at your convenience at place of work. I would wish to make an audio recording of the interview and may quote in anonymised form some of this material in the report of this project. The interview and all correspondence will be treated in strictest confidence and neither you nor the name of any organisation you work for will be mentioned.

The issues raised for discussion in the interview would include: a brief review of your professional experience with Growth Hormone, the expansion of the categories of treatment for which the hormone is acceptable (especially since the advent of synthetic GH in 1985), the social aspects of treating short stature, and professional perceptions of 'alternative' applications of GH such as in anti-aging medicine. I realise you are extremely busy but I hope that you will be able to participate in this research and I would value your contribution. Ideally I would wish to be able to arrange our interview between_____ and… [details]

Thank you for your time and assistance,

Yours sincerely

Michael Morrison

Interview Letter version 2 (deployed in main UK phase)

Dear _____,

I am conducting a research project exploring the historical development of human Growth Hormone from the early days of its discovery to the current range of applications The project is funded by the UK Economic and Social Research Council (ESRC) and aims to collect the personal testimonies of academic endocrinologists from the US and in the UK who have contributed to both the academic and clinical study of the drug.

I would greatly appreciate the opportunity to interview you as part of this study given your considerable experience with Growth Hormone across the spectrum of paediatric indications and the issues associated with its use.

The data from this research will be used to produce a contemporary perspective on the ways in which biopharmaceuticals emerge and change as therapeutic agents.

The interview would last approximately 60 minutes and will be carried out at your convenience in your office or other suitable place of your choice. The interview and all correspondence will be treated in strictest confidence and neither you nor the name of any organisation you work for will be mentioned.

The issues raised for discussion in the interview would include a brief review of your personal involvement with Growth Hormone, the growth of approved indications for hGH (especially after the advent of biosynthetic hormone) and [elements of project relevant to expertise]. This interview is not an exercise in collecting prescribing opinions on Growth Hormone and as such differs substantially from various pharmaceutical industry sponsored enquiries.

I realise you are extremely busy but I hope that you will be able to participate in this research as your contribution would be most valuable. The UK section of this research is scheduled to take place in early October 2006. With your permission I will contact your office to discuss possible arrangements.

Thank you for your time and assistance,

Yours sincerely

Michael Morrison

Interview Schedule

Section 1: Respondent background and experience with Growth Hormone

1. To begin with could you provide an overview of your work with Growth Hormone?
   - What has your work on/with human Growth Hormone entailed?
   - For example investigation of which applications or properties of the drug?
   - Approximately how long have you been working in this field?
   - When you began working with Growth Hormone, which indications was it approved for?

2. Did you have any experience of working with pituitary derived human Growth Hormone?
   - If yes, in what capacity and investigating which indications or properties?

3. Concerning growth treatment for childhood Growth Hormone deficiency:
   - When you began working in the field, what was the prevailing rationale for the administration of Growth Hormone in GHD?
   - Has this, in your experience, changed between then and the present?
   - If so, in what ways?
   - Which factors do you feel have been involved in effecting/driving this change?
   - Do you think that the switch from pituitary hGH to the biosynthetic product had any effect on the practice of endocrinology and if so, in what ways?
   - (And how has the involvement of pharmaceutical companies that this entailed affected the development of hGH)
   - In general does adult GHD treatment follow a similar rationale/ and is it viewed similarly to childhood GHD treatment even though it was identified at a much later stage in the history of Growth Hormone therapy?

Section 2: Expanded uses of Growth Hormone in children.

Concerning other approved applications for Growth Hormone:

4. Do you feel that other applications of Growth Hormone for childhood short stature due to other causes such as [for example but not limited to] Turner's Syndrome or Renal failure where there is not a classical absence of Growth Hormone production have been perceived differently to GHD?
   - Is the rationale for treatment [essentially] the same as with GHD or are there significant differences?

- [Specifically looking for mentions of the idea of 'the psychological burden of short stature' or ideas of normalisation]
- Has this changed over the time you have been investigating hGH?

5. Is there a role for Growth Hormone in treating so-called 'normal short' children?

6. Does this application or potential application raise any social or ethical issues?

- For example, is this case of medicine being applied to treat social difficulties in treating short stature?
- Raise issues about enhancement over therapy?
- Do you have any comment on the presentation/ awareness of the side effects of Growth Hormone in long-term usage (in terms of both severity and frequency) among patients/ professionals/ pharmaceutical companies?

Section 3: Expanded uses of Growth Hormone in adults

7. Do you think it is appropriate to use Growth Hormone to treat the symptoms of ageing in elderly patients?

- Is there a difference between using GH to treat middle-aged patients with adult GH deficiency and restoring declining GH levels in the elderly?
- Are there difficulties with anti-ageing as a valid goal for medicine?
-

8. How is GH replacement therapy for ageing different from or comparable to:

1) The idea of HRT for older women (now fallen from favour) and
2) GH in treating some of the wasting (cachexia) and lipodystrophy phenomena associated with HIV/AIDS which utilises the metabolic regulatory effects of GH in adult bodies – many of the effects labelled as 'anti-ageing' such as an increase in lean muscle mass are due to the same effects of GH?

9. In your view, what do you see as the social or ethical issues raised by the application of GH for anti-ageing?

10. Further Comments:

Invite interviewees to make any further comments on hGH and what they see as the main issues – scientific and social, or maybe a question about future developments.