Knowledge Accumulation and Vaccine Innovation: Lessons from Polio and HIV/AIDS

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I hereby declare that this thesis has not been submitted, either in the same or different form, to this or any other university for a degree.

Ohid Yaqub

To my parents and Corinne,
Two worlds that should not be separate.

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ABSTRACT

This thesis contrasts vaccine innovation efforts in the cases of poliomyelitis and HIV/AIDS. It addresses the question of why some fields of human endeavour can be seen to yield positive change more quickly than others.

The thesis develops a perspective that views innovation as a cumulative learning process. It employs the notion of a 'testing regime' to draw attention to the role of testing in driving this carefully managed learning process during the development of vaccines. Repeated testing, under conditions that are varied using instruments and skill, generates knowledge that is reliable and robust for technological purposes. Governance is needed to co-ordinate this process of testing to ensure the resulting knowledge growth is shared and cumulative. This lens is used to explore the creation of intermediate conditions, the development of instrumentalities, and the role of governance in vaccine innovation processes.

The thesis uses the notion of 'social visions' to explore how attention directed to poliomyelitis contrasted with neglect and apathy afforded to AIDS in its early manifestations. Shared, rather than competing, visions are found to play a significant role in setting the vaccine innovation process in motion. However, the thesis finds that key pathogenic features of the virus and certain ethical and safety stances make learning and the accumulation of technological knowledge inherently difficult. Importantly, the thesis finds policy measures can mitigate or exacerbate these learning challenges considerably. Whilst greater market support and increased research funding tend to be positive contributions to vaccine development, this research shows they are only part of what is needed to take ideas through to innovation.

The empirical evidence gathered in this thesis, when viewed through the testing regime lens, suggests that science and innovation are distinct activities but their inter-relationships can be enhanced with the development of an infrastructure focussed on nurturing skills, fostering the use of new techniques, encouraging the development of new instruments, and implementing governance measures to co-ordinate testing efforts and resources.

LIST OF CHAPTERS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

‘The demand for higher levels of food consumption, greater life expectancy, the elimination of infectious disease, and the reduction of pain and discomfort, have presumably existed indefinitely in the past, but they have been abundantly satisfied only in comparatively recent times. It seems reasonable to suppose that the explanation is to be found in terms of supply side considerations. It is unlikely that any amount of money devoted to inventive activity in 1800 could have produced modern, wide-spectrum antibiotics, any more than vast sums of money at that time could have produced a satellite capable of orbiting the moon. The supply of certain classes of inventions is, at some times, completely inelastic - zero output at all levels of prices… On the other hand, the purely demand-oriented approach virtually assumes the problem away. The interesting economic situations surely lie in that vast intermediate region of possibilities where supply elasticities are *greater than zero but less than infinity*!’ (Rosenberg 1974:106).

‘All effects follow not with like certainty from their supposed causes. Some events are found, in all countries and all ages, to have been constantly conjoined together: Others are found to have been more variable, and sometimes to disappoint, our expectations; so that, in our reasonings concerning matter of fact, there are all imaginable degrees of assurance, from the highest certainty to the lowest of moral evidence’ (Hume 1748/2007:Part I iii).

‘Theories are not verifiable, but they can be corroborated. A theory can be the better corroborated the better testable it is’ (Popper 1959:248, 268).

‘People have been talking vaccine, vaccine, vaccine for public consumption, and I have said it too. But I always scratch my head and say this [AIDS] is not the kind of situation where it is going to be easy to do the testing’ (Unnamed US public health official, quoted in Altman 1986).

Chapter 1

Introduction

What will it take for an HIV vaccine to be developed? Why is there not yet a vaccine after nearly 30 years of research? With treatment and prevention programmes alone unable to end the pandemic and with 15,000 new infections daily, how can vaccine discovery be accelerated? Some believe that HIV vaccine innovation suffers from a lack of money; others view it as a virus posing unusual scientific challenges.

Whilst economics and biology certainly reveal difficulties, as recognised and investigated in the thesis, these are not the only barriers. The thesis contends that a different set of difficulties is exposed when vaccine innovation is analysed as a learning process. Examining the path from science to innovation reveals that learning is controlled, co-ordinated and cumulative; and most importantly, this process can benefit from policy intervention. Policies are needed to support not only the generation of scientific knowledge, but also the accumulation of specific knowledge required for vaccine innovation. The thesis suggests that, in the case of HIV vaccine development efforts, weaknesses in science and technology policies may have hampered innovation.

There is a keen sense to let the 'power of science' overcome the challenges of HIV vaccine innovation (IAVI 2008b:3). This optimism is based on the idea that innovation has generally become more related to science[1]. This would argue that any public policy that strengthens science will inevitably support vaccine innovation too. However, as this thesis identifies, experience suggests this is far from the case.

The hope that scientists can turn their discoveries into products, in a simple and linear way, runs against research on the relationship between science and technology by historians of science, historians of technology, sociologists, scientists, engineers, patent and bibliometric

[1] See for example, Dosi (1988b:222) or Freeman (1982:31). However, Freeman notes that 'the expression *science-related*, is usually preferable to the expression *science-based*' (1982:29).

analysts. As Nightingale (1997:1) puts it, ‘scientists may like to think that technology is just applied science, but engineers know better’.

If the complexities of the science-technology relationship mean that simply funding science is not enough to generate vaccines, what else is needed? This thesis seeks to make this question clearer for policy makers by providing a framework for conceptualising the production and accumulation of vaccine knowledge.

The thesis starts by observing that some vaccines are made quickly, whilst others are not made at all. It argues that socio-economic theories provide incomplete explanations of this variation, and that an analysis of the way knowledge is accumulated further up the vaccine innovation process is required. The thesis draws on historical experiences in vaccine innovation, and reflects on the record of HIV research.

A recurrent theme emerges from this analysis: technologists must be able to generate knowledge that is reliable, robust and shared in order for it to accumulate and yield innovations. Moreover, there is an identifiable system underlying this process. Technologists test ideas with instruments and skill, under varying conditions, according to widely accepted standards and co-ordinating institutions. Together, the thesis calls this conceptualisation a ‘testing regime’.

The testing regime is intended for use as an expository device to gain insights into the problems faced during vaccine development efforts. The thesis characterises the role of a testing regime in the context of vaccine innovation, locates the testing regime in key innovation theory, and applies the testing regime to explore the cases of poliomyelitis and HIV vaccine efforts. The thesis shows that certain components of the testing regime are potentially fertile – but largely unrecognised – areas for public policy to accelerate and improve vaccine innovation.

The rest of this chapter proceeds in six sections. The first section underscores the need for policies that support vaccine innovation. The second section preludes a later chapter on the

economics of vaccines, and discusses the funding situation for HIV vaccine R&D. The third section argues that an 'upstream' analysis of vaccine innovation is required. This looks at the source of new ideas and how they are taken-up into development. The fourth section defines the focus of the thesis, and how it aims to explain the accumulation of technological knowledge. The fifth section outlines a broader science policy back-drop to this focus and the sixth outlines the remainder of the thesis.

1.1 The need for vaccines

It is difficult to overstate the desirability of vaccines. They have prevented more premature deaths, permanent disability and suffering than any other medical discovery or intervention[2] (WHO 2000; Andre 2001:2206). And they are cheap per life saved. For example, the cluster of vaccines against polio, diphtheria, pertussis and tetanus that are delivered by the WHO's Expanded Programme on Immunization can together be given for less than about $20 per year of healthy life gained in low-income countries (Jamison, Breman et al. 2006).

Vaccines are cost effective when the costs of treatment, hospitalisation and lost working days are taken in to account (IOM 2000; Bloom, Canning et al. 2005). For every dollar spent on the measles, mumps and rubella vaccine, $21 is saved in direct medical costs (IOM 1997). Similarly, the diphtheria, tetanus and pertussis vaccine saves $6.21 for every $1 spent (CDC 1999). The WHO has estimated that poliomyelitis eradication will save governments $1.5bn per year in treatment and rehabilitation costs (Barrett 2004). The elimination of smallpox is thought to have saved $275m per year in direct health costs (GAVI 2003) and the $100m invested in eradicating the disease after 1967 'saved the world about $1.35bn a year' (Barrett 2004:640). The US alone saves the total of all its contributions to the smallpox eradication programme every 26 days (Rappuoli, Miller et al. 2002). An influential World Bank report, *Investing in Health* (1993), concluded that child immunization is one of the most cost-effective health interventions available.

[2] I consider technologies that provide clean water and sanitation to be a likely exception to this claim.

Vaccines have positive externalities of group immunity, where people who are not immunised also benefit because of the reduced transmission of the pathogen (Ramsay, Andrews et al. 2003; Fine 2004). Thus, suffering caused by the *spread* of communicable disease is reduced in addition to the prevention of suffering for the vaccinated product-user. Vaccines are easier to administer than many drugs, especially compared to the complicated drug regime in AIDS therapy, and some vaccines require only one dose, placing less pressure on health infrastructures and budgets.

Immunisation also reduces poverty and inequality (Andre, Booy et al. 2008). These impacts stem from the fact that immunisation protects individuals not only against an illness, but also against long term effects of that illness on their physical, emotional and cognitive development. Enduring poor health through certain phases of life may be especially conducive to entering chronic poverty (Yaqub 2002; 2004:125). In contrast, improved health has a positive effect on economic productivity, savings and investment, and workers to dependents ratios (Bloom, Canning et al. 2004). Health inequalities within countries (let alone across the world) still persist but vaccines present us with a tool with which to promote equity in health (Bishaia, Koenig et al. 2003; Anand, Peter et al. 2005).

It is not surprising then that a vaccine to stem the HIV pandemic is so sought after. The UNDP's Human Development Report considers HIV to have inflicted a major reversal in human development (UNDP 2005). The workforce of entire countries are being decimated as they are laden with sickness, or lost altogether to death. Victims, and those around them, often suffer social and psychological costs, and the effects of discrimination are deeply detrimental to the economy. There are about 40 million people living with HIV/AIDS, 95% of them in developing countries[3] (WHO/UNAIDS 2006).

So far, the potential contributions of more than 25 million people have been lost to HIV/AIDS; their deaths have left 12 million children orphaned in sub-Saharan Africa alone (WHO/UNAIDS 2008). In some of those countries, one in five working age adults have HIV, and life expectancy has dropped to 30 years, the level of a century ago (CGDev

[3] Combating HIV/AIDS is the sixth Millennium Development Goal (IAVI 2005; UNDP 2005).

2006). The loss of household bread-winners and parents to HIV/AIDS has cost sub-Saharan Africa about 12% of its GNP (Sachs, Ahluwalia et al. 2001).

1.2 Funding for vaccine innovation

Given that an HIV vaccine is needed so much, one might expect significant private investments. However, their investments remained less than $25m in 1993, and only managed to reach $50m in 1999[4] (IAVI 2004a:3).

This led to suggestions of market failure and the need for corrective 'pull' policies. They include strengthening tax and intellectual property incentives, making advanced purchase commitments, offering tiered/differential pricing and the establishment of prizes (Danzon 1998; Kremer 2001; Kremer 2002; Kremer and Glennerster 2004; Kremer and Snyder 2004; Kremer, Glennerster et al. 2005; Kremer, Glennerster et al. 2006). Despite the assortment of 'pull' options, annual private investment in HIV vaccine R&D has never exceeded 10% of the global total (UNAIDS 2008:14).

In contrast the most prominent 'push' mechanism is funding research directly (IAVI 2004b)[5]. For 1993, total global funding for HIV vaccine R&D was less than $160m (IAVI 2004a:3). Several authors recognised this to be very low and called for increased funding using the global public goods argument (Archibugi and Bizzarri 2004; Arnold 2005; Barder 2005).

In the absence of private investment, governments funded 89% of total global investment in HIV vaccine R&D between 2000 and 2007 (UNAIDS 2008:14). Funding R&D is a relatively blunt policy tool because the outcomes are so uncertain, but it has been

[4] This compares to around $5bn in 2001 for worldwide expenditure on cancer research by the private sector (UICC 2006).
[5] Other 'push' policies include regulatory 'streamlining', tax credits, and liability protection (IAVI 2004b).

increasingly deployed. Total global investment in HIV vaccine R&D has increased steadily from $327m in 2000 to $961m in 2007[6] (UNAIDS 2008:12).

With an annual expenditure of almost a billion dollars, it is difficult to consider HIV vaccine development as a neglected effort, especially when compared to other diseases that have been 'neglected'[7] (Trouiller, Olliaro et al. 2002; Vogel 2006). Total worldwide spending on malaria vaccine R&D was only $42m in 1999 and $65m in 2003 (MVI 2004)[8]. For tuberculosis vaccine R&D, it was even less, estimated to have been between $100m and $150m over the 1990s (WHO 2002)[9]. That was the equivalent of spending less than a cent over the entire decade for every person infected with tuberculosis.

Funding for neglected disease R&D has increased in recent years to $2bn in 2004 (Morel, Acharya et al. 2005) and $2.5bn in 2007[10] (Moran, Guzman et al. 2009:142). Despite the increases, expenditure on HIV vaccine R&D still only represents a small part of the $20bn total annual spend on AIDS treatment R&D; and an even smaller part of the $70bn annual spend on all health product development (IAVI 2007).

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[6] A considerable part of that increase is explained by a $100m donation to IAVI by the Gates Foundation in 2002.

[7] The Commission on Health Research for Development (1990) showed that about 10% of health research funding is allocated to 90% of the world's health problems (the '10/90 gap'). This includes neglect by public expenditure. Medicins Sans Frontieres (2001) estimated that in 2000, non-commercial research was less than $100m for TB, malaria, trypanosomiasis, and leishmaniasis combined, compared to $3.1bn public expenditure devoted to cancer in the US alone. At the level of research activity, Lanjouw and Cockburn (2001) find that references to tropical diseases (which have 99% of their burden in poor countries) occurred in less than 1.5% of all citations in 1998. Closer to the product level, Pecoul et al (1999) find that 0.5% of total pharmaceutical patents in 1996 relate to these diseases. Only 8 out of 1,393 drugs licensed anywhere in the world between 1975 and 1997 were developed specifically for tropical diseases. Of these, five were intended for veterinary purposes and two were for military purposes.

[8] It is set to increase following the Gates Foundation's donation of $107m over six years to the Malaria Vaccine Initiative. Donation made on 30/10/2005. See http://www.gatesfoundation.org/StoryGallery/GlobalHealth/SGGHMalariaMVI-011019.htm

[9] According to the WHO's '*Global Plan to STOP TB 2006-2015*', it is set to increase to around $200m per year over the next decade (WHO 2006).

[10] Around 80% of these totals have been focussed on HIV, tuberculosis and malaria, whilst other equally high-burden diseases (as measured by disability-adjusted life years), such as pneumonia and the diarrhoeal illnesses, collectively received less than 6% (McCoy, Kembhavi et al. 2009; Moran, Guzman et al. 2009). Much of this concentration in funding is due to the priorities and policies of the Gates Foundation, as 90% of total neglected disease funding is provided by public and philanthropic sources (McCoy, Kembhavi et al. 2009; Moran, Guzman et al. 2009). This emphasizes the importance of the role for *public* policy in neglected diseases.

1.3 Uncertainties of the early innovation process

‘If, by doubling research and development spending over the coming five to 10 years we could bring forward the discovery of an Aids vaccine, we could save millions of lives’ (Brown 2005).

The difficulty with the view put forward by Gordon Brown is that successful innovation is not only a function of the amount of money spent on the project, especially in its early stages. It is a correct but incomplete view of innovation. Accordingly, one can observe immense heterogeneity in vaccine innovation. Table 1 shows that some vaccines have been developed in a decade whilst others have eluded development for over a century.

Table 1: High variation in the number of years to develop some vaccines

Infectious Agent (disease)	Agent linked to disease	Vaccine licensed in U.S.	Years elapsed
Measles virus (measles)	1953	1963	10
Hepatitis B virus (hepatitis)	1965	1981	16
Human papillomavirus (cervical cancer)	1981	2006	25
Rotavirus (diarrheal disease)	1973	2006	33
Bordetella pertussis (whooping cough)	1906	1948	42
Varicella zoster virus (chickenpox)	1953	1995	42
Poliovirus (polio)	1908	1955	47
Haemophilus influenzae (meningitis)	1889	1981	92
Salmonella Typhi (typhoid fever)	1884	1989	105
HIV (AIDS)	1983	2018, a minimum estimate*	35+
Human cytomegalovirus (birth defects, mononucleosis)	1960	-	48+
Mycobacterium tuberculosis (tuberculosis)	1882	1927, BCG**	126+
Plasmodium spp. (malaria)	1880	-	128+

Source: International AIDS Vaccine Initiative (IAVI 2008a:14). *Two thirds of leading AIDS scientists believe that a vaccine will not be developed for at least another ten years (Connor and Green 2008). **Although BCG vaccine is widely used in children, it is not as effective in tropical countries, and is not effective in adults.

Explanations of this wide variation have focused on downstream issues concerning product innovations. Economists have emphasised demand-side issues for vaccine products (Pauly, Robinson et al. 1995; GAVI 2007) or have analysed issues around the trade-offs in vaccine efficacies, costs and development times (Tangcharoensathien, Phoolcharoen et al. 2001; Esparza, Chang et al. 2003; Cropper, Haile et al. 2004). Sociologists are concerned with anti-vaccination movements (Blume 2006; Dempsey, Zimet et al. 2006), delivery and access (Aston 2001; IOM 2003) and selection of vaccine products (Blume 2005; Blume and Zanders 2006).

Explaining why something *did not* occur is obviously methodologically difficult. A focus on downstream issues has the weakness that it essentially attempts to explain the non-existence of a product at the end of the innovation process, by comparing with products that do exist. This does not pay attention to how the knowledge that drives the process is generated. A deeper analytical approach would involve exploring further upstream in the innovation process to trace the unpredictable turns that characterise the evolution of knowledge, the historical circumstances in which certain research paths were taken and others abandoned, and the local context in which technologies are developed[11].

Economic notions of market failure and sociological notions of neglected diseases are relatively silent on why HIV vaccine innovation is difficult. HIV vaccine research is well funded, has a potential market and is supported by a coalition of prominent social groups[12]. This thesis provides an alternative explanation that builds on innovation theory, draws on vaccine history, and is consistent with the HIV vaccine research record.

The first two sections of this chapter highlighted an urgent need for an HIV vaccine, and the substantial R&D investments being made for it. This section noted a wide variance in the innovation timeline. The next section discusses an important missing variable in

[11] Processes at work before the 'moment of invention' must not be neglected from analysis, partly because the notion of invention is itself so blurry and arbitrary. Invention is inseparably part of a broader process of innovation, the analysis of which unavoidably involves a critical and detailed analysis of the work and findings of scientists. This can make social scientists uncomfortable with the burden of mundane technicalities, and natural scientists uncomfortable with the possibility that their work might be sullied by political, social and economic influences.

[12] Possibly to the neglect of many other important diseases.

explaining that timeline: technological knowledge. Greater understanding of processes that create technological knowledge could be used to identify policy levers to accelerate vaccine innovation.

1.4 Focus of thesis: Technological knowledge accumulation

This thesis argues that vaccine innovation requires technological knowledge. This knowledge cannot be obtained 'as-is' from scientific knowledge, but has to be specifically generated and accumulated through its own dedicated and deliberate steps. Generating technological knowledge involves repeated testing. The purpose of testing is to align knowledge to the environment where the technology will actually be used. This requires varied, measured and controlled manipulation of experimental conditions with instruments, skills and experience. These allow a series of conditions that can mark milestones, or act as stepping stones in the path to an innovated product.

But central to the concern of this thesis is that intermediate conditions can range from the highly artificial, where it is easier to learn, to the highly relevant, where it is more reliable for the purposes of technological use. The creation of these intermediate conditions depends on what instruments, skills and experience are available and how they have been developed and used. A research process that lacks the basis for creating intermediate conditions has to advance in 'lumpy steps'. This can lead to researchers facing large leaps in selecting research strategies. The factors that determine intermediate conditions can be crucial in shaping the research and development path.

The manipulation of intermediate conditions needs to be governed so that the emergent knowledge is robust. Institutions are required to ensure the knowledge is true, shared and integrated. This is to recognise that the accumulation of technological knowledge is a social process. Critical instruments and skills are the foundations of the design of intermediate conditions and need to be made available or even developed. After a range of testing conditions have been developed, they also need to be institutionally standardised for more intensive testing.

The thesis brings these arguments about the accumulation of technological knowledge together in a conceptual framework it calls a 'testing regime'. It argues that the testing regime lens can provide important insights into the vaccine innovation process and, in doing so, may be used to help explain some of the variation seen in vaccine innovation. For vaccines against different viruses, in different instrumental, social and institutional contexts, the propensity to innovate varies systematically, and the testing regimes device may be able to characterise this variation to some extent.

Whilst traditional, decentralised 'peer review' governance of science may be cumulative for the growth of scientific knowledge, it may also contribute to fragmented output that increases uncertainty throughout the innovation process. The thesis therefore also needs to consider the role of institutions in contracting out targeted research projects, or co-ordinating investigator-initiated research, for the accumulation of technological knowledge.

1.5 Broader implications of the testing regime for science policy

Whilst the central focus of the thesis is the accumulation of technological knowledge, the notion of exploring technological change using the testing regime lens raises a set of wider questions within the governance of science. The issue of societal benefits of research and professional autonomy may be regarded as a notable back-drop to this study, which suggests why testing regimes may have been neglected in the past and why policies to support them may be resisted.

Sarewitz (1996) argues the notion that researchers are best left alone to work autonomously, because any scientifically reasonable line of research into fundamental natural processes is as likely to yield social benefit as any other, is a 'myth of unfettered research'. The argument is aimed at ideas such as Polanyi's 'Republic of Science' (1962),

Elzinga's view that external corruption of science leads to 'Epistemic Drift' (1985), and more recently Ziman's 'Real Science'[13] (2000a).

In principle, maximum autonomy in HIV/AIDS research would be achievable if science justified itself in terms of the cultural value of understanding a pathogen and disease that ravages society. As a cultural entity, there are no criteria by which to judge the merits of scientific work, so scientists can be left to decide amongst themselves what deserves support (Ronayne 1984). However, if science was justified on such grounds then it would merit no more support than the arts.

The noted increases in research funding, however, have *not* been based on such grounds. Rather, increased funding has been provided by governments principally for the purposes of making a vaccine. In recognising that technological innovation will require the embodiment of new knowledge, funding has been released for R&D. When science justifies itself in such practical utility terms it opens the activities of scientists to external control (Ronayne 1984). This is because technological concerns, such as those mentioned by economists and sociologists in section 1.3, and the role of institutions in testing regimes outlined in section 1.4, typically require more management and social organisation than scientific endeavours (Pavitt 1999). This gives rise to a tension between professional autonomy and accountability as summed up by MacLeod:

'In our day, we have become accustomed to situations where scientists urge the utility of science when asking for public money but defend the social autonomy of science whilst spending it' (cited in Balmer 1993:29).

Therefore the idea of guiding research towards innovation, in the form of testing regimes, can find itself meeting resistance, as part of a concern to defend the autonomy and political legitimacy of science. However, as will be seen in the next chapter, innovation literature from beyond vaccines, and beyond the platitudes of 'pure' scientists, indicates that research

[13] These arguments are responses largely to a movement in the 1930s led by JD Bernal (1939) who argued that science should serve the needs of the state.

can be directed towards innovation and that such tensions can be managed alongside more traditional models of science.

'Despite the uncertain and apparently random nature of the innovation process, it *is* possible to find an underlying pattern of success. Not every innovation fails, and some [organisations] appear to have learned ways of responding and managing it such that, while there is never a cast iron guarantee, at least the odds in favour of successful innovation can be improved' (Tidd, Bessant et al. 2001:45).

For the purposes of innovation then, certain steps can be taken to complement science and make the innovation process more consistent. This key message - that science on its own is not enough to secure persistent innovation - seems to have been misunderstood by policymakers of recent, and turned on its head to mean that the institutions of science are in need of whole-scale reform[14] rather than in need of further investment alongside policies to develop a skilled industrial workforce (OECD 2003; Dosi, Llerena et al. 2006; EC 2007).

[14] Reforms such as encouraging universities to patent and commercialise their research through intellectual property licensing deals are often framed in the context of a 'European Paradox', where Europe has a supposedly strong science base but is unable to turn it into business (see especially European Commission Green Paper 1995).

1.6 Outline of the thesis

The thesis is developed in nine more chapters. Chapters 2 and 3 introduce the idea of the testing regime in two steps: first, by discussing the innovation literature it draws on and second, by presenting it as an exploratory framework to analyse technological change. Chapter 6 applies it to poliomyelitis vaccine innovation and Chapters 7-9 to HIV vaccine innovation efforts. The analysis of HIV vaccine efforts is split into three chapters that use the testing regime lens to explore three fundamental aspects of innovation respectively: *rate* of technological change, *direction* of technological change and decision-making under *uncertainty*. Chapter 4 discusses methodology. Chapter 5 sets the background for the empirical chapters by discussing the economics and the biology of vaccine research and development.

Chapter 2 reviews evolutionary theories of technological change. This highlights shortcomings in 'push-pull' models of innovation and policies based on them. The chapter discusses how technological paradigms and their trajectories can help characterise innovation process in a much more realistic and policy relevant way. Whilst these concepts appear later in the empirical chapters, there is a notable issue in the literature in terms of understanding why some technological paradigms are overtly more powerful than others. The chapter suggests that future theoretical development might address this underlying question by focussing on how the deliberate development of instruments and skills in crafting varying intermediate conditions affects technological change.

Chapter 3 develops a framework to explore technological knowledge growth. Within this framework, the chapter introduces the notion of a 'testing regime', specifying its characteristics and suggesting its role in innovation. The chapter identifies three dimensions of the testing regime in terms of relevant learning conditions, instruments to manipulate them, and institutional roles in ensuring cumulative output. The discussion of the testing regime builds upon, and is presented in relation to, the theories discussed in chapter 2. The chapter also adds the concepts of social vision and operational principle to analyse disease construction and vaccine design respectively.

Chapter 4 explains the methods used. Recognising that historical and detailed case study approaches are useful for addressing process-oriented issues such as innovation, the thesis re-constructs the innovation of the poliomyelitis vaccines and HIV vaccine efforts, but with a new lens provided by the concept of the testing regime. Details are provided in this chapter of how cases were selected and built up. The difficulties of analysing contemporary cases, such as HIV vaccine research, and the strategy of synthesising secondary data are also discussed.

Chapter 5 analyses the economics of vaccine innovation and highlights the strengths and weaknesses of such an approach. It finds that a more detailed examination of the technological knowledge underlying vaccine innovation is needed. The second part of the chapter outlines basic concepts in immunology and vaccinology necessary to understand the biological parameters that define the innovation task.

Chapter 6 analyses the history of two successful poliomyelitis vaccines, and analyses the development of its testing regime. A coordinated vision helped encourage provision and development of instruments to improve learning conditions. The chapter shows how these conditions were related to the selection and development of approaches towards poliomyelitis vaccines. Research governance is discussed for its role in the accumulation of technological knowledge and in mediating differences in opinion between different research groups. Finally, the chapter also notes how differences across countries affect vaccine choice and use.

Chapter 7 uses testing regimes to explore the rate of HIV vaccine development. It draws a contrast between the strong social vision that drove poliomyelitis research and the weaker one in HIV research. The chapter explains how characteristics of HIV make the testing regime appear weak and describes under-explored efforts to strengthen it using animal models.

Chapter 8 applies testing regimes to discuss the direction of HIV vaccine development. It tracks the emergence of multiple HIV vaccine efforts in both private and public sectors. It explains how, for different vaccine designs, the learning conditions were either realistic but difficult, or simple but irrelevant. It suggests how instruments may help change these conditions, and highlights the importance of governance in taking up these instrumental opportunities to arrive at a vaccine with suitable and appropriate characteristics.

Chapter 9 uses the testing regime idea to focus on decision-making under uncertainty with respect to launching HIV vaccine clinical efficacy trials, the most expensive set of testing conditions in vaccine development. The chapter shows how the testing regime could, in principle, reveal ways to help reduce uncertainties around decisions to undertake such tests by drawing out how different decisions about the creation of testing conditions have different implications for the rate and direction of innovation. It questions not simply whether society really wants (or can have) a vaccine, but also what kind of vaccine it might want (or get). Conversely, the testing regime can highlight weaknesses that exist in HIV vaccine research policy and can be seen to exacerbate uncertainties. Clinical trials are not simply about testing if a vaccine works, but as discussed in the chapter, involve complex inter-relationships between the design of the trial and the research approach that led to the trial; and these can have effects on the final characteristics of the vaccine[15].

Chapter 10 summarises evidence in chapters 6-9 on poliomyelitis and HIV vaccine innovation. It then draws 'cross-cutting' conclusions across chapters about the use of testing regimes to explore innovation. Overall, the thesis suggests that the ideas embedded and emphasised by the testing regime lens play important roles in the accumulation of technological knowledge, which, if not anticipated and addressed, is likely to hinder vaccine innovation further. The chapter suggests that there are three principles which policy can follow, which broadly correspond to the three elements of the testing regime: supply and development of instruments and skills, supply and development of animal models, and strong institutional leadership and co-ordination.

[15] For example, it explains why there is an important distinction to be made between HIV vaccines and AIDS vaccines (discussed further in section 9.6).

Chapter 2

Evolutionary Theories of Technical Change: A review

This chapter will review evolutionary theories of technological change and their explanation of knowledge growth. It argues the field would benefit by including the development of instruments, a necessary but under-emphasised foundation for learning. The next chapter will take this argument further to suggest the notion of testing regimes be used as a lens through which technological change in vaccines can be explored.

2.1 'Science-push' or 'Demand-pull'?

The birth of innovation studies is typically dated to the 1950s when economic growth models[1] were left with a 'residual', unexplainable by the growth of labour and capital. This large leftover was attributed to 'technical advance' and referred to as 'a measure of our ignorance' (Abramovitz 1956; Solow 1957). Explaining technological change became a central research challenge.

Post-war science and technology policy drew on Bush's (1945) manifesto for public funding of free and fundamental science. Although his model left room for nuances, it encouraged a linear conception of innovation, where scientific discoveries feed directly into industrial engineering departments[2]. Early work in economics provided post-hoc justification for policy, by focusing on weak incentives to invest in basic research (Nelson 1959; Arrow 1962). Social returns to R&D were greater than private returns due to the low appropriability of knowledge. Knowledge as a non-rivalrous and non-excludable

[1] Aside from growth accounting exercises, economic historians also emphasised the importance of studying the effects of technological change. For example, a landmark text by Landes (1969) succeeds in placing technological change at the centre of industrial development, but is weaker in explaining where the new technologies came from, preferring to cast science and technology as autonomous entities, largely free from the influence of the social, political and economic institutions he so excellently detailed.

[2] The linear model is rooted in the successes of wartime projects, especially the Manhattan Project.

commodity meant that it could leak out of firms without them reaping the full benefits. Thus, science represented a market failure that required government intervention.

In contrast, Schmookler (1966) suggested that changes in demand determined innovation by showing that shifts in demand preceded shifts in inventive activity[3]. Marquis (1969) found that approximately 75% of 500 innovations were stimulated by 'demand pull'. Later, studies pointed to the importance of paying attention to users' needs (Rothwell, Freeman et al. 1974), the role of users in developing innovations (von Hippel 1988), and the skills and informal mobility of researchers between science and industry (Gibbons and Johnston 1974).

In addition, many examples existed to suggest that science benefited from, rather than pushed, technological change, such as investments in the steam engine driving advances in thermodynamics (see Rosenberg 1982a for more examples). Such findings may have implied that technological change and science[4] are determined, rather than influenced, by demand. Accordingly, in the 1970s and 1980s, science and technology policies around the world - especially those supporting 'blue sky' research in the UK - were reined in to make for a leaner state that relied more on markets than 'wasteful' subsidies (Balmer 1993:64; von Tunzelmann, Malerba et al. 2008:472).

Rosenberg (1976; 1982b) was a key opponent of this extreme emphasis on the determinacy of market forces: '…we are compelled to consider the rates at which different sciences have progressed. Many important categories of human wants have long gone either unsatisfied or very badly catered for in spite of a well established demand' (Rosenberg 1976:276). He argued science, research and knowledge are important variables in themselves. For him, economic forces can only operate within a framework of scientific and technical constraint and his historically based work drew attention to what exactly gets invented or attempted.

[3] Demand was measured by investment levels whilst inventive activity was measured by patent applications.
[4] See for example, Bernal's (1939) 'The Social Function of Science'.

He argued that it is deeply unsatisfactory to consign technology to a black box and study it by quantifying input resources and output efficiency gains[5].

Mowery and Rosenberg (1979) identified methodological flaws in demand-pull studies[6]. Explaining innovation by market demand requires more than merely showing its existence: it requires evidence that innovation was stimulated by a shift in demand only, rather than a shift in demand and knowledge supply together. They also identified theoretical flaws. They argue that the concept of demand is invoked inconsistently as the market cannot accurately evaluate demand for a future product of which it has incomplete knowledge. This is revealed especially by examples of revolutionary new products such as telephones and computers[7]. Furthermore, Schmookler concentrates on mechanical sectors where innovations are close to investment and neglects other sectors where the link is likely to be weaker. And most importantly, he neglects to analyse how the state of technological knowledge influences the choice and method of technical problems that are even attempted.

Mowery and Rosenberg's influential conclusion was that demand was necessary but not sufficient for innovation. Perhaps because they were so focussed on testing the demand-pull movement, they did little to explain the vast differences in technical change that were emerging from the empirical evidence[8] (Pavitt 1984). A new perspective was needed to appreciate innovation as an ongoing process[9] rather than an event that can be simply pushed or pulled.

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[5] As a result, Rosenberg (1976:278) finds 'the interesting economic situations… lie in that vast intermediate region of possibilities where supply elasticities [of technology] are greater than zero but less than infinity.'

[6] As Martin and Nightingale (2000:xvi) note, when the demand pull hypothesis was re-tested, using Schmookler's data and new data, significantly weaker relationships were found.

[7] In 1943, Thomas Watson as head of IBM, stated, "I think there is a world market for about five computers." Western Union declined the opportunity purchase Alexander Bell's telephone patent when 'it was offered to them for a mere $100,000!' (Rosenberg 1986:24; 1994). 'This 'telephone' has too many shortcomings to be seriously considered as a means of communication. The device is of inherently no value to us' (Western Union internal memorandum 1876, cited in Yates, Wilkinson et al. 2008:112).

[8] For example, science-push could be important in the early stages of an industry and economic factors more important in later stages; different classes of industry have their own distinctive sources and stimuli for technical change.

[9] Prior to evolutionary theories of innovation, Donald Campbell (1960) also did much to establish the growth of knowledge as a process of 'blind variation and selective retention'.

2.2 Evolutionary theories: Moving beyond push-pull debates

A defining feature of evolutionary theory was its stress on bounded rationality and inherent uncertainty throughout the 'groping' R&D process[10]. Nelson and Winter (1982:46) advocated 'appreciative theorising' in order to take into account 'ignorant uncertainty' where possible outcomes as well as their likelihoods were both unknown[11]. Such a conception of uncertainty cannot be used in elegantly bounded formal probability distributions (Nelson 2006). The result was a deliberate blurring between choosing how to execute or develop a technique and deciding what technique to use. The essence of the evolutionary argument is that these choices can be readily understood as a reflection of the past (as opposed to a rational decision making process).

The degree to which variations on the past are blind processes or deliberate goal seeking actions was left largely unanswered (see section 2.5). Suffice to say here that, in its early manifestations, evolutionary theory emphasised the disorderly and error-ridden nature of innovation (leaning to the blind) by amassing empirical studies into the details of the innovation process, and increased the appreciation of its diversity, complexity and immense uncertainty (Rosenberg 1976; 1982b; Clark and Fujimoto 1991; Pisano 1996).

Thus, the evolutionary perspective developed a more dynamic and differentiated perspective of technological change. Nelson and Winter's 'technological regimes' (1977:57; 1982:258) reformulated push and pull factors to explain the nature of technological knowledge as distinct from well-codified information: it was specific, tacit and embodied in people and organisations. They drew on behavioural theories of the firm (March and Simon 1958; Cyert and March 1963) to argue that firms do not optimise or maximise in their activities; instead they 'satisfice' (try to reach definable, realistic targets) through the establishment of 'routines' (heuristics, habits, rules of thumb) for action and

[10] As a result of the complexity and uncertainty emphasised by evolutionary theory, firms or governments are not able to explain fully or predict accurately either the outcomes of their innovative activities, or the technical performance of innovations. Another consequence is an emphasis on processes and institutions other than market organisation.

[11] Stirling (1998) developed Knight's (1921) conception of uncertainty into distinctions between risk, uncertainty, ignorance and ambiguity.

decision making. Importantly these included search routines for exploring technological improvements, which made it a theory of change that regarded the historical accumulation of skills and experience as very important.

The importance of tacitness was incorporated into the generation and flows of knowledge. Firms, industries and countries were differently able to innovate, and innovation was analysed inside the firm as well as outside. Firms were not just information processing/coordinating organisations, they were dynamic learning ones too. Firms' variation in rate and direction of learning depended on their accumulated competencies and search routines as well as their technological and market opportunities, and their ability to appropriate the benefits of their activities (Klevorick, Levin et al. 1995).

Thus, while technological knowledge was still thought costly to create, it was no longer assumed to be costless to transmit and re-use. Firms were not considered to be homogenous maximisers; moreover, they were thought to play critical and distinctive roles in the way in which new technological knowledge is embodied in artefacts.

2.3 Constraints and structure in the growth of technical knowledge

Dosi (1982) developed the evolutionary theory further by suggesting how technology changes in ways that cannot be characterised in terms of supply and demand. He applied Kuhn's (1962) ideas about paradigms in science, to technical change. His notion of an overarching 'technological paradigm'[12] highlighted that the innovation process does not just produce new artefacts and practices; it also generates its own body of growing knowledge, restricting innovation and the growth of technological knowledge to a path-dependent 'technological trajectory'[13].

[12] Nelson and Winter (1977) identified a similar concept of 'technological regime', mentioned earlier, but did not relate it to the opportunities afforded by Kuhn's (1962) notion of paradigm shifts.
[13] See David (1985) and Arthur (1989) for alternative explanations of 'lock-in' and path-dependence in technological change.

The incremental accumulation of technological knowledge is constrained by its inherently tacit and specific nature, by the emergence of technological tasks from other or older technologies, by technology's links to scientific principles and by the physical materials required for solving a technical problem. Perceptions of these factors influence what tasks are possible and how they are solved, the identification of dead ends and likely routes to success, and shape how new knowledge can be learnt from existing technological practice.

Dosi's theory emphasised that investments in research would not, on their own, be sufficient to yield innovations. Innovations were unlikely to emerge directly from academic research without considering concerns highlighted by Dosi, such as problem solving skills. It provided a more realistic model for exploring the substantial (but incomplete) role of science in innovation than the alternative focus on 'spill-overs', which carried an implicit but obvious linear assumption of catching and applying science emerging from universities (von Tunzelmann, Malerba et al. 2008).

By highlighting that technology had its own growing body of knowledge, and that it links to science, Dosi implied that there were two separate bodies of knowledge to link together. Thus, Dosi built on work by previous scholars who had argued that science and technology were distinct, and therefore, it was their relationship that needed clarification (von Hayek 1945; Polanyi 1958; Price 1965; Layton 1972; 1974; 1976; Vincenti and Rosenberg 1978). This contrasts with authors who have preferred to try and show science and technology to be essentially equivalent, or 'symmetrical' (Bloor 1976; Latour and Woolgar 1986; Latour 1987)[14].

Taking stock of technological regimes, paradigms and trajectories, (five) stylised facts of innovation emerged (1988a:222): uncertainty is inherent; there is increasing reliance on

[14] Microstudies by sociologists studying the social shaping of technology have provided a refined analysis of demand and user groups by taking into account class, gender, power and control (MacKenzie and Wajcman 1985; Bijker, Hughes et al. 1987). These models initially look useful for analysing the developments efforts for a vaccine that affects the poor and marginalised, but the theories are difficult to operationalise because they try to explain the social construction of, not only technology but also, science, knowledge and facts, all under the same 'symmetrical' framework of truth and falsity (Pickering 1984; Latour and Woolgar 1986). For a rebuttal of social constructivism, see Vincenti (1995). '[Technologies] …must conform to real-world constraints, such as laws of nature, that are not open to alteration by human agency' (Vincenti 2000:174).

scientific opportunities; search activities are undertaken by formal organisations; these organisations learn much by doing and using; and innovation is a cumulative activity and competences are built up over time.

2.4 Knowledge flows between science and technology

We have seen that attempts to explain changes in knowledge through needs, even when expressed as effective market demand, were problematic (likened to pushing a piece of string in Pavitt 1991). Since markets alone could not explain the relationship between science and technology, different aspects of technological regimes, paradigms and trajectories were explored by examining their knowledge flows across and within organisational and institutional boundaries.

R&D departments have remained close to manufacturing firms and production departments (Pavitt 1999). Where they have not, networks of people providing feedback and collaboration are especially important (Hicks 1995), forming 'national systems of innovation' (Lundvall 1992; Nelson 1993; Edquist 1997; Freeman 2008) or 'sectoral systems of innovation' (Malerba 2002; 2004). Whilst universities may be seen as knowledge producers and industry as innovators, in systems of innovation it is the knowledge flows and linkages between universities and industry that are most significant[15] (Mansfield 1995; Narin, Hamilton et al. 1997; Geuna, Salter et al. 2003).

In order to examine knowledge flows and linkages, a distinction is often made between products and their broader underlying bodies of knowledge in order to understand how the increasingly specialised production of knowledge is integrated by organisations, institutions, and governance for cumulative and persistent innovation (Granstrand, Patel et al. 1997; Pavitt 1998; 2002). This is because the division of labour between companies in production cannot be mirrored by an equivalent division of labour in knowledge: 'firms

[15] Indeed, some have suggested that such diffused 'mode 2' knowledge production should be studied as a new form (Gibbons, Nowotny et al. 1994) whilst others have encouraged a 'triple helix' of academia, industry and government (Etzkowitz and Leydesdorff 2000). Both the ontological and normative claims of the two groups respectively have been contested (Dasgupta and David 1994; David, Foray et al. 1999).

know more than they make' so that they can co-ordinate and integrate for innovation (Brusoni, Prencipe et al. 2001)[16].

2.4.1 Learning from outside the firm

The production of increasingly specialised knowledge and complex artefacts requires integrating an increased range of fields of knowledge that contribute to innovation (Pavitt 1999). The knowledge required to innovate is often acquired from external sources in a form that cannot be easily applied. So R&D has 'two faces', one where it enables firms to produce new technology, but another where it has to be undertaken in order to understand external sources of information and acquire an 'absorptive capacity'[17] (Cohen and Levinthal 1989; 1990).

This second external face of R&D is significant because underlying fields of knowledge do not advance at the same rate. Their uneven progress cannot be tracked solely by monitoring codified information. Tacit competencies, such as the ability to use and refine instruments developed elsewhere, must be retained in house to 'assimilate and exploit externally available information' (Cohen and Levinthal 1989:593).

So, as noted by the concepts of technological regimes, paradigms and trajectories, knowledge is highly idiosyncratic at the firm level. It does not diffuse automatically and freely through the system; rather, it has to be absorbed by firms through their differential capabilities accumulated over time. This raises deeper questions of why some knowledge fields are able to grow faster than others (Nelson 2003), and why some technological paradigms are less powerful than others in yielding innovations when demand is strong (Nelson 2008b).

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[16] Thus products are becoming increasingly multi-technology and firms increasingly multi-product.

[17] Similar explanations were put forward by others (Rosenberg 1990; Pavitt 1991), with strong supporting empirical evidence (Gambardella 1992; Malerba 1992; Hicks 1995). For example, Project SAPPHO highlighted factors common to successful innovation, many of which related to the external environment. Firms need to access external know-how, fundamentally incorporate users' needs into design and development, acquire skills and human capital readily, and need product champions and gatekeepers (Rothwell 1992; 1994).

2.4.2 Learning inside the firm

The way firms adapt to changes in their external knowledge environment and associate them with appropriable market opportunities is affected by their internal 'core competencies', 'core rigidities' and 'dynamic capabilities' (Henderson and Cockburn 1994; Prahalad and Hamel 1994; Leonard-Barton 1995; Teece, Pisano et al. 1997)[18]. Along with absorptive capacity, these concepts resonate strongly with the view that the firm's primary role is knowledge integration.

This knowledge-based approach to understanding firms has a long history, with Penrose (1959:78) arguing that the application of knowledge to produce goods and services requires the bringing together of many areas of specialised knowledge. The production process is not simply the transformation of inputs into outputs, but the creation of value by combining an array of knowledge specialisms in a co-ordinated, non-random way[19].

Knowledge integration can be recognised as an activity that defines the firm's existence. Injecting market incentives within the firm can be detrimental to intra-organisational learning and knowledge integrating capabilities because these activities require a high degree of co-operation and teamwork in the delivery of products and services (Kogut and Zander 1992). Accumulating increments in an existing stock may depend not just on the level of that knowledge stock, but also on the level of other (complementary or interconnected) stocks (Dierickx and Cool 1989). For accumulating new knowledge inside a firm, market incentives have inherent limits. So, to provide excessively strong individual incentives would in fact be destructive of the very advantages that a firm can bring for knowledge integration.

Nelson (1998; 2000) divides bodies of knowledge into two distinct but complementary and interacting bodies. 'Bodies of understanding' reflect competence in a specific technological

[18] This resonates with a long held view that the firm's primary role is to combine existing but heterogeneous sources of knowledge (Penrose 1959:78). These features are central to determining the way firms strike a balance between exploiting existing knowledge, and exploring for new knowledge (March 1991).
[19] Penrose states that the practice of combining specialised knowledge and the 'inherent heterogeneity in resources' allows the exploitation of 'productive opportunities'.

field. They are less dependent on the immediate context of products and are easier to codify and generalise, so they often give rise to publishing and patenting. 'Bodies of practice' are more esoteric, context specific, and tacit because they are based on experience and skills (see also Nelson and Winter 1982:74). As such they are closely related to design, development, production and marketing.

Firms are developing and bringing these bodies of knowledge together differently. Practice and skills play an important constraining role. This is supported by empirical findings showing that whilst firms' knowledge capabilities are diversifying, their product focus is increasing (Gambardella and Torrisi 1998). Firms can move into areas that utilise new bodies of understanding, but their production remains constrained by what they already know in terms of their bodies of practice. Pavitt (1998:442) takes this to indicate 'clear cognitive limits on what firms can and cannot do'. Thus, the direction in which firms' search activities seek to improve bodies of understanding is strongly influenced by their bodies of practice and what they actually make. In this way, electronics firms have moved into semiconductor technology (but not biotechnology), and pharmaceutical firms have moved into biotechnology (but not semiconductor technology) (Patel and Pavitt 1997).

Recent research has examined firms' techniques for improving their bodies of understanding. It frames learning as a cognitive process that is not only constrained by past activities, but one that generates new questions and new knowledge as solutions to problems (Nightingale 1998). Drawing on cognitive psychology literature, Padua (2008) has suggested that problems can be well defined or 'ill defined'. Mahdi (2002; 2003:246) has gone further in developing a taxonomy of technological search dependent on three factors: firstly, the degree to which technological problems can be 'parsed' into simpler sub-tasks; secondly, the level of 'rational' understanding of cause-effect relations; and lastly, the costs of experimentation with 'multiple' possible solutions. Analysis along these dimensions has been very revealing about the growth of bodies of understanding, presenting it as a cumulative, step-by-step cognitive advance involving incremental puzzle solving.

So, firms' bodies of understanding can be improved in a step-by-step fashion, but this cognitive advance is often constrained by bodies of practice. However this perspective underplays the possibility of firms strategically changing their bodies of practice so that it links up with their bodies of understanding better. There are some indications in the literature suggesting that instruments could play a vital role in this endeavour; in particular, the role of instruments in recognising when something valuable has been found in a search for new understanding. 'It is almost trite to point out that if you wish to achieve some material effect, your tools, not the theories, are the instrumentalities. A theory cannot be used directly to move or change something' (Price 1984b). Despite the importance of instrumentation (Price 1984a; 1984c; Rosenberg 1992; Irvine, Martin et al. 1997) it remains remarkably under-represented in current innovation literature in terms of how and why it is important.

2.4.3 Learning through instrumentation

This section argues that the use and development of instrumentation is a vital and deliberate aspect of technological change that deserves more focus. Whilst individual scientists may have distinct styles and perspectives of objectivity in bodies of understanding, their description at the socially aggregated level is more stable; scientific explanations share sufficient common ground for overlapping discoveries and contests over their priority to exist (Price 1984b:5). This may lead some to hypothesise that knowledge grows along universal paths that are determined by a process of cognitive cumulation.

However such a view of knowledge growth along a unitary path leaves little room for science and technology policy, because it implies that the paths of knowledge growth are largely predetermined. Kuhn's paradigm shifts (1962) leave an attractive loophole out of this pre-determinacy problem where knowledge growth is still constrained, but might be opened up to non-cognitive factors. Kuhn thought of shifts as emerging when, in order to accommodate a seemingly incomparable finding, an entire system of thought requires radical re-structuring. Major cognitive leaps are necessitated by incommensurable observations, which in turn may have important social or economic contingencies.

Unfortunately, there are difficulties in relying on paradigm shifts to explain technological discontinuities in this way. The history of technology can be structured into paradigmatic patterns (Dosi 1982)[20], but major technical shifts, that represent considerable cognitive advance, do not necessarily acquire the seminal importance that shifts brought on by lesser cognitive advance do. For example, silly putty and the Concorde jet were technical triumphs brought on by considerable cognitive advance respectively, but they did not acquire the importance of the supermarket or the printer, which required less cognitive advance. 'They are just not the type of event that can serve as even the thin end of a wedge to open the closed cumulation of science to the social, economic and general utilitarian determination that such theorists seek' (Price 1984b:5). Thus, relying on paradigmatic cognitive processes of cumulation to explain *shifts* in the socio-economic arena clearly has tight limitations.

Price notes that rather than simply testing theories and replicating experiments, a great deal of laboratory work involves developing '*instrumentalities*'. These involve practicing old techniques for doing something; producing a new technique by tinkering and fiddling with it; then perfecting, extending and using it on everything in sight. Usually this only yields new results that fit very well with prior expectations. But occasionally, it is hoped, the experimenter will produce, by luck or clever judgement, results other than those readily comprehensible within the paradigms of previous knowledge.

For example, Price noted how the telescope provided the conditions in which Galileo made his contributions, an experience which Price delightfully termed 'artificial revelation'

[20] This is not what Dosi's paper aimed to do; rather, as reviewed earlier, it was a theoretical persuasion that technological trajectories can exist. I do however believe this claim is supportable (see also subsequent evolutionary studies such as Ziman 2000b). For example, an IT expert expresses sentiment of almost inescapable progression, 'Precious little has happened over the past five years… steady increases in processor speed and storage size have become as predictable as child's growth… just as the computer industry is predicated on Moore's Law – that chips will double in speed every 18 months, which companies can literally plan on – the telecom industry can be predicated on the transparent network… change is routine and uneventful… the fiber-optic backbone has joined the microprocessor on a steady predictable climb. Processing speeds will double every 18 months. Bandwidth will quadruple every two years' (Steinberg 1998:80-84, cited in Pavitt 1998).

(1984b:9)[21] . The telescope provided 'unnatural conditions' that extended the common experience of the senses. 'Galileo realized that he had manufactured for himself a revelatory knowledge of the universe that made his poor brain mightier than Plato and Aristotle and all the Church Fathers put together….by clothing the naked eye…. His insight was that the new aid to the senses was generalisable to other experiences' and relevant to the real world (1984a:108, 110). This was not the testing of theories, but rather the trying out of new practices and techniques to create new conditions, hoping for learning opportunities, and then relating them to the world outside of these 'unnatural conditions'.

Price advocates the use of the term 'instrumentality' to carry the general connotation of a laboratory method for doing something to nature or to data in hand. But the significant point about instrumentalities 'is that they are not of themselves part of the knowledge system of science. They are clearly *technology*, an understanding of the way to do things, and often in their beginning, as with the telescope and voltaic pile, no one properly understands how and why they do work as they do, but only that they work and that they produce something new' (Price 1984b:13). The key point is that whilst instrumentalities may provide a means of doing something new in the laboratory, they might also conjointly do so for the world outside.

Price (1965) had suggested that science and technology move in linked but largely independent ways, related like a pair of dancers. Upon realising the significance and potential of studying the role of instruments in change, Price revised the imagery by arguing that what keeps science and technology linked is that both dance to the music of instrumentalities. 'Normal science begets more normal science. Normal technology begets more normal technology. But an adventitiously new instrumentality can make for a change in the paradigm within science, and an invention leading to new innovation within technology' (Price 1984a:113).

[21] Artificial Revelation: 'The term is not used lightly. Galileo was not so conceited as to think he was brighter than all previous authorities; he knew that he had been presented with decisive new evidence of the structure of nature' (Price 1984b:9).

Therefore, particularly for the purposes of analysing innovation that draws heavily on science, this thesis suggests that a fruitful line of enquiry would be to combine analysis of cognitive learning factors with an examination of how instrumentalities develop, within an institutional context that facilitates accumulation (rather than fragmentation) of socially produced knowledge. It is with these three incisors (learning, instrumentalities and governance) that the next chapter sets out a conceptual framework for exploring technological change in vaccine innovation, aspiring to incorporate science, as well as technology, in models of innovation and change.

2.5 From bounded to blinded-rationality: fertile ground for new theory

This section develops the notion of a testing regime, ahead of a more formal exposition of the analytical framework of the thesis. It reviews existing ideas on variation in evolutionary theory and situates instrumental testing processes within them.

Evolutionary theory is perhaps our most tactile approach to dealing with empirical challenges in studies of technological change[22]. This is particularly the case for sectors that deal with highly complex, systemic and difficult to predict patterns of behaviour such as biopharmaceuticals[23]. However, evolutionary theory tends to understate the extent to which deliberate and purposeful testing processes drive change. Testing processes are integral to

[22] The explanatory potential of evolutionary theory is suggested not only by the burgeoning empirical studies in this stream (for example Ziman 2000a) but also by the fact that historians of technology and scholars studying growth of knowledge have also arrived at similar points of view, acknowledging some form of variation-selection mechanism at work (Campbell 1987; Hull 1988; Vincenti 1990; Constant 2002). In particular, it has allowed us to account for enormous accumulated technical change in the past; for if we accept that variations are heritable and that selection allows some to be retained, previously unimaginable distances can be traversed given time. Adopting such a view makes us less prone to underestimating the potential future impact of long term technological change (Rosenberg 1986). 'In living bodies, variation will cause the slight alterations, generation will multiply them almost infinitely, and natural selection will pick out with unerring skill each improvement. Let this process go on for millions on millions of years; and during each year on millions of individuals of many kinds; and may we not believe that a living optical instrument might thus be formed as superior to one of glass as the works of the Creator are to those of man?' (Darwin 1859/1994:chapter iv).

[23] Biopharmaceuticals is a category of medical biotechnology (EC 2009:7). Biotechnology is defined as 'the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services' (OECD 2005:9). Biotechnology can be used for agricultural, industrial and medical purposes. Medical biotechnology is further categorised into devices, diagnostics and biopharmaceuticals (treatments and preventatives) (EC 2009:7).

any scientific or technological endeavour by selecting what ideas and approaches are prioritised or discarded; but less readily recognised is that the tests' design, set-up, and execution provide sources of new ideas and approaches for developing them. As the empirical chapters will show, testing concerns feature much earlier in the generation and development of ideas than is commonly assumed.

Crucial to all evolutionary theories has been the notion that variation is to some extent blind[24]. The emphasis on uncertainty in R&D served as an important reminder that it is not adequate to assume agents rationally devise and choose what they are doing from a large range of alternatives with known outcomes. But blind does not necessarily mean random or just effects of luck. Dosi (1982) and Nelson and Winter (1977; 1982) did much to show that the evolution of technical knowledge was not just serendipitous and a result of chance. In this sense, evolution was made less blind with the development of constraining concepts, technological paradigms and trajectories. Further advances have been made by scholars developing the bounded-rationality notion and highlighting cognitive limits (Gavetti 2005; Nelson 2008a).

However, as Dougherty (2007:265) finds[25], there remain difficulties in applying theory outside the 'old' world of 'autos, computers, and chemicals' where models emphasise 'linear, decomposable, scalable, and path-dependent processes that obey the laws of physics.' In contrast, 'many 21st century innovation challenges involve non-linear, non-decomposable, non-scalable and pathless activities that obey the 'laws' of life sciences and social sciences'. As a result, 'after more than a year' of trying, Dougherty sees 'patterns lurking in [her] data but cannot grab them conceptually' (2007:265). So theoretical refinements to the blindness concept are needed for analysing modern empirical data better, and 'people working on drug discovery [using bioinformatics for example] are figuring out limits to blind search the hard way' (2007:267).

[24] 'In going beyond what is already known, one cannot but go blindly. If one can go wisely, this indicates already achieved wisdom of some general sort' (Campbell quoted in Vincenti 1990:48).
[25] See also Pisano (2006) who recognizes there are difficult innovation challenges being faced by the biotechnology sector, but notes that, recently, the sector has become structured so that research is increasingly separated from production and marketing activities. He argues the sector will continue to struggle to remain innovative unless these activities are brought closer together again and co-ordinated more carefully.

There is a need to further particularise our models of R&D and innovation to take into account the diversity of holistic[26] knowledge systems, in particular the distinctive contributions of science and technology. Dougherty's findings indicate that industrial life scientists 'proceed in an emergent, stepwise, but deliberate fashion to feel out the possibilities in a way that preserves the whole problem space but begins to zero in on options' (2007:267). Simply acknowledging uncertainty is not helpful in such situations, where organisations need to engage in deliberate learning activities (Zollo and Winter 2002).

The need for evolutionary theory to adapt its models to challenging new forms of empirical data has been noted. Nelson (2007:31) suggests a new agenda. '..too much of the research within this tradition has stayed too close to certain features of the early work, which I think is causing the endeavour to run into sharply diminishing returns… we played down the role of cognition, understanding, and conscious-problem-solving… in effect we were playing down the importance of human knowledge in the advance of know-how, and in particular were repressing the important roles that the advance of science had played in the evolution of practice… It is time to build more closely into economic evolutionary models the nature and evolution of the knowledge that guides attempts to improve practice.' By deferring too much to behaviouralists (March and Simon 1958; Cyert and March 1963), evolutionary theory lacks agency and struggles to explain change, especially radical change (for example in bio-pharmaceuticals). Agency, on its own however, cannot explain the persistent and cumulative change that is consistently achieved.

Nelson's call to redress the balance is highly germane but, as the thesis discussed, it remains tied to what is essentially a cognition driven perspective. In contrast, the perspective put forward here seeks to emphasise strategic learning through testing with instrumentalities. The tests may still be designed by agents of bounded-rationality, but testing activities are nevertheless considered intentional, shaped by institutional forces and

[26] Dougherty (2007:268) notes that most pharmaceutical companies are reorganising into multi-disciplinary therapy teams to capture interdependencies since the life system cannot be decomposed.

built on previous knowledge and habits (Constant 1983). The question that emerges is how results from such tests can be and are applied to the innovation process.

Chapter 3

Testing Regimes: A lens to explore vaccine innovation

This chapter presents some building blocks from innovation theory with which to explore the inventive efforts documented in the empirical chapters of this thesis. It focuses on the production of technological knowledge in order to contrast with other explanations of vaccine innovation that emphasise the role of the market in vaccine innovation.

One can imagine a Schmooklerian (1966) explanation for poliomyelitis vaccine innovation. It would emphasise that the expectation of profit drove industry to allocate its resources towards inventive activity. Similarly, it might argue that the lack of an HIV vaccine is due to meagre expectations of profit relative to the risks of investment. This thesis will argue that such views are problematic because, firstly, industry involvement was limited in poliomyelitis vaccine innovation and, secondly, considerable resources have been invested into HIV vaccine efforts.

Following Rosenberg's studies (1976; 1982b), an exploration of technical details in upstream vaccine innovation processes is required for a more complete analysis. However this chapter also seeks to develop a lens for organising these details into technological paradigms (Dosi 1982) so that the empirical chapters should not simply be seen as a review of 'the science' underlying vaccine innovation. It uses the concept of operational principles as a device that explicitly distinguishes between science and technology, and opens up the possibility for exploring technical, path-dependent trajectories in vaccine development. The chapter defines testing regimes, charts its role in modern innovation and outlines some of its characteristics.

3.1 Operational principles in technology

Innovation is an iterative process in which problems are selected, and their solutions are generated and selected (Constant 1980; Laudan 1984; Vincenti 1990). Once a problem is selected, potential solutions are generated either by using existing knowledge and problem solving skills or by engaging in a process of testing and learning. Potential solutions become solutions through failure, revision and re-testing. Effective and established solutions can then be thought of as operational principles.

Operational principles are defined by Polanyi (1958:328) as 'how [a technology's] characteristic parts… fulfil their special function in combining to an overall operation which achieves the purpose'. The technological problem provides the function the device must fulfil (purpose) whilst the operational principle is defined by the way the device will perform (function). As such, Vincenti (1990:209) argues, it incorporates features of knowledge beyond science[1]. Thus, science is often necessary but never sufficient for innovation, and the technological knowledge needed for innovation cannot be obtained 'as-is' from scientific knowledge.

For example Sir George Cayley's 1809 statement of the operational principle of the fixed-wing aircraft is: 'to make a surface support a given weight by the application of power to the resistance of air' (quoted in Vincenti 1990:208). This separates lift from propulsion. 'It says that an airplane operates by propelling a rigid surface forward through the resisting air, thus producing the upward force required to balance the airplane's weight. It was fundamental in that it freed designers from the previous impractical notion of flapping wings. All designers have this concept in the back of their minds' (Vincenti 1990:208).

[1] The operational principle 'originates outside the body of scientific knowledge and comes into being to serve some innately technological purpose. The laws of physics may be used to analyse such things as airfoils… once their operational principle has been devised, and they may even help in devising it; they in no way however contain or by themselves imply the principle' (Vincenti 1990:209). Similarly Polanyi states, 'The physico-chemical topography of the object may in some cases serve as a clue to its technical interpretation, but by itself would leave us completely in the dark [about its operational purpose]… The complete knowledge of a machine as an object tells us nothing about it as a machine.' This detail is recognised by patent law in its distinction between discovery and invention (Polanyi 1958:177).

Tacit appreciation of the form and purpose of operational principles is crucial. 'These concepts may exist only implicitly in the back of the designer's minds, but they must be there. They are givens for the project, even if unstated. They are absorbed by engineers in the course of growing up, perhaps even before entering formal training' (Vincenti 1990:208). This also applies to how components are arranged or 'configured' to embody the operational principle. For example, 'automobile designers of today usually (but not invariably) assume without much thinking about it that their vehicles should have four (as against three) wheels and a front-mounted, liquid cooled engine'[2] (Vincenti 1990:210).

Engineering design is decomposable into a multi-level and hierarchical set of problems[3]. Successive stages 'resolve' problems 'into smaller manageable sub-problems, each of which can be attacked in semi-isolation. Problems at the upper level tend to be conceptual and relatively unstructured. People outside engineering think of design primarily in such terms; historians tend to focus predominantly on project definition and overall design. At the lower levels, where the majority of engineering effort takes place, problems are usually well defined and activity tends to be highly structured' (Vincenti 1990:9). However, the notion of decomposability should be employed with caution, particularly in bio-pharmaceuticals, where patterns of behaviour are highly complex, systemic and difficult to predict (Dougherty 2007).

Normally, operational principles and their configuration are well established throughout the hierarchy. Most technology is well understood and the challenge is to make steady incremental improvements at the lower hierarchical levels. Constant refers to this as 'normal technology' and Vincenti calls the process 'normal design'[4]. 'The engineer engaged in such design knows at the outset how the device in question works, what are its customary features, and that, if properly designed along such lines, it has a good likelihood

[2] 'They doubtless assume other things as well. Other features may be left open to be decided in the course of the design (whether for instance power is to be applied via the front wheels, the rear wheels, or all four). Whatever the details, the preferred configuration for a given device with a given application is knowledge that has to be learned by the engineering community, usually by experience with different configurations in the early stages of a technology' (Vincenti 1990:210).

[3] See Vincenti (1990:9) and Constant (1984:24-27, 33) for examples of multi-level and hierarchical design.

[4] Normal technology is what Constant's technological communities usually do – 'the improvement of the accepted tradition or its application under 'new or more stringent conditions'… like Kuhn's normal science of 'puzzle solving'' (Constant 1980:10).

of accomplishing the desired task' (Vincenti 1990:7).

But for radical design, or perhaps even normal design in bio-pharmaceuticals, familiarity with such design concepts cannot be assumed. 'How the device should be arranged or even how it works is largely unknown. The designer has never seen such a device before and has no presumption of success. The problem is to design something that will function well enough to warrant further development' (Vincenti 1990:8). Simply, operational principles are yet to be developed and the challenge is to find one that works at all in terms of function and purpose.

Despite the need for holistic approaches in bio-pharmaceuticals noted by Dougherty (2007), routines for establishing operational principles are likely to be dynamic and hierarchical; where progressively lower levels are sequentially fleshed out as a line of development or operational trajectory. This is because when there is uncertainty at a given level of operation, lower levels are also subject to the same or more uncertainties. As one operational principle is established, another needs to be established further down the design hierarchy. Solutions to one set of problems go on to define a new set of problems further along the design process (Laudan 1984:84; Vincenti 1990:9).

However, as operational trajectories proceed, designers learn about probable efficacy through preliminary tests. This means that the trajectory is not completely linear with time, and that knowledge acquired about lower hierarchical levels feeds back up to higher levels too. The degree to which testing, learning and feedback is possible within the operational trajectory is therefore a key factor in the rate of technological change. We return to how operational trajectories are selected later.

3.2 Formalised testing regimes

Testing and learning in the innovation process have perhaps become more common in recent times because the feasibility of inventions can be trialled more easily before going into full scale operation. An increase in the number of trained scientists in the workforce,

organisations that have accumulated capabilities in testing prototypes, technical and instrumental developments focused on testing, may all have contributed to a new environment that makes indirect testing more favourable than in the past (Nightingale 2000).

Situations where there is less scope for indirect trial still likely remain, for example an artisan working from conception through to fabrication with little more than the resolving eye and the skilful hand[5]. Whilst this form of technical development may have many favourable artistic attributes, products emerging from craftsmanship are likely to be of high unit cost, low standardisation and relatively low complexity. Learning and product refinement is largely confined until after the product is introduced to the environment directly. Knowledge accumulation and transmission relies heavily on traditions, rituals and apprenticeship, acquired mainly through interactions in person, involving tacit or procedural knowledge and skills transfer (Constant 1980).

These aspects of knowledge accumulation are still important for innovation where there is scope to trial products before exposing them to their environments. However, other characteristics of technological change start to emerge more prominently when knowledge specifically dedicated to testing is embodied in people (communities and organisations) and artefacts (equipment, tools and instruments).

For example, the rate of technical change can be markedly more rapid when designs are exposed to the environment vicariously through indirect testing and when feedback is quicker. Where vicarious development is not possible, such as craftwork, selection has to take place by direct trial in the environment, and traced back to which 'skilled master' introduced it, before imitation and distribution. So useful design improvements might be overlooked, and many of them may not be incorporated into cumulative and systemic change.

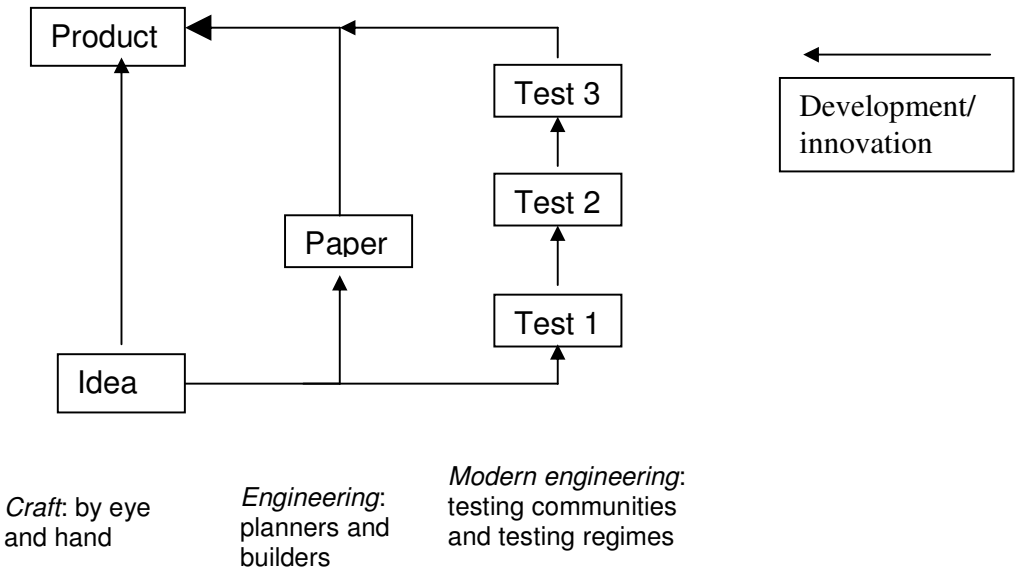
[5] Nightingale (2007) personal communication.

Dedicated testing regimes reflect a greater organised division of labour. For example, engineers and architects plan on paper by conceptualising their ideas visually (Ferguson 1977). With drawings, they transmit their ideas to workmen and labourers who build, construct, and might also add further creativity (von Hippel 1988). Crucially, plans can be refined and modified on paper because design and production is separated to a greater extent.

Testing regimes can be yet more formalised. Indeed, a prominent feature of many modern engineering sectors is a highly formalised testing regime with communities that are dedicated to their development through routinised and systematic testing practices. Constant goes so far as to suggest that 'bold total-systems conjecture and rigorous testing to large scale, complex, multilevel systems beginning in the nineteenth century created a fundamentally novel category of knowledge and knowledge processes distinct both from science proper and from craft technology' (Constant 1980:21). This form of organised engineering, with divided labour exploring the environment indirectly, is capable of much faster and more cumulative change than craft based technology and paper-planned design (Constant 1980; Constant 1987; Brusoni 2001; Brusoni, Prencipe et al. 2001). Their products are typically more sophisticated, standardised and of lower unit cost.

The various degrees of testability and testing regimes described in this section can be depicted as different modes of innovation process (see figure 1), where the route to innovation can range from the direct to the highly punctuated with several intervening steps. It should be noted that important and complex feedback loops have been omitted for the purposes of illustrative clarity. The diagram resonates strongly with recent evolutionary theory about 'offline' development (Nelson 2008a; Nelson 2008b).

Figure 1: Increasing indirectness of innovation



However, the advantages of increasingly being able to disconnect technical change from its environment need be to set against some important disadvantages. Industries that exhibit formalised testing regimes can be susceptible to large degrees of unresponsiveness to rapidly changing environments. Inflexibility and path-dependency can have harmful effects for society (Dosi 1982; David 1985; Blume 2005). Thus a central feature of testing regimes, vicarious 'offline' testing, can make possible an increasing intensity of production but can also limit choices about the direction of technological development by reducing direct engagement with the environment (Stirling 2009).

The questions that emerge are: 'What is it that is 'modern' about modern technology?' (Rosen cited in Vincenti 1990:256). What then do we mean by a formal testing regime? And how have they had such a profound effect on the rate and direction of technological change?

3.3 Constitution of a testing regime

The testing regime is defined in this thesis as a system made up of intermediate conditions, instrumentalities, and institutional structure. These core terms are in turn defined as follows:

1/. Intermediate conditions – A set of environments in which experiments are undertaken to learn and develop technology.

2/. Instrumentality – A way of carrying out an experiment, a skill or technique used in conjunction with an instrument or tool to create specific intermediate conditions.

3/. Institutional structure – An important context that provides problems to be worked on and influences ways of working.

Each of the components of a testing regime is examined in more detail below but it is important to note that these core concepts are highly interactive. When we examine a 'testing regime' we must be aware that we are dealing with an ensemble of all three elements.

3.3.1 Intermediate Conditions: the reduction of uncertainty

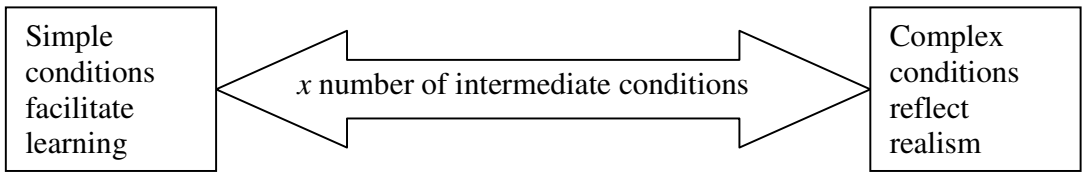
New operational principles are built up in a series of iterative and recursive steps, whilst complex phenomena are broken down and simplified (Nightingale 2000)[6]. This is conducted with a background, tacit knowledge of how an operational principle works and whether actors can intervene to create artificial conditions more suitable for analysing patterns of behaviour (Nightingale 1997). This analysis involves a process of recognising, mapping and theorising patterns of behaviour. Patterns of behaviour caused by features of the world that are external to the operational principle can be removed, in the mind first (during experimental design) and then in reality (experimental set-up). This leaves behind the explanatory factors that are of most interest. In this way, the strength and extent of key

[6] Mahdi (2002) refers to this breakdown of phenomena as problem parsing.

causal relationships can be assessed for their reliability; and the robustness of a new operational principle can be extended into practice.

Initial explanations formed in protected and purified laboratory experiments may not necessarily remain relevant in the more messy and unpredictable world outside the laboratory (Nightingale 2004). The ability to learn is facilitated by modifying and creating simplified conditions, where specific causal mechanisms can be isolated and tested (Hacking 1983). However, the resulting experimental knowledge needs to be iterated back and forth into more complex conditions of application to ensure relevance outside the laboratory. Thus, the development of new operational principles is permeated by constant trade-offs between conditions that facilitate the ease of learning and conditions that are relevant to the non-laboratory world[7]. Figure 2 depicts this trade-off.

Figure 2: A trade off in which the innovation process goes back and forth



Presenting intermediate conditions as a scale adds to Nelson's (2008a; 2008b) concept of 'offline' or 'online' development by indicating that there may in principle be a continuous spectrum of conditions that lie in between offline and online[8].

3.3.2 Instrumentalities: the manipulation of intermediate conditions

The ability to tinker with these conditions so that ideas work and become operational principles is important for knowledge growth. Its importance has been noted by several

[7] When a balance can be struck between the two, Nightingale (2004:1264) refers to such environments as 'artificially purified conditions where theories and the world coincide.'

[8] For example, temperature is often part of experimental conditions in biology and biotechnology, but it is not a discrete variable that can either be offline or online. It can be held constant or variable, but when it is variable it can be more, or less, realistic relative to the designer's intended operating environment of the technology in development.

scholars referring to 'research technologies', 'standardised packages', 'epistemic machinery', and 'thing knowledge' (Fujimura 1992; Rosenberg 1992; Knorr-Cetina 1999; Joerges and Shinn 2001; Baird 2004). Their use and application rely on tacit skills and techniques (Nelson and Winter 1982:74; Senker 1995; Hopkins 2004:15).

The impact of instrumentalities on technology is being explored, for example in the nano-materials sector (Rafols 2007; Olsen 2009); although, why they can have such immense impacts on the development process is not directly examined. Nelson (2008b:488) argues that the ability to 'identify, control and replicate' conditions influences progress along technological trajectories. Whilst variable conditions may enable learning and the development of theories, this does not, on its own, facilitate the development of a technology. Rather it is the intended and deliberate manipulation of these conditions with *instrumentalities* (Price 1984b:13) to allow the variation and selection of alternative explanations (Deutsch 1997).

The notion of instrumentalities has not been overly specified and tightly defined because it is intended for flexible application in empirical contexts. Its value is likely to lie in the way that it draws consistent attention across varying empirical contexts to the distinctive contribution of technological knowledge to innovation, as distinct from scientific knowledge. Instrumentalities: the use of certain objects (artefacts) in certain ways (skilled techniques), can be useful for learning in a laboratory[9], but it may also be conjointly useful for the world outside. In such circumstances, instrumentalities are critical for the creation of a set of intermediate conditions that lie in between the laboratory and the world outside, where the production of technological knowledge is most intense.

Instrumentalities provide a link between experiment and application by allowing iteration along intermediate points of conditions. Technologies develop as instrumentalities reduce uncertainty by winnowing the number of possible explanations for behaviour. This helps select out a large proportion of possible explanations. As Deutsch (1997) notes, while there

[9] For science, the ability to adjust our ideas for given conditions is given more primacy than our ability to adjust conditions to make ideas work.

are an infinite number of possible explanations for a phenomenon, there are only a finite number of actual ones. Technologies increasingly are too complex to explore unaided, and instrumentalities allow conditions to be created for a subpopulation of possible explanations to be selectively explored, analysed and tested. A well developed set of instrumentalities allows a more focused set of explanations from which to choose, reducing search time and costs.

Instrumentalities help technology to be reliable (in the sense that they function repeatedly) and valid (in the sense that they function across varied conditions). These selected characteristics of knowledge are implicated when instrumentalities allow the creation of a series of intermediate conditions in which realistic sets of explanations can be formed. Thus, instrumentalities allow rapid recursion between reliability and validity, resulting in 'strongly corroborated' but not necessarily 'true' knowledge (Constant 2000:221).

Learning and innovation can therefore be facilitated by improving the resolving power of instrumentalities, such that they increase the number of intermediate conditions. The greater their number, the easier it is to make reliable inductive inferences that can be shared across different sites with the minimum of 'tinkering'. This effect is appreciated by engineers, 'About half of the Institution of Electrical and Electronic Engineers annual list of the 200 top innovations is devoted to testing equipment' (Constant 1980:276). Since experimental conditions are created locally, their co-ordination requires the use of specialised technology, shared tinkering or standard operating procedures.

Cumulative learning is affected by how observations emerging from instruments are categorised. The technologist (and scientist) has to constantly make decisions over whether to take a new reading as highly significant or whether to put the observation down as an error in procedure or protocol (Polanyi 1964)[10]. Inevitably these personal judgements are

[10] These observations need to be related to the complexity and relevance of conditions but observations, often borrowed explicitly from science, are always laden with theoretical assumptions (Hanson 1958; Feyerabend 1987). They can serve to *frame* observations either as potential breakthroughs or as rendered contaminants. Instrumental equipment and criteria are therefore calibrated according to such assumptions and frames. For example, in order to keep the data output at manageable levels, the new Hadron Collider (particle accelerator)

subject to cultural, educational and social conditioning. We can, but only to a certain extent, protect against such subjective judgements by repeating and varying tests as many times as resources allow (Nightingale 2000; Nightingale and Mahdi 2006).

Cumulative innovation relies on instrumentalities being used to gather prescriptive, as well as descriptive, knowledge (see table 2 and figure 3)[11]. Procedural knowledge involves knowing what to design *for*, as opposed to knowing *how* to design to a given requirement. Amorphous, ill defined, qualitative goals must be translated into specifiable, attainable, quantitative goals couched in definite technical terms. Without such technical performance specifications, the designer cannot contrive the details that are ultimately required. For the designer these quantities are objective ends, for everyone else they are objective means to an associated subjective end.

Table 2: Description and Prescription

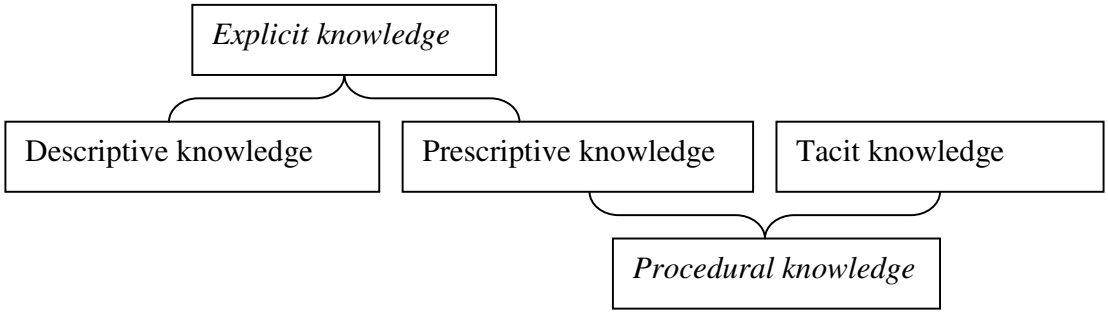
Descriptive Knowledge	Prescriptive Knowledge
Describes things as they are	Prescribes how things should be to attain a desired end
It is knowledge of fact or actuality; judged in terms of veracity or correctness	It is knowledge of procedure or practice; judged in terms of effectiveness, degree of success/failure
While it may be more or less precise, it is not subject to wilful adjustment by engineers to serve their needs	Can be altered at will to be more or less effective

Source: Compiled from a summary of Vincenti (1990:197-8, 216-7, 236-7).

is being fine tuned and calibrated to detect and allow for certain observations predicted by string theory (Shiga 2007).

[11] As earlier scrutiny of operational principles suggested, a full descriptive understanding of the way things are is not sufficient for technology. Prescriptive and tacit elements are necessary, which indicate: in order to accomplish this, arrange things this way.

Figure 3: Explicit and procedural knowledge



Source: Taken from Vincenti (1990:198).

For example, applying this to vaccine development, criteria need to be set in the development of vaccines. The qualitative goal of immunity must be translated into quantitative goals such as the proportion of antibodies that need to be neutralised, or the number of T cells that must be activated, or the required concentration of immune system support molecules such as cytokines or chemokines. Specifications about what is meant by a 'working vaccine' are required. Vaccines can be designed to provide immunity quickly for a short length of time, or can be designed to become gradually more effective through the use of boosters to provide immunity for longer periods of time.

For technology, observations emerging from instruments need to be framed within a set of theories that may not, accurately, be called science. They are distinct because they are 'device specific, have little explanatory power or scientific standing… Engineers devise them because they must get on with their job and the phenomena in question are too poorly understood or too difficult to handle otherwise… They are used because they work, however imperfectly, and because no better analytical tools are available' (Vincenti 1990:214). Even more expedient tools exist but these are 'too crude even to be dignified as theories.' They are often realised to be wrong and used for practical reasons because they are known from experience to give conservative or otherwise acceptable results.[12]

[12] The role of these tools is merely to establish a relative order between observations that need not be absolute. Properties of the technological systems (such as size, weight and conformation, composition) measurable or observable by instruments are related to predictable and unpredictable conditions to make 'educated,' experienced guesses about function and failure. The exact number of antibodies is not as important, as establishing when they are more or less, and critically when they are *enough*.

3.3.3 Governance in testing regimes: coordinating instrumentalities

Leadership of, and co-ordination between, research and development groups completes the triad, by ensuring that the new knowledge arising from experimental practice with instruments is accumulated, assimilated and utilised. For the purposes of a research and development community, the testing regime is a 'shared utility' that forms an important part of the 'invisible' research infrastructure (Nightingale 2004) because testing regimes do not develop autonomously alongside technological opportunities. They are created at high fixed cost and need governance to set up and maintain.

Testing regimes exist in an institutional context where there are 'basic rules of the game' derived from laws, norms, customs and costs for organising labour and transactions (Granovetter 1985; Williamson 1985; Hodgson 1988; North 1990). Within that context, as noted in section 3.2, testing regimes develop technologies in niches protected from these direct market and social forces (to varying degrees). As a consequence, governance is needed to organise the division of labour, coordinate the distribution of testing materials, allocate resources for testing, ensure comparability of methods and results, and make choices about the development of parallel R&D paths.

The particular set of governing structures required for establishing and maintaining a testing regime requires further separate characterisation. Instrumentalities are 'physical technologies', but the way in which work is divided and coordinated across multiple parties using instrumentalities can be conceived as 'social technologies' (Nelson 2008c). The two technologies co-evolve but the social is more difficult to direct and control than the physical (Nelson 2008c), and so it is likely that the testing regime changes slower than the technology it tests and develops.

Variations in experimental practice and instruments can mean that comparison is not possible; conditions or standards between tests may be different, accuracy and relevance may be checked with different instruments. With low comparability, the interpretation of testing data in order to eliminate less suitable trajectories becomes subject to intense social negotiation as interests form around particular trajectories. Governance structures can either

co-ordinate various activities and instruments to increase comparability across conditions or it can provide leadership that mediates arguments about how the instruments are calibrated and the criteria for success or failure (this forms part of the procedural knowledge).

Standard-setting is a principal way to divide labour and co-ordinate activities dimensions; one can set certain quality standards to aim for, use technical standards to compare across, and establish reference standards to track progress[13] (David and Greenstein 1990). Processes of standard setting, both within and across organisations, can result in standards being explicitly published or remaining 'private' (Farrell and Saloner 1988; Hawkins, Mansell et al. 1995). One can imagine that technologies can still develop in contexts of privately held standards, but as Steinmueller (2003:134) notes, the standards literature has not yet analysed such contexts.

Governance is also needed to play a strategic role in selecting between possible operational trajectories. It is of course possible to conduct development on parallel trajectories to hedge against uncertainties about function and purpose, but this quickly becomes impossible as the costs of developing multiple trajectories become too expensive to maintain and choices must be made along the way (Nelson 1961; Scherer 1967; Arditti and Levy 1980; Scherer 2007). Where costs allow, parallel trajectories may survive all the way through to full development, such that broader market or socio-political forces have greater impact on choice.

The testing regime itself can take on alternative trajectories of development and may raise issues in need of policy guidance. Testing regimes and technological change are bidirectionally related, and can be conjointly or independently dynamic. Sometimes to unlock innovation, the development of the testing regime needs to be addressed directly. Policies might be put in place to encourage the development of techniques and skills, and

[13] Instruments can also be calibrated or designed to provide a way for standardisation. For example, rulers can be designed and distributed to allow distance to be measured in centimetres and not inches. Similarly, time can be measured by radioactive half life, but the watch is a more practical way of providing measurements in minutes and hours. In some cases of technological development, the range of instruments available for use may be wide, the scope for manipulating conditions large and the number of possible intermediate conditions high. In these circumstances governance becomes even more important.

instruments and analytical tools so that test results feed back quickly. Efforts might be directed towards reducing the costs of supplying prototypes and models so that testing can be high volume. These are overt governance challenges and attention to the evolution of such supporting infrastructure can be easily overlooked if a particular innovation is being zealously pursued.

3.4 Application to vaccine innovation

This section situates the notion of testing regimes within the specific context of vaccine innovation. In the vaccines literature, Blume's focus has been largely sociological, Muraskin's largely political and Galambos' on the private firm. Focusing on the gradual and persistent accumulation of technological knowledge is likely to complement social, political and industrial analyses of vaccine innovation, rather than duplicate them. The section will then highlight pertinent questions about the way testing regimes affect vaccine development.

3.4.1 Incorporating revolutionary technologies into existing knowledge

Many authors have written about revolutions (impending or past) in vaccine science and technology (Galambos and Sewell 1995; Muraskin 1998; Galambos 1999; Andre 2001; Plotkin 2005a). These perspectives tend to emphasise science as the major contributor to vaccine innovation. The biotechnology revolution and, more specifically, the ideal of 'reverse vaccinology' through rational design (Pizza, Scarlato et al. 2000; Capecchi, Serruto et al. 2004; Danzig 2006) envisage potential vaccine targets being identified from the genome sequence rather than pathogen cultivation or manipulation (see chapter 5).

Perspectives that emphasise the revolutionary potential of new scientific breakthroughs often come at the cost of overlooking the broader technological context into which they must enter, where there is considerable prior accumulated knowledge that also needs to be integrated. In effect, they are prone to understating the additional research and development that is required to bridge the gap between science and innovation. As such, breakthroughs

that were expected to revolutionise the pharmaceutical sector have on their own failed to reinvigorate product pipelines and are yet to yield a windfall of new therapeutics (Nightingale and Martin 2004; Hopkins, Martin et al. 2007). Thus, many of the divisions between past revolutions or cycles seem artificial or even arbitrary because past strategies continue to be useful rather than completely displaced.

The impacts of major discontinuities need to be related to and assimilated into a system of old technologies for cumulative technological change. Even where old is completely displaced by new, the origins of revolutions can be traced. '…'creative destruction' is no more prevalent than 'creative accumulation' since revolutionary new technologies either grow out of old technologies, or must be combined with changes in them in order to develop useful artefacts'[14] (Pavitt 1999:xv). This thesis does not seek to identify the next revolutionary technology to sweep the vaccine industry; instead it focuses on the steady accumulation of technological knowledge as it leads up to innovation[15].

International efforts to encourage vaccine innovation have tended to overlook the steady cumulative aspects of the process. The Children's Vaccine Initiative was created on the hopes of a biotechnology revolution and on fears that the market place was responding only to effective demand[16] (Muraskin 1998). The CVI was founded to improve communications throughout the vaccine innovation system, from basic research and product development through to supply delivery. At its core was the assumption that better co-ordination of

[14] Pavitt here is discussing the nature of the micro-electronics revolution, but Constant (1980) holds and almost identical view with regard to what is termed 'the turbojet revolution'.

[15] This thesis therefore reflects scepticism about the extent of the discontinuities generated by 'revolutionary' technologies. Revolutionary changes in understanding rarely make redundant all of the techniques that feed into –and are necessary for - a complete product. 'A new paradigm does not discredit and displace all of the knowledge generated in earlier paradigms, but instead adds to them. Newtonian physics still has major theoretical and practical uses, and at least a quarter of all the new technology created today is still in mechanical engineering. The development and commercial exploitation of technological discontinuities turns out to be a more cumulative process than is often supposed' (Pavitt 1998:443). The thesis emphasises that innovation draws on stocks of knowledge other than science and represents more than the application of pure science.

[16] The CVI was founded to develop new improved vaccines by bringing together actors in the health community network. These included scientists, health bureaucrats (national and international) foreign aid donors, and vaccine manufacturers (private and public). The network communicated with each other through personal links, publications and conferences but rarely worked together. The kind of private public sector switching that occurs in science was not thought to occur as much with administrative officials (Muraskin 1998).

economic information about the biotechnology revolution and about social demand would solve the problem, a static view that understates the role of dynamic tacit and technological knowledge growth.

The CVI was initially focussed on developing an oral tablet that protects against a dozen diseases (a 'magic bullet'), before turning its mission to field delivery of existing vaccines. The CVI was considered unsuccessful and disbanded[17]. But the reasons put forward for its failure have been centred on various polities, overlooking the need for organisations that engender tacit skills and infrastructure capable of accumulating technological knowledge (Muraskin 1998). Muraskin's Machiavellian analysis of turf wars and political infighting serves to underscore the need for effective governance in a testing regime that may cross political borders.

3.4.3 The industrial organisation of the vaccine system

The most prevalent organisational context for testing regimes has been firms, which dominate the development and marketing of vaccines (Douglas 2004). Galambos and Sewell (1995) provide detailed insight into industrial vaccine innovation at Merck, and some of the organisational capabilities required to undertake innovation[18], but do not afford explicit attention to the testing regimes at work.

Galambos and Sewell (1995) find that a number of 'cycles' of revolutionary technologies and vaccines have emerged from a mixed system of public, profit and non-profit making institutions. By focussing on the varying incentives and disincentives for inventive efforts at Merck, they suggest that threatening the market conditions faced by private sector actors

[17] In the late 1990s, the CVI was replaced with a new initiative called The Global Alliance for Vaccines and Immunization (GAVI), which focused on ensuring equity in access to new vaccines (Muraskin 2004; Hardon and Blume 2005).

[18] Galambos and Sewell (1995) focus on Merck's ability to read signals from scientific and medical networks, forge new links and ultimately manage the firm through a changing knowledge environment, where many others failed. Some of Merck's absorptive capacity resided in the fact that the executive leadership used to be research leaders themselves, such as Maurice Hilleman, who turned out to be a crucial catalyst for innovation. Although the authors do not make any reference, their description of Hilleman may well fit that of the network builder or the systems leader (Hughes 1983).

would cause a fundamental and detrimental shift in the tripartite system that has so far fostered vaccine innovation[19].

The role that public policies might play in strengthening a testing regime is left largely unexplored by Galambos and Sewell (1995). This is particularly significant because, since their caution about altering the status quo, two conspicuous shifts in the pharmaceutical industry have emerged. Firstly, the industry has become increasingly disaggregated (McKelvey and Orsenigo 2006). Secondly, and perhaps relatedly, public-private partnerships have become more prevalent (for example Chataway and Smith 2006). The next section discusses some implications of these shifts in turn.

3.4.4 The role of the public sector in shaping norms, values and choice

Whilst the pharmaceutical industry continues to be dominated by large firms undertaking most of their innovative activity in house, recent decades have seen significant vertical restructuring of the industry such that firms increasingly rely on externally sourced R&D coming from small biotechnology firms (McKelvey and Orsenigo 2006). The causes of this restructuring of R&D activity are complex, ranging from changes in patent law and practice that have extended exclusionary IPRs further 'upstream' in science (Heller and Eisenberg 1998; Mazzoleni and Nelson 1998), financial market innovations that have eased access to venture capital for early stage companies (Hall and Lerner 2009), and the development of institutions[20] that have encouraged universities and public laboratories to actively promote commercialization (Debackere and Veugelers 2005; Candemir and Van Lente 2007).

One consequence of these changes is that a larger market for knowledge has emerged where knowledge is traded between small technology firms and large integrating firms

[19] 'The private firms read a combination of scientific/technical and market signals; the professional institutions read scientific/technical signals and blend them with signals about their members' functional concerns; the public institutions blend political signals from the electorate, interest groups, and governmental bureaucracies with information of a scientific, technical and professional nature. The public interest in disease control is best served, we believe, by having all of those signals read and responded to by an innovative, mixed system' (Galambos and Sewell 1995:250).

[20] Examples of such organisations are science parks, technology transfer offices, incubators, spin-offs, contract research consultancies (EC 2004:10). Much of the literature resorts to referring to them as bridges or intermediaries to cross undefined regions between university and industry (Webster 1994; Bozeman 2000).

(Brusoni and Geuna 2003). Pharmaceutical innovation now exhibits a complex network of contractual agreements linking a variety of actors at various stages of the development process. Empirical evidence on strategic technology alliances also shows an explosion of collaborative activity since the early 1990s, with many of these alliances spanning national boundaries[21] (Powell, Koput et al. 1996; Powell, Koput et al. 1999; Roijakkers and Hagedoorn 2006).

Even where there are weak market incentives, private firms (both small and large) still interject because R&D networks extend to public sector research organisations. Public-private partnerships, particularly those involving philanthropic entities, have emerged as a dominant solution to co-ordinating R&D activities in neglected diseases, where markets are weak (Buse and Waxman 2001; Widdus 2003; Arnold 2005; Moran 2005; Chataway and Smith 2006; Chataway, Brusoni et al. 2007).

Many authors view these changes in the industry as a worrying trend that is systematically undermining public sector competences (Gréco 2001:1609; Yamey 2002a; Yamey 2002b; Foladori 2003; Barder 2005; Lorenz 2007). However, one author goes further in suggesting that these shifts change the nature of products emerging from testing regimes (for example Blume and Zanders 2006). This thesis seeks to build on work by Blume in particular, whose histories focus on the nature and social acceptability of the vaccines that are produced. By disclosing the values, assumptions and social negotiations through which vaccines are endowed with particular features[22], Blume aims to show that gradual privatisation of public sector activities and services is detrimental for public health and social welfare.

An important step in this argument is to show that industrial restructuring and public-private partnerships results in a shift in social values, norms and assumptions. By

[21] Between 1963 and 1999 over one-third of new drugs approved originated in industrial alliances (Danzon, Nicholson et al. 2005).

[22] In this way, Blume's work resonates with the social construction of technology literature, which carries strong differences in emphasis when explaining rate and direction of technical change to the literature reviewed in chapter 2. For example, Blume pragmatically avoids drawing explicit boundaries between science and technology.

examining rival theories of knowledge production (Gibbons, Nowotny et al. 1994; David, Foray et al. 1999), Blume and Geesink (2000b) find that 'vaccinology' is now highly privatised and fits the more diffused 'mode 2' model. They suggest that privatisation has a detrimental shift in the values, norms and incentives that structure existing disciplines and institutions of vaccine R&D. Although, they do not go as far as David et al. (1999), who argue that 'mode 2' skews incentives in 'parasitic' way, drawing resources away from traditional scientific work; Blume and Geesink (2000b) remain more concerned by the impact on vaccine technology in society.

Another step in the argument is to show how the changes take effect on the nature of vaccines and their incorporation into social systems. Blume and Zanders (2006) argues that under new organisations of vaccine R&D, such as public-private partnerships, public sector competencies are undermined and ultimately, the scope for vaccine choice is diminished. The paper suggests the need to critically examine the implications of having various nations' public sectors under increasing encroachment by a globalised and privatised vaccine industry. An over-dependence on the private sector may develop as public sector competencies in evaluating, developing or manufacturing vaccines are lost. A growing and concentrated industry has an interest in standardised products that can be marketed globally. Increasingly vocal advocacy groups are in tune with global opinions, where individual rights and responsibilities have acquired much greater emphasis over collective interest. Blume shows that these forces are now impinging heavily on public health officials and consequently health policy outcomes.

The importance of coupling vaccine development and production to a national vaccination programme, and insulating them from such collective forces is illustrated in a series of papers (Blume and Geesink 2000a; Blume and Lindner 2004; Blume 2005). Blume uses histories of poliomyelitis vaccines and the shaping of vaccine policy to show why public sector vaccine institutes should respond to quite different incentives to innovate than do multinational pharmaceutical companies[23].

[23] Drawing on the concept of lock in and path-dependence (David 1985; Arthur 1989; Arthur 1994), these papers by Blume highlight the influence of national characteristics and institutions on vaccine selection and deployment. By comparing vaccine policy in the USA with that in the Netherlands, he charts the practices and

Two of the themes Blume identifies in his exploratory paper (1998), safety and data collection, are explored in more detail in this thesis. Blume (1998:170) views questions such as 'can the next step be justifiably taken?' as reflections of a relative process of negotiation between social groups. This thesis adds to these views by emphasising that such questions are also an indication of an inherently iterative process of using instruments to guide cognitive processes in garnering technological, as distinct from scientific, knowledge. Institutional norms play an important role in the testing regime, but even if social negotiations could somehow be quenched, such questions about taking 'the next step' would still arise, where instruments and testing play key roles.

3.4.5 Diagnosis, expectations and visions

Expectations have been argued to be a crucial part of technology dynamics because promises are vital to network formation[24] (van Lente 1993). They are seen as a resource for actors when they legitimize arguments and mobilise funds and attention. In his cyclical model, 'opportunities presented as promises, get accepted and become part of an agenda; and are subsequently converted into requirements that guide search processes' (1993:198). It is an inherently forward looking perspective that sees technological change as essentially ideas being turned into world-altering actions through expectations that are either pre-existing or constructed. Whilst expectations are important, focussing analysis on it detracts from how, through testing processes, we may unexpectedly learn from the world to change our ideas about how a technology should or can function.

However, the notion of a '*social vision*' of the future (Blume 1992:64-70) is important for vaccine innovation. The 'Tyranny of Diagnosis' (Rosenberg 2002) highlights how the specification of disease concepts has played a pivotal role in 'how we organize health care delivery, think about ourselves, debate and formulate social policy, and define and manage

interests that was likely to have 'locked out' one of the vaccines that was later improved and found to be very useful were it not for the strength of the Dutch public sector health institutions.

[24] Van Lente (1993:37) defines promises or expectations as explicit statements uttered in public or written down in order to stress their social and shared character. Expectations have a performative element to them as they transform statements into actions. 'The statement alters social reality; it creates, reinforces, or destroys a social connection or *linkage*' (1993:191).

deviance' (2002:236). By providing an essentialist taxonomy, the act of diagnosis has allowed the development of specialised bodies of clinical knowledge and medical technologies to address mechanisms of disease. Employing definitions of disease is also the link through which clinicians can use these technologies (and bring institutions to bear) on patients in a routinised and predictable way.

Thus, the construction of a vision for the technological community depends on an essentially scientific endeavour of establishing an observable causal relationship, hence the technological importance of an accepted explanation of disease. Once a cause is established, the notion of developing a vaccine (or other technological strategies) becomes possible. Following Thagard (1999), there are two stages before experimentation and mechanism elaboration where such an approach to developing medical technologies can break down.

First, before a causal inference can get underway, there needs to be a disease to be explained (Thagard 1999:20). *Characterisation* (Thagard 1999:129) is harder for diseases which have many different symptoms (typically called syndromes). It is easier when symptoms are distinct and do not change much over time. The indeterminacy of symptoms can be a serious impediment to diagnosis, and hence the development of causal understanding. Second, for *cause specification* (1999:130), there can be too many causes to sort out and a disease may correlate with many possible causes. Or the causal factor may not have the power to impose a readily observable effect with current diagnostic instruments (1999:117). Or there may be background theories (such as religious disease concepts) that impede the recognition of plausible causes (Thagard 1999:22; Hilleman 2000b:1436).

3.4.6 Laboratories, animals and humans

This section identifies emerging questions to lead the empirical analysis.

Following Thagard and Charles Rosenberg, a social vision is formed as a disease is characterised, its causes established, and resources and institutions reorganised towards developing a solution to the problem. The key questions that inform this vision are:

- What are the causes and origins of the disease?
- Are resources and institutions being reorganised?

In the case of vaccines, there are essentially two operational principles new vaccine knowledge may build on: a passive immunisation, or active immunisation with a live or killed pathogen (see chapter 5). The testing regime can either be weak or strong in terms of accumulating this technological knowledge. Subjective goals are translated into more feasible, objective and specifiable criteria (Vincenti 1988). One can expect the development process to go back and forth between intermediate conditions, and the transitions to be difficult. The jumps from concept to animal modelling, and from animal modelling to clinical trials, are likely to be fruitful points of analysis. They will involve making inferences and judgements as conditions vary between artificially simplified learning conditions, and real and complex technological conditions (Nightingale 2004). The most crucial questions that emerge are:

- How does a testing regime help accumulate technological knowledge?
- What makes a testing regime weak or strong?

3.5 Summary

The previous chapter reviewed how evolutionary theories of innovation moved debates beyond science-push and demand-pull explanations. This chapter builds on that stream of theory (Nelson 2008a; Nelson 2008b) by exploring how a testing regime may affect the power of technological paradigms and trajectories to accumulate its own knowledge. Together, the chapters emphasise that knowledge growth is not only a cognitive process, but that knowledge is also socially accumulated. They argued that cognitive perspectives could be usefully augmented with analysis of how instruments develop and interact with the innovation process.

This chapter presented the testing regime as a lens for exploring the empirical chapters. The testing regime consists of instrumentalities for the creation of intermediate conditions, and governance for shared learning and technical development.

Chapter 4

Appreciative Synthesis: Methods and methodology

This chapter discusses why a case study approach was adopted, why poliomyelitis and AIDS were selected as cases, the challenges of studying a contemporary case, and the benefits of analysing data through synthesis.

4.1 Reasons for adopting a case study approach

4.1.1 Getting 'dirty' with the details

The development of a new vaccine tends to be seen as an event transpiring in a 'black box'[1]. Innovation can either be pushed by science, or markets can be corrected to exert stronger demand pull forces[2]. This thesis recognises the importance afforded by these policies to vaccine innovation, but seeks to open up and examine the contents of the black box, into which vaccine innovation has been consigned[3]. I believe this will not only allow for further complimentary innovation policies to be developed, but will also illuminate why there are differences in rate and direction of technical change. This is because specific characteristics (of viruses, techniques, instruments, and science policies), together with historical contingencies and tendencies, have ramifications that cannot be understood without a close and detailed examination of those characteristics.

As Rosenberg explains (1976:2), we must be willing to 'dirty one's hands' in acquiring a familiarity with the relevant details of the technology itself. Only in this way is it possible to develop an appreciation for the characteristics of particular technologies and the

[1] As Latour (1987) explains, the now widely used black box concept is borrowed from cybernetics, where they were customarily used as a short hand way of alluding to some complex process. If it is deemed unnecessary to get into the details, one denotes this by simply drawing a box with the inputs and outputs.
[2] Similarly, for sociological explanations of vaccine innovation, diseases can either affect relevant or irrelevant social groups (Bijker, Hughes et al. 1987). Precisely what makes them irrelevant to the vaccine innovation process is less well understood, and remains 'black-boxed'.
[3] See sections 1.3 and 5.1 for examples of such consignments.

consequences that flow (or fail to flow) from them. It is not possible to analyze the effects of technological change independent of the particular context within which it appears, for the availability of the same technology will exercise very different kinds of consequences in societies that differ with respect to their institutions, their values, their resource endowments, and their histories' (1976:2). Rosenberg is certainly not alone in this view and this study follows in the tradition of many other scholars' contributions in this way (Constant 1980; Hughes 1983; Vincenti 1990; Blume 1992).

The thesis draws on my understanding and experience acquired through prior studies in biochemistry in order to detail the role of certain biological and chemical processes. However, references to well known textbooks were often necessary to better appreciate findings in journal articles (Stryer 1997; Murray, Rosenthal et al. 1998; Madigan, Martinko et al. 2000; Alberts, Johnson et al. 2002; Levine, Kaper et al. 2004; Plotkin and Orenstein 2004; Voet and Voet 2004; Janeway, Travers et al. 2005).

4.1.2 For complex questions, context counts

The case study method is appropriate for this thesis because the 'how' and 'why' nature of its goals are too complex to be able to use survey or experimental methods (Yin 1994:6). Survey methods are unsuitable because such questions do not seek to determine the prevalence of established phenomena and experimental methods are unsuitable because we have no control over behavioural events.

The complexity and breadth of human activities involved in innovation renders suspect attempts to discuss vaccine innovation in highly aggregated quantitative ways[4]. The working assumption has been that while policy and social science literature treats vaccines as an almost homogenous category, the scientific literature makes a series of important distinctions in their work, that have yet to be brought into the social science or policy discourse (for example, natural sterilising immunity is an important consideration in

[4] 'After all, man is, in his ordinary way, a competent knower, and qualitative common-sense knowing is not replaced by quantitative knowing… This is not to say that such common-sense naturalistic observation is objective, dependable, or unbiased. But it is all we have. It is the only route to knowledge- noisy, fallible and biased thought it be' (Campbell 1975:191 quoted in Flyvbjerg 2001:73).

vaccine design; see section 7.2). A detailed study approach will be able to do this and explore the currently unknown consequences for theory and policy.

Theory formulation in vaccine innovation is difficult because there is such wide variety in the outcomes of innovative efforts. The heterogeneous phenomenon under study is assumed to interact with its context in many ways, blurring the boundaries between the two making them virtually indistinguishable. Therefore a study in vaccine innovation processes should not, and cannot, be readily divorced from its context. Yin (1993:3) highlights some challenges of studying such a situation, 'First, the richness of the context means that the ensuing study will likely have more variables than data points[5]. Second, the richness means that the study… will likely need to use multiple sources of evidence. Third, distinctive strategies will be needed for research design and for analysis.'

4.2 Case study as a tool for context-based learning

The aim of the thesis is a critical exploration of the concept of innovation in vaccines, highlighting its substantial variation and historical contingencies. The emphasis is on developing context-based theory because developing predictive theories and universals in the study of human affairs is difficult. For Flyvbjerg (2001:73), 'concrete, context-dependent knowledge is therefore more valuable than the vain search for predictive theories and universals'.

Case studies on their own are not supposed to be broadly generalised to populations or universes, but act with theory to provide to an adjusted understanding about innovation that may be generalised in tandem with other evidence. Yin (1994:30) characterises this process as making 'level two inferences' through 'analytic' rather than 'statistical generalisation.'

The thesis is in keeping with Mayr (1976:664) who 'is fundamentally inductive rather than deductive; it begins with microscopic research done in depth and detail on the level of

[5] With less than a hundred vaccines invented (Plotkin and Orenstein 2004), 'more variables than data points' is a very likely situation.

individual episodes, in hopes that the empirical data thus gathered will lead to generalisations on some higher level' (quoted in Vincenti 1990:10).

This study does not, however, reach for completely grounded and empirically-led theory; it proceeds more by appreciative theorising (Nelson and Winter 1982:46). In grounded theorising, the researcher (supposedly) has no preconceptions guiding the research at all (Strauss and Corbin 1998); this leaves the researcher with data from which new theory may not necessarily emerge. Although I do not have a detailed preconceived theory already set out, I have developed a basic framework with which to expect a reasonable theoretical contribution.

Theoretical contributions are appreciative because the thesis seeks to iterate back and forth with triangulated empirical data, which is used to test hypotheses about testing regimes. As Balmer (1993:55) notes, 'there is therefore a two-fold research objective: to use theory to say something about the data and to use the data to say something about the theory'.

4.3 Case selection and data collection

4.3.1 Disease as a unit of analysis

The 'disease' was chosen as the unit of analysis because it is assumed that inventive efforts coalesce around the symptoms, tragedies, and challenges posed by the diseases we are faced with. For example, most pharmaceutical companies are now organising their efforts into therapeutically focussed teams (Dougherty 2007:268). Public policies and programmes are structured around single diseases such UNAIDS, STOP TB, and Roll Back Malaria.

'Disease' is taken to be a discrete unit of analysis because vaccine innovation processes are necessarily targeted at disease-causing agents such as viruses (rather than disease symptoms). Viruses, in turn, are assumed to be sufficiently different enough to warrant the development of unique innovation systems. Although most vaccines are developed for a single disease, some are available for multiple diseases, such as measles, mumps and

rubella. However, these are essentially combinations of single vaccines developed from earlier innovation processes (Levine, Kaper et al. 2004; Plotkin and Orenstein 2004).

4.3.2 Importance of 'failure' in case selection

The two cases I selected, poliomyelitis and AIDS, were primarily chosen to represent variation across the dimension that informed my preliminary judgements the most. AIDS affected socially neglected groups, poliomyelitis affected all social classes; so innovation (or lack thereof) was socially determined in these cases, and they would be amenable to social analysis.

Case selection was also driven by two other concerns[6]. I selected diseases caused by viruses in order to avoid unnecessary biological differences, and I was influenced by the availability of data. Vaccines against poliomyelitis virus and HIV were two of the major research programmes of the last century, and consequently, much has been written about those efforts. They seem ready for theory building through a close inspection of their 'black boxes'[7].

Poliomyelitis was widely documented as an 'American success story' (Oshinsky 2005) driven by the determination of a popular US President (akin to the goal of landing on the moon) (Gallagher 1985). Such Panglossian histories indicated to me that the case was probably in need of further critical review, or at least one that incorporated other powerful social groups.

In contrast, HIV/AIDS by the turn of the century had rapidly gained broad media coverage as a disease of inequity, with antiretroviral drugs being accessible to some but not others

[6] Screening out other potential cases represented a significant portion of my research effort.
[7] I considered malaria and tuberculosis, which are also major killers of neglected populations. However, in addition to not being viruses, considerably less financial resources were committed to them, compared to AIDS and poliomyelitis vaccine efforts (see chapter 1). I studied them to a certain depth and this has informed my views.

(McGreal 2000; Boseley 2001; Boseley and Astill 2001)[8]. Indeed, vaccines were hardly mentioned at all, except to say that they were a neglected technical option that needed more funding (Archibugi and Bizzarri 2004). Moreover, there was an increasing awareness that global health inequities were being exacerbated by a broader lack of R&D for neglected diseases (Trouiller, Olliaro et al. 2002). In this context my preconception that innovation was socially determined seemed reasonable. However, my studies in biochemistry and awareness of the challenges faced by natural scientists in these neglected diseases piqued suspicions that this was neither a full nor sufficient explanation of innovation in this field.

The methodological strength of the cases selected lies in replication, *not* sampling, logic (Yin 1994:46). According to sampling logic, a small set of cases is assumed to 'represent' a larger universe. In contrast, the reliability of this study is rooted in replication logic which aims to use the same method across the cases, such that similar results are predicted (literal replication) or contrasting results are produced but for predictable reasons (theoretical replication). This study follows the latter, where one case of successful innovation and another of not-yet successful innovation will be examined with 'maximally similar methods'[9] (Campbell and Fiske 1959; Campbell 1969).

The importance of such a strategy has been noted by many scholars referring to 'failure' but has not been followed up with as much conviction (Staudenmaier 1985). This is strange because analysis has focussed on successful innovations despite abundant empirical evidence indicating that the majority of innovation attempts result in failure (Freeman 1982) and cogent theoretical arguments about the importance of failures in engineering[10] (Petroski 1992; 2005).

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[8] This 'Dying for drugs' series of newspaper articles were highly influential on the development of my thoughts at the time as a biochemistry student. It would not be an exaggeration to say that they led me to studies in the social sciences, particularly in innovation policy.

[9] Campbell conceives reliability as 'the agreement between two efforts to measure the same trait through maximally *similar* methods' whereas validity is 'represented in the agreement between two attempts to measure the same trait through maximally *different* methods' (cited in Constant 2000:200). Constant argues that recursive practice aiming for consistency and convergence lead to increasingly reliable and valid knowledge as Campbell conceives it.

[10] Petroski's conception of failures in engineering bears similarities to Popper's notion of falsification in the growth of knowledge. Technologies can be seen as hypotheses waiting to be disproved and corrected.

Given the emphasis on failure by the scholars above, the case of AIDS seemed pertinent as significant resources and inventive effort are now committed to it (see chapter 1). While it may be more accurate to describe the case as 'not yet successful', it is certainly difficult to currently consider it 'successful' when prominent AIDS researchers remark, "the virus is winning" and "HIV is currently beating the crap out of us" (Hilleman 1992:1052).

It should be noted, however, that the cases were not selected with the aim of answering a counterfactual question: 'why did innovation ostensibly *not* occur in this case?' This would involve consideration of, potentially, an infinite number of rival theories. Instead, as Rosenberg emphasises, much can be learnt about the innovation process from the difficulties and challenges encountered in less innovative endeavours, such as the AIDS vaccine efforts. 'It is highly relevant to ask why it took so long to do certain things, and why inventors failed for so long at some inventive efforts while they succeeded quickly at others… If we want to probe the relations between science, technology and inventive activity more deeply, we must learn much more about what was *not* possible as well as what *was* possible. We need to understand what scientific and technological discoveries were needed for key breakthroughs in invention. For knowledge not only permits - it also constrains. For this reason we can learn much from the study of unsuccessful attempts to invent something for which the market was perceived to be ready. In this respect, the study of failure is essential to a determination of the precise role of supply side variables in the inventive process' (Rosenberg 1976:278).

4.3.3 Flexible data collection

Although the study was rooted in theoretical replication logic, where the aim was to use similar methods for both cases, greater weight has been given to AIDS in terms of its empirical and analytical content. This was to draw out features of the AIDS virus which presented vaccine designers with unique sets of challenges. The implications required further research and analysis in order to build appreciative theory. This resulted in the rapid expansion of the AIDS case and has to a certain extent led to its characterisation as a deviant or extreme case.

These case studies are not primarily intended to unveil new historical data, but to test certain theoretical concepts by bringing together sources on a wide range of topics. Data validity was corroborated using a triangulation approach with a varied range of sources. Secondary sources of data used were reviews of the scientific literature, histories, biographies, contemporary journals such as *Vaccine, Virology*, *Nature* and *Science*, reports by policy makers, newspaper articles and publications by non-governmental organisations such as advocacy groups and charity foundations. It should be stressed that many of the eminent scientists and key actors involved with the poliomyelitis and AIDS vaccine endeavours were known personally by the authors of the histories I have drawn on[11]. In some instances they themselves are the authors.

This method of data collection leaves the study prone to several forms of bias (Becker 1958; 1967; Thatcher 2006). The first is secondary bias, effectively a recycling of the primary author's inaccuracies or prejudices. In order to minimise this effect, documents were carefully used and not readily accepted as universal truths or as literal recordings of events that have taken place. As mentioned before, multiple sources were used to gain a consistent picture. When they were contradictory rather than corroboratory, it was used as a signal for further investigation.

The second is researcher bias, a tendency to affirm rather than falsify my own assumptions and biases. I have tried to be reflexively careful about this by being alert to it and resisting simplistic verification where possible. It should be noted that my preliminary views about AIDS as a neglected disease have altered during the course of the research. This may not qualify as falsification proper, since there were no formal hypotheses at the outset, but does suggest that this investigation was open to the possibility of falsification.

A third form of bias may be geographical. Most of the sources used to build both case studies focus entirely on the US, and the convenience of access to this data may have skewed the analysis. At first sight, epidemiology does not seem to justify the US focus. As

[11] For example, John Paul, Jonas Salk, Richard Carter, Saul Benison, Frederick Robbins, Stanley Plotkin, Robert Gallo, Jon Cohen, Maurice Hilleman, Patricia Thomas, Myron Levine.

hygiene and welfare standards improved globally, poliomyelitis epidemics broke out across the globe, not just in the US (Carter 1965; Paul 1971). For AIDS, two thirds of all cases (and 80% of female cases) live in sub-Saharan Africa (deCock and Weiss 2000; Piot, Bartos et al. 2001). The region is home to ten out of the eleven people who contract HIV every minute (Kalipeni, Craddock et al. 2003).

However, most vaccines have been developed, produced and funded in the US (Pauly, Robinson et al. 1995; Levine, Kaper et al. 2004; Plotkin and Orenstein 2004). For HIV vaccine R&D, the US accounted for 85 to 90% of public sector funding between 2000 and 2004 (UNAIDS 2005:10). About two-thirds of total global HIV vaccine R&D funding was disbursed by the US's NIH alone between 1999 and 2007 (Batson and Ainsworth 2001:721; UNAIDS 2008:13). A closer examination of epidemiological trends also reveals an American focus. Hygiene standards improved foremost in the US and, as such, faced severe poliomyelitis epidemics before most other countries. For example, by the time the 1957 poliomyelitis epidemic struck the Soviet Union, two vaccines had already been developed in the US (Carter 1965:359; Paul 1971). A few vaccines are developed in Europe, but the rate of AIDS in the US in the mid-nineties was 8 times higher than that of the UK or Germany, and 3 times higher than that of France or Switzerland (deCock and Weiss 2000:3). By 1999, the US had more than 3 times the total number of cases in Europe (deCock and Weiss 2000:6).

4.4 Difficulties of examining contemporary events

Soderqvist (1997) identifies a temporal imbalance in the history of science where contemporary science heavily outweighs earlier historical periods in terms of size and activity[12]. Recent science is more 'dense' and poses the problem of 'documentary overload' to the historical researcher. Hughes (1997) therefore emphasises the need to tighten and restrict the scope of the study.

[12] See also Ziman (1994).

However, this approach is less easy in a policy environment, where the unit of analytical concern is necessarily large, like the disease. Decomposing the unit into variables divorced from their context is likely to hinder the policy relevance of the findings. Therefore, large bodies of literature were used, but they were managed by using review articles and histories to identify and triangulate key papers. Over the course of this study I was able to recognise significant actors and became familiar with key researcher names.

Secondly, the danger of exaggerating the documentary overload can lead to the neglect of other problems such as the politics of history. Hughes argues that history is always contested by competing interests and partisan accounts, but that this problem is especially pertinent in contemporary history. 'History is never for itself; it is always *for someone*' (Jenkins quoted in Hughes 1997:26; see also Tatarewicz 1997). Fee and Fox (1989:307) explain why this is so: 'In dealing with the distant past, historians have only the dead and each other with whom to contest their interpretations; in dealing with the recent past and the present, they must also confront the living – who have memories of their experience, and who may also have powerful and perhaps partisan explanations of the same events. The political and ideological struggles over interpretation of the present are usually waged with a special intensity rarely displayed in arguments over the more distant past'[13].

Thirdly, there are problems associated with being temporally too close to the events being studied. 'Contemporary history is the most interesting thing. In my time it used to be called journalism' (Hennessy cited in Hughes 1997:19). Whig history is criticised for interpreting past events in today's context but the main critique of contemporary studies is that the lack of temporal perspective compromises one's ability to analyse rigorously or be able to judge which events are (most) significant. However a counter side to this argument can be made. Close temporal proximity means that it is not just the history of 'successful' technologies that is told, but the much richer story of failures is also told. Contemporary studies of innovation have the advantage of not knowing which technological option will emerge successfully and are therefore able to provide a fuller account of events as they happened.

[13] It is interesting to note that Fee and Fox make their point by using the case of AIDS.

Even with this advantage however, several well known works on the AIDS epidemic (for example Shilts 1987; for example Grmek 1993; Thomas 2001) succumb to a teleological account of events, reading history backwards by projecting the certainties of hindsight back onto past events. So some events that were important at the time but later emerged to be non critical are often omitted or events that were thought to be unimportant at the time are invoked with greater emphasis and intensity. They tend to cast actors as either heroes or villains and rarely move beyond the position that if only science and technology were free from politics and society, everything would be fine. This view contrasts sharply with theoretical perspectives of science and technology presented in chapter 2. This thesis is careful to highlight contingencies, uncertainties and failures where they were apparent and resists re-constructing scientific developments to follow a rational order.

4.5 Analysis through Synthesis

In comparison to the natural sciences, progress in the social and behavioural sciences 'has been exceedingly slow' (Rosenthal 1991:3). Rosenthal identifies two sources of pessimism in social science: problems of 'poor cumulation' and 'small effects'. Although the thesis partly argues that the natural sciences have problems of cumulativeness of their own, better cumulativeness might be achieved in social research if more effort was spent on analysing and conceptualising the data that already exists. This is particularly the case for a phenomenon that is so acute, the burgeoning literature has led to establishment of a biannual *Aids Book Review Journal*. Rather than to search for a few major determinants of social phenomena, synthesising existing evidence of small effects on variation may combine to provide a better overall picture of variability and heterogeneity (Scott 2004; NESTA 2006:6).

The importance of quantitative meta-analyses and systematic reviews has been recognised by organisations such as the Cochrane and Campbell Collaborations that promote 'evidence based' medicine and social policy (Sackett, Rosenberg et al. 1996; Chalmers 2003). Systematic review techniques have been developed there to pool the results of randomised controlled trials, such as meta-analysis (Chalmers and Altman 1995). However, researchers

have also begun to explore methods that allow the synthesis of qualitative research (Pope and Mays 1996). One such method, used in this thesis, is narrative synthesis, which seeks to go beyond summarising studies and highlighting recorded events by attempting to integrate them into a narrative analysis. These syntheses aim to identify key themes and threads that run through the collected evidence (Greenhalgh 2004).

The synthesised data was analysed using two forms of pattern matching: 'non equivalent dependent variables' and 'rival explanations' (Yin 1994:106). In the first, one seeks to find a variety of outcomes that are consistent with an argument and in the second, one takes the outcome as given but focuses on how and why the outcome occurred. These methods are not very precise and, until better methods are developed, Yin (1994:110) discourages postulating very subtle patterns. However, the strong differences between the cases in this thesis, combined with synthesised sources that are stable (allowing the investigator to assume reliability by revisiting repeatedly) and varied (allowing the investigator to assume validity by visiting multiple sources), have allowed me to identify relatively nuanced patterns.

4.6 Summary of methods used

I adopted an exploratory case study approach in order to subject the black box of vaccine innovation to a detailed examination, using prior experience in biochemistry. I sought to develop contextualised theory by making analytical generalisations to the growth of knowledge standard. I used disease as the unit of analysis, and selected poliomyelitis and AIDS from a range of viruses because they provided interesting technical similarities and social contrasts. Importantly, they provided a contrast between 'success' and 'failure' in vaccine innovation. I synthesised a variety of documentary sources, using a multidisciplinary approach, to build case validity and reliability. The methods minimised secondary bias, researcher bias, geographical bias and difficulties in contemporary studies.

Chapter 5

Contextual Analysis of Vaccines: Economic and technical dynamics

This chapter aims to establish a context in which to situate the forthcoming empirical chapters. The first part will show how economists have focused on the nature of the vaccine market and its effect on industry incentives to invest in R&D for new and improved vaccines. The perspective may help to understand why blunt science-push and demand-pull explanations of vaccine innovation have dominated policy formulations. The second part will provide a basic introduction to the technicalities of vaccines so that the reader may engage with 'the details of the technology' (Rosenberg 1976:2) in chapters 6-9.

An economic analysis of the vaccine sector

Economic models seem to underlie most analysis and policy discussions about vaccine innovation[1] (Grabowski and Vernon 1997; Barrett 2004; Finkelstein 2004; Milstien and Candries 2005; Kremer, Glennerster et al. 2006; Stephenne and Danzon 2006). 'There is a common root to most of the problems [in vaccines]: economic fundamentals' (Vandersmissen 2001:1612). And the World Health Report states, 'You cannot make real changes in society unless the economic dimension of the issue is fully understood' (WHO 1999:viii). This section will highlight some of the strengths and weaknesses of this approach.

Most economists have argued that poor market conditions, together with certain industry characteristics have led to less than desirable levels of vaccine innovation. They tend to do this by splitting the factors into supply and demand. 'Two avenues can be considered: one can attempt to solve the problem by addressing the supply side, to ensure plentiful availability. Alternatively one can strengthen demand, to provide the incentive of an

[1] The references to HIV/AIDS as a threat to notions of progress and economic growth in section 1.3 support this assertion further.

attractive market' (Vandersmissen 2001:1614). Aside from the problems of divorcing interacting factors in this way, such categorisation is also rather arbitrary because all of the characteristics listed below as supply may easily be considered part of market conditions as a whole, perhaps excepting rising R&D costs. Nevertheless, the categorisation below should be sufficient for gaining a familiarity with the broad context of vaccine innovation.

Section 5.1 will examine the demand for vaccines by exploring certain characteristics of the market. It notes that the vaccine market is considerably smaller than that of pharmaceuticals and the following sections examine why this might be. It examines the centralised way in which vaccines are often purchased, varying disease environments, and social resistance to vaccination.

Section 5.2 will examine the supply of vaccines by exploring certain characteristics of the industry. It notes the importance of limited liability and regulation, and strong intellectual property protection in the context of rising R&D costs. It suggests that in the absence of these factors many companies have exited the sector, leaving vaccine supply largely in the hands of a few manufacturers.

5.1 Demand for vaccines: the vaccine market

5.1.1 Small market size relative to pharmaceuticals

Worldwide annual vaccine sales have been growing from about $1bn in 1980 to $6bn in 2001 and $10bn in 2005. The market is expected to continue growing by 10 to 12% per year; to $17bn in 2010 (Gréco 2001; Gréco 2002; NIH and NIAID 2002; Vandersmissen 2002; Douglas 2004; Costello 2007; NIH and NIAID 2007). Despite such rapid growth rates, the vaccine market still only represents about 1.5% of the pharmaceutical market[2]. For example, the global market for a major cholesterol lowering agent was $10.3bn in 2003, exceeding the entire vaccine market for the year (NIH and NIAID 2007).

[2] In 2001, the pharmaceutical market was estimated to be $350bn (Gréco 2001; Gréco 2002; NIH and NIAID 2002; Vandersmissen 2002). In 2006, it grew to $650bn (IMSHealth 2006). These figures suggest that the *relative* size of the vaccine market has remained largely unchanged.

Small market size is significant because it reduces incentives to invest in R&D. As Acemoglu and Linn (2004:1084) suggest with a temptingly direct link between demand and supply, 'a 1 percent increase in the potential market size for a drug category leads to approximately a 4 percent growth in the entry of new non-generic drugs and new molecular entities.' The small size of the vaccine market may be due to the presence of oligopsony, distinct disease environments, and social resistance, which are examined further below.

5.1.2 Oligopsony: centralised public demand

The introduction of a new vaccine to the market typically follows a 20 year pattern (Gréco 2001). In the early stages, fragmented sales are made predominantly to the private market at low quantities but high prices. The market as a whole grows, but the private market is gradually displaced by public procurement. In the later stages, sales are almost exclusively to governments and a few organisations (such as UNICEF, PAHO, WHO, GAVI) at high quantities but lower prices.

In the US, the Centers for Disease Control estimate that up to 80% of paediatric vaccines are purchased by government. Given that paediatric vaccines represent 50 to 70% of the vaccine market (Gréco 2001; Scrip 2002), centralised government purchases have considerable concentrated purchasing power to lower aggregate demand. Whilst private prices are set by manufacturers, public prices are negotiated and purchased below those paid by the private sector (see table 3).

Table 3: Public-Private Vaccine Prices ($) in the US by year and vaccine

	DTP		MMR		OPV/IPV	
Year	Private	Public	Private	Public	Private	Public
1985	2.8	2.21	13.53	6.85	6.15	0.80
1995	5.54	1.40	21.43	11.27	10.18	1.92
2005	22.04	12.75	40.37	16.67	21.80	10.42

Source: National Centers for Disease Control and Prevention[3]. DTP is diphtheria-tetanus-pertussis vaccine; MMR is measles-mumps-rubella vaccine; OPV is oral poliomyelitis vaccine; IPV is injected poliomyelitis vaccine.

Perhaps because of the product-market cycle identified by Greco, there is an expectation that all vaccines will eventually be abundantly available at low prices, and the role of centralised purchasers should be to accelerate this process. However, it is unlikely that the prices being paid by the end of the cycle, or even over the whole cycle, really reflect the full value of vaccines to society when considering the reduction in health care costs and related costs, suffering, and death (see chapter 1).

Many have argued that pricing is critical to protecting vaccine innovation incentives because R&D costs are compensated for by large profits (Grabowski and Vernon 1997); profitability and R&D outlays were found to be strongly correlated in the pharmaceutical industry (Scherer 2001; Giaccotto, Santerre et al. 2005; Vernon 2005). Frank (2001) adds a more dynamic dimension by emphasising that the link is more specifically to do with R&D investment today and expected - but uncertain - future profits. Since vaccine companies are often subsidiaries of pharmaceutical companies, vaccines must compete with other product areas for resources in this context of uncertainty (Vagelos and Galambos 2004; 2006).

Internationally, centralised purchasing and public pressure continue to depress prices. The growth of the global vaccine market is driven by new vaccines sold to North America and Europe, which represent 70% of the market by dollar sales (Gréco 2001). The impact on the direction of innovation is therefore heavily geographic and disease specific.

[3] http://www.cdc.gov/nip/vfc/cdc_vac_price_list.htm

5.1.3 Different disease environments

Distinct disease environments and specific epidemiologies can segment or shrink a market. Whilst developing countries have obtained substantial benefits from pharmaceuticals developed originally for rich country markets (Scherer and Watal 2002), little research is conducted on diseases that primarily affect poor countries.

For some diseases, at least 99% of cases are located in low- and middle-income countries[4] (Lanjouw and Cockburn 2001). In 1998 alone, these 'tropical' or 'neglected' diseases are estimated to have caused the loss of almost 200 million DALYs[5], and over five million lives, a large share of them children. The A-strain of the HIV virus is also particularly widespread in poor countries but not in the developed world. For these diseases there is simply no free ride.

Estimates suggest that infectious and parasitic diseases account for only 3% of the disease burden in high-income countries (WHO 2006). Yet this figure rises to one-third in low-income countries and to nearly one half in Africa. In contrast, 83% of the disease burden in high-income countries is made up of non-communicable conditions such as cancer and cardiovascular disease. This impacts on vaccine innovation because the people who would benefit the most from vaccines (developing countries with high communicable disease burdens) are the people who can least afford it, and offer satisfactory returns to firms' R&D investments.

Even for diseases that affect developed countries as well as developing countries (such as cancer), characteristics of poor countries make the products designed for developed markets unsuitable. Developing countries have weak infrastructure and so for example, need vaccines that can withstand breaks in refrigerated distribution chains and survive a long shelf life. Vaccine candidates that are potentially cheap, but are technically less effective, may not be acceptable to rich consumers and hence not be developed by firms even though

[4] For the disease list see Lanjouw and Cockburn (2001).
[5] Disability-adjusted life years (DALYs) are estimates of years of life lost or lived with a disability, adjusted for its severity. Mortality and DALY figures are found in WHO (1999).

they would be of great benefit to poor consumers. Developing countries have weaker health care systems and so for example, need products that do not require intense supervision by medical personnel. Whilst Europe has 39 trained physicians per ten-thousand people and the US has 27, sub-Saharan Africa has only 1 (World Bank 2001). In addition, new vaccines may not provide immunity to some strains prevalent in developing countries.

Thus whilst developing countries benefit from products based on other countries' R&D efforts, few products are tailored to the specific needs of the developing world. For the vaccine manufacturer, the key implication of these differences between developed and developing country disease environments is a reduction in available market size.

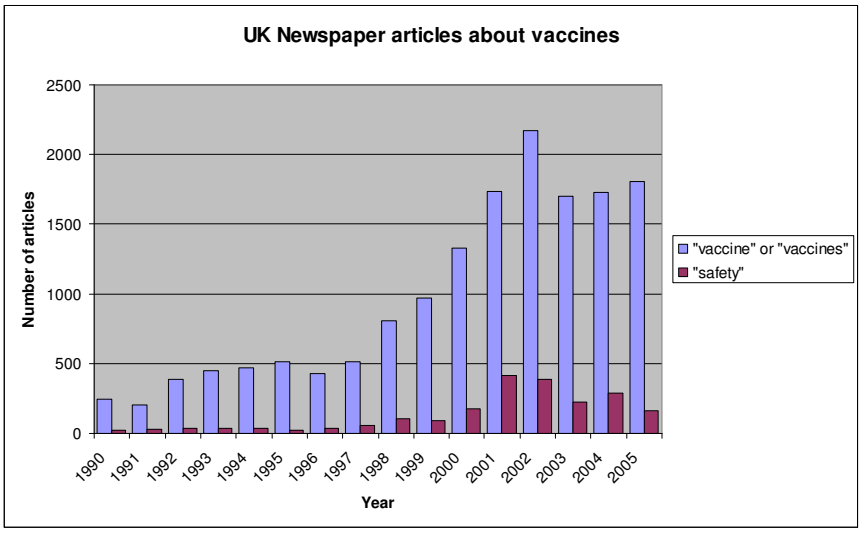
5.1.4 Social resistance

Social and cultural factors that centre on risks and benefits of vaccines also affect the popularity of vaccines as a product. This is likely to have a diminishing effect on market size. As they succeed in dissipating disease, vaccines become a more feared entity (Gréco 2001). The prevalence of disease and that of anti-vaccine attitudes therefore have an inverse relationship, presumably because populations become unaccustomed to the ravages of disease and overestimate risks of vaccines while underestimating their benefits.

Even if an effective AIDS vaccine were available, Brandt (1988) raises the issue that it is highly unlikely that a sufficient number of people will identify themselves at risk and actually use the vaccine. Furthermore, some may oppose the vaccination of others arguing that it would alter social behaviours, such as the use of recreational drugs or the practice of deviant or promiscuous sexual activity. Brandt draws on the history of other sexually transmitted diseases such as syphilis to show that where there is fear, hostility and intolerance of a group affected by a disease, attitudes to vaccination are likely to be especially negative. The recent difficulties in encouraging parents to vaccinate their children against cervical cancer seem to support this, with some parents believing that vaccination will encourage sexual activity in their children (Dempsey, Zimet et al. 2006).

Vaccines currently feature heavily in the media and interest seems to have been driven by safety concerns. Using the Lexis-Nexis Professional database, I searched for 'major mention' to the words 'vaccine' or 'vaccines'. The search covered all UK national newspapers, but excluded newswires. The graph below shows the results of the search and its secondary bars show that between 10 to 25% of these articles were exclusively about safety issues.

Figure 4: Vaccine safety in the media



Source: Compiled from Lexis-Nexis database.

Table 4 provides a brief list of reasons why vaccines may be perceived as excessively risky. Although generalizations are made in the table, it should be noted that many non-vaccinating parents have their own localized knowledge systems with which public health officials need to engage if vaccine uptake is to be maintained (Blume 2006; Leach and Fairhead 2007).

Table 4: Risks in vaccination

Generalisations from the Risk literature	Attributes of vaccines/vaccination pertinent to risk perception
A risk accepted *voluntarily* causes less dread than one which is required by obligation, law or coercion.	Vaccinations are sometimes regarded as obligatory and some are required by law.
When the consequences of accepting risk are *immediate*, there is less fear than when the consequences lie at some indeterminate time in future.	The risks of vaccination are immediate but the benefits of vaccination may or may not be needed in the future.
People seem to be more acquiescent to a risk which is presented as the *only possibility*, rather than a risk that may not necessarily be incurred because there is an alternative course of action.	The increasing popularity of Alternative Medicine (Ernst 2000) suggests that vaccines are not seen as the only way of avoiding disease, making vaccination seem less obligatory.
If a risk is regarded as *essential*, it is more acceptable than one which is regarded as unnecessary.	At the time of vaccination, it does not seem essential as the putative vaccinee is well and free from disease. The vaccine effect may not be perceived because it will only be apparent by the expression of the normal healthy state of the individual and the absence of disease. This is in stark contrast to therapeutic interventions, where risks are tolerated more readily.
When the consequences of having been exposed to a risk are *reversible*, that risk is more countenanced than one where the effects are irreversible.	Vaccination is seen as an irreversible health choice and there is a sense of dread at the vaccinial contamination of a clean, pure and healthy body.

Source: Compiled from Stirling (2003) and Spier (2001).

A key characteristic of vaccination, known as herd immunity, is that the reduction in susceptibility for one person benefits all unvaccinated persons (see chapter 1). So not all members of the community need to be vaccinated in order for everyone in the community to be protected (Ramsay, Andrews et al. 2003; Fine 2004). Thus, the externalities of vaccination mean that it is possible for individuals to free ride on the costs and risks incurred by other members of the community. It is likely that increasingly consumerist cultures centred on the individual, prevalent in North America, have contributed to some of the difference in immunization rates across America and Europe through an under-appreciation of the benefits of vaccination to wider society.

This is of concern to the democratic political process because once half the population is vaccinated, it would not be possible to obtain majority approval for any increases in vaccination rate, assuming that non-altruistic parents of vaccinated children cease to place any value on vaccination of other children.

Many unsubstantiated claims have endangered vaccination programmes in many countries (Andre 2003). The origin of these claims, usually promoted by a few zealous champions, is often country specific. For example, social amplification models have been applied to the rapid spread of autism claims regarding MMR vaccine in the UK[6] (Hillman 2001). A non-exhaustive list of such beliefs with their sources is shown in table 5. It is worth noting that the origins and causes of these health conditions, often claimed to be directly caused by the implicated vaccine, are (or were) not well understood.

Table 5: Vaccine Safety debates

Health condition	**Vaccine implicated**	**Source**
Neurological damage	DTP	Scotland
Unexplained death	DTP	Japan
Chronic fatigue syndrome	Hepatitis B	Canada
Sudden infant death	DTP	France
Multiple sclerosis	Hepatitis B	France
Crohn's disease	MMR	UK
Autism	MMR	UK
Diabetes	Hib	US
AIDS	OPV	A US journalist (Hooper 1999; 2000)
Mental retardation / Autism	Thiomersal	US
Arthritis	Lyme	US
vCJD	Bovine serum	UK
Immune overload	Combinations	US

Source: Based on Andre (2003).

It is important to acknowledge that vaccines can indeed cause unwanted side effects. Even if such adverse reactions are difficult to establish scientifically (temporal associations with vaccinations does not necessarily mean causality) serious errors have occurred more than

[6] Following the 1998 autism claims, MMR vaccination rates in the UK dropped to under 80%. In 2006 and 2007, there were more cases of measles than in the previous ten years put together. One of the cases led to the first measles death in 14 years. (http://www.dh.gov.uk/en/News/Recentstories/DH_086861)

once in the past. Examples are the Cutter incident, when one batch of killed poliomyelitis vaccine that had not been properly inactivated caused many cases of paralytic poliomyelitis, or the Lubeck disaster when the use of pathogenic mycobacteria for the production of BCG vaccine was responsible for cases of tuberculosis. Mass immunization programmes mean that such errors involve large numbers of people. Errors are acute and conspicuous because those affected are otherwise healthy children. As the section below notes, exposure to liability is a major disincentive for the vaccine industry.

5.2 Supply of vaccines: characteristics of the vaccine industry

5.2.1 Liability and Regulation

Whilst the liability of products should promote efficient levels of product safety, misdirected liability efforts are argued to be harmful to innovation because they increase the cost of R&D (Viscusi and Moore 1993). This effect is seen across most manufacturing sectors but there is evidence to suggest that liability costs are a particularly important consideration in the vaccine sector (Vandersmissen 2002; Sloan, Berman et al. 2004; Hinman 2005). One reason the vaccine sector is prone to high liability costs is because, unlike most drugs, vaccines are usually administered to healthy and young people.

Evans et al. (2004) report that the litigious atmosphere of the early 1980s brought a series of lawsuits against vaccine manufacturers. When the lawsuits were successful, they often exceeded the gross sales of all vaccines in a year. Vaccine suppliers decreased and prices rose sharply. DTP vaccine went from $0.19 in 1980 to $12.00 in 1986.

In response to lobbying by medical and biological professionals, as well as industry, a reluctant Reagan administration passed the National Childhood Vaccine Injury Act in 1986. The program was essentially a way to compensate vaccine victims quickly and easily without punishing vaccine manufacturers. Negligence and blame was removed under a quite unusual ‘no fault system.’ Although similar schemes were already in place in other

countries (for example the UK's 1979 Vaccine Damage Payments Act[7]), the United States' scheme represented a significant improvement in the legal situation for vaccine manufacturers since this was where the majority of claims were being made.

However, the scheme has reportedly been plagued by money shortages (Cohen 1992c) and the solution would not be applicable for adult vaccines such as AIDS. In addition, the varying stringency of the California liability regime correlated with companies' entry, exit, re-entry, and re-exit from AIDS vaccine development. Interview evidence with Genentech's lawyer indicated that the alternating leniency in liability was directly affecting their investment decisions (Cohen 1992c).

Another factor argued to be responsible for depressing vaccine innovation by increasing R&D costs has been the role of an increasingly complex regulation (Gréco 2001; Vandersmissen 2001; Gréco 2002; Vandersmissen 2002; Douglas 2004). Recently, for pharmaceutical drugs, this link between strict regulation and lowered innovation has been directly and persuasively criticised (Abraham 2008).

Relative to pharmaceuticals however, it is likely that regulations for vaccines are more stringent, and have been increasing in their complexity. Significant shifts have occurred in the interpretation and intensity of enforcement of those guidelines by the Food and Drug Adminstration[8] over the last decade or more (IOM 2003). For example, acceptable levels of Thimerosal (ethyl mercury) were suddenly changed in 1999 after the FDA reassessed the risk and required its removal from all paediatric vaccines (Freed, Andreae et al. 2002:1154). This decision necessitated major alterations in production and bottling processes and resulted in an estimated 20 to 30 % losses on various vaccines.

Whilst manufacturers may try to suggest that the FDA's decisions are heavily influenced by an irregular, unpredictable and powerful media and anti-vaccination movement, this author considers it more likely that such inconsistencies reflect limited knowledge of the ways in

[7] The UK scheme has recently been strengthened (Government, UK Dept of Pensions 2002).
[8] The Center for Biologics Evaluation and Research (CEBR) of the FDA is responsible for regulating vaccines in the US.

which vaccines work. The evolution of the vaccine safety system has been shaped in large parts by lessons learnt from past experiences and controversies rather than on a strict understanding of vaccine development (Abraham 1995; Ball, Ball et al. 2004). Modern challenges for regulation principally focus on the vast array of changing technologies used in developing and manufacturing vaccines (Baylor, Midthun et al. 2004; Levine, Kaper et al. 2004; Plotkin and Orenstein 2004).

5.2.2 Rising R&D costs

Studies investigating the overall costs of developing a new vaccine have not been undertaken in the systematic way that they have for drugs; as such, estimates vary widely. However, they do indicate that similar amounts are spent on developing vaccines and drugs, despite vaccines having a much smaller market. DiMasi et al. (1991; 2003) estimate that drug costs have risen from $231m in 1991 to $900m in 2001[9]. Estimates for bringing a new vaccine to market currently range from $600m to $800m (Douglas 2004; Plotkin 2005b), although a recent influenza vaccine cost more than $1bn (NIH and NIAID 2007)[10].

Clinical development involves studies of the effects of vaccines on patients for safety and efficacy typically over a longer period of time than that of drugs (Ebbert and Mascolo 2004). This is due to the preventative nature of vaccines where proving a negative occurrence for the purposes of satisfying regulatory conditions is difficult and takes longer. As a result of this difficulty, more indicators and proxies are often required for vaccine trials (Levine, Kaper et al. 2004). Because clinical trials take longer, they are more expensive too. A commonly quoted figure for trials was $30m (Batson and Ainsworth 2001:723), but a recent HIV vaccine trial that enrolled just 8000 volunteers cost $130m alone (NIH and NIAID 2007).

Manufacturing plants are also expensive costing between $50m and $200m, and unique manufacturing requirements usually mean they are suitable for only one product (Douglas

[9] 1991 figure based on 1987 dollars; 2001 figure based on 2000 dollars.
[10] Next to these figures, the expenditure of a billion dollars *per year* on HIV vaccine R&D (chapter 1) seems particularly noteworthy.

2004). Outlays for production plants need to be committed early on, 4 or 5 years before licensing if there is to be no gap between the product's licensing and its market launch. Choosing to commit such large funds represents an uncertain decision with large financial risk. Moving to manufacturing plants is a difficult process, often requiring long investigations on how laboratory procedures can be transferred to mass production techniques with consistency and safety (Pisano 1996). Since vaccines are biological (rather than chemical) products, their essential components work in more complex ways that cannot be measured (or reduced) easily. As such, they require more assays that must be validated for each stage of manufacture, which adds to costs and makes schedules harder to follow.

Pisano's (1996) case studies show that changes in multiple manufacturing tasks must be timed carefully because they need to be approved by regulatory authorities. This means that strong management systems and controls are needed, and clinical and process development tasks must be closely co-ordinated (Pisano and Slack 2001; Douglas 2004; Pisano 2006). This is perhaps why the later stages of development have remained intact through current trends of industry disintegration.

5.2.3 Intellectual property regime

For more than 50 years, large empirical studies from across the world have found consistently that patents are extremely important for the pharmaceutical sector [11]. Indeed the sector is somewhat unusual in valuing patents so highly (Schankerman 1998). It is estimated that pharmaceutical R&D outlays would be reduced by 64% in the absence of patent protection; while for other industries, the corresponding reduction was only 8% (Grabowski 2002).

[11] The largest empirical surveys into IP are drawn from the UK (Taylor and Silberston 1973), the US (Scherer 1959; Mansfield 1986; Levin, Klevorick et al. 1987; Cohen, Nelson et al. 2000), Japan (Cohen, Goto et al. 2002) and Europe (Arundel, van de Paal et al. 1995; Arundel and Kabla 1998; Arundel 2001). Other factors for appropriating benefits from research-intensive innovations included trade secrecy, first mover advantages and associated brand loyalty, establishment of effective production, sales and marketing functions, and the complexity of the learning curve and production technology. Silberston's (1987) follow-up categorised survey responses and analyses of patent and R&D intensities into 3 groups, where patents are 'essential', 'very important' or 'less important'. He concluded that the first group 'consists of only one industry - pharmaceuticals'.

The reason why patents are so critical to pharmaceutical firms in appropriating the benefits from innovation lies principally in the characteristics of the pharmaceutical R&D process. New drugs cost in the region of $1bn and take around a decade to develop and gain regulatory approval (see above). In the absence of patent protection, imitators can free-ride on the innovator's regulatory approval and duplicate the compound for a small fraction of the originator's costs.

Imitation costs in the pharmaceutical industry are exceptionally low, relative to the innovator's costs for discovering and developing a new product[12]. Generic compounds need only demonstrate that they are bio-equivalent to the pioneering brand in order to receive market registration. This process only takes a few years and costs $1m to $2m (Reiffen and Ward 2006). Furthermore, the prospect of success is very likely, as reflected by the fact that many generic firms typically receive FDA approval and enter the market within a short time of the patent expiration of the pioneer brand. The case of Praziquantel – which was discovered, developed and licensed by Bayer, then immediately copied, improved and sold at a lower price by a Korean pharmaceutical company – is illustrative of this (Reich and Govindaraj 1998).

Patents are similarly important for vaccines but probably less than for drugs. As vaccines are more complex biological products than drugs, it is likely that more tacit knowledge would be required to imitate innovators. Furthermore, the small market size of vaccines reduces the incentives to imitate and 'production, control and regulatory constraints will keep the barriers to entry high' (Gréco 2001:1609). Nevertheless, strong - but of limited scope - patent protection may still be useful as part of a package of policies to improve innovation and access across the world.

[12] While R&D may cost in the region of $1bn and take longer than a decade, imitation costs are around $1m and can be undertaken in a year. There are few other comparable industries where there is such a large disparity between the costs and dynamics of innovation and imitation.

5.2.4 Oligopoly: concentrated industrial structure and wider actors

The industry has been increasing in concentration such that only a small number of companies are left producing vaccines. In 1967, there were twenty-six companies with US vaccine licenses; by 1980 there were seventeen; and by 2002 there were twelve (Cohen 2002b). The exodus began as half of all commercial vaccine producers stopped manufacturing vaccines between 1966 and 1977 (IOM 2003). In 1996 there were six firms producing recommended childhood vaccines for the US market (Sing and William 1996); and by 2002 an oligopoly of only four remained (IOM 2003).

Part of the decrease in number of suppliers can be explained by mergers and acquisitions[13]. Such a trend towards increasing industry concentration has worried many observers about the stability of vaccine supply (Cohen 2002a; Sloan, Berman et al. 2004; Hinman, Schwartz et al. 2005; Salinsky and Werble 2006). It is argued by these authors that a fragile vaccine supply is a sufficiently serious public health risk to warrant the formulation of policies to address this directly. Underlying their arguments is the discussion over what factors influenced the consistent exit of firms out of the industry. Regulatory costs, liability costs, and poor returns relative to pharmaceutical and other products in the corporate portfolio seem to be the key factors.

Danzon (2005; 2006) goes further by suggesting that the inherent nature of the vaccine market is such that only one or very few suppliers can exist at any point in time. Small and concentrated demand for standardised products mean that competition between firms with large sunk costs and low marginal costs is likely to drive down prices to marginal cost, leading ultimately to the exit of all but one producer.

However, such an orthodox view overlooks two important features of industrial organisation highlighted by innovation scholars. First, innovation is a key factor to changing the structure of industries. Second, the knowledge required for innovation is

[13] Greco (DeNoon 1998) listed several examples of industrial concentration, of which one is: Merieux Institute and Pasteur Vaccines became Pasteur Merieux Serums & Vaccines. Then, Pasteur Merieux Serums & Vaccines and Connaught became Pasteur Merieux Connaught.
Pasteur Merieux Connaught joined with Merck's European division to create Pasteur Merieux MSD.

socially distributed across multiple institutions and not just private companies. A closer look at the innovative dynamics and the broader actors in the network suggest that the vaccine supply need not be as inevitably fragile as Danzon suggests, provided a strong public infrastructure can be maintained. The innovation systems perspective (Lundvall 1992; Freeman 2008) notes the significance of deliberate investements in intangibles – specifically, learning activities – in a variety of institutions (firms, schools, and universities) and links among them. Highlighting knowledge flows between different institutions allows for an explicit appreciation of industrial change, and such a view emphasises that the accumulation of vaccine development skills and capabilities may not necessarily occur within the confines of a single organisation developing vaccines.

Although there are few vaccine producers, there are many more small firms undertaking vaccine R&D, whose primary source of funding is risk capital from private investors but who may have spun off from public research or universities (Sisk 1995:177). Innovation drawing on the public sector seems to be a common way for private newcomers to gain entry. Once entry is gained, another route, similar to the rest of the pharmaceuticals and medical device industry (Powell, Koput et al. 1999; Malerba and Orsenigo 2002), is for small firms involved in vaccine R&D to seek merger or acquisition when what they have developed demonstrates some commercial viability (for example Chiron).

There are several government departments in the US that play important roles in vaccine research and development (Douglas 2004). Their relative contribution to the vaccine network is depicted in table 6 below. The National Institutes of Health is a major funding agent of research, usually in academic institutions. The Food and Drug Administration is the regulatory body, charged with licensing new products. It establishes standards for manufacturing processes, facilities, and clinical studies to ensure that licensed vaccines are safe and effective. It also maintains some research capacity to assist in its evaluations. The Center for Disease Control and Prevention conducts epidemiological studies and evaluates the public health impact of disease in order to establish public health priorities for vaccine R&D. This department is an important factor in determining the demand for a vaccine and how profitable a vaccine can be. It exerts its influence in two ways. Firstly, it makes

recommendations for vaccine usage (along with other professional organisations), and secondly, it is responsible for most of the public purchases. Some additional directed research is also supported by two other departments, the Department of Defense and the US Agency for International Development, on vaccines that might be relevant to military service and on vaccines for children in developing countries respectively.

Table 6: Relative contributions of US government departments

	Research		Development			
	Basic/Related	Targeted	Process	Clinical	Manufacture	Postlicensure studies
NIH	+++	+++		++		
CDC						++
FDA		+	+	+		+
DOD	+	+	+	+		+
USAID		+		+		
Large company	+	+++	+++	+++	+++	+++
Small company	+	+++	+-	+-	+-	
Academia	+++	+++		+++		
NGOs		+		+		

Source: Reproduced from Marcuse et al. (1997:1017). +++, major; ++, intermediate; +, minor; +-, varies by company. NIH is National Institutes of Health; CDC is Centers for Disease Control and Prevention; FDA is Food and Drug Administration; DOD is Department of Defense; USAID is US Agency for International Development; NGO is non-governmental organization.

5.3 Shortcomings of an economic approach

Vaccines tend to be overshadowed by pharmaceuticals because vaccines are produced by pharmaceutical companies and the vaccine sales market is much smaller than that of pharmaceuticals. The consternation of most public health officials and analysts is that the vaccine market is much smaller than their social value. Economic models dominate policy discourse by emphasising oligopsony effects on prices, and highlighting social resistance and disease categories as factors that shrink the market. However, the models are weak on explaining where the social resistance comes from or why and how disease categories shrink the market.

Economic models are also often invoked by pharmaceutical companies to identify 'ever increasing regulatory, quality [liability] and R&D costs' (Gréco 2001:1609) as unfavourable barriers to industrial innovation. These rising supply side costs are not explained easily and indeed explanations are not often attempted. This thesis argues that this is largely due to a failure to appreciate the product complexity of vaccines. Thus R&D costs may be high, and there may be resultant intellectual property issues, but the causes of these effects should not be relegated to 'exogenous factors' and excluded from analysis.

Without a more thorough investigation of the technological knowledge underlying vaccines, its growth and socially distributed nature, the ability to develop economic policies to stimulate and shape the innovation process in the pre-market phases will be limited. Whether of a 'demand-pull' or 'science-push' type, they are not sensitive enough to capture the dynamics of technological change or the subtleties in the relationship between science and technology. Dependence on such models is likely to lead to the development of blunt policy tools.

Technical dynamics of vaccines

This part of the chapter introduces how vaccines work. The first section introduces some important background concepts in immunology that are exploited by vaccines. It then presents a short history of vaccination outlining its principles. The second section compares and provides an overview of the types of immunisations that are currently possible. And the final section comments on the possibility of genomics as the platform for future vaccines.

5.4 Principles in immunology and vaccination

5.4.1 Two distinct arms of the immune system

Pathogens are handled by two distinct arms of the immune system. When a pathogen enters the bloodstream, the immune system responds, firstly, to prevent it from infecting cells and, secondly, to eliminate any cells that do become infected. These two aspects are called the humoral and cellular responses respectively.

The humoral response aims to prevent entry into cells. The immune system's B lymphocytes (B cells) secrete antibodies which patrol the bloodstream and intercellular spaces. Antibodies are Y shaped proteins that can identify foreign substances in the blood and lock onto them in a highly specific fit. (The model of antibody-antigen binding commonly used is of the two arms of the Y locking on to the point of a V, with key-like ridges interspersed along the interfaces providing specificity.) With antibodies latched onto it, a pathogen cannot infect cells readily and is rendered inert. The memory B cells stored in the lymph nodes 'remember' the conformation of the pathogen so that if the immune system were to come across it again, its antibody response would be even swifter. Killed vaccines (see below) tend to be effective at training B cells to perform these functions (Nathanson and Mathieson 2000).

If the pathogen finds shelter inside cells, it is beyond the reach of the antibodies, so a different arm of the immune system's response is engaged. The cellular response or cell

mediated immunity is used. T cells scrutinize the exterior of cells looking for traces of infections. For example, after a virus infects a cell, it copies itself. During replication, bits and pieces of its proteins (viral debris) are moved to the cell surface (exocytosis) where they work as warning flags for T cells to detect.

There are two routes to the cell surface resulting in two different kinds of signal for the T cells. Both routes involve specialized MHC (Major Histocompatibility Complex) molecules. In the first disposal mechanism, MHC Class I molecules attach to viral antigens and make them visible to a specific kind of T cell, the killer T cell (cytotoxic T lymphocyte or CTLs). Killer T cells take on the infected cell by ingesting it (phagocytosis) and releasing extremely potent cytotoxic chemicals. Once killer T cells are primed to a particular pathogen, they kill every cell infected by that pathogen they can find. Copies of different kinds of killer T cells are archived and can be reactivated if the same antigen ever returns. In the second disposal mechanism, MHC Class II molecules take the viral antigens and display them in a way that is recognizable to helper T cells (CD4 T lymphocytes). Having recognized the antigens, helper T cells do not attack the virus directly. Instead helper T cells signal a general siren that boosts production and localisation of antibodies and killer T cells.

Live vaccines (see below) tend to be effective at stimulating the cell mediated arm of the immune system because they exploit the normal way T cells learn to find and destroy infected cells. Live vaccines can infect cells and express the proteins that, via the MHC, signal T cell activation (Desrosiers 2004). Killed vaccines, in contrast, penetrate cells much less and are more limited in their ability to express proteins, but the antibody response is stronger.

5.4.2 Vaccination in historical perspective

A vaccine is a substance sufficiently like the organism to generate a specific response in the immune system, but sufficiently different that the vaccine itself does not cause the infectious disease. The response in the immune system that is looked for is one that will

protect from future infections, known as acquired immunity[14] (Murray, Rosenthal et al. 1998; Madigan, Martinko et al. 2000).

Acquired immunity (as opposed to innate immunity) can be achieved in several ways. The early strategy was to deliberately cause a mild infection with unmodified pathogen (Plotkin and Plotkin 2004a). This was the principle of variolation, established in 1798, in which inoculation of a small amount of dried material from a smallpox pustule would cause a mild infection followed by long lasting protection against reinfection. However, infection after variolation was not always mild: fatal smallpox ensued in about 3% cases (Jenner 1798/1966).

Jenner's achievement was realising that infection with a bovine analogue of smallpox, vaccinia (L. *vacca*, cow) which caused cowpox, would provide protective immunity against smallpox in humans without the risk of significant disease. He named the process vaccination[15], and as a tribute to him, Pasteur later extended the term to the stimulation of protection to other infectious agents (Plotkin and Plotkin 2004a). Humans are not a natural host of vaccinia, which establishes only a brief and limited subcutaneous infection. But it contains antigens that stimulate an immune response that is cross reactive with smallpox antigens and thereby confers protection from the human disease (Elgert 1996).

This established the underlying principles for safe and effective vaccination, but they lay fallow until late the 19th century, when the germ theory of disease was established[16] (Hilleman 2000b). Both of these were, in large part accomplished by Louis Pasteur (Plotkin and Plotkin 2004a). However, Pasteur was far more interested in preventing disease than studying it. Before leaving on holiday, Pasteur accidentally left a chicken cholera culture out on the shelf for two weeks. On his return, he noticed that the culture, weakened by exposure to air, provided immunity to the disease rather than cause the disease itself (Elgert 1996).

[14] Acquired immunity is also known as adaptive immunity (Janeway, Travers et al. 2005).
[15] In this thesis, the terms vaccination and immunisation are used interchangeably.
[16] The germ theory suggested that disease is caused by microorganisms rather than by an imbalance of body humors or the position of the moon (Elgert 1996).

Pasteur's contribution was recognising[17] that attenuation had occurred. The principle was the same as Jenner's but attenuation had been achieved in a different way. Using a weakened form of chicken cholera itself to prevent disease was preferable to using a related organism in the Jennerian way because it may provide better immunity and less chance of transmitting other diseases. The idea was quickly developed into a chemically attenuated rabies vaccine five years later (Plotkin and Plotkin 2004a). Thus, the modern concept of immunisation, involving the development of vaccines in the laboratory using the same agent that caused the disease, was really introduced by Pasteur.

The next major step in vaccine development was the killed vaccine concept, where bacteria are killed by heat (Hilleman 2000b). In the space of a decade, this approach yielded vaccines against typhoid, cholera and plague (Plotkin and Plotkin 2004a). The focus on bacteria and antibodies in the late 19th century originated from key discoveries in immunity that were being made by no less than four Nobel prize winning scientists.

In 1890, Robert Koch established procedures for proving that a particular living agent was the source of a specific disease[18]. This was by identifying agents through staining and growing single strains of bacteria (pure culture). These procedures are known as 'Koch's postulates'[19]. In 1883, Elie Metchnikoff was the first champion of cellular immunity and his studies uncovered the central role of phagocytes in host defence (Janeway, Travers et al. 2005). In 1897, Paul Elrich's receptor theory of immunity was an equally strong contribution to vaccine development because it pointed out the difference between active and passive forms of acquired immunity (Hilleman 2000b). In 1890, Emil von Behring's work defined the origin and role of antibodies, which established the field of passive immunotherapy (Elgert 1996). Elrich's development of methods for specific quantification of antibodies made von Behring's passive immunity a practical reality. Elrich's concepts

[17] Pasteur is quoted to have said "Chance favours the prepared mind" (Elgert 1996).
[18] Koch isolated both the cholera and tubercle bacilli as the causal organisms of the respective diseases.
[19] The postulates consist of four requirements. First, the causal agent must be found in all cases of the disease. Second, the agent must be isolated from a carrier and grown in pure culture. Third, when the culture is injected into a susceptible laboratory animal, the animal must contract the disease. Finally, the causal agent must then be recovered from the diseased animal.

for specific complementarity of cellular side chains with chemicals and with other proteins gave birth to what was later called specific receptor-ligand binding (Stryer 1997). This concept dominates modern understanding of biochemistry and underpins all technological assets related to immunology.

The majority of the fundamental concepts of vaccinology had been introduced by the end of the 19th century. Vaccine development in the early 20th century followed two empirical roads, gradually refining these theoretical underpinnings. The first was the search for *live attenuated* organisms with reduced pathogenicity, which would stimulate protective immunity; the second was the development of vaccines based on *whole inactivated* organisms that would be as effective as using live organisms (see table 7 below).

Table 7: Learning and instrumentalities in vaccines since 1798

Disease causation and instrumentalities	**Live, Attenuated**	**Killed, Whole**	**Protein or polysaccharide**	**Genetically engineered**
18th Century				
Gods and devils cause disease until… Germ theory of disease	Smallpox (1798)			
19th Century				
Focus on bacteria and antibodies. Pasteur (attenuation), Koch's postulates, von Behring (antibodies), Metchnikoff (phagocytes), Elrich (specific receptor binding)	Rabies (1885)	Typhoid (1896) Cholera (1896) Plague (1897)		
Early 20th Century				
Antibody mechanisms described, Immunotherapy dominates field	Tuberculosis (1927)(BCG) Yellow Fever (1935)	Pertussis (1926)(whole cell) Influenza (1936) Rickettsia (1938)(typhus)	Diptheria (1923) Tetanus (1927)	
Post World War II				
New culture techniques, Goodpasture (fertile eggs), Enders et al (human cell culture) Conjugation technology Adjuvant technology Recombinant genetic technology	Polio (oral) (1958) Measles (1963) Mumps (1967) Rubella (1969) Adenovirus Typhoid (1990) Varicella Rotavirus (1998) Cold adapted influenza	Polio (injected) (1955) Rabies Japanese encephalitis (1965) Tick borne encephalitis (1937,1980) Hepatitis A (1991) Cholera	Pneumococcus (1972) Meningococcus (1976) H. influenzae (1988) Hepatitis B (plasma derived protein) (1981) Typhoid Acellular pertussis Anthrax (in development, bioterrorism act)	Hepatitis B recombinant (yeast or mammalian cell derived) (1986) Acellular pertussis (some components) Lyme (*E.coli* recombinant) (1998)

Sources: (Andre 2003), (Hilleman 2000b), (Plotkin and Plotkin 2004b)

Although the instrumentalities are not clearly defined in table 7, the table does serve to confirm suggestions made in chapters 2 and 3; the development of instrumentalities have been crucial influences in the rate and direction of vaccine innovation. Significant changes and achievements throughout the history of vaccination against viruses have been subject to

the co-evolution of instruments and techniques for growing them[20]. The initial challenge was due to viruses requiring living and multiplying cells for their growth, so no inanimate growth media (such as agar gel, used to grow bacteria) would suffice, no matter how it was enriched. It was not until the first decade of the 20th century, when cells could be cultivated in vitro, that the possibility of culturing viruses opened up. Even as cell culture techniques became good enough to grow cells seemingly forever (immortal cell lines), viruses did not grow and some even began to doubt their existence (Paul 1971:371).

In 1931, Ernest Goodpasture introduced the use of embryonated hens' eggs for growing viruses (Plotkin and Plotkin 2004a). This technique represented a major advance, because until then human viruses could only be grown in expensive animals, such as horses and sheep (Markel 2007). 'Nearly all the later practical advances in the control of virus diseases of men and animals sprang from this single discovery' (Burnet cited in Chase 1982:286). It facilitated the production of a crude influenza vaccine, as well as vaccines against rickettsia and yellow fever.

Then in 1949, Enders, Weller and Robbins propagated poliovirus in human tissue (see section 6.3.2). The ability to grow human viruses outside a living host, in a relatively easy and safe way, led to a flood of creative activity in vaccinology. This technique, in addition to greater knowledge of pathogens and host responses, led to what Plotkin and Plotkin (2004a:6) call the 'golden age of vaccine development' in the 1950s and 1960s, the development of effective viral vaccines against poliomyelitis, measles, mumps and rubella.

The eradication of smallpox through a global vaccination campaign in the late 1970s is one of the most important accomplishments of medical science[21]. It returned vaccines to the spotlight as an indispensable tool for public health administrators and provided an impetus for the development of new vaccines (Muraskin 1998). This optimism renewed interest in discoveries made in the 1930s which fell by the wayside for forty years due to the success of antibiotics (Plotkin and Plotkin 2004a). The discoveries showed that the immunogenicity

[20] This seems to be consistent with Hopkins's thesis (2004) that technological change in medicine can be 'technique-led.'
[21] Poliomyelitis and measles, whose only reservoir is human beings, have also been targeted for eradication.

of a capsular polysaccharide, which is generally a poor immunogen, could be increased by chemically binding (conjugation) to a carrier protein (PRP) (Janeway, Travers et al. 2005). This new protein conjugation technology was finally developed in the 1970s and 1980s yielding three effective bacterial vaccines: a meningococcal vaccine, a pneumococcal vaccine, and a Haemophilus Influenza type b vaccine[22] (Plotkin and Plotkin 2004a).

In addition to conjugation technology, the use of adjuvants is another important approach to enhancing the immunogenicity of vaccines. Purified antigens do not usually trigger a strong immune response on their own, and most acellular vaccines require the addition of adjuvants to boost their immunogenicity (Madigan, Martinko et al. 2000). Adjuvants use bacterial cell wall components, synthetic polymers, or liposomes and they influence the type of immune response induced by the vaccine (Madigan, Martinko et al. 2000)[23].

In 1981, a hepatitis B vaccine, made from surface antigen derived from human plasma, was licensed, and this was followed in 1986 by a recombinant hepatitis B vaccine, the first of its kind (Hilleman 2000b). As will be discussed, the advent of molecular biology and the development of new techniques in genetic manipulation and recombination greatly expanded the number of possible approaches for vaccine development.

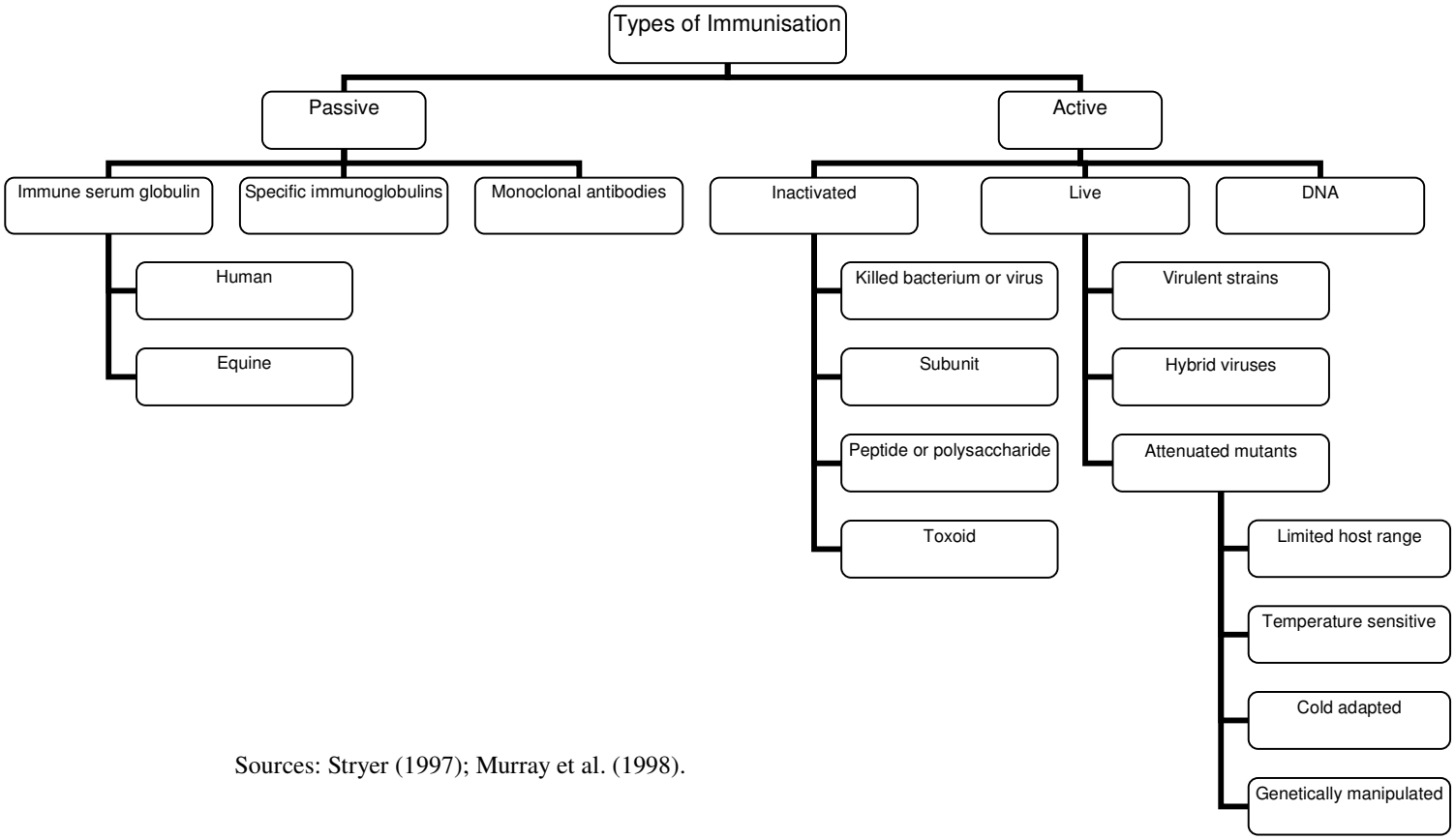
[22] These were important improvements over previous non-conjugated vaccines because children under the age of two, who are most at risk from these diseases, cannot make good antibody responses and could not be effectively vaccinated by polysaccharides vaccines (Janeway, Travers et al. 2005). New conjugated vaccines meant that children could be vaccinated by having their immune systems recognise the protein and launching a cellular response.

[23] For example, tetanus vaccines often contain aluminium salts, which bind polyvalently to the immunogen by ionic interactions and stimulate antibody responses (Janeway, Travers et al. 2005). Pertussis toxin has adjuvant properties in its own right and, when given mixed with tetanus and diphtheria immunogens, not only vaccinates against pertussis but also acts as an adjuvant for the other two immunogens (Janeway, Travers et al. 2005). This mixture makes up the DTP triple vaccine.

5.5 Types of immunisation and their development

This section reviews and compares the types of immunisations that are possible (figure 5).

Figure 5: A typology of immunisations



Sources: Stryer (1997); Murray et al. (1998).

The injection of purified antibody or antibody containing serum for the rapid, temporary protection or treatment of a person is termed 'passive immunisation' (Murray, Rosenthal et al. 1998). It can be used to prevent disease after a known exposure, to alleviate the symptoms of an ongoing disease, to protect immune suppressed patients like those infected with HIV, or to block the action of bacterial toxins and prevent the diseases they cause (for example diphtheria antitoxin grown in horses (Markel 2007). Immune serum globulin preparations are derived from humans (preferred) or animals.

‘Active immunisation’ occurs when an immune response and immunological memory are stimulated in response to a challenge with an immunogen (Elgert 1996). Such immunisation occurs after each exposure to an infectious agent (natural immunisation) and through exposure to microbes or their antigens in vaccines.

Inactivated vaccines, rather than live vaccines, are used to confer protection against most bacteria and the viruses that may be too virulent or that can cause recurrent infection (Janeway, Travers et al. 2005). Inactivated vaccines can be produced through the chemical or heat inactivation of bacteria, bacterial toxins, or viruses or through the purification of the components or subunits of the pathogen. These vaccines are usually administered with an adjuvant, which boosts their immungenicity (Madigan, Martinko et al. 2000). Inactivated vaccines are generally safe, except in people who have allergic reactions to vaccine components (Murray, Rosenthal et al. 1998). However, even with adjuvants, the immune response evoked by the inactivated vaccines is much more limited than that evoked by live vaccines (Madigan, Martinko et al. 2000). The immunity is not usually life-long, may be limited to humoral (molecular) and not cell-mediated (cellular) immunity, requires booster shots, and requires a larger dose of an inactivated vaccine than of a live vaccine (Madigan, Martinko et al. 2000).

A subunit vaccine can be developed after identification of the bacterial or viral components that elicit a protective immune response. Either the immunogenic component is isolated from the bacterium, virus, or virus-infected cells by biochemical means or the vaccine is prepared through genetic engineering involving the expression of cloned viral genes in bacteria or eukaryotic cells. Vaccines against *H. influenzae* B, *N. meningitidis, S. typhi* and *S. pneumoniae* are prepared from capsular polysaccharides enhanced by conjugation to a protein carrier, such as diphtheria toxoid (inactivated toxin) or *N. meningitides* outer membrane protein (Madigan, Martinko et al. 2000).

Live vaccines are prepared with organisms limited in their ability to cause disease (avirulent or attenuated). Most live vaccines are used to protect people against viral

diseases, especially infections caused by enveloped viruses, which can require T-cell immune responses for the infection to resolve (Elgert 1996). Immunisation with a live vaccine resembles the natural infection and elicits both the humoral and cellular immunity. It generates an immunity that is generally long lived and can mimic the normal immune response to the infecting agent (Murray, Rosenthal et al. 1998).

However, there are two problems with live vaccines: (1) the vaccine may still be dangerous for immunosupressed people or pregnant women who do not have the immunological resources to resolve even a weakened virus infection, and (2) the vaccine may revert to a virulent form, a process that is rare. It is hoped that these shortcomings will be alleviated with the application of recombinant DNA technology to the development of live attenuated vaccines, making them safer[24] (Janeway, Travers et al. 2005).

Live virus vaccines consist of less virulent mutants (attenuated) of the wild type virus, viruses from other species that share antigenic determinants, or genetically engineered viruses lacking virulence properties (Madigan, Martinko et al. 2000). Wild type viruses are attenuated by growth in embryonated eggs or tissue culture cells at non-physiological temperatures (32˚C to 34˚C) and away from the selective pressures of the host immune response. These conditions select for or allow the growth of viral strains (mutants) that are less virulent because they grow poorly, do not replicate well in any human cell, or can replicate at a benign site but do not disseminate, bind, or replicate in the target tissue affected by the disease (Madigan, Martinko et al. 2000).

5.5.1 Reverse vaccinology

Recent breakthroughs in life, and information, sciences have opened up a radically new approach to developing vaccines. This approach has been termed ‘reverse vaccinology’ because potential vaccine targets are identified from the genome sequence rather than elucidated from the pathogen cultivation. Genome sequences are fed into computer

[24] One example of this is Salmonella typhi, the causative agent of typhoid, which is manipulated to develop a live vaccine. Specific genes are targeted for mutation that makes the bacteria dependent on an external supply of an essential nutrient. These bacteria grow poorly in the gut but survive long enough as a vaccine to induce an effective immune response (Janeway, Travers et al. 2005).

software that can provide a list of possible antigens - without needing to grow pathogens *in vitro* and empirically derive which parts of the pathogen are antigenic. Although no vaccines have been developed in this way yet, the reverse vaccinology approach has been applied recently to Meningococcus B[25] to focus efforts more precisely (Pizza, Scarlato et al. 2000; Capecchi, Serruto et al. 2004; Danzig 2006).

Reverse vaccinology may be able to generate a range of possibilities, but it does not select them for us. Software might be able to screen or prioritise some of the possibilities for us, but that software in turn needs to be designed, with programmatic assumptions that are likely to have been derived from empirical labour as well as genomic analysis. There is nothing inherent in genomes that will, by itself, indicate a social purpose – a vaccine – without human interpretation, based on tacit knowledge and empirical testing. The immense challenge of developing assays, measurements and efficacy tests (and then codifying them into programs!) will therefore still remain. Developing these tests is especially problematic in cases where there is a lack of natural sterilising immunity, such as HIV, TB and malaria. In these cases, we cannot readily observe a natural immunity, and then use it to illuminate a design pathway for us by developing a body of tacit and empirically tested knowledge. This is supported by the fact that the HIV, TB and malaria pathogen genomes have all been sequenced for many years now, but successful vaccines have not been developed.

As shown in the empirical chapters, broader genetic recombination techniques may also help to develop better delivery (vector) technologies. However, the value of knowing '*what*' to present to the immune system, as well as how to present it, is unlikely to be diminished by these technologies. They do not represent an unequivocal, all competence destroying, technological revolution in vaccines.

[25] The pioneer case of reverse vaccinology was Meningococcus B (Pizza, Scarlato et al. 2000). As its genome was being sequenced, computer software was used to screen the genome for putative pathogen-surface exposed or pathogen-secreted proteins (2158 possibilities). These proteins are then screened again for potential antigens (600 possibilities). Of the potential antigens, only half could be expressed and purified (350). These were tested in bactericidal assay, an assay which is known to correlate with protection in humans (91). The antigens that were able to induce bactericidal antibodies (29) are then subjected to immugenicity testing in mice. This left us with 15 promising vaccine candidates for developmental investigation, a number greater than the total number of candidates found over the previous 40 years.

5.6 Reflecting on technical dynamics

The first part of this chapter analysed shortcomings in an economic approach to vaccine innovation issues.

The second part of the chapter discussed biological principles in immunology and basic concepts in vaccine development. It noted that the immune system has separate responses for when the pathogen is inside or outside cells, known as the cellular and humoral responses respectively. Live vaccines tend to exploit the cellular response more effectively, whilst killed vaccines tend to exploit the humoral response more effectively.

A historical perspective was used to outline how the knowledge of vaccination has accumulated over time (rather than simply changed). The role of instrumentalities was emphasised by highlighting the co-evolution of instruments and techniques. New instrumentalities were integrated into existing bodies of knowledge. Thus, the early strategies of killed pathogen and live attenuation have remained useful over time, despite 200 years of knowledge accumulation.

Chapter 6

Knowledge Accumulation in the Road to Poliomyelitis Vaccines

This chapter proceeds in seven sections. The introductory section explains why poliomyelitis drew attention and became recognised as a problem. It describes the construction of a vision, led by a US President, as well as by scientists establishing a cause for the disease. The second section describes some of the failures and barriers faced by researchers, which might otherwise be overlooked in a history of poliomyelitis successes. The third section describes the development of a testing regime, which involved improving learning conditions, instrumentalities, and knowledge co-ordination and integration. The fourth section describes the development of field-based testing capabilities to manage the move out of the laboratory. The fifth and sixth sections follow the development of two different operational principles, disagreements between people working on the different approaches, and the significance of ethics and path-dependency to certain testability issues. A final section concludes the chapter.

6.1 The emergence of a problem and the vision of a solution

Poliomyelitis was eventually given its name as a disease in the middle of the 19th century[1] after physicians learnt to associate a distinctive paralysis with damaged spinal cords in children. This formed the basis for early clinical recognition (Paul 1971:26). It was sometimes fatal, and the damage was found to be inflammation (*itis*) of the grey (*polios*) matter of the spinal cord (*myelos*) (Paul 1971:7). Initially, it was thought to be caused by teething (Carter 1965:8), perhaps due to the temporal proximity of the events. The

[1] The earliest evidence of poliomyelitis is an Egyptian stone carving depicting a man with a deformed limb dated to 1500BC (see Paul 1971:15 for an image of the stone). The disease was given a series of changing names as the characterisation of the condition became increasingly specific. For example, names range from morning paralysis in 1843, to tephromyelitis anterior acuta parenchymatose in 1872 and later, infantile paralysis (Paul 1971:5).

clustering of cases in single households however, suggested the disease was of an infectious nature.

6.1.1 A vision for the technological community

In 1908, Landsteiner and Popper, showed more conclusively that poliomyelitis was spread by an infectious agent (Robbins 2004:17). The researchers caused monkeys to develop the disease by inoculating their brains with spinal cord tissue taken from a human who had died of the disease[2] (Paul 1971:98). The following year, Flexner and Lewis went further by passing the human infection from monkey to monkey (Carter 1965:9). Although the infectious agent responsible for poliomyelitis could not be seen under microscope, the flurry of experiments between 1908 and 1910 showed it conclusively to be a living parasitic microorganism[3], able to reproduce in the cells of its victims.

This line of enquiry was likely to have been informed by Koch's postulates, which had laid the foundations of germ theory[4] (Paul 1971:100). The Metropolitan board of health in New York had recently formed, and was keen to exploit such freely available ideas (Mullan 1989). It allowed public health officials to be less concerned with intractable environmental tasks such as cleaning up the city, ridding pests and animals, promoting personal hygiene and sanitation, or dealing with overcrowded slums, hunger and poverty (Tomes 1990). The establishment of a causal agent also helped initiate a shift in disease management policies away from quarantinism (Baldwin 1999).

For the technical community, the discovery of a disease causing agent for poliomyelitis allowed them to search for past experience of similar situations. They were able to conceive a solution based on Jenner's and Pasteur's vaccines, which tackle diseases known by then

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[2] It is important to note that the animal model was not a perfect simulation of humans. The monkeys only contracted paralytic poliomyelitis if the agent was injected directly into their central nervous systems (Paul 1971:98).

[3] The infectious agent was recognised to be a virus because it could pass through the finest filters (Carter 1965). The relationship between infectious agent and disease is relatively simple for poliomyelitis. As we shall see, the relationship between HIV and the onset of AIDS is more complex and when modelling in monkeys, SIV infection, *not* HIV infection, is needed to bring about AIDS-like disease in monkeys.

[4] Pasteur had already applied these principles a few decades earlier for vaccine protection against anthrax, cholera and rabies (see chapter 5).

to also be caused by a specific agent. The poliomyelitis researcher Hortsmann (1985) wrote, 'Recovering the etiologic agent of a disease immediately conjures up dreams of developing a vaccine to prevent the infection. This was as true in 1908 when Landsteiner reported the isolation of poliovirus as it is today, when the identification of HTLV3 [the early term for HIV] as the probable cause of AIDS burst on the horizon.' However, beyond having a target to take aim at, the operational principles such a poliomyelitis vaccine might have were completely unknown, and further knowledge about the epidemiology of the poliovirus was needed to assert that the notion of a vaccine was a technological possibility.

By 1910 it was demonstrated that monkeys that survived poliomyelitis often resisted re-infection. It was also shown that the blood of surviving monkeys contained a substance that neutralised virus in a test tube (Paul 1971:108). This served as further clues to the possibility of a vaccine, and ensured that further work towards the idea of a vaccine was not eliminated as unworthy of resources. In 1911 Flexner issued a press release declaring that within six months[5] a specific remedy would be announced, 'We have already discovered how to prevent the disease, and the achievement of a cure, I may conservatively say, is not far distant' (full press release in Paul 1971:116). For Flexner the nut had already been cracked and all that was needed was to turn the laboratory discovery into a fully developed and tested technology. He was appealing to a common intuition in which the difficulties of moving from science (of establishing cause) to innovation (of a vaccine) were underestimated. Perhaps this was necessary in order to sustain the belief that the vision or proposed idea is not ridiculed as a technological impossibility[6].

However, there were several early obstacles to establishing operational principles (aside from world wars). Laboratory diagnosis of poliomyelitis was dependent on testing spinal fluid, obtained through a painful and dangerous procedure that few physicians could perform. So serum harvested from the blood of sick patients or animals remained scarce and unreliable, and was critically dependent on skilled people (Paul 1971; Rogers 1992).

[5] A similar, more public, announcement was made by Margaret Heckler, US secretary of health, about the time needed (a couple of years) to develop an AIDS vaccine (Shilts 1987; Cohen 2001b).
[6] The eminent polio researcher John Paul concedes, '[Flexner] can be forgiven for making mistakes about poliomyelitis' (Paul 1971:125).

As such, accumulating knowledge about the properties of the virus (and viruses generally) was slow. Little was known about how poliomyelitis established itself in man (pathogenesis), or how it was transmitted (Robbins 2004:17).

It is now known that various types of poliovirus may enter through the mouth and nose from droplets such as saliva or microscopic pieces of faeces (Paul 1971:2). The virus then slides into the gut where it reproduces. Normally the immune system can limit this infection before it causes serious disease, but on rare occasions the virus travels through the blood and into the central nervous system, causing meningitis. Paralysis occurs only if the virus then enters nerve cells. It is estimated that in an unvaccinated population, poliovirus paralyses 1-2% of the people it infects (Madigan, Martinko et al. 2000).

This model of polio-pathogenesis accounts for the transmission of its immunity, as well as the patterns of disease spread during epidemics. Before poliomyelitis epidemics emerged, poliovirus was usually spread by faecal contact. Paradoxically, increasing sanitation and better standards of hygiene promoted its spread because children were less exposed to mild forms making them more susceptible to severe infection (and also because mothers did not pass immunity to foetuses[7])[8].

The model postulated by Flexner in 1913 was significantly different and, in short, mistaken (Rogers 1992). In this incorrect model, poliomyelitis was caused by only one type of virus, which travelled through the sinuses directly to the brain and spine, and grew in living nervous tissue. These assumptions led to problematic inferences. First, it mistakenly led researchers down the path of aiming to culture (grow) virus in nervous tissue, rather than any other kind of culture medium. Second, if the poliovirus did not enter the bloodstream, there was little point in trying to put any antibody there. Furthermore, monkeys that recovered from the disease did not develop noticeable amounts of antibody in their blood

[7] However, Immunoglobulin A, which contains antibodies, is passed on to newborns in the colostrums in their mothers' milk (Chase 1982).

[8] The general implication is that our pathogenic environment is constantly evolving in response to our behaviour and in turn new health technologies will need to 'keep up' in order to remain effective. The most important innovations in healthcare then are not one-off vaccines, but instead lie in the processes that can consistently innovate and a system that can sustain the distribution of such innovations. It is with this in mind that we explore which aspects of the *vaccine innovation process* were important.

until long after recovery. Antibodies were therefore seen as a by-product of illness rather than of central significance to immunity.

The early work that followed Landsteiner and Flexner was expensive and produced unclear results. Experiments were often confusing because researchers did not know they were dealing with multiple types of virus at the same time. Furthermore, the only polio-susceptible animal was the monkey, 'a cranky, expensive creature, which in those days (prior to antibiotics) had a way of succumbing to other diseases before the researcher could measure its responses to polio. No laboratory combined sufficient interest with enough funds to buy and maintain all the monkeys needed for thorough study of the poliovirus and the disease it caused' (Carter 1965:19). Apart from a few researchers like Flexner and Lewis, the consensus of the scientific community in 1913 (and up to 1935) was that a vaccine was possible and desirable, but not likely (Carter 1965:58; Paul 1971:113).

6.1.2 Finding wider support and a war chest to chase the vision

By 1916, the annual incidence of paralytic poliomyelitis in the United States was over 27,000, killing more than 7,000. New York, in particular, was panicked where there were 9000 cases with over 2000 deaths that year (Rogers 1992:10). Reported cases had never exceeded 7.9 per 100,000 but in 1916 the rate jumped to 28.5 (Paul 1971:148; Rogers 1992:10). Hospitals refused to admit cases for fear of infecting others, and some cities began insect control programmes with DDT whilst others impounded cats and dogs, all of which authorities mistakenly thought could transmit the infectious agent discovered by Landsteiner (Paul 1971:149, 291). Parents sealed their windows and refused to let their children play outside (Oshinsky 2005). By 1953, poliomyelitis afflicted more than 20 per 100,000 (Robbins 2004:17).

Although the rate was not as high as some other diseases, such as measles, much public concern was generated by the media portrayal of poliomyelitis because of its seasonal occurrence, its disfiguring nature and its propensity for paralysing the respiratory muscles (Oshinsky 2005). The disease was highly visible because paralysed patients often needed help breathing with large apparatus dubbed 'the iron lung' (Paul 1971:327). In addition, the

disease was visible to all social classes because, unlike other leading causes of infant mortality and infectious diseases (such as tuberculosis), it was not restricted to the poor. Given Landsteiner's finding, public health officials are likely to have known that the middle and upper classes could not be insulated from poliomyelitis very well using current methods (such as quarantine).

In 1921, Franklin Roosevelt[9] was struck by poliomyelitis aged 39 (Carter 1965:11; Paul 1971:301; Gallagher 1985; Oshinsky 2005). Roosevelt's condition altered public perception of poliomyelitis and boosted scientific research. His misfortune was beneficial not only to poliomyelitis victims but also to those with other disabilities too because physical handicaps were judged harshly. Afflicted individuals were kept out of sight by families that felt ashamed (Longmore 1987). An influential orthopaedic text of the time supported the idea that disabilities are punishments from God, stating, '…a cripple is detestable in character, a menace and burden to society, who is only apt to graduate into the mendicant and criminal classes…' (Longmore 1987:357).

Roosevelt's public relations were carefully coordinated so that he would appear less like the cripple described above and more as a triumphant hero despite being burdened with physical limitations; this significantly contributed to the transforming structure of disabled identity (Gallagher 1985). The lack of photographs of Roosevelt in a wheelchair support this notion and contribute to what Gallagher (1985) calls 'FDR's magnificent deception'. In 1924, after it was reported in newspapers that he bathed in Warm Springs, Georgia, to ease his paralysis, many other sufferers made their way there. Roosevelt spent two thirds of his personal fortune renovating, and expanding it to become the Warm Springs Foundation (Gallagher 1985). It was directed by his former law partner, Basil O'Connor, whose commitment was further reinforced by his daughter's death from poliomyelitis (Oshinsky 2005:271).

[9] Although Roosevelt's presidency did not begin until 1933, he had by then already risen to national prominence. He was born into a wealthy and powerful family. In 1905 he married his cousin, who was the niece of the then President Theodore Roosevelt. By 1920, he had won his party's Vice-presidential nomination (Gallagher 1985).

In 1934 Roosevelt staged nationwide charity balls on his birthday 'to dance so others may walk' (Carter 1965:14) and also to relieve debts accruing at Warm Springs (Rose 2003). Given the stock market crash of 1929, the campaign achieved extra-ordinary success (Rose 2003). It raised $1m that year[10], $0.75m the following year and it reserved $100,000 to 'stimulate and further the meritorious work being done in the field of infantile paralysis' (Carter 1965:14,15 and 18). The first sixteen research grants totalled $250,000, one of which, for $65,000, was distributed to Maurice Brodie (Carter 1965:20; Benison 1967:179).

6.2 Brodie-Kolmer vaccine failures: A weak testing regime in need of strengthening

Part of Flexner's bold optimism was based on the successes of tetanus and diphtheria vaccines, which by 1910 had rapidly saved millions of lives[11]. This passive immunisation was achieved by using immune sera drawn from the blood of horses previously immunised with graded doses of bacteria. Flexner and Lewis attempted to repeat the achievement with polioviruses but had to report 'the failure to produce neutralising serum in the horse by repeated injections of filtrate… The horse serum, when mixed with the virulent filtrate and incubated [as in monkeys], displayed no power whatever to inhibit the action of the virus. The monkeys injected with the mixture of horse serum and virus became paralysed in the same average period as the controls' (cited in Chase 1982:302). Poliovirus could not be grown in horses, or any other animal[12], and further research and development would have to involve either humans or monkeys.

6.2.1 Failure of 'witches' brew'

Despite the confusing data emerging from monkeys, the overall vision was strong and stable enough for two investigators to overlook the problems. They independently conducted field trials of ill-conceived vaccines prepared from spinal cord of infected monkeys in 1936 (Chase 1982; Robbins 2004). They envisaged rudimentary operational

[10] All dollar figures in this thesis, unless stated otherwise, have not been adjusted for inflation.
[11] For example, the United States' death rate for diphtheria halved between 1900 and 1909 (Chase 1982:302).
[12] Although, in 1939, a poliovirus strain was adapted for certain rodents, its growth was limited and rare (Paul 1971:276; Robbins 2004:19). Humans and monkeys seemed the only alternatives.

principles and wanted to test them promptly to refine them into a vaccine. Brodie and Park used a formalin-treated preparation of mashed up spinal cord, whilst Kolmer used live virus from spinal cords which he treated with chemicals and refrigeration to achieve immunity. In retrospect Kolmer's was probably the more dangerous of the two, described by some as 'a veritable witches' brew' (Paul 1971:258).

The investigators wanted to progress quickly with tests, and using what Paul (1971:259) refers to as 'kitchen chemistry', the two hurried their 'vaccines' into perceived readiness, each fearing the other would succeed first. The rivalry was perhaps all the more intense since Kolmer was not funded by Warm Springs money. The failure killed and paralysed many of 12,000 children he 'vaccinated' (Paul 1971; George 1996). In a public health association meeting, Kolmer is reported to have said "Gentlemen, this is one time I wish the floor would open up and swallow me" (Paul 1971:260; Chase 1982:284). Many have alleged that Brodie killed himself four years after the trials (Paul 1971:261), but his death certificate only offers thrombosis as the cause (Chase 1982:284).

The failures stifled vaccine development and dampened enthusiasm to an extent that Paul considers 'blown out of proportion'. The impact of the experience traumatised researchers and sparked 'a wave of revulsion against human vaccination attempts in poliomyelitis' that lasted for two decades (Paul 1971:260).

6.2.2 Learning from failure with a testing regime

The failed efforts are indicative of the norms and traditions of those testers. They saw vaccinology largely as an empirical art, and if the vaccine worked, it worked. Vaccines for diseases such as smallpox and rabies had been developed without formal identification and characterisation of their infectious agents. How or why a vaccine protected a human was relevant but not all important. Their aim was to protect public health and livestock; if understanding was improved along the way, so much the better.

But if the vaccine did not work in a single attempt, as in this instance, the testing regime needs to be able to ensure that researchers have a way of finding out why the test failed.

The knowledge generated from these trials did not accumulate and further social investment in the testing regime would be needed. The failures served to highlight that more systematically gained know-how was needed before injecting people.

The testing regime was weak for three reasons. Firstly, feedback loops were weak because there was so little virus available to work with. Few were skilled at diagnosing infection quickly by extracting spinal fluid, so most researchers had to wait for symptoms when testing for any immunity. Secondly, iterations, refinements and adjustments could not be made, because monkeys were so difficult to use and they were not used intensively because they were so expensive[13]. Thirdly, the community did not establish the types of poliomyelitis virus they were working with before trialling. Each of these three issues needed to be addressed for successful vaccine innovation as the next section shows.

The failures moved Roosevelt to abandon the Birthdays Balls after 1937 and rename the Warm Springs Foundation to the National Foundation for Infantile Paralysis (Rose 2003). Its mission was not just to 'make every effort to ensure that every possible research agency in the country is adequately *financed* to carry out investigations into the cause of infantile paralysis and the methods by which it may be prevented' (Carter 1965:15). But significantly, Roosevelt also announced that the Foundation would, '*lead, direct, and unify* the fight of every phase of this sickness' (Markel 2005:1408) [my italics]. It would form a major institutional part of the testing regime for poliomyelitis vaccine development, and it formed a focal point for the co-ordination of resources – fiscal, labour, skills and materials.

The first fund raiser held by the Foundation was a radio promotion. One of the radio promoters enthused 'we could ask people to send their dimes directly to the White House…think what a thrill people would get…we could call it the march of dimes' (Carter 1965:16). The Foundation received over $1.8m in a week and with each new campaign the proceeds increased. For example, the 1945 receipts totalled $18m, and 1955 contributions

[13] Brodie only tested his vaccine on 20 monkeys before trialling with 300 children whilst Kolmer only tested on a few monkeys, himself, his children and 22 others before distributing the vaccine to physicians around the country (Paul 1971).

totalled $67m (Carter 1965:26). A considerable war chest was established for the research and development of vaccines[14] (Carter 1965; Paul 1971:312).

Figure 6: March of Dimes Posters

Sources: US FDA[15]

6.3 The construction of a more sophisticated testability regime

In 1947, Harry Weaver was appointed as Director of Research at the Foundation. With the support of O'Connor, and to the resistance of many others, he went about directing poliomyelitis research much in the style of large war time projects. Weaver began by inviting leading poliomyelitis researchers to conferences and had the Foundation publish their remarks in regular reports (Carter 1965; Smith 1990). He instituted a series of round table discussions with the Foundation's grantees. The more long term purpose of this was to 'encourage communication and intellectual cross-fertilisation in a field notable for its lack of both' (Carter 1965:57). The more short term goal was to bring himself up to speed with the current wisdom about poliomyelitis.

In this way, Weaver immediately played an important co-ordinating role between different groups of scientists. With O'Connor, Weaver would also play an intermediary role between

[14] Between 1938 and 1962, the Foundation's overall income was $630m. 59% was spent on hospital and patient support (treatment and care), 13% was spent on fund-raising and advertising, 8% on educational programmes, and 11% ($69m) was spent on vaccine R&D (Paul 1971:312).

[15] www.fda.gov/cber/summaries/cent092302pp.htm and http://polioclinic.com/history/dimes.htm

the scientific community and the wider public interest. The Foundation was entrusted with co-ordinating the scientific community and preventing the failures of the 1930s vaccines resurfacing, but it was also constantly in the media spotlight and funded by mothers with tins collecting door-to-door. With Weaver, the Foundation was able to juxtapose scientific concerns with those of the technology-demanding public. Researchers wanted incremental advances of certainty, and poliomyelitis sufferers wanted tangible advances urgently.

The tensions between these two aims quickly became apparent to Weaver. The round table discussions and conferences led Weaver to the view that whilst researchers who are free of direction establish more certainties about a disease, they often choose to investigate questions of little practical application. Weighing up the field Weaver wrote to O'Connor,

'Only an appalling few…were really trying to solve the problem of poliomyelitis in man….If real progress were to be made, more exact methods of research would have to be clearly defined, procedures and techniques would have to be developed to permit attaining those objectives and individual groups of workers would have to sacrifice to some extent their inherent right to roam the field, and concentrate their energies on one, or at most, a few of the objectives' (Carter 1965:57).

Prior to Weaver's appointment, the National Foundation simply funded projects that independent researchers chose (Benison 1967; Smith 1990), similar to many of the foundations of today (Arnold 2005:34; Boddington 2008; McCoy, Kembhavi et al. 2009; Moran, Guzman et al. 2009), upholding the traditional view that burdening scientists would suffocate their creativity and output. Weaver believed that part of the problem was allowing this form of investigator-initiated research to dominate the research agenda at the expense of more carefully co-ordinated research. As Weaver was a doctor of philosophy and not of medicine (Carter 1965:58), he set up a Scientific Research Committee with whom he could direct research at the technical level. The head of this Committee was Dr Thomas Rivers, who shared Weaver's view of targeted research,

‘During the first year of the Foundation’s existence, the Scientific Research Committee received any number of applications from individual investigators and, while many were worthwhile in themselves, together they did not seem to be going anywhere. They were too haphazard for a program and I thought that the Foundation would be better served if a committee surveyed the field of polio research and blocked out problems that needed solution. With such a guide in hand, I felt that the committee should seek out the men and institutions capable of researching such problems and support them with grants’ (Benison 1967:231).

‘Several members of the committee didn’t like my idea.... They felt that the Foundation would be better advised if it simply continued to give grants to competent investigators of accredited institutions who voluntarily expressed their wish to do research into causes and prevention of polio’ (Benison 1967:232). For example, one prominent Foundation grantee wrote, ‘Are we now employees who are ordered about?’ (Paul 1971:405).

Despite the resistance to such interference in research, Rivers and Weaver led the enterprise ‘by seeking out men and institutions’ to undertake an 11 point research plan they felt needed doing[16]. To begin with, there were three major impediments to poliomyelitis vaccine development which Weaver tackled directly. Firstly, Weaver felt that a monkey shortage had delayed poliomyelitis research. Secondly, it was not known how many wild types of poliovirus existed against which a prospective poliomyelitis vaccine would need to protect. Thirdly, it was not possible to grow viruses successfully in the laboratory; they had to be grown in living animals, in the brains of monkeys. This was time consuming, expensive and of low yield.

6.3.1 “Monkey Business”: Co-ordinating the supply of Testing Resources

Weaver complained to O’Connor that ‘experiment after experiment had been botched by scientists who used too few monkeys or made the error of reusing monkeys whose systems

[16] The eleven priorities are fully listed by Benison (1967).

were misleadingly immune to one or another type of the virus.' O'Connor resolved, "We'll go into the monkey business" (Carter 1965:73).

After decades of trying, researchers had been unsuccessful (except in a very limited way) in giving poliomyelitis to mice, rats, rabbits and other small, inexpensive and readily available laboratory animals (Robbins 2004). They could do it with monkeys, but working with monkeys was expensive, messy, and sickly. Even with the ethics of animal research being less high profile compared to today, working with monkeys was still troublesome. Monkeys required special animal quarters distinct from the usual cages or bins for smaller laboratory animals such as guinea pigs and mice (Paul 1971:101).

Aside from the extra space required, monkeys needed an entirely different kind of care from that of smaller animals. 'Salk had spent a significant proportion of his time arranging the housing and feeding of his monkeys, as well as placating the assistants who had to work with them' (Smith 1990:123). For it was these skilled keepers who had to watch for their welfare and keep up their spirits, whilst also cleaning their messes and feeding them. They were skilled in handling them, exercising them and observing their behavioural tendencies. They also had to contend with the constant threat of bites and thumps, as well as the chance of catching disease from them. The possibility was frightening enough for Salk to request from the Foundation 'a $10,000 life insurance policy for each of the individuals in this extra-hazardous work'[17] (Carter 1965:75).

Despite these difficulties, laboratory demand for monkeys outstripped supply. Capture of wild monkeys was not always a simple affair, free of outside considerations[18]. Many

[17] One physician working with monkeys suffered a fatal case of encephalitis. The Foundation referred Salk to University administration on his request for insurance against such fatalities.

[18] Cynomolgous monkeys suffered from poliomyelitis in ways that were close to human and their temperament made them easier to work with, but their extreme scarcity meant they were very expensive imports from the Philippines and Indonesia (Time 1954; Smith 1990). Rhesus monkeys, the type most commonly used for laboratory research, were abundant in India, but they are sacred to Hindus, regarded as incarnations of the monkey God Hanuman (Lutgendorf 2007). Only Muslims, (or other non-Hindus) would catch monkeys and then only during specific seasons, for example not over the month of Ramadan (Time 1954). Supplies were also susceptible to Indian government regulations and restrictions rooted in Hindu religious pressure groups, fears about what they were being used for, or concerns about mistreatment in transit (Time 1958).

researchers complained about monkeys arriving dead or diseased. Salk complained to a supplier, 'In addition to the three monkeys from the first shipment that were dead on arrival (in one instance there was obvious head trauma), we have lost three more. I wonder… whether you will replace the animals that die… The monkeys of the 18th seem to be much cleaner, more content and evidently well fed; however they seem very small' (Carter 1965:75).

O'Connor established Okatie Farms to address these problems. Weaver would organise massive monkey 'airlifts' from India and Indonesia (Time 1954:7) and have them sent directly to the Farms. There they would rest, recover their bearings, and recuperate from whatever diseases they might have had. Only when they were nursed back to health would they be dispatched to laboratories. In this way, the Farms saved laboratory time, effort and space.

Smith (1990:121) describes the Farms as 'a rehabilitation facility that was also a center [sic] for research in the solution of problems nobody else much cared about.' The Farms developed carefully formulated dry monkey feed in conjunction with researchers like Salk, 'I am wondering if the low cost of your [monkey] diet is not due to the fact that there has been some substitution in content' (Carter 1965:76). The Farms also provided instructions on how to mix the feed and tips on when and how to get the monkeys to eat it. Among the tips were to divide the rations so that the monkeys would not have enough in one go 'to fling around and mash into each other's ears and stuff down drains and such like' (Smith 1990:122). In all, there are considerably long correspondences regarding the minutiae of delivering, feeding, handling and disposing of monkeys (Carter 1965).

6.3.2 Tissue Culturing: a new technique for growing virus

The effort to develop better methods for propagating the virus was attempted by various investigators throughout the 1930s, but failed to find a solution (Robbins 2004). By the end of the decade two exceptional groups reported the growth of poliovirus in cultures of human embryonic brain tissue, however they failed to take the technique further with cells from non-nervous system tissues (Sabin and Olitsky 1936; Burnet and Jackson 1940:373;

Paul 1971). Robbins (2004:18) laments on their efforts, 'Unfortunately, they did not pursue these findings; otherwise the vaccine might have been available almost a decade earlier.'

Their failure to persist was in part due to the orthodoxy that poliovirus was essentially a nervous system virus, which occasionally spilled over into the blood. Unfortunately their findings served only to reinforce the notion that poliovirus was more neurotropic than it really was. Thus it was thought that a poliomyelitis vaccine was highly impractical because, if it would only grow in the nervous systems of monkeys, it was impossible to remove all of the animal-nerve cells when harvesting the virus for vaccine preparation. This in turn meant that a vaccine would be very dangerous for humans because, when they are injected with foreign nervous tissue, they may suffer fatal allergic inflammations of the brain, or encephalitis (Rogers 1992).

However, some other Foundation grantees made significant findings about virus growth. Paul and Trask observed the presence of virus in human faeces, implying it could reproduce in the alimentary tract (Paul 1971:281). In 1940, Bodian and Howe gave chimpanzees poliomyelitis by feeding them the virus and, in 1947, Melnick and Hortsmann demonstrated that the animals developed antibody and resistance to re-infection after such feeding (Paul 1971:287). This provided strong indications that poliomyelitis was an intestinal infection.

Then, with Weaver at the helm, the Foundation funded a more persistent effort on tissue culturing than before. The Foundation provided funds for training personnel to acquire practice and skills in culturing. In order to achieve good yields, cultures have to be kept at precise temperatures, in very clean containers, of the right shape and size, with the right kind of lids and stoppers (Smith 1990). Sourcing the tissue with which to culture was not a straightforward matter either. The Foundation kept laboratories in close contact with local maternity hospitals because embryonic tissue grows much faster than that of adults, and is less prone to disease, so it is the preferred tissue. Given the contentious nature of acquiring genuine embryonic tissue, the closest the Foundation could get was to acquire small quantities of foreskins from circumcisions of newborn boys. Placentas, miscarriages and

still-born tissue were also used but the supply of these sources were less predictable and were also quite controversial (Smith 1990).

The Foundation commissioned a group at Harvard University, who had been developing culturing techniques on mumps virus and chicken pox virus with considerable success, and supplied them with abundant poliovirus and funding to match (Chase 1982:292). In this attempt, Enders, Weller and Robbins succeeded in making the breakthrough most eagerly sought by the Foundation – that is, cultivating poliovirus in human non-nervous tissues (in human embryonic skin muscle). It was not long before poliomyelitis was found to propagate in cells from a variety of tissues (Robbins 2004:18).

Initially, the scientist John Paul undervalued the breakthrough. 'For the moment, I was stupidly unaware of the implications that this finding held. At least it did not appear to me as an electrifying piece of news. Instead, I visualised it as just another repetition of the results which Sabin and Olitsky had reported twelve years earlier…However remarkable their technical triumph was, it hardly seemed to me to be a trick... How utterly mistaken was my preliminary judgment of this discovery to prove!' (Paul 1971:373). Their technique marked the start of the tissue culture era.

Tissue culture transformed the testing regime by providing a safer and simpler environment to learn in, with tighter feedback loops with new knowledge derived from tests accumulating quickly. Firstly, the tissue culture era did not simply represent a method of growing more of the virus. It was a source of better quality virus because it was relatively free of protein and, crucially, it could be free of nerve cells, which meant it removed the chief safety concern of encephalitis (Robbins 2004:18).

Secondly, tissue cultures drastically reduced the need for monkeys which were being imported at great financial and temporal expense (Chase 1982). In 1953, human embryonic tissue was substituted with the testicles or kidneys of monkeys, a single one of which, according to Salk, could provide enough tissue culture for two hundred test tubes (Carter 1965:114). One monkey, then, did what used to require two hundred. 'Worse than the costs

of buying and maintaining these animals were the temporal limits they placed on the investigative progress' (Chase 1982:286). With the need for experimental animals vastly reduced, feedback loops were much shorter. More ideas could be tested, and the results of such tests could be assessed quicker. Thus testing became dramatically cheaper and quicker.

Thirdly, tissue cultures were used to set up standards and criteria. It was observed that early in the course of poliovirus cultivation, infected cells were rapidly destroyed (Chase 1982:292; Robbins 2004:19). This cytopathic effect was used as an indicator of viral replication, meaning that the presence of viruses were observable with microscopes rather than with monkeys. With some technical modifications, tissue cultures were also used for virus titration, antibody quantification, virus isolation from clinical specimens and antigenic typing of virus isolates (Paul 1971:374; Robbins 2004:19).

Robbins (2004:18) reflects, 'There is no ready explanation as to why [our] experiments succeeded whereas those of Sabin and Olitsky did not. The principal technical difference was that, in Enders' laboratory, the cultures were maintained for a longer time, with periodic changes of nutrient medium…'. Sabin himself acknowledged this at a Danish conference (Carter 1965:115). Persistence and simply trying harder and for longer, however, were not the only reasons they succeeded. Rivers also saw the experiments as very similar, as he recounted, '[Sabin and Olitsky's] work was so meticulously done that I believed it was absolutely correct… I read [Enders'] paper over and over looking for a flaw. In the end I had to believe he was right. It wasn't easy because I damn well knew that Olitsky and Sabin were also right' (Carter 1965:90). But Rivers realised that whilst Enders was supported by the Foundation in the form of grants and supply with plenty of virus, the other groups were not. He reasoned that Sabin and Olitsky's technical downfall had been the virus they had used. As Sabin subsequently proved, possibly at Rivers' suggestion, the MV virus was the only poliovirus that would not grow in non-nervous tissue. Rivers noted, 'If Olistky and Sabin had worked with another strain… the chances are that… we would have had a breakthrough of major proportions in making a vaccine [much earlier]' (Carter 1965:91).

So Rivers felt that working without a clear cataloguing of the various poliomyelitis strains had impeded vaccine development by delaying tissue culturing.

6.3.3 Virus typing: $1.37m for a "dull" and "menial" program

In 1948, Weaver pushed forward this important, but theoretically unexciting, strategic research project. For a long time it was suspected that multiple strains of poliovirus existed[19] but to establish this with more certainty would involve a long and systematic effort. It would entail immense cost in terms of laboratory space, monkeys, technical personnel, and equipment. Weaver was aware that senior researchers would be reluctant to take on such 'drudgery' (Carter 1965:61) because it would involve giving over their laboratories and several years to mechanical and boring work.

John Paul (1971:318) says of the co-operative typing program, 'This was not exploration; rather it was the application of established methods to solve a specific problem. In the planning and implementation of this type of medical 'research and development,' the foundation was at its best' (Paul's inverted commas).

The protocol of immunological testing was difficult, imprecise and time consuming. A group of monkeys was infected with a strain of poliovirus, say Type I virus. After waiting for them to get sick, and waiting for them to recover (if they did recover), they were then challenged with 'standard' doses of unknown viruses and their responses were charted. If this group of monkeys that was infected with known Type I virus and then subsequently infected with a virus of unknown type, got sick again on the second infection, one infers that the unknown virus is a different strain from Type I, say Type II or Type III. This different strain of virus can then be injected into another group of monkeys known to have recovered from infection with Type II virus. If there were no ill effects, the unknown strain can be confirmed as Type II, but if the monkeys got sick the procedure is repeated with another group of monkeys known to resist Type III viral infection so that the unknown

[19] There were indications that monkeys immune to one strain of poliovirus could still be infected by another strain (Burnet 1931, cited in Chase 1982:284).

virus can eventually be confirmed as a Type III virus strain when the monkey shows no ill effects (Smith 1990).

The whole protocol, even when executed perfectly and with a lot of luck, would have required a lot of monkeys to confirm immunological test results. But there are many inaccuracies in making the deductions. Preparing 'standard' doses, also known as challenge stock, was a delicate, time consuming and frustratingly immense job because the viruses differed greatly in pathogenicity and infectivity. Thus the standard dose was significantly different for just about every virus strain and it could be miscalculated easily given such high variance. Too weak a dose and one might mistake a very mild infection for prior immunity. Too strong a dose and the monkeys end up dead, which would reduce the efficiency of monkey use. To guard against such miscalculations, each step of the process needed to be repeated with dozens of monkey groups (Smith 1990). Only then can a challenge stock database be compiled and shared with other groups as a sort of 'public good' of knowledge for further research.

Weaver set up an eminent advisory committee to lead the virus typing project but the task itself did not inspire any of them so Weaver went looking for other young and fresh researchers. An ambitious Jonas Salk had just set up a new laboratory of his own after having worked on a formalin-inactivated influenza[20] vaccine with his mentor, Thomas Francis, for the US Armed Forces (Carter 1965; Galambos and Sewell 1995:47). Salk was looking for his laboratory's first grant when Francis encouraged him to take on lucrative work being offered by the Foundation (Carter 1965; Smith 1990). This project was seen by Salk as 'a dull but dependable investment that would provide a regular dividend of money for his lab' (Salk quoted in Smith 1990:117). Smith writes 'The Foundation's virus typing program would be menial but liberating [Salk] told himself – a simple job… and a means to expand both the size and the equipment of his laboratory in ways that would remain long after… The Foundation directors who had chosen Salk's laboratory didn't mind a bit of careerist greed as long as it got the job done' (1990:110).

[20] The Army were interested in influenza vaccines because more people died from the influenza epidemic of 1918 than were killed in combat (Crosby 1976).

The large scale experiment spanned four universities and two years, classified over 200 clinical strains of poliovirus isolated from patients all over the world, cost $1.37m and used up 30,000 monkeys[21] imported at great expense (Chase 1982). It showed conclusively that there were three, and only three[22], immunologically distinct types of poliomyelitis virus (Bodian 1949).

This was crucial information for developing a vaccine that was fully protective and not just partially protective against local strains. The virus typing set another standard for all future vaccine candidates to be compared against. Indeed when successful results were announced to the public in Francis' final evaluation report, it was in terms of this standard; Salk's vaccine was '60-70% effective against disease caused by Type I virus and 90% or more effective against that of Type II and Type III virus…' (Carter 1965:275). The Foundation also devoted significant funds to epidemiological studies which established which of the three strains were prevalent and where the strains were distributed across the country. Such epidemiological data would be useful in deciding where to locate field trials of future vaccines (Paul 1971:357).

6.3.4 Summary

Weaver ensured that the Foundation worked to open channels for communicating research results, encourage the sharing of unpublished data and establish criteria and specifications with which to frame those results. The Foundation's scientific advisors, led by Rivers, commissioned the development of key research tools such as tissue culturing, and important epidemiological studies such as identifying and classifying the three strains of virus.

On the one hand, tissue culturing drastically reduced the need for monkeys but on the other hand, the virus typing programme offset that reduction and made the need for monkeys

[21] To put the figure in context, the US Department of Agriculture reported the use of 52,000 monkeys, chimpanzees and other primates in 2002 for the *all* R&D http://www.aphis.usda.gov/ac/ar2002.html
[22] The three strains were named Lansing, Prunhilde and Leon strains (Time 1953).

even more intense than it was before[23]. Weaver's careful watch on monkey procurement from Asia and O'Connor's efforts in the establishment of Okatie Farms relieved scientists of many of the administrative and handling problems associated with monkeys.

The community was well prepared to appreciate any new ideas and, following these key advances, were well positioned to start thinking about how they might test and assess them in monkeys and, eventually, people. With the chances of making a poliomyelitis vaccine much improved, a number of groups worked towards that goal but with different operational trajectories. Hammon chose to pursue a passive immunisation approach, whilst Salk and Sabin successfully pursued active immunisation approaches[24]. Salk took the line of a formalin-inactivated vaccine, whilst Sabin chose to pursue a live attenuated vaccine.

6.4 Passive immunisation: Testing for design and field-based capabilities

By the 1950's, the emphasis shifted from establishing these operational trajectories in monkeys, to creating learning conditions in humans. These conditions would be more relevant and realistic, but this section highlights how the associated complexity was managed through governance so that testing resources were co-ordinated and tests on humans resulted in the accumulation of technological knowledge. A critical part of the vaccine design process is also described as a difficult and uncertain translation of qualitative goals into objective ones. I begin by outlining the feasibility of passive immunisation as an operational principle, before analysing considerations made about vaccine design and organisational capabilities during the move to human testing.

Hammon believed that gamma globulin, an antibody obtained from pooled plasma with known neutralising activity, might protect against natural infection. His immediate goal was to prevent poliovirus causing disease on the nervous system, rather than infection in

[23] The Virus typing program used 30,000 monkeys but before the program, 17,500 monkeys were used in tests (Carter 1965; Chase 1982).

[24] Passive immunisation refers to injection of blood gamma globulins that transfer specific antibodies to the virus, in contrast to active immunisation, in which an antigenic substance is injected that induces specific antibodies to the virus. See chapter 5.

the first occurrence (Carter 1965; Paul 1971; Plotkin and Vidor 2004). Permanent immunity through repeated infection might be achieved, but without the symptoms of poliomyelitis. The idea carried weight in part because passive administration of serum achieved some success against measles virus (MRC 1948).

In 1948 Morgan and Bodian were able to protect monkeys from one type of poliomyelitis[25] (Carter 1965:64; Paul 1971:405). By using graded doses of virus with the purpose of producing varying levels of antibody, they effectively constructed an index of the degree of immunity in monkeys. This represented an improvement in the knowledge infrastructure because future antibody experiments could be compared to this index. Hammon argued that the role of antibody was still uncertain in humans, and that the antibody index would allow a safe start to ascertaining 'how much was enough for humans?' and 'how long do they last in the blood?'.

The Foundation created a 'Committee on Immunization' to manage strategic and logistic aspects of human vaccine trials[26] (Carter 1965:125; Paul 1971:407). It was a daring role given the traumatic failures of the Brodie-Kolmer trials two decades earlier. Fear about using killed or live virus was a common theme voiced by Sabin and coloured the views of most in the field (Rinaldo 2005). However, Hammon's vaccine did not contain any virus and answered Rivers' call for boldness, 'I think it is time that we got ready to go somewhere, and somebody ought to come up with some concrete experiments that will be done in human beings on a small scale in order to get going' (Carter 1965:126).

Hammon's preliminary field trial showed that relatively low levels of antibody could prevent invasion of the central nervous system[27] (Hammon, Corriel et al. 1953). The results provided vaccine designers pursuing different operational trajectories, such as Salk and Sabin, not only with the confidence that infection could be prevented, but also a tangible

[25] Although the following year the Foundation's virus typing committee (of which Hammon was a member) found that there were three types.
[26] Members included most of the eminent virologists of the time: Bodian, Enders, Francis, Hammon, Howe, Paul, Rhodes, Sabin, Salk (Carter 1965:125; Paul 1971:407).
[27] This indicated that Hammon's lower goal, of preventing disease rather than infection, may have been excessively modest.

performance criterion. The subjective aim of immunity had become an objective goal of putting antibodies in the blood[28]. The testing regime had a bar, against which potential designs could be compared.

Questions of how quickly and safely immunity could be established in the blood, and how long it would last for in the blood under various conditions remained. Antibodies produced by the body through active stimulation were thought to last longer than those passively given to the body. Hammon argued the other operational trajectories' also provided only transient immunity[29]. In addition, he noted their safety concerns and their need for multiple injections, saying that with his gamma globulin, its effect would be immediate and would represent no danger to any child' (Hammon 1950:702).

Although passive immunisation might not need multiple injections, Hammon apparently overlooked the fact that passive immunisation would require up to 10cc of gamma globulin given in the buttocks, a painful and taxing task (Rinaldo 2005). Although he cited the availability of gamma globulin as an advantage (Hammon 1950), his subsequent clinical trial seriously depleted all reserves of gamma globulin[30]. A further trial with more people, and hence more slightly varied conditions, was needed to address these issues of speed, durability and quality of immunity[31].

The Foundation funded Hortsmann (1952) and Bodian (1952) to see if passive immunisation protected monkeys from very high, lethal doses of poliovirus of all three

[28] By helping to ascertain how much antibody was needed to prevent infection, Hammon effectively provided what can be called a correlate of immunity. Many HIV vaccine researchers lament on the lack of correlates of immunity (see section 7.2.2).
[29] In support of this view, Morgan (1948) had showed that repeated large doses of formalin-inactivated virus induced only temporary immunity in monkeys.
[30] The limited availability of gamma globulin restricted its use. Obtaining gamma globulin was an expensive and time consuming process and depended on voluntary blood donations. At the same time, the Korean War and hospital needs were drawing on supplies. O'Connor warned that there was not enough to provide 'even temporary protection to the 46 million children and adolescents most susceptible to poliomyelitis' (Rinaldo 2005:795). Nevertheless, the Foundation spent $7m boosting gamma globulin production and a further million children were protected in the poliovirus season of 1953 (Rinaldo 2005).
[31] The Immunization Committee initially turned down Hammon's request for a larger scale controlled trial (Rinaldo 2005). They wanted to see more animal and human data before embarking on a complicated and expensive clinical trial (the trial ultimately cost the Foundation $1m). They were also concerned about using placebo controls, which had never been used before, and its moral and social acceptability (Rinaldo 2005).

strains. Compared to Morgan's experiment in 1948, these conditions were more stringent, more technologically relevant, and perhaps even scientifically less interesting because the theoretical concept of neutralising antibodies had already been established. The protection achieved under these conditions convinced the panel to fund a pilot study of 5000 children. Panel members realised that this size would not yield statistically significant results, rather the study's purpose was 'to gain experience in organisation and administration, as well as to evaluate the public's and medical profession's reaction to such a trial' (Rinaldo 2005:793).

The details of the trial which needed to be organised were very broad and included how to: blind the vaccine vials, select a type of control inoculum, source and set dosage of gamma globulin, types of syringes, packaging, venue, injection administration site on the body, consider legal aspects such as written informed consent, select geographical areas undergoing epidemics of a suitable magnitude, gain approval by local population, manage publicity and preparation of clinics, and follow up studies to identify incidence cases. Most critical was 'the definition of the severity of the paralytic disease, for which they used a carefully graded scale of muscle function loss' (Rinaldo 2005:793). This is another example where the Foundation set up an infrastructure to compare future observations to a set of known conditions, thereby ensuring that those observations would contribute to cumulative knowledge growth. It might otherwise have been seen as a chore, with little, if any, scientific merit.

The pilot results were encouraging and public support was very strong, with hundreds of volunteers being turned away by day four (Hammon, Corriel et al. 1953). Problems included such issues as lack of access to large autoclaves to sterilise the syringes and needles. A larger trial was quickly approved, which involved 55,000 children. The result of this trial was considered, 'conclusive evidence of a very significant reduction in the total number of cases of paralytic poliomyelitis' (Hammon, Corriel et al. 1953:758).

Hammon concluded that, 'perhaps the greatest contribution of the gamma globulin trials… demonstrated that a very low concentration of antibodies will protect man' (Hammon,

Corriel et al. 1953:1283). Aside from taking this design standard from monkeys and establishing it in human conditions, a graded scale of paralytic disease was also developed. The trials were seized as an opportunity for the Foundation to build up organisational capabilities in acquiring local knowledge for testing outside laboratory conditions, and co-ordinating people, resources, logistics and public support. The Foundation had already begun setting up the organisational decision-making process for moving, potentially, more dangerous vaccines to trial in humans.

6.5 Killed vaccines: Testing regimes for taking 'calculated risk'

This section discusses how a more risky vaccine was tested, and selected to be tested, in humans. The vaccine was more risky than Hammon's because it contained killed virus, but less risky than using live vaccine. The initial risk appears to have been borne by certain sections of society, who provided the conditions that were both relevant for technological development and suitable for learning. Key techniques used to ensure these conditions for knowledge growth was the design of double-blind, placebo-controlled trials, and institutional leadership to mediate differences of opinion. This was critical for choosing which of the different operational trajectories to test.

By 1953, Salk had showed that poliovirus could be inactivated by formaldehyde (Salk 1953). Moreover, he determined how much formalin affected inactivation, and conducted safety and immungenicity studies in animals (Benison 1967; Robbins 2004). If there was any doubt as to whether such animal findings could be translated to children, Howe's (1952) paper made it clear, entitled 'Antibody response of chimpanzees and human beings to formalin inactivated Trivalent poliomyelitis vaccine'.

Howe tested six children at the Rosewood school, whom he noted as, 'low-grade idiots or imbeciles' (1952:265), and was able to report that 'both children and chimpanzees develop readily demonstrable neutralising antibodies at comparable levels following the injection of small quantities of clarified monkey cord suspensions containing formalin inactivated poliomyelitis virus' (1952:265). Salk, too, had started preliminary studies in humans which

showed that antibodies could be increased to relatively high titres in children already infected at the Watson Home for Crippled Children[32]. But these advances, aside from any modern day ethical testing concerns, were leading to a somewhat problematic vaccine.

Conventional wisdom held that only a live-attenuated vaccine could confer long lasting immunity because it more closely mimicked a true infection (Carter 1965; Klein 1976; Smith 1990). Several of the Committee's senior virologists, including the Nobel Laureate John Enders and Albert Sabin, in particular questioned the relation of antibodies to permanent immunity and doubted the safety of a vaccine prepared from virulent poliovirus, regardless of 'inactivation' method, especially after the failed vaccines of the 1930s (ibid). Enders cautioned, 'the ideal immunising agent against any virus infection should consist of a living agent exhibiting a degree of virulence so low that it may be inoculated without risk'[33] (Enders 1954:88).

But, for Salk, the notion that only natural infection, or a vaccine made of living pathogen, could offer durable protection was nonsense. Salk felt the orthodoxy was based on unverified lore received from the past, conflicted with some observed realities and premised on the idea that the effectiveness of a vaccine depended not on chemistry but on some occult life force. Salk therefore saw his challenge to orthodoxy as not only experimental but an ideological claim for empiricism and pragmatism in science[34] (Carter 1965; Klein 1976; Smith 1990).

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[32] Like Howe, Salk tested children who were not infected but were 'mentally retarded' and found that the levels of antibody production were equally encouraging (Chase 1982).

[33] This adheres to the classic Jenner-Pasteur model where a live, but attenuated, strain creates immunity by producing less severe form of the real disease. It is notable that the development of such attenuated strains in animals was extremely time consuming and difficult but the feasibility of this operational trajectory was now vastly improved by the culturing techniques that Enders developed (see above). It is understandable then that Enders would want to see his technique be used in the development of the final poliomyelitis vaccine.

[34] It is likely that Salk's deviation from the orthodoxy resulted from his newness to the field of poliomyelitis prophylaxis. In fact, his previous experience in developing inactivated influenza vaccine most probably directed his choice of approach to the poliomyelitis problem (Galambos and Sewell 1995:47). Brodie and Kolmer had tarnished the killed approach and Salk was careful in his relations with the public to set apart his methods from theirs; for example, a Time magazine article pointed out, in unusual technical detail, that Salk's vaccine used purified mineral oils to hold the vaccine in the body for longer as a way of distinguishing his from previous efforts (Time 1953).

The professional controversies directed at Salk's unconventional vaccine were 'waged with the intensity that man usually reserves for his holy wars' (Carter 1965:6). Sabin persistently objected that a massive investment of time, money and public faith in a [killed] vaccine of only temporary use would hurt efforts to find a live virus that would really solve the problem (Smith 1990). Flexner declared that 'only an infectious vaccine compounded of living virus could protect' (Carter 1965:86). Enders is even quoted as having confronted Salk and calling his work, "quackery" (Carter 1965:88).

Members of the Foundation did their best to calm such 'sharp differences between this group of opinionated scientists' in the Immunization Committee (Paul 1971:407). For example, regarding the concerns about the lack of certainty over whether an inactivated poliomyelitis vaccine really was inactivated, Rivers said at a Committee meeting, "I think we will all admit that there is no *test* to be sure the stuff is inactive. Why not just accept that? Why kid ourselves? Why use the word inactive? Why not just say, 'safe for use?' It won't produce disease, and that's all there is to it" (Carter 1965:126, my italics).

Such 'nervous brawling' often crippled progress (Carter 1965:129). So, in 1953, the Foundation set up a new and smaller committee because, as Weaver is quoted as saying, 'The immunization committee was not able to function with the necessary dispatch. It could get entangled for months in technical debates. Furthermore, its members were virologists and the decisions on which we needed help were not exclusively virological. The Vaccine Advisory Committee with experienced public health men… was a far more efficient group' (Carter 1965:176; Paul 1971:411). The need for a second committee suggests that the design of tests is not an entirely objective and technical matter, and includes broader considerations. It was also established in part to limit conflicts of interest that may arise from having competing designers playing the role of 'architect, carpenter and building inspector' all at once (Weaver quoted in Carter 1965:179).

Supporting Salk's vaccine into trials was a difficult choice made under conditions of high uncertainty and social conscience. A member of the Vaccine Advisory Committee said, "I think… progress can be made even in the light of the fact we have so little knowledge. It

would seem to me the time has come to really go at the inactivated material… The live virus is fine, but if you think about it as a public health measure, it is a difficult thing to use… I don't think you have a good excuse morally to go into infectious material until we have shown that inactivated material was unsatisfactory" (Carter 1965:128).

Salk recalls the arbitrary nature of deciding when to test. "We did not have a vaccine yet. There really was not *a* vaccine until an arbitrary decision was made prior to the national field trials of 1954, and *the* vaccine, so to speak, was not developed until later than that. In 1952 all we had were several dozen experimental preparations, some with adjuvant, some without, some containing one type of virus, some another or a third or all three, some made with monkey tissue, some with testes, some inactivated for ten days, some for thirteen, some for twenty one" (Carter 1965:130). Although, Salk here attests to the landmark significance of the major clinical trial, the possible permutations of experimental conditions he describes seem endless, and arriving at any one combination to test in a 'major field trial' is likely to have been subject to a series of many tests prior to that point in development.

Salk seemed initially uncomfortable with being pushed into a state of readiness by members of the Foundation. Salk insisted, 'I don't know that we even have a vaccine yet. That term was used, but I think it should be understood that we are using it as a colloquial expression. We have preparations which have induced antibody formation in human subjects' (Carter 1965:152).

Rivers asked, "Wouldn't it be silly to wait 50 years or to wait 10 years to develop the ideal vaccine when there is the possibility of a vaccine being developed very rapidly that will last, say, for two or three years with one injection perhaps? We don't know anything about that, but have we the right to wait until the ideal vaccine comes along?" (Carter 1965:151). Salk emphasised the trade-off in a telegram to convince sceptics, 'It is said that to await certainty is to await eternity' (Smith 1990:295). Despite the many and strong objections, Weaver and O'Connor believed that the Foundation had a mandate from its volunteers and donors to proceed and, although Rivers thought the Salk vaccine was 'something slightly

better than gamma globulin, something by definition imperfectible,' he felt it was 'worth a try' (Carter 1965:152). The Foundation began to plan for a major field trial.

Harry Weaver wrote, 'The practice of medicine is based on a calculated risk…the physician elects to follow the course that provides the greatest benefit with the least risk of incurring any untoward effects… If [we wait until more] research is carried out, large numbers of human beings will develop poliomyelitis who might have been prevented from doing so… our work must be governed by scientific and sociological concerns' (Carter 1965:147; Benison 1967). This implies that the vaccine development process was not simply a scientific puzzle, with a technical solution that could be found and optimised; rather, the urgency of the historical and social context of the actors played important roles in their decisions about an 'imperfectable' vaccine.

In the design of the trial, the planned use of placebo controls was problematic, but the precedent seemed necessary. Initially, Weaver sought simplicity and economy, and suggested that the poliomyelitis rate be compared between vaccinated and non-vaccinated school-children of the same age (Carter 1965:176). However, the Vaccine Advisory Committee suggested that socioeconomic differences between those who volunteered and those who did not would weaken the study.[35]

Salk felt that his vaccine was not up to such a stringent test, and lapses in the manufacturing process or unimpressive results of a double-blind test might scupper the opportunity to improve it (Carter 1965:178). I quote him at length in the paragraphs below to show that the design of the tests was at the centre of his concerns at the time, and that the parameters of the tests left an indelible mark on the nature and characteristics of the vaccine most widely used.

[35] High income, well educated families were more likely to submit their children to experimentation of this kind. In contrast, less well educated families living in poorer areas were less susceptible to paralytic poliomyelitis, tending to contract the non-paralytic form in infancy and gaining immunity. Thus, a project to vaccinate all volunteers, would immunize the children most susceptible. The poliomyelitis rate might be unimpressively similar to that among the unvaccinated. Therefore the vaccine might be good, but the test would not have the resolving power to prove its efficacy. In addition, poliomyelitis diagnosis was still difficult despite the scale developed in the Hammon trials, and any biases emerging from knowing who had been vaccinated and who had not, would serve to exacerbate the problem.

"The sensible thing, I thought, was to accept the urgencies of the situation and continue improving the vaccine. I thought the field trial should be designed to permit this, not prevent it… I thought we should concentrate on polio prevention and be less concerned about making epidemiological history with an elegant double-blind study. I was afraid that, for some people, the *kind* of test had become more important than the kind of protection the vaccine might be able to provide."

"I wanted a field trial not only because it was simpler but because it was suited to the realities. I wanted to know who had been vaccinated so that blood samples could be taken promptly. If tests then showed that a certain batch of vaccine was producing unsatisfactory results, the children could be revaccinated with better material. At the same time, we could be taking steps to improve the manufacturing process and avoid new batches of inferior vaccine. Finally I was uncomfortable about giving placebo shots to children, depriving them of immunity in what might turnout to be an epidemic year. Many public health officials agreed with me on this."

"The issue of field-trial design was typical. Here you had someone like myself, trying to adapt to the needs and circumstances, and there you had this rigid insistence that a 'product' be submitted forthwith for ceremonious testing. The emphasis on 'product' and on ritual and on looking good in the eyes of certain elements in the scientific community was being allowed to obscure the real purpose of everyone's work, which was the prevention of polio. For arguing this as often as I did I earned scorn as an eccentric nuisance. My desire to continue my experiments so that the vaccine might be as close to 100 per cent effective as possible was considered intolerably presumptuous. What a dreadful inconvenience to impose on designers of field trials and on pharmaceutical manufacturers and on government officials!" (Carter 1965:178).

Salk went on to describe the use of placebos as 'a fetish of orthodoxy… a 'beautiful epidemiologic' experiment over which the epidemiologist could become quite ecstatic but would make the humanitarian shudder and would make Hippocrates turn over in his grave… the worship of science involves the sacrifice of humanitarian principles on the alter of rigid methodology' (Carter 1965:192). In order to address the concerns of parents, teachers, and such 'humanitarians' O'Connor announced that an observed control plan would be used, in which children would not be injected but only observed (Meldrum 1998).

The Foundation asked the nation's health officers for advice and support, who suggested that the Foundation may not be able to maintain impartiality in such evaluation (Meldrum 1998). So O'Connor appointed Thomas Francis to head the evaluation of the trials, a critical but unglamorous task, based on 'his deft direction of complex field trials of influenza virus vaccines during World War II' (Markel 2005:1408). However, Francis would not accept until he manoeuvred between health officers, paediatricians, clinical poliomyelitis specialists, statisticians and virologists to engineer a change in the trial design (Meldrum 1998). He suggested a placebo design run in some areas at the same time as an observed design run in other areas.

Addressing concerns about volunteer recruitment in the placebo plan, the evaluation group decided that it could rely on the widespread fear of the disease; members agreed that 'it would not be difficult to sell as there is a high attack rate… [and] there would still be a 50% chance of a child receiving the vaccine' (Meldrum 1998:1235). Francis compromised with Salk and others to a certain extent with observed design in some areas, but his insistence on the placebo plans in other areas was particularly important in the context of the vociferous criticisms from Enders, Sabin and others about the validity of the killed-vaccine concept.

Firstly, results emerging from double blind trials might be more convincing, and facilitate quicker and more widespread vaccine adoption. Secondly, it was important given the possible conflict of interest arising from the Foundation evaluating a vaccine they, as an

organisation, developed and sponsored. Thirdly, the placebo plans were also a part of the Foundation's effort to legitimise an institution governed by non-experts.

The trial for the vaccine went ahead in 1954 and was the largest of its kind to be run. It was not a cheap gamble, grants for the field trial and its evaluation cost the Foundation a total of $7.5m. The results of nearly 2 million children were presented on 12th April 1955, and the vaccine was found to be safe and 70% effective (Smith 1990). Although not completely effective, the breakthrough cases[36] were judged to be less severe (Smith 1990). With financial guarantees from the Foundation, industrial production facilities were already built and ready to operate (Blume and Geesink 2000a). The Foundation paid a further $7.5m to the manufacturers for 10 million Salk vaccine doses (Chase 1982). The products of six producers were licensed within days, one of whom was Cutter Laboratories in Berkeley[37] (Offit 2005a). Poliomyelitis cases dropped from 58,000 in 1952 to 5,600 in 1957.

Writing of the 1935 and 1955 vaccines, Paul, whose career in poliovirus research spanned both eras, noted how different the testing regimes were. 'The situations were in no way comparable, for the Brodie-Kolmer vaccines had been launched in the face of colossal ignorance, whereas the Salk-type vaccine had been promoted under circumstances which from the start almost guaranteed success. And yet one cannot help feeling a twinge of sympathy for the two figures of 1935 who were so alone in the midst of their disgrace, in contrast to the powerful forces of the National Foundation, the US Public Health Service, and innumerable advisory committees that stood back of the Salk type vaccine' (Paul 1971:420).

[36] Cases where volunteers are diagnosed with poliomyelitis despite being vaccinated in the trial.
[37] The Cutter incident represented 'one of the worst pharmaceutical disasters in history' (Offit 2005b:1411). In a batch of Salk vaccine manufactured by Cutter, there remained some active virus which had not been killed. It caused over two hundred cases of poliomyelitis, of which 150 were paralytic and 11 were lethal (Nathanson and Langmuir 1963). The error paralysed 15 times more children than the earlier Brodie and Kolmer vaccines combined.

6.6 Live vaccines: in the shadow of the killed vaccine

This section reviews how improvements to the testing regime enabled the establishment of live vaccine operational trajectory. The section emphasises the path-dependency of such trajectories by highlighting the role of non-fiscal testing resources. It also emphasises how context-dependent such operational principles become by highlighting testability constraints, and different decisions taken by public health authorities in the USSR and USA.

As he had done with the yellow fever virus, Max Theiler passaged the poliovirus continuously through the brains of living mice until, without losing its capacities to produce antibodies, the attenuated virus no longer caused paralysis (Chase 1982). He reported it to the Foundation in 1946, which then funded research to demonstrate that poliovirus could also lose its ability to infect the central nervous system on repeated passage through non-nervous system tissues (Robbins 2004). The idea of attenuating the poliovirus, rather than killing it outright, appealed to many because it was presumed to mimic the natural situation more effectively, resulting in a longer and more effective immunity[38].

The live attenuated poliomyelitis vaccine approach was feasible only with the possibility of intense empiricism because it relied so much on striking a balance between efficacy and safety (see section 8.5.3). This entailed searching for virus that is not pathogenic (disease causing) but retains some of its virulence (ability to infect). By strengthening the testing regime, the Foundation reduced barriers to empiricism. The development of tissue culture techniques[39] facilitated the rapid emergence of variation in strains, whilst the availability of monkey models allowed designers to select for pathogenicity and virulence traits, and the typing project allowed putative vaccine preparations to be challenged without added

[38] However, Salk, and other proponents of killed vaccine, resisted the notion that immunity provided by live vaccine would be somehow longer lasting. 'One cannot say how long immunity may last, one can report only how long it has lasted' (Carter 1965:377).

[39] Viral culture techniques were significantly improved by Dulbecco and Vogt (1954). Adapting techniques for growing bacteria, they grew virus in microscopically thin mono-layers of chick embryo tissue cells. The colonies proliferating from the growth of a single viral particle could be identified, counted and isolated. This made it easier to purify specific lines of virus, which was extremely valuable for those looking to prepare a live vaccine (Paul 1971:406; Robbins 2004:19).

confusion. Selecting strains with monkeys meant that live vaccine development did not need to rely on few and imprecise in-vitro markers of virulence, such as growth at higher temperature (Paul 1971:458). Instead, a more authoritative test for neurovirulence, adopted as the standard by the regulatory agencies, was devised where monkeys had to be inoculated through their central nervous system (Robbins 2004:20).

6.6.1 Scarcity of testing resources

Sabin was one of several groups[40] working in this way (Paul 1971; Robbins 2004). In light of the improvements to the testing regime noted above, the Foundation provided him with $1.2m between 1953 and 1961, and $2m in total (Carter 1965:357; Chase 1982:303). In 1955, Sabin began a trial on inmates in Chillicothe Federal Prison in Ohio (Carter 1965:357; Smith 1990:301). His vaccine was successful, but the Foundation saw little reason to take chances with a larger scale trial of an infectious live vaccine when Salk's field trial had demonstrated efficacy the previous year. Large scale trials of Sabin's vaccine, and those of others, would be difficult to interpret because the Salk vaccine had been licensed and was being used widely. For example, when, in 1959, Herald Cox had the opportunity to test his live vaccine in Miami, Florida, Sabin dismissed any excitement by pointing out that too many people had taken Salk vaccine for the test to mean anything (Carter 1965:365).

There is clearly a strong path-dependency element to testing processes in vaccines (see also Blume 2005), but I would like to draw attention to a slightly different view. In the early experiments, poliomyelitis researchers faced a shortage of virus; Evans and Green, who were beaten to the Nobel Prize, faced shortage of human embryonic tissue; Hammon faced issues with a shortage of gamma globulin; whilst Sabin faced a shortage of people to test on. These cases represent a scarcity of testing resources. These resources are not fiscal, as is commonly emphasised in health and vaccine development literature (see for example Archibugi and Bizzarri 2004; Barder 2005), but can be anything from the availability of

[40] Other groups were led by Hilary Koprowski at the Wistar Institute, Herald Cox at Lederle Laboratories, and Joseph Melnick at Yale, all of whom tested their prototype live vaccines on institutionalised children (Chase 1982).

monkeys, gamma globulin, primary isolates, to simply people as test subjects. They were unlikely to have been resolved by policies that focussed on pecuniary issues alone.

6.6.2 Testing to see which vaccine is better

The safety concerns to this approach extended beyond simply whether the virus in the vaccine was sufficiently attenuated to prevent it from causing disease. The major concern centred on its genetic stability and whether the attenuated virus would *remain* safely attenuated. One of the advantages of the live vaccine was that after it passed through the intestines and was excreted by the vaccinee, it might then go on to confer immunity to someone else in the community. But the same advantage became a disadvantage for those who thought that, after several passages through the community, the altered vaccine strain might undergo progressive genetic changes such that it reaches a degree of virulence comparable to that of wild epidemic polioviruses. The success of the entire live approach therefore turned on proving that any cases of poliomyelitis were not caused by the vaccine reverting back to virulence after multiplication in the host.

Melnick found that live vaccine virus passaged through children was sometimes virulent enough to paralyze monkeys (Carter 1965:381). This caused serious concern, but there was no way in which a test could show that a given case of poliomyelitis in humans had been caused by the live vaccine, even if the victim was struck by poliomyelitis shortly after taking a live vaccine. If virus recovered from the victim resembled the wild type, one could suppose that it had taken over the intestines, and driven away the vaccine virus, before causing the disease (wild type-induced disease). Alternatively, one could decide that the vaccine virus had changed to resemble the wild type and become virulent, thereby causing vaccine-induced disease. Either way, testing primary isolates would not be able to prove a vaccine guilty.

This made choosing between the alternative operational trajectories on any kind of objective basis of safety technically difficult. However, this did not prevent the two

different operational principles being perceived differently as more or less risky[41]. And closely tied with these perceptions were the assumptions of the designers, embedded in the operational principles, about the social context in which their designs would be used. The next section shows that safety, as a relative measure, became more readily observable as protagonists argued risks and benefits in different contexts.

6.6.3 Vaccines as part of a public health system

The continued existence of distinct operational trajectories was dependent on different social contexts and the success of their protagonists in 'suiting' their vaccines to them. This is because notions of vaccine safety, and indeed other attributes of the vaccines, are relative measures which protagonists can highlight as merits in different social contexts (or as drawbacks by opponents in others).

Due to the safety concerns, testing problems, and the use of Salk's vaccine, all described above, Sabin was forced to look abroad to conduct large scale trials. In 1958, 200,000 children in a Singapore trial received Sabin's live vaccine in an effort to curtail their epidemic (Paul 1971:454). By 1960, approximately 100 million people in the former USSR and Eastern European countries had received the vaccine. By the end of the year enough evidence had been established to secure licensure in the US for Sabin's live vaccine[42] (Paul 1971:456).

However, the success of one vaccine over the other depended on the social context of its use. As a Soviet public health official remarked, 'Our inoculation program was a public-health measure, not a field trial. It was designed to suit our medical services. In attempting

[41] Tommy Francis saw the operational trajectories differently. 'The two outlooks are, then, simply, this. Inactive virus is apparently a test of the straightforward hypothesis that antibody induced by the administration of antigen can provide protection without subjecting the recipient to harmful effects of even apparent infection. The other, through the use of modified active virus, seeks to induce antibody formation but wishes to add some undesignated advantage derived from assumedly harmless infection (I am not certain that any significant infection may not create undesirable tissue reactions…). Which of these approaches to poliomyelitis will be the more effective is, then, not a decision to be arrived at by authority and debate but by… making the observations. When the conditions are appropriate, tests should be made. This is the beginning not the end…' (Carter 1965:357).

[42] Thus, just over a decade after concerted efforts to strengthen the testing regime began; not one but two effective vaccines against poliomyelitis were available for general use.

to inoculate a population the size of ours, could there be any serious confusion about whether to give away candy drops, when the alternative was injection requiring so much more apparatus and personnel? Our work with the Sabin vaccine must be viewed in terms of public health and not as a strictly controlled scientific experiment' (Carter 1965:359).

If the Sabin vaccine could actually be shown to cause paralytic poliomyelitis, the finding would have been more significant for the US than for the Soviet Union. The Soviet Union was suffering poliomyelitis incidence rates of 94 per million (Carter 1965:363), much higher than that of the US, so any vaccine that could reduce that figure would be allowed the deficiency of a few vaccine-caused cases. It simply represented one dimension in a broader set of criteria for the health system as a whole.

The protagonists of each vaccine worked hard to promote their interests and preferred choice[43]. Cox was benefiting from an aggressive publicity campaign by Lederle touting its advantage of a single dose vaccine that still protected against all three strains (trivalent) (Carter 1965:365). Koprowski managed to trial his vaccine in 9 million people but had his vaccine turned down by the US government because it caused some lesions in monkeys (Paul 1971:454). Salk argued that his vaccine was effective and that they needed to wait longer, without introducing other vaccines, to see definitive results of an imperfect vaccination program. And Sabin's appeared to be the newer more modern vaccine with which the public health service could have a second chance of executing a vaccination program of more complete coverage (Carter 1965:372). Sabin's field trials in the Soviet Union were even doubted, and it took a report by Hortsmann, who was dispatched there by the WHO, to verify the standards and evidence (Paul 1971:455; Robbins 2004:20).

[43] Salk describes his changing experience of attending poliomyelitis conferences. 'It was like sitting in on the plans for one's own assassination. The atmosphere of intrigue and hostility was even more intense than in 1953 and 1954. In those years mine was the only vaccine in the picture. But now you had Sabin and his vaccine, Koprowski and *his* vaccine, Herald Cox and his Lederle vaccine, and each of them had their coterie. There were actual plots hatched to keep one or another vaccine report off one or another scientific program. And, long before a particular report was read, you heard a dozen whispered allegations about the lies contained in it and the number of deaths unmentioned by it. It was like Lisbon during the war' (Carter 1965:364).

The ensuing history of the changing relative merits and drawbacks of the Salk and Sabin vaccines is considerably well discussed but much of this lies outside the scope of this chapter (Blume and Geesink 2000a; Blume and Lindner 2004; Blume 2005). It is worth noting, however, that as incidence of poliomyelitis decreased in the US over the next thirty years, the perception of risks and benefits changed and so the choice of vaccine changed too. 'The conclusion [of a comparative analysis of live and killed vaccine] is heavily dependent on assumptions of risk of exposure to wild virus in the US. Major declines in risk of exposure… could alter the balance significantly' (Hinman, Koplan et al. 1988:295). Despite the high costs of switching from live to killed vaccine, the Advisory Committee on Immunisation Practices recommended the change in 1996 and US vaccine policy delivered killed vaccine exclusively from 2000 onwards (Plotkin and Orenstein 2004:1484).

6.7 Summary

The development of vaccines was dependent on a vision. This vision needed to be convincing not just for the community of technological practitioners, but also for wider society. It was constructed by key actors from different communities. Landsteiner may have shown an infectious agent to which inventive vaccine efforts could be directed, but the social landscape was undoubtedly reshaped by President Roosevelt. The relationship between scientists as technological-producers, and the public as 'science'-consumers, was not forged until a specific and dedicated mediating organisation, the Foundation, was born to ensure the cumulative growth of technological knowledge.

The path to two poliomyelitis vaccines required the development of a testing regime, and the Foundation played important governance roles in setting that up. The Foundation facilitated research by finding specific researchers to do the work and provided them with funds, virus, tissue and reagents. It cultivated an atmosphere that ensured there would be people to test on, as well as an immensely supportive public tolerant of failures (such as those by Brodie-Kolmer and Cutter Laboratories).

But the Foundation played a yet more active role in vaccine development than that. It fostered communication across research groups and in doing so gained an overview of what was needed for innovation. It directed technological research in critical areas that were seen by scientists as unstimulating. It mediated between personal agendas, conflicts of interests, and managed differences of opinion. It even displayed the leadership to make the uncertain and unpopular decision to enter field trials with Hammon and Salk vaccines.

Once culturing techniques were developed, a steady supply of monkeys was secured and the results of a virus typing project were established, ideas could be tested quickly and in varying conditions. The Foundation then turned its attention to transforming subjective issues of vaccine design into more specifiable, objective criteria for vaccine use in human conditions (rather than in laboratory monkeys).

In doing so, the Foundation played a central part in the choice of operational trajectories. The antagonism between the orthodoxy, of which Sabin and Enders were part, and newcomers such as Salk, might have mired development efforts were it not for a mediating organisation. The fact that the patterns of institutional rewards and credit accorded to Salk and Sabin differed so significantly[44] suggest that elegant science and urgent technology development do not always sit comfortably next to each other.

The Foundation also co-ordinated with many different actors to ensure that the field testing of vaccines ran smoothly. Clinical trials were greatly facilitated because the Foundation ensured officials from health departments across the country were on board. They provided local knowledge and support when the Foundation needed to navigate through the sensitive issue of using placebos in the trials for the first time. In addition, the prevailing and very eugenically oriented medical ethics of the first half of the 20th century (see for example Martin 1998), which considered mentally and physically handicapped children and

[44] Salk was a household name but his colleagues in the world of science never afforded him the recognition and awards accrued to Sabin (Oshinsky 2005:270). Although Salk received the Congressional Gold Medal and other such public medals, Sabin was lauded by fellow scientists, elected to the National Academy of Sciences and embraced by virologists worldwide. 'Many attributed the professional discrimination against Salk to the flamboyant backing of O'Connor and the resultant media frenzies, which were offensive to 'pure scientists'' (Katz 2004:187).

prisoners to be the subjects of choice for medical experimentation, undoubtedly had the effect of strengthening the testing regime by providing easy access to accurate testing models.

The cumulative growth of knowledge emerging from these field trials was ensured by providing scaffolding, or knowledge infrastructure. This took the form of careful trial design, indices of immunity, graded scales of poliomyelitis diagnosis, and finding critical viral infection doses.

The Foundation had at its core a public mandate whilst creating an atmosphere that was conducive to technological research and development. The fact that volunteers for trials were so willing and abundant made the introduction of double-blind, placebo-controlled clinical trials possible. Such protocols indicate an emphasis on the role of trials as rigorous testing rather than as experimental treatments; it is an example of how well the Foundation juxtaposed public concerns with those of the scientists. The design and timing of clinical trials most likely had a lasting effect on the characteristics of the Salk vaccine when it was licensed.

The Foundation's concerns did not stop at the development of the Salk vaccine. By providing purchase guarantees before the vaccine was even finished, the Foundation managed some of the uncertainties involved in industrial production and facilitated prompt distribution by ensuring manufacturers were ready to produce as soon as possible. It also turned its attention to the development of a second vaccine that had developed under the strengthened testing regime. However, the Sabin vaccine faced a scarcity of resources that forced it abroad. The different decisions taken by the public health authorities suggest that the efficacy of vaccines is heavily dependent on the context in which they are used.

The following chapters will show how AIDS vaccine research and development was presented with many challenges that were, in some ways, similar to those described above. However, the researchers, faced with a much weaker testability regime, have so far been less successful than their poliomyelitis vaccine predecessors.

Chapter 7

Dead-ends and Detours in the Road to HIV Vaccines

This chapter proceeds in four sections. The first section describes how the emergence of AIDS was generally met with antipathy, making visions for a vaccine weak. Uncertainties about the origins and causes of AIDS exacerbated problems in drawing wider support to develop measures against it. The second section explains why characteristics of the HIV virus make the establishment of a strong testing regime difficult, and the third section shows that there have been strategic efforts to strengthen the testing regime. The fourth section concludes the chapter.

7.1 The beginnings of a testing regime

In contrast to poliomyelitis, where certainties about its origins and causality enabled a shared technical vision of a vaccine solution to be formed quickly, AIDS vaccine development was burdened with uncertainties from the outset. It took the best part of a decade to attain consensus over what caused AIDS (Epstein 1996). The relative newness of the AIDS virus and its unclear origins made visions of a vaccine hazier still[1]. In addition, the groups that were emerging as most at risk from AIDS (homosexuals, injecting drug users and sex-workers) were already subject to heavy social prejudices (Fee and Fox 1988; 1989).

7.1.1 The origins of HIV and the cause of AIDS

Although there is agreement that HIV arose from SIVcpz in chimpanzees in Africa and SIV in monkeys (Weiss 2003; Keele, Van Heuverswyn et al. 2006), how the viruses crossed over to human beings is debated. The most prevalent theory is that SIV was transferred as a

[1] Notwithstanding the fact that the earliest case of AIDS is now thought to be that of a man in Kinsasha in 1959 (Carlsen 2001), the perception of a virus-related public health risk requiring government action, came decades later.

result of primates being eaten, or their blood entering wounds or cuts in a human hunter. Others have argued that mass injection campaigns during the 1950s not only accelerated the spread of virus but also contributed to its transformation from SIV to HIV by a process of 'serial passage' in weakened immune systems[2] (Chitnis, Rawls et al. 2000; Carlsen 2001). In contrast, Hooper (1999; 2000) argued that the epidemic began because Hilary Koprowski's experimental live poliomyelitis vaccine, which was tested in Africa in 1957-60, was contaminated with SIVcpz[3].

The first well-documented AIDS case was discovered in late 1980, by an immunologist at University of California teaching hospital, who came across previously healthy young men dying from everyday infections that normally only claim the immuno-suppressed (CDC 1981b; CDC 1981a; Shilts 1987:47). Medical researchers quickly focussed on the men's status as homosexuals[4] and hypothesised that the syndrome was linked to 'some aspects of homosexual lifestyle' (CDC 1981b:252). Although Gottlieb later reported cases of the syndrome in exclusively heterosexuals, and others reported the syndrome in injecting drug users, attention in the medical literature remained fixed on the male homosexual sufferers (Shilts 1987; Oppenheimer 1988). Speculation about cases proceeded from the premise of the centrality of male homosexuality.

Although the US Congress repeatedly offered more money for AIDS management (and R&D) than the Reagan administration requested in the budget (Shilts 1987:493), powerful

[2] The virus adapts to its host through mutations, becoming stronger before it is passed on, until it eventually becomes more virulent, lethal and transmittable. Simian viruses have been made 1000 times more pathogenic by serial passaging in as little as 3 monkeys (Carlsen 2001). Jim Moore argued that during colonial rule in Africa, many people were placed in labour camps with poor sanitation, scarce food supply and extreme physical demands. To improve productivity, they were immunised against smallpox with the same syringe allowing for 'serial passage'. The conditions were sufficient to create poor health in anyone, so SIV could have exploited their weakened immune system to become HIV (Chitnis, Rawls et al. 2000).

[3] Hooper provides convincing circumstantial evidence: for example, the timing and location coincide and the fact that other monkey viruses have been known to pass to humans from poliomyelitis vaccines, one of which was harmful (SV40) (Sweet and Hilleman 1960). The vaccines were given to infants so the SIVcpz could adapt in an under-developed immune system into HIV. However, evolutionary analysts have dated the HIV to 1930 plus or minus 15 years (Korber, Muldoon et al. 2000) and others examined old samples of Koprowski's vaccine to find no DNA from chimpanzee cells, no genetic material from SIVcpz and none from HIV either (Cohen 2001a). This makes Hooper's theory extremely unlikely. However, such theories probably exacerbated the anti-vaccination forces (Blume 2006).

[4] AIDS was initially called GRID (Gay-Related Immune Deficiency) (Shilts 1987:121; Oppenheimer 1988; Epstein 1996:50).

groups consistently opposed any funding for AIDS management on moral grounds. For example, senator Helms declared "Let's talk about who's *causing* this, *caused* this from the very beginning [my italics]. I've never heard once in this chamber, anybody say to the homosexuals, 'Stop what you're doing.' …No federal funds can be used to encourage or promote homosexual, sexual activity" (Barker 2004:45).

Framing the disease as a 'gay disease' and as a lifestyle problem distorted its public health significance for the population as a whole, and led to a lacklustre political and scientific response. Transcripts of White House Press Briefings reveal that in the years 1982-84, the Reagan administration viewed the AIDS problem with indifference. Even when it was brought up in terms of possible epidemics, the press officer treated the topic as unworthy of serious attention and laughed-off questions from journalists (See appendix for transcripts). Reagan did not say the word 'AIDS' in public for the first seven years of his presidency because, as his policy adviser reveals, he was 'irrevocably opposed to anything having to do with homosexuality' (Kramer 2005).

The moralising wasted time and resources because a central question of early AIDS research was whether the disease was caused by an infectious agent or by the excesses of lifestyle choices. The answer to that highly contested question drove the degree to which society organised itself for the development of technologies such as vaccines, rather than measures to adjust social behaviours. For a long time, the latter dominated. The newness of the syndrome placed further special concern on 'deviant' social conditions of those that were affected and did not encourage the search for a technical solution. This history of events indicates the importance of support from the wider community outside of science. It bears close resemblance to the theories put forward by Rosenberg (2002) about the reorganisation of social resources around a disease diagnosis.

The possibility of an AIDS vaccine as an operational principle became much more compelling when it was shown to be caused by viral infection. Epstein's (1996) study explores how that causality came to be slowly established over time. The 'immune overload' hypothesis represented the initial medical frame for understanding the epidemic,

by claiming that hedonistic lifestyles were subjecting the immune system to too many sexually transmitted diseases and recreational drugs all at once and essentially pushing the immune system to give up (Epstein 1996:48).

The search for a causal agent of AIDS was guided by a well known set of causation criteria[5]. 'Implicitly or explicitly, researchers had Koch's postulates – or similar criteria – in the backs of their minds' (Epstein 1996:88). They provided a common reference point for considering the causation of AIDS and were a core part of the operational principle. (This principle was defined as how the parts of a technology come together to serve its purpose.) Luc Montagnier's group at the Pasteur Institute, Paris, and Robert Gallo's group at the National Cancer Institute, Washington DC, isolated the HIV virus and linked it to AIDS[6].

Proponents of the immune overload hypothesis argued that HIV did not fulfil all of Koch's postulates whilst critics argued that, for contemporary biomedical research, the exact relevance of the postulates were questionable, especially for viruses, which were undiscovered in Koch's time (Epstein 1996). They suggested researchers nowadays tacitly work with 'modern' or revised interpretations of the postulates, and have argued that Koch himself did not intend them to be followed rigidly (Gallo 1991:277). As more was discovered about HIV and more evidence of its presence in AIDS patients was gathered, the immune overload hypothesis was eventually discredited.

In the scientific community, Gallo led the charge for HIV's causal role in AIDS (Blattner, Gallo et al. 1988; Cohen 1994b) against Peter Duesberg's claims which argued that HIV did not cause AIDS (Duesberg 1995; 1996; Duesberg and Rasnick 1998). Gallo's

[5] Koch's postulates of disease causation (see section 5.4.2).
[6] The assignment of credit for this discovery was disputed and later developed into a protracted legal case that was eventually settled in 1987 involving the two heads of state, Reagan and Chirac. Although interesting, it lies outside the scope of this chapter. I offer as a rather coarse simplification that Montagnier discovered a novel virus, whilst Gallo established its association with AIDS. (See back to back articles by Montagnier, Gallo, and Gallo and Montagnier in Science 2002, Vol 298, pages 1727-1731.)

autobiography included an entire chapter entitled 'About Causes of Disease (and, in particular, Why HIV is the Cause of AIDS)' (Gallo 1991:276).[7]

As Gallo and Montagnier gained ground in the debate, a vision of a vaccine started taking a hold. In 1984, the US Health Secretary, Margaret Heckler, announced with little mention of the French group led by Montagnier, "Today we add another miracle to the long honour roll of American medicine and science…. The probable cause of AIDS has been found" (Shilts 1987:451). In response to widespread complaints of inactivity on AIDS by the Reagan administration, Heckler added, "Those who have said we weren't doing enough have not understood how sound, solid, scientific medical research proceeds" and declared that "a vaccine would be ready within two years" (Shilts 1987:451).

The prediction was similar to that of Flexner's, the poliomyelitis researcher, in its optimism and confidence about the possibility of a vaccine. Unlike poliomyelitis researchers, however, Gallo had never made a vaccine before (Gallo 1991). He reflected on the vaccine prediction with a reporter (Cohen 2001b:8), "I just said, 'I think, you know, due to the fact we have an unlimited amount of virus now and we're sure it causes the disease, I can't think that this should take that long.' I didn't perceive the difficulties. You can't imagine the level of my own feeling of confidence at that time. There was so much data pouring in that I, too, thought – probably believed – we could have solved the whole bloody thing, you know?" (Cohen 2001b:8).

The announcement was a turning point and marked a start for the search of an HIV vaccine[8]. Almost as soon as the cause of the disease was perceived to have been established, talk of a vaccine followed.

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[7] In response to critiques that he was not offering an alternative hypothesis, Duesberg later aligned himself with the 'immune overload' hypothesis. His credibility was used most notably by South African President Thabo Mbeki, who, in November 2007, admitted that he is 'still an AIDS dissident' (McGreal 2007). More accurately, Mbeki is an HIV dissident. At the International AIDS Conference of 2000, held in Durban, South Africa, Mbeki opened with HIV denial, "It seems that we cannot blame everything on a single virus" (Barker 2004; http://virusmyth.net/aids/news/durbspmbeki.htm).

[8] 'Regardless of the political settlement concerning who discovered the AIDS virus, and who will garner Nobel prizes or public opprobrium, the May 1984 acceptance of [HIV] as the cause of AIDS irreversibly changed the nature of managing the epidemic. Prior to that time AIDS research was groping: now it had direction. Scientists could go on to real targeting of specific tests and prevention strategies' (Panem 1988:30).

7.1.2 Testing for HIV: diagnosis and surrogate markers

The FDA approved the first blood test to screen for antibodies to HIV in 1985[9] (Gallo 1991:205; Kates 2006). 'From that precise moment when the blood test became available, AIDS became a problem that could be measured and scientifically evaluated' (Gallo 1991:206). The enzyme-linked immunosorbant assay (ELISA) test was an important development because it allowed researchers to track the spread of the infectious agent through a population. Before, epidemiology could only chart the course of the epidemic through full-blown AIDS cases, which meant that researchers were in effect following the route the virus had travelled several years behind. This is because of the long and varied incubation period between HIV infection and symptoms of AIDS, which can range from a few years to a decade. Some people do not seem to progress to AIDS at all (Johnston 2000).

The tests helped to quickly associate cases of AIDS with HIV, and hence establish a stronger link between the two. It also served to establish AIDS in social groups other than homosexuals and injection drug users, such as 'ordinary' heterosexuals, haemophiliacs and children[10]. The US health secretary, Margaret Heckler, made a key note address at the first International AIDS conference in 1985 that marked a change in tone. She said that AIDS was "our number-one public health priority until it has been conquered" and added that, "we must conquer AIDS before it affects the heterosexual population and the *general population* [italics added]… we have a very strong public interest in stopping AIDS before it spreads outside the risk groups, before it becomes an overwhelming problem"[11] (Shilts 1987:554).

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[9] http://www.fda.gov/oashi/aids/miles81.html

[10] The tests also served to highlight tensions between public health and civil liberties (Gostin 2006). For example, there were concerns about how insurance companies might use the data to shield themselves from expensive treatment costs (Shilts 1987:469). Test results effectively became a decisive marker of a person's identity because no treatments existed.

[11] Activists were quick to point out firstly, that AIDS was already an overwhelming problem, and secondly, that homosexuals, intravenous drug users, and people with AIDS were also among the 'general population'. Furthermore, it is notable that the first technology to emerge was a blood test which was of no help to those already with AIDS, and only made it possible for them to be cordoned-off from the 'general population'.

Even though the blood test allowed the scale of the problem to be more accurately perceived by indicating who was infected, it did not represent an instrument which could provide a way to gather knowledge about disease progression by varying learning conditions (Plotkin and Orenstein 2004:1220). Such knowledge would be needed to evaluate whether a vaccine that did not prevent infection was still of any value in slowing disease progression or reducing the intensity of disease symptoms (see section 8.2).

Many indicators of disease progression, apart from death, were developed. The problem was that within a few years too many of these new indicators, or surrogate markers, began to emerge. In addition to neutralising antibodies, the list of other possible markers was long, including: viral counts, viral RNA, CD8 cell counts, CD4 cell counts, p17 antigen, p24 antigen, β-microglobulin or neopterin levels (Plotkin and Orenstein 2004:1220).

The wide range of potential markers reflected the uncertainty about what was actually going on in the progression to AIDS. But part of the diversity in markers reflected differences in emphasis on what vaccines against AIDS should aim to do. For example, activists emphasised quality of life and argued for markers of apparent health, such as a doctor's ranking of the patient's overall state of being. In deciding which surrogate marker to use for developing tests, there was a challenge for the accumulation of knowledge. There needed to be some co-ordination, standardisation and common agreement about these definitions so that technologists knew what would be counted as 'working' by the rest of society. This is an institutional role, where the 'objectivity' in stable definitions of markers is established to enable further knowledge accumulation (Eichler, Pignatti et al. 2008:820).

A good marker was agreed to be one with 'face validity' and 'biological relevance'; terms that refer to how easily, reliably and objectively measurable they are (Moss 1990). Epstein (1996:270) provides a historical account of how the markers were contested through NIH conferences with titles such as 'Surrogate end-points in evaluating the effectiveness of drugs against HIV infection and AIDS'. Although debate remains, it seems to have stabilised around CD4-cell counts (also known as T-cell counts) and viral load as measured

using polymerase chain reaction techniques (see for example Gallo 2005; Johnston and Fauci 2007).

These now most likely form part of what Rosenberg (2002:238) calls the 'predictable course' of a disease that a patient expects their life to take when they discover they have been infected by HIV. In the contest to define what AIDS is, immunologists seem to have dominated. The progressive deficiency in the immune system is characterised by low CD4 counts as opposed to, say, a doctor's assessment of how often a patient suffers opportunistic infections, the latter being too variable and dependent on idiosyncratic patient behaviour or subjective observations.

The blood test and the issue of surrogate markers represented the beginnings of a testing regime. Firstly, the blood test formed was a key diagnostic instrument which helped track the spread of AIDS. Secondly, for the spread of AIDS in individuals, various surrogate markers needed to be developed to represent discrete and different conditions in disease progression. The triad is completed when the social co-ordination and decision making process to set standardised markers is included in the analysis.

Such a synthesis allowed the problem to then be set in technical terms: a problem with a virus target. Numbers could be applied to the scale of the problem and patterns could be studied in how the virus spread through the population and in individuals. A specifiable aim was for a vaccinated person to be able to take a blood test after exposure, and return a negative result. For that, an acceptable testing regime, and a pass-mark, was required.

7.2 Difficulties in strengthening the testing regime: A virus of 'outstanding success'

By 1985 a causal agent of AIDS was found, a blood test could detect HIV, and viral markers were being understood to represent different sets of conditions in the progression of AIDS. The goal now was to develop a vaccine that could return a negative test result after exposure to the virus[12]. However further developments in the testing regime stalled, and part of the reason was the virus itself.

'In Darwinian terms, the recent emergence of HIV is an outstanding success' (Weiss 2003). As researchers have learnt more and more about HIV, it is not surprising that Weiss and many others have expressed sentiments of respect and admiration for the virus' ability to survive. The virus has two important characteristics: its extreme variation and its ability to evade 'natural sterilising immunity'. These two properties make ideas relating to an HIV vaccine harder to test and make devising operational principles for vaccination problematic. This consequently placed greater emphasis on safety issues in testing regimes compared to poliomyelitis, many of which have not been resolved even today.

7.2.1 Extreme variation of HIV creates moving goalposts

The ways in which HIV attacks its host and causes disease are extremely diverse and complex. In addition to HIV targeting the immune system cells that are supposed to protect the host from the virus, the virus also possesses elaborate means for escaping detection by the immune system[13] (Nabel 2001; Girard, Mastro et al. 2004). Perhaps the most important of them is its genetic and antigenic variation which makes HIV extremely adaptable. In chronic infection, HIV variants with mutations at every (single nucleotide) point in the genome, are believed to arise thousands of times per day (Johnson and Desrosiers 2002). Influenza is thought of as a highly variable virus, 'yet the HIV population present in a single individual six years after infection can be as great as the global variation for an influenza outbreak' (Weiss 2003:12). The swarm of viruses within an individual are so variable they are known as 'quasi-species' (Cichutek, Merget et al. 1992). Klein and Ho

[12] Rather than wait ten or so years for identifiable clinical symptoms to develop (see chapter 9 for more on 'end points').

(2000:304) think that HIV may be 'the most adaptive and genetically variable virus discovered to date'.

Two of the most significant sources of variation lie with HIV's low fidelity through replication cycles and extremely high turnover rate. In one day, $1x10^{10}$ virus particles are produced (Ho, Neuman et al. 1995). Like other retroviruses, HIV genome exists as RNA[14]. It uses reverse transcriptase[15] to convert its viral RNA into DNA, which is then integrated into the host genome. This enzyme, reverse transcriptase, is highly error prone and the absence of 'proofreading' safeguards means that, on average, one mutation is introduced every replication cycle (Letvin 2006). In addition to these two factors, HIV also has a strong propensity to genetically recombine with itself and other quasi-species (Garber, Silvestri et al. 2004). When two viral particles with different genetic sequences enter the same cell; they can both integrate and produce entirely new viral RNA genomes.

The result is that only about a third of nucleotide positions in the coding sequence of HIV are invariant (Alberts, Johnson et al. 2002:1450), which stands in contrast with the finding that humans and chimpanzees are 99% invariant (Wildman, Uddin et al. 2003). Nucleotide sequences in some parts of the viral genome, such as *env* gene, can differ by as much as 30%. Even conserved parts, such as *gag* gene, differ by up to 20% (Letvin 2006:936). By comparison, amino acid changes of only 2% between a vaccine strain and wild types of influenza virus necessitate a change in vaccine strain and the formulation of a new influenza vaccine each year (Garber, Silvestri et al. 2004:405).

Attempts to get around the variability of HIV by targeting functional, more conserved, regions, such as the critical binding site, have been foiled so far because HIV's highly

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[13] For example, HIV has evolved mechanisms that disrupt the Major Histocompatibility Complex proteins, the antigen-presenting proteins that T cells rely on to recognise foreign antigens on the cell surface. One of these mechanisms involves HIV's *nef* gene product, which down-regulates expression of CD4 and class I MHC cell surface proteins that are essential for T-cell recognition of cells that harbour virus (Girard, Mastro et al. 2004).

[14] RNA is inherently less stable than DNA due to the 2'-OH group on the ribose sugar, giving it the ability to be more chemically reactive and change its genetic bases. It is therefore yet another source of variation.

[15] The discovery of reverse transcriptase earned Baltimore, Temin and Dulbecco a Nobel Prize because it challenged the central dogma of molecular biology that all genetic information exists in the more stable DNA form that Watson and Crick outlined.

glycosylated, hypervariable[16] loops serve to shield and cloak its more conserved functional regions (Garber, Silvestri et al. 2004:399; Girard, Osmanov et al. 2006:4065). Antibodies are physically occluded[17] from 'where the action is'; whilst the regions that antibodies can reach are changing too quickly to be recognised for infection to be blocked.

Given that HIV is so much more variable than influenza, and influenza is too variable to eradicate through vaccination, one might be led to assume that the same applies to HIV. However, a key difference is that HIV is far harder to transmit than influenza. HIV can only be transmitted in two ways: sexual or blood contact[18] (Bloor 1995). This means that a rapidly executed mass immunisation programme, with a fact-acting vaccine, could control the HIV pandemic before the virus mutates too much. This implication for HIV vaccine design is explored further in the section below (7.2.3).

Rapid evolution of a pathogen complicates whether to progress with prototypes. One effective strategy against a pathogen that evolves so rapidly is to develop multiple targets and take aim at all of them at the same time. This means that in order for the virus to survive, viral mutations need to confer resistance to all of the attacks at the same time. Although this is less likely to happen than mutation conferring resistance to only one form of attack, it does, however, raise the theoretical possiblity that a strain could arise which is resistant to all form of attacks presented to it (McMichael and Rowland-Jones 2001). Therefore, there is a strategic aspect to vaccine design, as there is in drug design, that involves gambling on how many targets represents 'enough' to ensure that completely resistant strains will not emerge. As Smith puts it, 'It becomes a moral issue of whether or not to wait for better vaccine candidates or to move ahead with the ones showing at least, some promise' (Smith 2002:108).

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[16] 'Hypervariable loops mask the critical receptor binding sites' and 'viral escape is facilitated by changes in glycosylation' (McMichael and Hanke 2003:875).

[17] In addition to hypervariable loops and glycosylation, conserved regions are also protected because they are embedded deep within the inside surfaces of envelope proteins that are arranged in trimeric (3xgp160) sets of heterodimers (gp120 and gp41) (McMichael and Hanke 2003:875; Girard, Mastro et al. 2004:399).

[18] (Blood contact includes mother to child transmission.) The fact that there are so many people who are living with, or have died from, HIV/AIDS, despite the HIV network having only two avenues for growth, suggests that HIV is incredibly well suited to modern society and can be considered a highly human virus in the sense that it taps in to the most human of behaviours and relationships.

In describing the results of a failed monkey experiment, one reviewer reports, 'The researchers discovered that the SHIV [discussed later] had mutated its way around the killer-cell response. It's an ominous development, Letvin thinks, because it threatens in time to undermine every vaccine that relies on the killer cells alone' (Cohen 2002c:2325). Letvin here is suggesting that a multi-pronged approach will be necessary without defining the extent of the multiplicity required.

The extent of multiplicity required is another inherently empirical question that requires the ability to test ideas against reality frequently and easily. Similarly, in discussing how closely to match the virus in the vaccine with the wild type virus, McMichael and Hanke (2003:878) write, 'Intuitively, it seems preferable to match as closely as possible…[because] interactions are very sensitive to change… [but] The danger of too narrow a response is that escape mutants could be easily selected for by the vaccine, particularly if protection is incomplete.'

In summary, the extreme variation of HIV causes uncertainties in the vaccine innovation process. There is uncertainty in whether, firstly, the prototype is still relevant to tackling wild strains, and secondly, if the prototype has attacked enough targets to be effective. However, these are known uncertainties, and so the ability to test ideas frequently and easily means that robust knowledge may be gathered to address them. This requires a strengthened testing regime.

7.2.2 Humans lack natural sterilising immunity against HIV

The lack of natural sterilising immunity, the ability of the immune system to teach itself protection against a virus, is another unusual aspect of HIV. People who recover from an infection are often immune from subsequent attack by the same pathogen, and previously this has provided clues in the development of vaccines. This is not so for HIV because no one is known to have recovered from, and completely cleared, acute infection, let alone developed natural immunity to re-infection (McMichael and Hanke 2003; Garber, Silvestri et al. 2004; Girard, Mastro et al. 2004). 'Natural infection with HIV does not result in virus clearance by the host immune system and the development of natural immunity to re-

infection' (Girard, Osmanov et al. 2006:4065). Humans can therefore be said to lack natural sterilising immunity to HIV.

In spite of intense and sustained immune responses, HIV is able to resist eradication. Even when treatment reduces the viral load to undetectable levels[19], the virus still remains and can continue depleting immune system cells, eventually leading to AIDS (Johnston and Fauci 2007). Since natural immunity to re-infection is not seen in HIV infections, it is not surprising to find that superinfection with a second HIV isolate[20] can readily occur in infected persons. A lack of natural sterilising immunity therefore exacerbates the inherent variability of the virus by having multiple variants in the body at the same time, leading to the emergence of recombinant virus variants and generating increased virus diversity (Altfeld, Allen et al. 2002).

Theoretically, even if the virus was completely cleared, the virus could return from latency. To prevent the 'return' of virus, any cells with the provirus integrated within the host genome, along with all of the copies of the cell after it was infected, would need to be identified and killed. It has been calculated that it would take up to 60 years to eradicate a reservoir of as few as $1x10^5$ latently infected cells (Gallo 2005; Girard, Osmanov et al. 2006). This suggests aiming to completely cure AIDS by clearing HIV infection is not feasible, and that it may be better to try and prevent infection.

The lack of natural sterilising immunity against HIV means that 'the potential correlates of protection are not known, leaving us without a definite model of protective HIV immunity to emulate through vaccination' (Garber, Silvestri et al. 2004:398). This situation contrasts strongly with the challenge poliomyelitis researchers faced, as Albert Sabin succinctly put it, 'The objective is clear: to imitate what nature does for 99-99.9% of the population but without incurring the 1-0.1% risk of paralysis which in many parts of the world is the price for acquiring immunity to poliomyelitis' (Carter 1965:180).

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[19] Treatment is by a combination of antiretroviral drugs collectively known as cocktail therapy or (HAART). Undetectable levels are <50 RNA copies per millimetre (Johnston and Fauci 2007:2704).
[20] HIV from another source.

Maurice Hilleman (1992:1054), who has made many vaccines, laments, 'The time proven approach of trying to mimic the immune response to natural infection makes little sense for a virus to which the natural immune response by the host fails and is ineffective'. One famous AIDS researcher said that the AIDS vaccine field was 'flying without a compass' (Cohen 2005:99).

This has led some commentators to identify natural sterilising immunity as *the* major criteria for judging whether a vaccine is possible or not. 'It is now theoretically possible to develop a safe and efficacious vaccine against any infectious disease to which natural specific immunity develops on recovery from infection' (Andre 2001:2207). It is a declaration that carries great promise and excitement for vaccine development efforts against the many diseases where natural sterilising immunity can be seen. It is also a disheartening one for the diseases that are most in need of vaccine development (AIDS, tuberculosis and malaria), where natural sterilising immunity is not seen.

7.2.3 Implications for vaccine design: A small window of opportunity

Extreme variation and lack of natural sterilising immunity have immediate implications for the establishment of operational principles in vaccine design.

From the moment of transmission into a host, the window of opportunity in which chronic HIV infection might be prevented by a vaccine is very small. Nearly all CD4 helper T-cells, the immune system's cells that HIV attacks, are located in mucosal tissues such as those lining the vagina, airways and gut to provide mucosal protection. Only two per cent of CD4 cells are estimated to actually circulate in the blood (Aldhous 2006). This highly skewed distribution of CD4 cells is possibly because pathogens typically enter the body through such tissues. And yet, despite this, infections acquired by this route have historically been difficult to prevent through vaccination (Klein and Ho 2000:305).

Most HIV infections are transmitted sexually through the mucosal surface (Hilleman 1992:1055), so a protective vaccine will probably have to provide 'mucosal immunity' in addition to immunity in the blood. This is difficult because, to provide mucosal immunity,

the induction of specific immunoglobulin (Ig)A antibody is needed in the thin layer of fluid at the mucosal interface. IgA neutralisation of the virus must occur at this narrow interface between the mucosa and the circulation. If neutralisation does not occur, the virus can easily encounter lymphocytes or macrophages and cause infection long before traditional IgG and IgM antibodies can respond in the bloodstream (Schultz 1996). In short, the virus has to be tackled effectively at the body's first line of defence.

But even a functional mucosal antibody would not be enough because HIV can be transmitted within cells as well as outside of them. So a protective vaccine would need to prevent cellular transmission. The fact that the virus can be transmitted either free of cells or within cells led Albert Sabin, the poliomyelitis vaccine developer, to suggest that an HIV vaccine is impossible (Sabin 1992). As chapter 8 will show, researchers came to realise that the operational principle of an effective vaccine would need to be more than a functional antibody response to kill the virus. A cellular immune response would also be required to clear any infected cells and prevent further cellular transmission.

Mucosal surface transmission and intracellular transmission are not the only reasons the window of opportunity is narrow. Graham explains that once the virus enters the bloodstream, rapid evolution of HIV and the lack of natural sterilising immunity come into play and severely reduce the chances of a vaccine working effectively. 'The timing of the immune response with respect to initial virus infection and spread is particularly important in the case of HIV infection. One reason is that the longer HIV replicates in the host, the more diverse variants evolve, which may allow the virus to escape immune responses. In addition, once HIV resides in the extracellular space of lymph node germinal centers and in latently infected cellular reservoirs, or is sequestered in the central nervous system and other sites that are relatively protected from immune responses, it probably cannot be fully eliminated from the host.' Thus the confluence of these factors serve to reduce the window of opportunity such that, 'the success of vaccination may hinge on altering events that occur in the early hours following HIV exposure' (Graham 2002:209).

HIV poses some unique challenges (see table 8). The lack of natural sterilising immunity leaves vaccine designers few clues with which to design operational principles. The pathogen diversifies quickly due to the lack of immunity against super-infection and the virus' inherent variability. This means that the operational principle has to get to work quickly in order to fulfil its purpose. The pathogen is usually transmitted through the mucosal surface, either within cells or outside of them. This means that the operational principle must prompt mucosal, cellular *and* humoral immunity.

Table 8: A summary of technical obstacles to HIV vaccine development

Common elements in vaccine preventable disease	**Some unique attributes of HIV infection**
Virus shows limited antigenic variation, if any	Hypervariability of antigen specificity
Spontaneous recovery is the normal event	No, or extremely rare, spontaneous recovery from natural infection
Genetic integration is not part of virus life cycle	Obligatory integration of virus into host cell genome where the infection may be silent/latent and immunologically undetectable
Virus does not destroy immune system	Infection and progressive destruction of the immune system itself
Transmission of disease is by free virus Transmission of disease is non-mucosal	Transmission of infection by virus hidden inside cells as well as by free virus Transmission of infection by mucosal route
Vaccine efficacy is by induction of neutralising antibody and sometimes cytotoxic T cells in addition	Appropriation of infection in the CNS, where it is inaccessible to a peripheral immune response
Viral antigens presented to immune system by Major Histocompatibility Complex	Down-regulation of MHC class I antigens by viral gene product (*nef)*

Sources: (Hilleman 1992:1054; Girard, Mastro et al. 2004:1220)

These are formidable design specifications, but they have been established through a collective judgement, experience and understanding[21]. They have become increasingly well-known uncertainties (as opposed to unknown uncertainties) about the development

[21] There are a few individuals who offer further ways forward. A small cohort of sex workers in Nairobi has been found to be exposed but uninfected; however, their immunity seems dependent on continued exposure (Nabel 2001:1002; McMichael and Hanke 2003:875). There are also some infected people who have managed to fend off the onset of AIDS for more than a decade, known as long term non-progressors or elite controllers (Johnston 2000:268). A highly focussed, co-ordinated and well-resourced effort to find, and study, such rare individuals may help provide a 'roadmap' to inducing immune resistance.

process. This places heavy pressure on the need to test designs against these specifications to show that they are robust enough to meet them. Test-results need to be incorporated in a systematic way that allows incremental accumulation of knowledge.

Sophisticated testing regimes allow the development of technologies through intermediate conditions to provide varying degrees of indirectness to real technological conditions. One such set of intermediate conditions is provided by the use of animals as a stepping stone to dealing with the problems posed in humans by the HIV virus. Ideas can be tested, shared and refined with careful use of animals as an indirect representation of conditions in humans. However, the next section shows their use for testing and refining ideas is contingent on the creation of these conditions through instrumentalities, and is in no way inevitable.

7.3 Efforts to strengthen the testing regime with animals

This section will show that there have been strategic efforts to strengthen the testing regime in the field of animal modelling. The section organises these efforts into the three constituent parts of the testing regime, explained in section 3.4.

Animals provide an important environment from which novel hypotheses can emerge, in which new ideas can be tested, and which allows dead ends to be eliminated and new leads to be built on. But such a drive for animal-led HIV vaccine research and development has been problematic for a number of reasons. Foremost is that HIV is a primate virus capable of infecting only few animal species. Although HIV infects chimpanzees, the virus replicates to a lesser extent than in humans, the virus does not congregate and systematically destroy the lymph node architecture as in humans, and does not culminate in disease (Klein and Ho 2000; Nath, Schumann et al. 2000; Van de Perre 2000). By 1999, over 150 chimpanzees had been infected but only one was reported as progressing to AIDS (Koopman, Haaksma et al. 1999).

In reviews of HIV vaccines, few fail to readily acknowledge the lack of an animal model as a significant obstacle to vaccine development (Nabel 2001; Letvin 2005; Singh, Jeang et al. 2005; Slobod, Bonsignori et al. 2005; Johnston and Fauci 2007; Titti, Cafaro et al. 2007). 'Another roadblock encountered in HIV vaccine research is the lack of a truly representative animal model in which to gauge the effectiveness of vaccine strategies' (Klein and Ho 2000:304). 'A second obstacle to an HIV-preventive vaccine is that we have no truly useful small animal model for studying HIV infection' (Gallo 1991:1894).

And yet, for all researchers who have commented on the unsuitability of animal models in mimicking real world conditions, the majority of the scientific literature I have reviewed has discussed data derived from animals. Nath et al (2000:430) conclude that 'primates have provided a great deal of information that has significantly advanced vaccine design.' There is an inconsistency between the complacency about animals and the use of animals. I suggest the phrasing in the quotes above by Klein and Ho and by Gallo, using verbs such as 'lacking' or 'having a useful model', are *passive* descriptions or observations of the state of the natural world as it is. They have the tendency to downplay the role of human agency in the use and interpretation of animal models to mimic real world conditions as much as is technically possible. Girard et al. (2006:4066) expresses the difficulties more *actively* by using the word 'developing', 'A significant obstacle in HIV vaccine research has been the difficulty in developing an appropriate animal model.' This choice of words reflects more of the human effort that is expended in 'making the best of what we've got,' in moulding what is provided in the real world to our technological needs.

Unlike the construction of prototypes and testing chambers in engineering, which are seen as clearly man-made endeavours, the use of animals as 'testing chambers' is quite rightly not seen in this way because animals are not man-made. But scope for man-made interventions that structure the environment provided by animals do exist, and this role is perhaps somewhat underestimated when barriers to vaccine innovation are being explicitly articulated.

Chapter 6 showed that monkeys were used to guide the way to poliomyelitis vaccines despite the fact that they did not closely mimic what happened in humans. Monkeys do not normally become infected with poliomyelitis, but when injected directly into their brains the virus is infectious and able to paralyse, thus giving an animal model with clearly visible test results. Isabel Morgan's experiments thus facilitated the *development* of monkey models such that they could become incorporated into an effective testing regime. Similar efforts to achieve this seem to be underway for HIV models.

7.3.1 Learning conditions in animals

These efforts are considerable and are what consume much of the debates in the literature. The first issue is in our understanding of the conditions represented by animal models. Despite the shortcomings of the chimpanzee model, it is still useful to researchers, provided they know what aspects of the vaccine they are testing for. For example, since chimpanzees do not readily progress to AIDS in a human-like way (Klein and Ho 2000; Nath, Schumann et al. 2000; Van de Perre 2000), using it to study how a vaccine might reduce disease progression would not be as helpful as say, testing vaccines that prevent infection outright. Feinberg and Moore explain, 'For instance, a virus that replicates very poorly in a host [as is the case with HIV-in-chimpanzee models] may be misleadingly easy to protect against by vaccination, and is of little value for studies of viral pathogenesis…'

'…Conversely, vaccine studies that employ particularly virulent viruses, as is the case with SHIV-in-macaques [discussed below], or experimental challenges delivered at high doses via intravenous inoculation may underestimate the potential protective efficacy of some vaccine strategies' (Feinberg and Moore 2002:207). Thus the usefulness of a model depends both on our understanding of the conditions that the model presents us with and on our ability to standardise what we are testing for.

In the case of HIV, some researchers express extreme uncertainty about our understanding of these testing conditions and suggest reluctance to draw interpretation, 'Even a vaccine that has 100% efficacy in all three [animal] challenge models discussed here might still be ineffective in humans. Conversely, a proficient vaccine developed in humans might never

show benefit in the animal models' (Nath, Schumann et al. 2000:430). Similarly Feinberg and Moore (2002:209) caution interpretation of data arising from animals, 'Animal models cannot determine whether a vaccine will be effective against HIV infection of humans; only Phase III trials in humans will do so.' However, they also note that they can be used to 'explore the potential protective efficacy of vaccine concepts' (:207), 'add important insights' (:209), and that 'it is essential for models to be *improved* [my italics] so as to mimic, as closely as possible, the actual circumstances of HIV infection in humans.'

7.3.2 Animals as instruments

The second issue involves the craft of developing animals as instruments. It is evident that researchers do not simply 'make the best of what they've got'. They actively construct models and techniques to use them. This can be illustrated by the two main animal models used in HIV vaccine development (a third less used model is the chimpanzee): SIV and SHIV in monkeys.

Shortly after HIV was discovered, SIV was also discovered as researchers in primate centres noticed that Asian monkeys (macaques) were dying of an illness which bore remarkable similarity to the newly observed AIDS syndrome that was killing young men (Gardner 1996). The causative agent of this simian AIDS was found to be SIV, a virus closely related to HIV in gene sequence homology. SIV is naturally found in African monkeys (sooty mangabeys), to which it does no harm but quickly causes AIDS in Asian monkeys, none of which are infected in the wild (Gardner 1996; Smith 2002). Smith says that '…several different, but closely related, strains (including SIVmac, SIVsm, and SIVmne) of SIV *were developed for research purposes*' (Smith 2002:101 [my italics]).

With respect to the first issue of understanding modeling conditions outlined above, the development of SIV-caused AIDS in macaques was quickly recognised as providing, 'the flexibility to test not only potential vaccines but also to test and verify theories of pathogenesis or immunological correlations with disease. Accordingly, there are a multitude of pathogenic and non-pathogenic viral strains that can be used in therapeutic and

challenge studies to answer such questions as correlates of protection or progression to disease' (Nath, Schumann et al. 2000:429).

The SIV model was developed further when an SIV genome was engineered to carry the *env* gene[22] from an HIV isolate. These SIV/HIV chimera (hybrid viruses) became instruments known as SHIVs (Johnston 2000). SHIVs can replicate in macaques and, after serial passages in the animal, eventually lead to the emergence of highly pathogenic variants that are capable of decimating CD4 T cell population of the animal within a few weeks of infection and generating a lethal AIDS-like syndrome within a year (rather than the ten or so years often needed for HIV) (Girard, Osmanov et al. 2006).

The use of multiple SIV 'strains of differing virulence' (Feinberg and Moore 2002:207) allow researchers to control iterations between stricter, more real world conditions and lenient, simplified laboratory conditions. And the use of different chimeric SHIVs provides even more control over the opportunities to examine and test particular issues in the development of vaccines. For example, one notable difference between SIV and HIV is when and which of the two seven-transmembrane chemokine receptors CCR5 and CXCR4 on CD4 cells, the virus binds with for viral uptake into cells (Nath, Schumann et al. 2000; Girard, Osmanov et al. 2006). In about half of HIV infected humans, HIV that binds to CCR5 predominates early and throughout the asymptomatic phase, but a shift towards binding to CXCR4 is observed as these humans progress to AIDS. This shift in tropism to CXCR4 has not been reported in SIV infected macaques (Johnston 2000). SHIVs provide an opportunity to take a controlled look at each of these tropisms in turn.

The great variety of animal models that have been developed allow researchers to firstly examine different aspects of infection in turn, for example 'R5' and 'X4' receptor tropisms, and secondly adjust testing conditions to slowly iterate towards more and more real world conditions. For example, by using more or less virulent strains, varying challenge route and dose, and using more or less genetically diverse strains between vaccination and

[22] *rev, tat, and vpu* genes are also used in the chimera (Nath, Schumann et al. 2000; Feinberg and Moore 2002).

challenge[23]. Thus, as instrumentalities help provide controlled variation of conditions, knowledge may grow reliably.

7.3.3 The need for institutions and R&D governance

As noted in the theory chapters, reliable knowledge gathered in an array of conditions may, however, remain fragmented. This effect may be particularly acute in a research environment that rewards individual achievement and relies on competition to drive forwards. In contrast, for robust technological knowledge to accumulate, it needs to be not only true but also shared and integrated. This can be facilitated by agreeing on which intermediate conditions to set experimental standards around. Thus, it is the inter-relationships between different groups of knowledge producers that are most important for technological development.

As Norley and Kurth point out, 'There are a number of [primate] models available, each with its advantages and disadvantages, and unfortunately the model selected can have a large impact on the result. Which model is the most relevant is therefore a matter of debate' (Norley and Kurth 1996:537). This would seem something of an understatement when compared to the account of a journalist, Cohen, on animal use, 'Salk's chimpanzee data [for AIDS vaccine candidates] were peculiar for several reasons, not the least of which was the way in which he attempted to use animal studies to gain support for human experiments he had already quietly begun. It would become an all too common gambit: rather than having animal experiments guide them in developing an AIDS vaccine, Salk and other researchers would use experiments *ex post facto* to justify the paths they had already chosen' (Cohen 2001b:88).

When primate models are used in this way, or without coordination between research groups, commensurability between the results of testing becomes problematic. For example, 'With the variety of challenge viruses and primates, comparison of one study to

[23] At 2002, all SHIV challenges employed vaccine immunogens that are genetically identical (or nearly so) to the challenge virus, yet a single amino acid change was reported to be sufficient to enable SHIV to escape from immune containment (Feinberg and Moore 2002).

another is often not possible' (Smith 2002:107) and 'These [SIV] species differ substantially. Since each of these SIV strains produced similar disease in a given macaque species and no macaque/ SIV model was clearly more relevant than another, researchers chose to study different SIV strains in different species of macaques. The resulting experiments, of course, often make direct comparison impossible. Additionally, researchers have now begun using SHIV as the challenge virus…' (Smith 2002:101).

To ensure that results between different groups are comparable would require a carefully planned strategy for co-operation. The very factors that provide researchers with flexibility and the ability to adjust testing conditions incrementally would need to be set constant and agreed for cumulative learning. This is needed in addition to careful documentation and understanding of the conditions used in tests and experiments. Thus, governance is required to ensure co-ordination and transparency.

'Comparative studies of candidate vaccines in animal models have been proposed as an approach to determining which candidates are most worthy of accelerated development. For example, comparison of viral vectors would require that the candidates express identical HIV genes, be of similar quality and be evaluated using the same protocol with the same challenge virus, route of challenge and endpoints' (Johnston 2000:269). Such a comparative study does not seem to have been undertaken (Cohen 2001b). It would therefore seem that there has been a significant failure in the organisation of HIV vaccine R&D since such grand experiments have been designed and executed before (chapter 6).

7.3.4 Some costs of not having wider support for a vision

Attempts to shape the testing regime in such a direct and deliberate way has ethical implications. For example, attempts at creating HIV strains that were capable of not only infecting chimpanzees but also killing them caused concern. These lethal virus strains, previously not lethal to chimpanzees, would be undeniably man-made and, for some, their

creation and introduction marked an exploitation of our relationship to the animals[24]. Major meetings were convened for such debates (Gardner 1996).

Smith (2002:101) notes, 'macaque studies are expensive, and the supply of macaques is limited' but relative to chimpanzees they are cheap and abundant. 'It can cost more than $100,000 to care for a single [chimpanzee] animal' (Nath, Schumann et al. 2000:428). In addition, as a rare species, chimpanzees are protected by a 1975 international treaty that allows them to be used for research only if they are bred in captivity and not caught from wild. This restricts supply much more than macaques. Macaques, in contrast, cost about $2000 each (Cohen 2001b:80) and, once infected, die from AIDS; unlike chimpanzees which need longer term care. Furthermore, chimpanzees can weigh up to 80 kilograms and possess strength three times that of an adult human male. Enclosures that can hold chimpanzees need to be made from durable steel and therefore add to the expense and difficulty of their use in vaccine testing (Nath, Schumann et al. 2000:428).

These practical, legal, ethical and cost obstacles to the use of primate models in AIDS vaccine development led to a shortage in supply. For example Gallo is quoted to have said, "To do the studies I would like to do over the next two years, I need 75 chimps, but I will be lucky to get two or three" (in Cohen 2001b:83). Gallo goes so far as to say, "It is conceivable that we may already have an effective vaccine, but we will never know unless we can get the chimps to fine-tune different dosages of different compounds" (in Smith 1990:397). Smith says, 'Macaque studies are expensive and the supply of macaques is limited. Therefore, most macaque studies involve small numbers, usually well less than 20 total, of animals' (Smith 2002:101).

[24] Jane Goodall, a prominent anthropologist, was a vocal advocate for chimpanzee welfare and their right to be free from testing. Using her well known studies of chimpanzees in Tanzania, she wrote, for example, to Science journal, '…it is their humanlike behaviors that most fascinate people: their tool-using and tool-making abilities; the close supportive bonds among family members, which can persist throughout a lifetime of 50 or more years; and their complex social interactions - the cooperation, the altruism, and the expression of emotions like joy and sadness. It is our recognition of these intellectual and emotional similarities between chimpanzees and ourselves that has, more than anything else, blurred the line, once thought so sharp, between human beings and other animals' (Goodall 1998:2185).

The existence of strong leadership and co-ordination has been shown to ameliorate such problems with solutions such as the dedicated breeding programme O'Connors set up for poliomyelitis vaccine research. Similarly, strategic research can be supported to strengthen the testing regime in other ways. This section has shown that researchers have already been active in developing animal models, but has suggested that in the presence of strong support and co-ordination, researchers explicitly dedicated working on developing animal models may have made more breakthroughs. This includes the possibility of developing smaller animal models such as rabbits or rats.

7.4 Summary

This chapter has shown how visions for an AIDS vaccine were constructed in a considerably different way to that for poliomyelitis vaccines. It was dependent on the establishment of HIV as its cause, but uncertainties about the virus and the lack of wider support further weakened this vision and allowed other competing visions to draw resources away from co-ordinating efforts. Nevertheless, development of a blood test marked an important starting point in the search for a vaccine.

This chapter has also reviewed the properties of the AIDS virus and its behaviour in animals so that their implications on vaccine design and development can be considered. The next chapter will examine how they have affected the development and selection of various approaches to AIDS vaccination in more detail.

Chapter 8

Which HIV Vaccine? Competing directions of technical change

This chapter explores the role of the testing regime in selecting between competing operational trajectories. It seeks to establish the notion that some operational principles are less likely to come about due to testing difficulties, and therefore that the direction of innovation is influenced by the testing regime. This idea complements the previous chapter which argued that the biological features of HIV, in comparison to other viruses for which vaccines have been found, requires the development of a far more sophisticated testing regime. This chapter continues by showing how, within the biological parameters of HIV, the testing regime can continue to shape progress in and direction of science and technology.

The first section describes the operational trajectory that most AIDS researchers were forging and explains its relative popularity. The second section describes some of the experiences of small companies in the private sector and seeks to explain their choice of a new operational trajectory. The third section explains how and why the strength of the testing regime may support the development of some trajectories over others. The fourth section examines yet more operational trajectories that emerged in the 1990s. The fifth section describes how a weak testing regime may have contributed to the 'closure' of older vaccine approaches, apart from considerations of their effectiveness. A sixth section concludes the chapter.

8.1 Whole-virus vaccines making way for viral-subunit vaccines

In the 1980s two approaches were available to AIDS researchers: live-attenuated and killed vaccines. These were the same options as when the poliomyelitis vaccines were being researched half a century earlier. But with the advent of biotechnology, AIDS researchers now have other approaches open to them.

8.1.1 Safety in reductionism and efficacy in empiricism

Live and killed vaccines present a modified version of the whole virus to the immune system. A new approach was to present proteins, or bits of protein, from the virus. This is known as the subunit approach. The idea of using genetically engineered proteins to make vaccines was elegant in its use of science and understanding, and seductive in its use of recently developed basic technologies in molecular biology. It has dominated AIDS vaccine research and development (see for example, Gallo 2005:178; Johnston and Fauci 2007).

Whilst the live and killed vaccines 'worked because they worked', it was felt a subunit approach was possible based on newer understandings about the virus[1, 2]. The NIH's leading AIDS vaccine researcher, Gallo, favoured this more refined approach (Fischinger, Gallo et al. 1986), "What can be done with a killed whole can be done with a protein and a little brains… The country has enough brains to do it. Let people who can't do it with their own abilities or brains work with it as killed whole, and let the rest of the country figure out how to do it with proteins, and don't stop either one" (in Cohen 2001b:44).

[1] Although it is debated how much HIV vaccine development should be empirically driven, there is no doubt that vaccines developed in the past have involved a considerable degree of empirical art. For example, Bolognesi, who has followed a not-so-empirical approach to making HIV vaccines, acknowledges that, 'The science of vaccinology has been largely empirical. The use of vaccines based on selected components of a pathogen is only a recent development and the efficacy of these vaccines is still being evaluated. The underlying principles of vaccination are poorly understood despite vaccines' successes, particularly against viruses' (Bolognesi 1990:41).

[2] With the benefit of several decades of hindsight, the words of poliomyelitis researcher Hilary Koprowski seem almost ironic as he predicted a diminishing role for empiricism in vaccine development. 'And soon the dispute between the killed- and live-vaccine schools will be ancient history. Now that it is becoming possible to isolate and purify and even synthesize the viral protein that confers immunity, the infectious part of the virus becomes unnecessary. Perhaps undesirable. Why introduce viral infection – even supposedly harmless infection – when you can supply the specific antigenic protein you need for immunization?' (Carter 1965:355).

Jonas Salk made his poliomyelitis vaccine using the whole-killed approach and he favoured the same approach to developing an HIV vaccine (Carter 1965; Salk 1987; Cohen 2001b). He saw contemporary visions of the subunit vaccine as hopelessly reductionist and unsubstantiated compared with the successes of the whole-killed approach in developing vaccines for poliomyelitis, influenza, pertussis, plague, typhoid, cholera and rabies, many of which are effective with little understanding of their disease causing mechanisms[3] (Plotkin and Orenstein 2004). Salk was of the view that understanding form and function, should come second to getting the vaccine to actually work.

Gallo (2005), and others, argued that using genetically engineered protein was safer because, as happened in the Cutter incident of 1955, whole virus may not be killed properly during manufacture. Since genetically engineered vaccines feature only a small part of the organism and crucially none of its genetic material, they can never cause the disease they are trying to prevent.

Another whole approach that was severely undermined by the safety issue was the live-attenuated vaccine, where the virus is alive but is weaker and cannot cause disease[4]. If the whole-killed approach was met with safety concerns, the live-attenuated approach was met with ridicule. Plotkin, who had made other vaccines using this approach, was repeatedly turned down for grants on the basis that developing an HIV vaccine this way was too risky. Gallo says in an interview in 1990, "I think I would argue to put people in jail who did it, OK? This would be so seriously nuts, beyond belief" (Cohen 2001b:48).

Gallo and some prominent colleagues expressed three key criticisms (Fischinger, Robey et al. 1985). Firstly, there was the risk that the weakened strain of HIV could cause cancer through a process called insertional mutagenesis, where viral genes cause problems when

[3] For example, vaccines against smallpox and rabies were developed before their causal agents were even fully identified (Chase 1982:167, 172; Plotkin and Orenstein 2004).

[4] One advocate for this approach was Stanley Plotkin, a prominent vaccinologist who had made vaccines for rubella and rabies. Like AIDS, rabies is also a disease for which humans have no (or very little) natural sterilising immunity. He had also developed a live varicella chickenpox vaccine, and a live poliomyelitis vaccine that never came to market. He co-authored an important medical textbook, *Vaccines*, featuring a chapter on each vaccine (Plotkin and Orenstein 2004).

they integrate with DNA in the host cell. Secondly, with such extreme variation, the weakened HIV could revert back to virulence. Thirdly, the weakened HIV virus might cause AIDS at a slower pace than the wild type virus with vaccinees developing AIDS thirty years after infection rather than ten years. These are all difficult criticisms to deal with because to respond effectively would require testing to prove that something does *not* happen. And, in the last case, testing for at least thirty years.

In addition to these criticisms, there was concern about the reaction of an increasingly reluctant public to a vaccine that was developed using the live approach. 'The public fear associated with vaccinating individuals with living HIV make using live-attenuated virus an unattractive prospect from the perspectives of marketing and compliance' (Klein and Ho 2000:308). 'Although most of the population has accepted [live] vaccines, the fear of AIDS is powerful, and even a l-in-a-million chance of contracting the disease from the vaccine is too great a public safety risk' (Klein and Ho 2000:309).

The whole virus approaches, both live and killed, were seen as old fashioned and unable to stand up to the challenge of a dangerous new pathogen (Cohen 1992a). Gallo insists that 'An HIV vaccine cannot consist of attenuated, actively replicating (live) HIV, even though the best vaccines for other viral diseases have usually used live viruses. There is inherent danger that attenuated HIV would cause AIDS. Killed whole virus, usually the next best approach, might also be precluded both because of the hazard (one cannot be certain that all virus particles would be inactivated), and because killed whole HIV has worked poorly in animal tests…we are restricted by the need to use one or more HIV proteins or peptides (subunit vaccines)' (Gallo 2005:1894).

8.1.2 Testing regimes and vaccine approaches: Inter-relationships

Of the three approaches (live-attenuated, whole-killed and subunit), subunit was the dominant approach both in the public sector, represented by Gallo's group at the NIH, and in the private sector (described in the section below). In the previous chapter, the testing regime was characterised as weak because of the lack of natural sterilising immunity (inability to clear virus), high variation of HIV, and limited scope for animal models to act

as intermediates to human testing. This section shows that these features have different implications for the different vaccine designs. It emphasises a lack of evolved capabilities, experience and skills in the testing regime.

As discussed at the end of chapter 5, the design of a vaccine based on viral pieces or fragments faces the challenge of finding out which pieces are the most important for the immune system to recognise HIV correctly and accurately (for example Eggink, Melchers et al. 2007). Then, even once the right protein or pieces of it have been selected for a vaccine; there is the worry that HIV's extreme variation would allow it to evolve resistance to the vaccine (see section 7.2.1). There would also be manufacturing challenges in either cloning enough copies of the protein (in vivo) or synthesising pieces of it in a machine accurately (in vitro). These issues are inter-related with the testing regime because they are design uncertainties which need to be addressed through repetitive testing in varying conditions.

The whole virus approaches face different obstacles to the subunit approach, particularly related to the issue of conducting tests with a deadly virus and without a reliable animal model. Advocates claim whole virus approaches rely on careful, 'rational empiricism…based on hard data' (Hilleman 1998:788). However, the lack of natural sterilising immunity and the lack of well developed animal models both result in a testing regime that is weak, and makes collecting 'hard data' on effectiveness difficult.

Hilleman notes that vaccines have been developed without animal models, and vaccines have also been developed for very dangerous pathogens, but for HIV, the two hurdles exacerbate each other: 'There are no meaningful animal models for measles, mumps, rubella, human adenovirus and varicella, but clinical tests of attenuated live virus vaccines could be carried out in human beings by a 'guts and judgement' approach and without prior animal safety studies because these diseases are not usually life threatening in their natural occurrence. Poliomyelitis, Hepatitis A and B, are potentially very dangerous, but it was possible to develop *in vitro* markers and tests in susceptible animal models… [for] safety

and protective efficacy… before initiating first clinical investigations' (Hilleman 1989, quoted in Grady 1995:96).

So unlike measles, mumps, rubella, diphtheria, pertussis, smallpox and many other vaccine-preventable diseases for which humans have some form of adaptive immunity, and animal models, HIV had neither. This combination of difficulties represented a major problem for all vaccine approaches, but dealt its heaviest blow to empiricist methods which formed the basis of previous whole vaccine development methods.

Capabilities, skills and experience evolved through successful use of whole vaccine approaches in the past; one might refer to them as part of a path-dependent technological paradigm. The paradigm has benefited from the development of ever more sophisticated testing regimes with key social elements.

Piot et al. (2001:972) note, 'Smallpox vaccination seems the ultimate 'magic bullet' — an example of a purely medical technology resulting in the total eradication of disease. But even the response to smallpox cannot escape its social determinants, such as the observation of natural immunity in cow-herding communities, the power relations that enabled vaccine testing, and the 200 years of social, political and economic organization required for vaccination to occur globally.'

Grady also uses the smallpox example to suggest that strong understanding may not be necessary for innovation, but emphasises that this is the case only if natural sterilising immunity can be observed (1995:95). 'At the 1977 smallpox conference, 200 years after the first effective vaccine was used, researchers still did not understand the correlates of immunity. A major difference exists, however, between previous efforts at vaccine development and efforts at developing an HIV vaccine… Previous vaccine work almost always started with an empirical observation about natural protection (sometimes without understanding much about the microbe, for example, even though correlates of immunity were not known, it was observed that exposure to cowpox protected people from smallpox,

and this observation is what led Jenner to try his experiments), followed by attempts to copy or elicit the same type of protection using various vaccine preparations.'

8.2 Selection of the subunit approach by the private sector

As noted in section 2.4.1, firms associate their market opportunities with their knowledge environment through their 'core competences, 'core rigidities' and 'dynamic capabilities' (Leonard-Barton 1992; Henderson and Cockburn 1994; Prahalad and Hamel 1994; Teece, Pisano et al. 1997). These capabilities are acquired through time, as argued by evolutionary theories reviewed in chapter 2. Thus, for firms, the relationship between the testing regime and vaccine approaches is examined in this section by analysing not only their experiences of pursuing an HIV vaccine, but also some previous experiences.

As noted in chapter 5, most private sector vaccine innovation capabilities resided with a few major pharmaceutical firms. However, they had declared their disinterest in the AIDS vaccine from the outset because of concern about longer development times, increased liability, and smaller profit margins, compared to therapeutic drugs (Chase 1984; see also chapter 5). The market was left to smaller biotechnology firms who drew investments by riding on the wave of optimism generated by genetic engineering. The few firms that did enter the race adopted the subunit approach to developing an HIV vaccine[5]. The associated lack of capabilities is noted in this section.

8.2.1 Chiron

A considerable degree of credibility for the subunit approach stemmed from Merck's recent Hepatitis B vaccine, which was the first genetically engineered vaccine (Vagelos and Galambos 2004).

[5] This approach appealed more to venture capitalists and the novel techniques were also creating excitement in other projects (Thomas 2001).

Initially the Hepatitis B vaccine was based on a surface protein of the virus, recovered from the blood of Hepatitis B carriers. Manufacturing it in this way was not only laborious and expensive, because it involved extensive separation and purification, the process was also vulnerable to contamination from other viruses in the blood, such as HIV.

Merck invested in several groups in order to find a better way (Vagelos and Galambos 2006). One of those was an academic laboratory of the University of California run by William Rutter. He was the first to clone a human gene, the insulin gene (Cordell, Bell et al. 1979), but genetic engineering caused much concern in the general public. Rutter is quoted as saying "I became very concerned about developing a model that demonstrated the benefit over risk [of recombinant DNA technology], I thought vaccines would be a tremendous model" (Cohen 2001b:52). Rutter and his colleagues established a firm called Chiron in 1981 (Chiron 2006). By cloning Hepatitis B surface antigen, Chiron simplified its production.

Chiron does not appear to have arrived at a vaccine approach by testing different strategies, comparing them and selecting the best one[6]. Rather, given Rutter's agenda of promoting the uses of genetic engineering and Chiron's experience with a subunit vaccine for Hepatitis B, it is likely that they sought to repeat the success for HIV, by cloning an HIV gene which codes for a surface glycoprotein[7].

Chiron quickly faced difficulties with this approach however. Whereas for Hepatitis B the epitope was already known, for HIV it was not certain which one would elicit the strongest immune response. Being a large glycoprotein on the HIV's surface, it was guessed that gp120 would be the most immunogenic.

Manufacturing gp120 in yeast raised problems (Pantophlet and Burton 2006). The protein yielded was not coated with carbohydrates; whereas it was in the wild (Wyatt and Sodroski 1998). This difference between the wild type and vaccine contravened a basic principle of

[6] Searches of the ISI Web of Science in 2006, and the accounts of Cohen (2001b) and Thomas (2001), have not returned any evidence of Chiron attempting to pursue whole vaccine approaches to HIV.
[7] A glycoprotein is a protein coated with small carbohydrate chains.

designing vaccines, which is to mimic the natural infection in order to elicit the strongest possible response from the immune system when it comes across the wild type virus[8] (Burton 1997).

A further problem with using this epitope is that truncated surface proteins unwind. Loss of conformational integrity is extremely important because protein recognition processes are highly discriminatory and specific to shape and form (Huang, Barchi et al. 1997; Stryer 1997). Antibodies would learn to recognise the unwound version, but remain less effective against the tightly coiled versions found on the wild type virus itself.

Despite these problems, Chiron had set itself along a subunit trajectory as it sought to emulate its previous market successes.

8.2.2 Genentech

Genentech was also looking to emulate Merck/Chiron's Hepatitis B vaccine by focussing genetic engineering techniques on envelope proteins of herpes simplex virus and HIV. Genentech was already a highly successful firm[9], and entered the vaccine business mainly through the research interests of its scientists rather than from a 'top down management strategy' (Thomas 2001:44).

In keeping with their popularity with the stock market[10], Genentech's strategy decisions were based firmly around profitability (Bass 1985; Stipp 2003). Genentech refrained from entering the vaccine market and emphasised therapeutic drugs because 'pills taken daily will earn more than vaccines every few years' (Thomas 2001:43).

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[8] However, staying too close to a wild type means that that the immune system is being prepared for a very specific response, which may be a disadvantage against a virus that varies rapidly (see also section 6.2.1).

[9] In 1972, biochemist Herbert Boyer of California University was working on restriction enzymes and geneticist Stanley Cohen of Stanford University was working on bacterial plasmids. Together they pioneered the recombinant DNA technology field (Cohen, Chang et al. 1973; Banting 2000). Boyer founded Genentech in 1976 with venture capitalist Robert Swanson (Genentech 2006). Within Genentech's first year, the company engineered the first human protein, somatostatin. The following year it engineered the hormone somatostatin regulates, human growth hormone (Bass 1985).

[10] Within an hour of Genentech's initial public offering in 1980, the stock jumped from $35 per share to $89 per share (Bass 1985).

Genentech's initial attempts were therefore focused on an AIDS therapy based around competitive inhibition of the gp120 receptors (Berman and Lasky 1985). The idea was to block the gp120 from docking with the CD4 immune system cells by flooding it with dummy docking stations. The rationally-engineered 'Soluble CD4' gave good results in the test tube and Genentech hailed it as, 'one of the most important steps we have ever been able to take' (Thompson 1988). But the approach did not work in vivo conditions because the virus could 'recognise' the difference and could selectively dock with genuine receptor sites (Berman and Lasky 1985). In this case, animals had provided a crucial change of conditions.

In the early 1980s it is likely that most of Genentech's resources were focussed on bringing their next big project to fruition, engineering human insulin. When they succeeded in bringing it to market, it was the first recombinant DNA drug and was licensed to Eli Lilly (Genentech 2006). Similar to Rutter's concerns about the public image of genetically engineered products, Genentech were concerned about their human growth hormone and insulin. Since they were used in young children, 'they needed them to appear as safe as milk' (Thomas 2001:34).

As such, Genentech did not want genetic engineering being linked with pathogenic viruses and did not allow HIV virus into their premises. One Genentech scientist recalls, "There was never any virus here, it was always the [harmless] nucleic acid. It was like we were fighting the battle with HIV with one hand tied behind our back" (Thomas 2001:34). All HIV research needed to be conducted in an annex (Thomas 2001). As was the case in poliomyelitis research, this scarcity of testing resources could only have hampered research efforts.

However, even with such top level discouragement from HIV vaccine research, some Genentech scientists pursued their own interests anyway and followed up with a vaccine similar to Chiron's gp120 vaccine. However, unlike Chiron who developed gp120 from yeast cells, Genentech used animal (Chinese Hamster Ovary) cells. This use of different

instrumentality resulted in the gp120 being glycosylated more accurately. Genentech found early success with the virus being neutralised in test tube and in inoculated mice. Phil Berman, scientist at Genentech, said, "It worked great in small animals and in test tube experiments, and then we rushed to test it in chimpanzees" (Thomas 2001:39).

The rushed experiment failed to protect against viral challenge. Despite a clear progression through intermediate conditions, learning in test tubes and mice, testing in the more realistic conditions of chimpanzees failed due to poor instrumentalities (instruments, skills and techniques). First, it is possible that the gp120 was not pure enough. Scaling up to chimpanzees meant that more gp120 was needed placing more demand on the purification process. Second, there was not enough time between doses according to Salk (Lasky, Groopman et al. 1986). HIV is quick to adapt and a partial immune system response is likely to have been evaded easily. Leaving more time between the doses might have given a stronger immune response.

The rush to move to testing on more chimpanzees was probably influenced by two broader factors. Firstly, Gallo published a study at the time that seemed to show chimpanzees to be a realistic animal model, where the human pathogen caused signs and symptoms that mirror human disease[11] (Alter, Eichberg et al. 1984). Despite the failure in chimpanzees, the results from preliminary tests in mice were enough to retain the attention of scientists working in a firm whose management focussed its interests elsewhere.

Secondly, there was a lack of skills and capabilities in testing vaccines in chimpanzees. Reflecting on their failure to schedule the immunisations and challenges correctly, the Genentech scientists said, "There were not more than a handful of people around who really had serious vaccine experience… we were just young and foolish and in competition, rushing blindly ahead. That was the whole spirit of the early days of biotechnology" (Thomas 2001:42).

[11] But, as section 7.3 showed, problems would emerge with the model later on, which meant that the model was not as ready-made as Gallo's study initially suggested. Results from the model need to be moderated because chimpanzees are more resilient to HIV infection and AIDS than humans (Koopman, Haaksma et al. 1999).

This feeling would seem consistent with the views of other commentators who criticise a broader ignorance of vaccinology and a loss of crucial competences and tacit skills (Goldberg and Salk 1984; Gandy and Zumla 2003). 'Expertise has been lost; the last generation of truly experienced 'field hands' are leaving the scene, lost to age and disuse. They are being replaced both in the West and in the research centers of the tropics by the 'molecular types,' more concerned with the exquisite intellectual challenges of modish science than with seeking practical solutions. The razzle-dazzle and promise of biotechnology….' (Desowitz 1991:16). The view that infectious disease had been defeated in principle was becoming prevalent in institutions of science and medicine, despite contrary warnings from many public health officials (Gandy and Zumla 2003).

Berman and his colleagues realised that the experiment could have yielded better results, so they persisted and tried again. The second was devised without the knowledge of management and, with the help of Jonas Salk from the older generation, the gp120 glycoprotein was purer and the immunisation schedules were less rushed. The vaccine was more successful as it managed to protect[12] chimpanzees from infection (Lasky, Groopman et al. 1986).

However, the vaccine received criticism on several issues. First, a less virulent HIV strain was used to challenge the inoculated chimpanzees. Second, the validity of the chimpanzee model was brought into question since they were found to be better than humans at fighting off HIV infection (Alter, Eichberg et al. 1984; Saxinger, Alter et al. 1987). These problems meant that the chimpanzee model was not as ready-made as Gallo's study initially suggested. Instrumentalities were required in executing the tests, and interpreting the results required skill. Results needed to be moderated to take into account that chimpanzees are more resilient to HIV infection and AIDS than humans (Koopman, Haaksma et al. 1999).

[12] Although the vaccine was protective, it provided only transient protection (Lasky, Groopman et al. 1986).

Genentech felt that even with these problems, the candidate held promise either as a therapeutic (treatment) or prophylactic (preventative) vaccine, and set itself on a subunit trajectory.

8.2.3 Other entrants and summary

Companies such as Vical, Oncogen, MicroGeneSys, Repligen, Virogen were all small biotechnology companies who were trying to establish their 'dynamic capabilities' (Teece, Pisano et al. 1997) around new emerging platform technologies. They were looking to apply their new techniques to attractive markets such as cancer or diabetes, and were willing to hope for a little luck in HIV research along the way. None of the entrants had the exclusive aim or dedicated goal of developing an HIV vaccine and few had any experience in developing vaccines (see also Batson and Ainsworth 2001).

In this setting, Salk's views and ideas were not generally received well[13]. To Salk, the human body was infinitely complex and the goal of science was to understand only what was needed to be known to solve problems and improve life for humans (Carter 1965; Goldberg and Salk 1984; Cohen 2001b). His intellectual curiosity in HIV did not reach beyond developing a way to stop it; just as his interest for poliomyelitis was intensely focussed on practical, pragmatic, technological concerns. His approach was seen as crude and perhaps out-dated by the scientists adopting the subunit approach. Largely on the strength of his name, Salk quickly raised $20m to start a biotechnology company of his own, focussed entirely on developing an HIV vaccine[14]. On its initial public offering, Immune Response Corporation managed to generate $100m (Thomas 2001:54). It was a seemingly large amount, but the company still needed to operate in the same, expensive, testing regime that other companies and public actors were working in.

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[13] However, they were received well by activists who wanted to see a sense of urgency in scientists' endeavours. For example, one activist newsletter contended, 'in the context of a raging epidemic… How much does one have to know about the scientific nature of combustion when the house's burning down?' (quoted in Epstein 1996:272).

[14] Salk began with an idea to immunise seropositives (people who had already been HIV infected) on the suspicion that a vaccine might boost their immunity to the virus (Salk 1987). This effect had been shown for rabies infection by Pasteur over a century ago (Plotkin and Orenstein 2004). The company today has several whole-killed HIV preparations in Phase II trials intended to boost the immunity of those who are HIV infected patients (ImmuneResponseCorporation 2006).

8.3 Why did gp120 rise above the other approaches?

One might expect all of the various approaches to have been developed somewhat evenly until formalised testing revealed that one approach was better than the other. But this does not seem to have been the case[15]. Chapter 7 discussed weaknesses in the testing regime in HIV vaccine development. Section 8.1 explained how these weaknesses dealt their heaviest blows to whole-virus approaches. Section 8.2 suggested that there was a lack of cumulative and shared knowledge growth between Chiron and Genentech. This meant that, in the absence of incremental improvements driven by regular comparative testing, other factors helped select the subunit approach, and along with it gp120 as its operational principle. This section discusses these factors.

Previewing the next chapter, it is worth noting here that whilst weaknesses in the testing regime at early stages of the vaccine development cycle allowed gp120 to establish dominance, it was recognised as ineffective and dropped later in the vaccine development cycle, when it encountered a stronger testing regime. But by this stage, considerable time and resources had been wasted.

The rise of the subunit approach is even more striking given that the only vaccine that had hitherto followed this approach was for hepatitis B[16]. All other vaccines have been made using whole approaches, as noted in section 8.1. One historical achievement was given preference over others on the basis that it was 'newer' technology. Other approaches were untestable due to safety concerns and were given little credence. 'The rapid development of an AIDS vaccine seemed a realistic goal in light of the remarkable advances in molecular biology…The highly effective hepatitis B vaccine…seemed to be the natural model for a vaccine…Unfortunately extrapolation from the hepatitis B model proved to be

[15] See also Klein and Ho (2000:308), who note, 'The possibility of using inactivated virus as the source of an HIV vaccine has been insufficiently investigated.'

[16] The subunit approach has been used to develop an effective influenza vaccine as well, but it is not as good as other influenza vaccines, and is only used in children who may be at more risk to adverse reactions. Hepatitis B is still widely regarded as being 'the landmark example of a subunit vaccine' (Klein and Ho 2000:308).

inappropriate because hepatitis B surface antigen is conserve' (Hilleman 1995:1126). The previous chapter showed that HIV's surface antigens were known to undergo extreme variation and such an approach was unlikely to work because the vaccine would be too different from the wild type pathogen.

Nevertheless, the period of 1984-1995 was characterised by an almost exclusive focus on the subunit approach[17]. Extreme viral variability was the eventual downfall of the approach, but many researchers still held the notion that a non-variable region could be found, especially in the V3 loop, a neutralising domain of the virus. Targeting this loop was a form of ultra-reductionism, given that the V3 loop is only 35 amino acids long[18] (Catasti, Fontenot et al. 1995). The belief in the subunit approach, and consequent focus on the V3 loop, has implications for HIV even today because the V3 loop is the basis of the existing typology of HIV variants (discussed later).

Although the early exclusive focus on the subunit approach is acknowledged, Klein and Ho (2000:308) are amongst those who try to justify it[19], 'Initial HIV vaccine design focused on the proteins expressed on the virus surface (V3 loop, gpl20, and gpl60). This was a logical first choice, because… targeting surface antigens was highly effective in producing the Hepatitis B vaccine.' Hilleman (1998:787) says that 'the zeal' of the subunit approach overlooked strain diversity at its peril, and that the failure of the V3 approach was 'predictable' given experiences with the diversity of influenza surface antigen.

Viral diversity and the lack of natural sterilising immunity affected the various approaches differently. The lack of natural sterilising immunity undermined the safety of whole-virus vaccines. In contrast, the subunit approach was safer because it relied on small antigenic

[17] Hilleman (2000a:352) calls it 'a near exclusive' search for 'antibody against the hypervariable surface antigens of the viral envelope.'
[18] The 1st and 35th amino acids are invariable cysteine residues forming a disulphide bridge between the two ends of the loop. The rest of the structure seems conservative relative to other parts of the virus, but is still so variable that up to 12 different amino acids may be found in any one position within the sequence (Klein and Ho 2000).
[19] Many other researchers invoke the success of Hepatitis B vaccine (see for example Moore and Anderson 1994).

parts of the virus, but it was most susceptible to ineffectiveness through viral diversity and hypervariablity.

Whilst problems of safety and the lack of sterilising immunity were acknowledged by those pursuing whole-virus approaches (discussed later), problems of diversity were downplayed in several ways by advocates of the subunit approach. One was a belief that a conserved region would be eventually found but another was that subtype diversity was geographically specific so different vaccines could be made for different geographical regions. Both of these assumptions were unprecendented in vaccine development for other viruses. 'Because phylogenetically diverse HIV subtypes are prevalent in different geographic locations, the use of HIV subtype-consensus sequences as vaccine immunogens have been proposed as a scientifically justifiable and feasible approach toward trying to diminish the problem that diversity poses against selecting relevant antigens for inclusion in candidate AIDS vaccines' (Garber, Silvestri et al. 2004:405).

In addition to global health equity implications[20], this raised the prospect of needing to achieve the 'impossible' not once but several times. The answer to this - somewhat optimistically – was that the subunit technology might find a way of provoking an immune response strong enough to deal with the diversity problem. 'This misguided choice of target antigen' coupled with 'the unfortunate intent to achieve a high level humoral antibody response' meant that 'the pursuit of the AIDS vaccine was one of initially serious flaws'[21] (Hilleman 2000a:352).

Meanwhile, there were reasons to think whole-virus approaches might prepare the immune system for diversity better than subunit approaches. However, the development of such

[20] This had rather worrying implications for developing countries. The head of AIDS vaccine development at WHO, Joe Esparza, warned that developing countries would need products designed specifically for them, 'There's a need here to encourage manufacturers to make strain specific vaccines' (Cohen 1993a:981). Advocates such as IAVI further argued that whilst R&D incentives for an HIV vaccine were weak generally, they were woefully inadequate or non existent in poorer countries.

[21] Hilleman (1998:786) goes so far as to call it a 'spurious dedication to achieving humoral response against surface antigen.' As explained in chapter 5, the humoral antibody response deals neutralises pathogens outside of cells, before cells might be infected.

approaches were stalled because the testing regime was particularly ill-equipped to deal with the safety issues raised by the lack of sterilising immunity (discussed later).

8.4 Chasing the cellular response: second round approaches to the HIV vaccine

Even with highly successful vaccines *complete* sterilising immunity is seldom achieved, and some cells become infected and must be removed. 'Because some HIV variants might escape our best efforts at sterilising immunity, and a low level infection could occur, a cell-mediated immune response that generates killer T cells that can eliminate the few infected cells should be part of the vaccine strategy' (Gallo 2005:1897). 'Although vaccines that stimulate the cellular arm of the immune response are not expected to provide protection against infection, they should allow vaccinees who get infected to control virus replication and reduce viral loads, thus resulting in lower probability of virus transmission to seronegative partners' (Girard, Osmanov et al. 2006:4068).

By the late 1990s, the rationale for a cellular response had become strong and widely recognised[22]. This section describes attempts to address the cellular response. The essence of the problem was to find a delivery vehicle that could enter into cells, carrying the kinds of materials that would trigger an immune response to kill infected cells. Rather than lead to more intense development of whole-virus approaches, as Hilleman had hoped[23], this process led to even more sophisticated recombinant techniques; and amongst these, the subunit approach still reigned.

[22] This contrasts with aiming for a very strong humoural antibody response alone and hoping that no cells would be infected at all. 'The period 1994-1995 gave *belated* recognition to the role of CD8+ T lymphocytes in destroying virus infected cells and in suppression of viral replication by cytokines' (Hilleman 1998:787).
[23] Hilleman wrote in 1995, 'The tool of molecular genetics, which had been the central driving force in vaccine research in its decade, has now become subservient to the larger view of the biology of AIDS.'

8.4.1 Vical and DNA Vaccines

In 1987 Vical was established as a spin-off from University of California on the basis of a new idea at first derided[24] but one which Vical now refers to as its 'core technology' (Vical 2006b). It was initially developed to improve gene therapy (Felgner 1997), particularly for cancer, but there have been toxicity problems for the development of any oral drug possibilities (Filion and Phillips 1998).

The aim was to package specific bits of DNA, using a positively charged fat vesicle as carrier, so that it would be drawn towards negatively charged membranes, and thereby into cells (Duzgunes and Felgner 1993). However, it was realised that DNA was being drawn into cells without the need for such packaging.

Once inside the cell, the DNA could be expressed as protein and transported back to the cell surface. Although the amounts of expressed protein were not enough to treat diabetes or cystic fibrosis, it was thought possibly enough to stimulate a cellular immune response (Cohen 1993b; McDonnell and Askari 1996; Weiner and Kennedy 1997).

When it was confirmed that DNA, on its own, could be drawn into cells and stimulate a response (Vical 2006a), Vical believed they were on the cusp of developing a new vaccine delivery method and quickly filed for a patent[25] (Wolff, Malone et al. 1990; Tang, DeVit et al. 1992). However, Vical encountered problems when they needed further finance to develop the operational principle. 'Any company that we went to had to be interested in developing vaccines, and there weren't that many' (Thomas 2001:63).

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[24] "We were considered out on the fringes of science," and "People would laugh at us, or abuse us publicy for our presentations." (DNA vaccine researchers, quoted in Thomas 2001:74).

[25] Vical's scientist said, "As soon as we got the naked DNA results, we knew that this was quite different from a business and from a patent perspective. Nobody was doing anything with naked DNA, so we had a blocking position that was very broad. And when you start a biotechnology company, that's what you're looking for" (Thomas 2001:56). Such defensive patenting strategies have been noted and discussed (Freeman 1982). For this analysis however, it serves to show that biotechnology companies were more concerned with their own survival through the establishment of platform technologies, than with HIV vaccine innovation.

They approached Merck whose vaccine division was headed by the well established vaccinologist Maurice Hilleman[26] (Galambos and Sewell 1995:238). With Merck's funding, Vical began developing the new vaccine approach. Vical scientists immunised mice with influenza genes, looked for immune responses and then challenged them with influenza virus. The reason they used influenza genes and virus was because mice resist infection with HIV. As Thomas (2001:58) puts it, 'nature has made mice safe from AIDS.'

The experiment was successful, in protecting mice against influenza virus better than control mice, but convincing Merck to continue support was difficult (Ulmer, Donnelly et al. 1993). 'One reason it took so long was that [Vical and Merck] were on different coasts. It's much easier to show somebody how to do it than to describe how to do it[27]' (Thomas 2001:69). Even after achieving successful replication of the mice experiments, there was still not much to suggest that the approach would work with influenza in humans, let alone with HIV in humans. The fact that there were no tests using primates or HIV meant that the effectiveness of the approach could not be compared to the dominant subunit approach, which at the time was being tested in macaques by Chiron and in chimpanzees by Genentech, itself another issue of comparability.

Chapter 7 took a different position to Thomas in arguing that animal models need not be seen as unchangeable 'nature has made' models, but as man-made technologies that can be deliberately developed and refined. Even without resorting to the use of chimpanzees or monkeys, efforts to develop a mouse model that was more suitable (for example by making it HIV-infectable) might have made judging the potential of this approach as compared to the subunit approach easier.

Instead, Vical faced intra-firm competition for resources as a new drug, a protease inhibitor, was being developed at Merck. There was a large incentive for a new drug because of increasingly apparent shortcomings of AZT, the reverse transcriptase inhibitor (Epstein

[26] Hilleman's enthusiasm for eliciting both cellular and humoral immune responses was critical in Vical striking a deal with Merck. "If he had been against it, we definitely would not have gone ahead, that's for sure. But he was really keen on it, and that's what it took at Merck Vaccine at the time" (Thomas 2001:68).
[27] The experimental procedure clearly contained tacit knowledge that was difficult to codify (Senker 1995).

1996:241), including severe side effects and that it did not work in a growing number of people. Merck's new drug was going through clinical trials, the most expensive phases of drug development, (Young, Anderson et al. 1990; Wlodawer and Vondrasek 1998), and most likely used much of its AIDS budget with little left over to develop Vical's approach.

8.4.2 Viral Vaccine vectors

Vaccination with vaccinia[28] virus was directly responsible for smallpox eradication (Levine, Kaper et al. 2004). Its potential use as a carrier for delivering foreign genes was explored in 1979 by Paoletti and Panicali in a New York state laboratory[29]. The idea was to insert cloned HIV genes into the viral vector as a delivery mechanism to cells in order to elicit an immune response.

The approach held theoretical and practical advantages (Panicali and Paoletti 1982). The theoretical advantage was the greater likelihood of prompting a cellular response[30]. The practical advantage was that engineered vaccinia injected into the body could make the HIV protein inside human cells, rather than in yeast or hamster cells. So there was no need for separation or purification in the production process. Furthermore, the protein would be glycosylated in its native configuration, helping to provide a more effective immune response.

Paoletti and Panicali did not, however, have access to HIV – it was a scarce testing resource, a weakness of the testing regime identified earlier (6.6.1). As with Vical, researchers had to progress with the development of the new approach on non-HIV pathogens. These viruses, more feared by the public at the time, were herpes (Panicali and

[28] Vaccinia can be thought of as the Escherichia coli of viruses. It has been the workhorse of virology and has been much manipulated and studied (Stryer 1997; Plotkin and Orenstein 2004).
[29] The application of this new technique had been delayed because the regulatory framework governing genetic engineering was so poorly formed. Boyer-Cohen's experiments were only six years old at the time, and fears about the technology were precautionary (Thomas 2001:83).
[30] because proteins would be made inside cells and exported to cell surface.

Paoletti 1982), influenza (Panicali, Davis et al. 1983), and hepatitis B (Paoletti, Lipinskas et al. 1984)[31].

The New York Health Commisioner, David Axelrod, hailed the new approach a result of the state's long term investment in basic biomedical research. Axelrod helped set up a spin off, called Virogenetics, to claim patents and exploit the technology further. However, with only incomparable results on viruses other than HIV, the firm struggled to find finance.

Paoletti and Panicali sought to set up a collaborative agreement in which they could find finance and could access cloned HIV genes to splice into vaccinia. They tried to source some from Montagnier, the French discoverer of HIV at the Pasteur Institute, but he declined to share his clones for the new vaccine idea[32]. Paoletti said, 'It wasn't that they didn't want to deal with Americans, it was that they wanted the vaccine to be a French effort' (Thomas 2001:88). In terms of virus and finance, the firm remained undercapitalised for several years. This, coupled with regulatory system delays, meant that progress was slow and allowed others to become involved in the development of the technology.

One of those who was quick to appreciate the potential of vaccinia was Lok Hu. Hu had just been recruited by Oncogen, a subsidiary of Genetic Systems Corporation, and his remit was to develop novel diagnostics and treatments for cancer. However, he did not have a project ready to get involved with, so he worked with what was at hand. By chance, the Pasteur Institute had sent Genetic Systems their gp160 clones to develop and market its version of the HIV blood test. 'These were the very HIV genes that Paoletti had tried and failed to obtain from Montagnier' (Thomas 2001:89). Hu inserted the gp160 into vaccinia constructing an impromptu HIV vaccine candidate. Oncogen's entry into the HIV vaccine

[31] Infact the possibility for delivering genes from multiple pathogens in one vaccine, making vaccinia a polyvalent vector, made the technique very popular and excited public health officials (Perkus, Piccini et al. 1985).

[32] Although Paoletti does not mention it, it is possible that the French American dispute between Gallo and Montagnier over the ownership of credit for HIV discovery and patent rights had a bearing on Montagnier's decision to decline.

sector was thereby circumstantial and could be described, at best, as researcher motivated[33] rather than part of a corporate strategy, or indeed any form of R&D governance.

Similar to the Vical-Merck case above, Oncogen's vaccine approach faced intra-organisational barriers as Genetic Systems allowed Lok-Hu to follow his interests initially, when resource requirements were minimal, but were mainly interested in targeting the cancer market. The success of Genetic Systems in the cancer drugs market however attracted the pharmaceutical firm, Bristol Myers Squibb, to purchase the company, along with its subsidiary, Oncogen. Hu made it clear that Bristol was not keen on his project in later interviews with journalists (Cohen 2001b:55; Thomas 2001:90), but the pharmaceutical company did let the project continue alongside his principal work on cancer vaccines[34, 35].

To develop the vaccinia approach further though, the developers would need to resolve testing problem related to its past use. The successful smallpox eradication programme had already introduced vaccinia to much of the world, and it was possible that people who are smallpox immunised might still mount an antibody response to it. Thus, the materials relevant to stimulating an HIV immune response (the vaccine) might be stifled by an antibody response to vaccinia (the carrier).

So the test needed to be designed so that it included people who were smallpox immunised and those who were not (Corey, Collier et al. 1989). They also needed to give the smallpox vaccine to half the volunteers and the trial vaccine to half so that they could distinguish how much of the immune response was to vaccinia (the carrier) and how much was to the gp160 (the vaccine) (Corey, Collier et al. 1989).

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[33] See also Augdorfer's (1996; 2005) analyses of bootlegging in R&D.

[34] "Bristol has all along taken a semi-interested [position], tolerated more than anything else. We're just a bunch of guys fooling around. We clearly generate publicity based on our work, but does Bristol need that? I doubt it. Number two, it might not want it. But really, it comes down to a bottom line with vaccine: because of the liability and because of the business of vaccines in general, big companies like Bristol, for that matter most of the companies shy away from it" (Hu, quoted in Cohen 2001b:55).

[35] Hu published his findings extensively, and perhaps made it harder for Bristol to terminate the project. His initial monkey experiments showed T-cell responses that were strong enough to support a clinical study (Chakrabarti, Robert-Guroff et al. 1986; Hu, Kosowski et al. 1986; Zarling, Morton et al. 1986; Hu, Fultz et al. 1987).

The results were encouraging enough to be reported in the *Lancet* favourably, but it was not the blockbuster the researchers hoped for (Cooney, Collier et al. 1991). The vaccine managed to stimulate a transient cellular immune response but no antibody response at all in vaccinia-primed subjects. A significantly stronger cellular immune response was observed in vaccinia-naïve subjects but again, no antibody response was detectable and the cellular immune response was transient. However, when followed with gp160 subunit vaccine in a prime-boost immunisation schedule, antibodies were stimulated.

The vaccine was concluded to be of value only to a vaccinia-naïve population (Cooney, Collier et al. 1991). Considering that the smallpox eradication programme had so successfully managed to immunise a large number of people, this fact served to shrink an already small potential market for investors. Furthermore, there was concern that the vaccinia vector may become virulent and re-introduce smallpox, despite there being little evidence from the vaccine trials to support this possibility.

It would seem then that unfavourable issues can emerge even from a programme widely acknowledged to be a success, like the smallpox eradication programme. Indeed it is precisely the success of the programme that made, firstly, so many people vaccinia primed and, secondly, the risk of reverting to virulence loom so large for potential investors. At this point Bristol withdrew its support for the project[36].

Other viral vectors were searched for, with special consideration given to the viruses that were unable to replicate in humans to allay fears of any vector virulence. In 1986, Axelrod and Paoletti managed to persuade Charles Merieux of the Pasteur Merieux Institute to invest in the undercapitalised Virogentics[37]. With the new money Paoletti and his team

[36] However, as the years after smallpox eradication passed, the proportion of the population who would be vaccinia naïve would also be increasing, making this approach one that would not be forgotten. Swedish researchers have recently run a vaccinia based prime-boost HIV vaccine through Phase I with strong results (MedicalNewsToday 2006).

[37] The Pasteur Merieux Institute bought out 51% of Virogenetics (Cohen 2001b:237). In 1989, Pasteur Merieux increased its share to 85%.

explored other vectors such as fowlpox, and canarypox[38, 39] (Cox, Tartaglia et al. 1993; Paoletti 1996).

In 1989, Pasteur Meriuex acquired Connaught Laboratories to become the world's largest vaccine company[37]. This resulted in Pasteur Merieux's HIV vaccine project portfolio increasing from one to four. The increase in resource competition, coupled with Axelrod's death in 1989, deteriorated relations between Pasteur Meriuex and Virogenetics.

Pasteur Meriuex Connaught's director, Stanley Plotkin, believed that the viral vaccine vector technology could only work in a prime-boost approach where, following canarypox immunisation, a gp120 boost would also be administered (Salmon, Excler et al. 1994). Pasteur Meriuex Connaught's strategic priority, to the frustration of Virogenetics[40], was to keep options open and wait for NIH to fund clinical trials into one of the approaches rather than to invest in comparing and selecting any single approach.

[38] Fowlpox was safer than vaccinia because it could not replicate in humans, and could be more lucrative in the veterinary sector. Similarly canarypox was also safer and expressed more antigen.

[39] The US Army, in the interest of protecting troops, provided New York State university with a grant to study the Venezuelan Equine Encephalitis (VEE) virus as an alternative vector to vaccinia (Thomas 2001). VEE might have been appropriate for two reasons (Johnston, Johnson et al. 2005). Firstly, the virus stimulates an immune response in mucosal surfaces. Secondly, it has a high affinity for lymph nodes, which correlates with a response from both arms of the immune system. For safety concerns, they made the vector unable to replicate (Grieder and Nguyen 1996; Caley, Betts et al. 1999). This resulted in a lower antibody response than that of the replicating version. Furthermore, the word encephalitis in the vector was thought to have exacerbated concerns about the vaccine's public image (Caley, Betts et al. 1999:108; Thomas 2001). So the project was denied further money and the researchers following this approach found no other sponsors (Thomas 2001).

[40] There were arguments about the viability of the prime boost approach because Paoletti wanted to test canarypox without the subsequent boost because he felt it was not necessary. Plotkin was convinced that both humoral *and* cellular responses would be needed in a successful HIV vaccine. There were also arguments about evaluating the results of experiments and arguments about manufacturing (Thomas 2001).

8.4.3 Summary

The private sector efforts to develop an HIV vaccine were lacklustre and narrowly focussed on biotechnological processes. 'An aggressive effort would test and adapt many AIDS candidate vaccines in parallel. However, few companies were pursuing multiple options and a number of approaches appeared to be shelved before their potential value had been determined' (Batson and Ainsworth 2001:724).

To explain the investment decisions, one needs to examine, as this thesis does, the technical problems faced by the companies and their previous experiences. Market pull explanations are particularly weak in such situations because if these problems are perceived by the companies, correctly or incorrectly, to be intractable, the size of the reward becomes irrelevant.

Similarly, if the perceived time to commercial revenue is long and far away, any rewards that may accrue is substantially discounted, thus relegating market characteristics and policies when considering investment. Accordingly, even by 1998, 'fewer than 200 scientists in the private sector were dedicated to work related to HIV vaccines, and some of them were probably supported by grants from the public sector. The private funds dedicated annually to R&D on AIDS vaccines were estimated to be between $50m and $124m' (Batson and Ainsworth 2001:722).

Although the more standard approaches to developing a vaccine had been claimed by Chiron and Genentech, small biotechnology companies continued to come up with new approaches. Two key technologies were naked DNA vaccines and viral vector vaccines, but the companies involved were severely constrained by the scarcity of testing resources, in terms of access to plentiful virus and animals as well as money. The lack of organised comparability between preliminary experiments most likely hampered the ability to sell their approaches to investors despite the stock market's fondness for biotechnology companies at the time. In addition, the vaccinia-based approach faced some unusual challenges of previous vaccinia use. It was also a time of biotechnology company take-overs by large pharmaceutical houses and with this, companies such as Vical, Oncogen and

Virogenetics had their aspirations for developing the new vaccine approaches quashed by the larger firms who were much clearer and more explicit about avoiding high-risk, low-return projects such as HIV vaccine research.

Despite belated recognition of the need for a cellular response, and the potential of these refinements to the subunit approach to provide a cellular response, the original gp120 subunit approach was still the one that reached clinical efficacy trials. This is discussed further in the next chapter. With little comparability between the approaches, and few instruments to learn safely, gp120 vaccines remained in the milieu. The next section shows how the other approaches would effectively drop out of the running.

8.5 The subunit approach becomes the last approach standing: selection by testing?

The dominant approach was centred on the hope that genetically engineered pieces of the HIV virus would be enough to trigger an immune response, perhaps with the help of a vector. As discussed, live-attenuated and whole-killed vaccine approaches were not commonly considered as feasible options. However, in the early 1990's, two research groups were developing vaccines that caused a rethink: James Stott's whole-killed vaccine and Desrosier's live-attenuated vaccine.

8.5.1 The whole-killed approach is killed off

The UK Medical Research Council co-ordinated a programme between two primate research groups run by James Stott and Martin Cranage[41] (Stott, Chan et al. 1990; Cranage, Stott et al. 1994). They were developing a whole-killed SIV vaccine with monkeys and found considerable success as their vaccine prevented infection from an intravenous challenge with SIV (Stott, Chan et al. 1990). They then pushed the vaccine further by testing in more rigorous conditions. It withstood more realistic situations as rectal challenge and mismatched strains[42]. Even without the confidence that comparative testing brings, most considered this vaccine to have provided much better results than subunit vaccines (Cohen 1992a).

Stott's vaccine was developed by growing SIV in human cells and then killing the whole mixture. Compared to separating the virus out from the cells they were grown in, then purifying the virus, and then killing the pure batch of virus, this was a much cruder one-step approach (Stott 1991). The resulting vaccine was essentially human cells with killed SIV. It was unlikely to be deemed clean enough to consider for human use, but the protection it achieved in monkeys was exceptionally good[43].

Then the group gave control monkeys human cells alone, with no SIV in them. The results astonished them so much that they wrote to *Science* noting, 'We are performing definitive experiments to confirm these observations…In the meantime, we wish to publish our unexpected findings quickly so that others working with SIV in macaques or HIV in chimpanzees can evaluate their results in the light of this information' (Stott 1991:393).

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[41] Hollingsworth's (1986) study of medicine in Britain and America notes differences in the styles of medical research between the two countries. Over the course of the twentieth century British research has been smaller, more centralised, more co-ordinated, and less competitive. Since the National Health Service came into existence research has also been more tightly linked with clinical practice (Hollingsworth 1986:222; see also Hopkins 2004). James Stott was based at the National Institute for Biological Standards and Control in Hertfordshire and Martin Cranage, at the Centre for Applied Microbiology and Research in Salisbury.

[42] Rectal challenge is innoculation of HIV through the rectum after vaccination (see also Sabin 1992). The term mismatched strains refers to conditions where the strain used in the vaccine is different to the strain used to challenge.

[43] Stott's previous publications indicate a background in developing veterinary vaccines where such an approach would be more acceptable (Brown, Newman et al. 1974; Nyack, Willard et al. 1981; Osburn, McGowan et al. 1981; Osburn, Stott et al. 1982; Stott, Scibienski et al. 1987; Angel, Stott et al. 1991).

What they found was that two doses of the vaccine protected three of four monkeys against subsequent SIV challenge. But crucially, two of four control monkeys did not become infected either (Stott 1991). The key principle that allows us to understand this result is that immune systems, whether they are of humans or monkeys, develop the strongest reactions to the things that are most foreign to them. This meant that the monkeys developed a strong antibody response to human cells, and since this was given to both test and control monkeys, both groups were primed in this way. So when control monkeys were subsequently challenged with human cells containing SIV, they were partly protected, albeit not as strongly as vaccinated monkeys.

Stott repeated the experiment with purified virus (virus with no human cells), but still got the same finding. This was because the virus was grown in human cells and it incorporated human cell proteins into its own structure[44].

The New Scientist's report on these results did not shy away from declaring the implications (Brown 1991; Maddox 1991). The control monkeys' antibodies explained away the protection seen in all vaccines where the virus had been grown in human cells. And since all primate researchers grew SIV this way, it brought into question all SIV vaccines. They were all contaminated. Its opening sentence, 'The search for an AIDS vaccine was thrown into disarray with the disclosure of stunning findings..' (Brown 1991:14) and the article's accompanying cartoon reflected a mood of disorganisation (figure 7).

[44] The protein shells (capsids) of SIV and HIV contain pieces of the host cells which they infect. As these viruses infect a cell, they abandon their capsid and inject their genetic material. The genetic material then integrates with the human cell's chromosome and codes for new viral proteins to be synthesised. These proteins assemble into a new virus which buds from the cell surface. During exocytosis, the virus incorporates some of the cell's proteins into its capsid. The virus therefore has both viral proteins and cellular proteins in its capsid regardless of whether it is purified afterwards or not.

Figure 7: SIV shock

Source: taken from Brown (1991).

Jonathan Weber[45], said he was 'gobsmacked' by the findings but, in response to criticisms about the MRC's overemphasis on the study of monkeys, defended the MRC, 'These findings prove there is a point to animal models. Although this hiccup is extremely important it is better that it happened in animals than in man' (Brown 1991:14). After testing in animals, Weber was perhaps hoping for incremental improvements and redirection of the approach rather than a response of abandonment.

Other scientists were angry that the vital control experiments had not been done earlier but Stott countered that everyone tries to minimise the number of monkeys they use, 'It's terribly easy to say that afterwards, it would have been such a bizarre experiment to suggest. You have to try and save animals' (Brown 1991:14). Similar to Weber's hope for refinement, Stott cautioned, 'Some people will view this negatively; I think it is also opening things up. The new finding could turn out to be very important…' (Brown 1991:14). Stott's and Weber's comments illustrate the importance of having firstly, access to cheap testing, and secondly well developed animal models. These issues were flagged in the theoretical framework of chapter 3, also emerged in the account of poliomyelitis vaccine development provided in chapter 6.

[45] Jonathan Weber is a Professor of communicable diseases at St Mary's Hospital in London and directed Britain's only human trial of a potential AIDS vaccine (Brown 1991).

Subunit researchers, such as Bolognesi's group, promptly capitalised on Stott's findings (Langlois, Weinhold et al. 1992). They analysed antibodies in blood from 200 monkeys used in vaccine experiments and showed high levels of human cell antibodies in those that had received whole-killed vaccines. After acknowledging that 'whole-killed SIV preparations induce the strongest and most consistent protection thus far experienced in experimental animal studies,' the paper concluded that more research was necessary into understanding how protection induced by inactivated SIV preparations was achieved (Langlois, Weinhold et al. 1992:293).

An alternative reaction to Stott's results would have been to harvest SIV in monkey cells and use the resultant virus both to make whole-killed vaccines and challenge stock (Cohen 2001b). This monkey-monkey approach to vaccinating and challenging would represent technological conditions more accurately. This is because if a whole-killed vaccine was to be used in humans, it would be made by growing HIV in human cells whilst the wild type virus that exists out there to 'challenge' the immune system would also be grown in human cells.

In order to pursue this approach, however, there was an instrumentality problem that needed to be resolved. Techniques for growing virus rely on immortalised cell lines. These cell lines carry mutations that make them more like cancer cells than normal cells in that they live longer and copy faster (see section 5.4.2). These characteristics are required for growing SIV because the cells need to replicate faster than the SIV can kill them. Many such cell lines exist based on human cells, but none existed for monkeys. This is the reason why all the vaccines featuring SIV had been grown in human cells.

Stott and Cranage did subsequently manage to grow some SIV in monkey cells, but only to use it to challenge monkeys vaccinated with human grown SIV (Cranage, Polyanskaya et al. 1993; Stahlhennig, Voss et al. 1993). It served only to emphasise their results more severely as they did not take the opportunity to vaccinate with monkey-grown virus. It is possible they did not have enough monkey-grown SIV to do both vaccination and challenge

because growing SIV in monkey cells is a difficult task without an immortalised monkey cell line.

These experiments, and also those of Le Grand, Vogt et al. (1992), confirmed the idea that earlier attempts were successful largely because of antibodies to the human cells. But the experiments effectively obscured the need for the monkey-monkey challenge and contributed to a sense that the whole-killed approach was no longer worth pursuing. My searches from 1984-2007 have not returned any records of a full scale monkey-monkey SIV vaccine experiment (see also Cohen 2001b).

Another scientist, Murphey-Corb, recounted her attempt to conduct a monkey-monkey experiment without the aid of an immortalised cell line (Cohen 2001b:126). After nearly a year of hoarding the spleens of SIV infected monkeys that died from AIDS, she had enough to make a vaccine. "I spent a considerable fortune and time trying to make virus." But it was too impure and the resultant vaccine "was really crap" to even stimulate an immune response. Murphy-Corb soon gave up and changed research focus[46].

The way in which the Stott paper was handled suggests that a stronger testing regime was needed. More liberal use of monkeys might have allowed the vital control experiment to be conducted earlier. Instrumental research issues such as the development of a monkey cell line for the purposes of harvesting SIV might have been made an explicit priority, in order to make comparisons and draw out implications for human vaccines. These are specifiable goals and are therefore amenable to strategic contracting. Since monkeys have been farmed before and many cell lines have been developed before, they are likely to be feasible too. The failure to overcome such hurdles suggests that the testing regime is inadequate, making

[46] Murphy-Corb says "I didn't want to be sacrificed. Everyone took Stott's work and said, 'OK, this vaccine is not doable.' You have to respect their opinion. I abandoned my whole-killed vaccine work. Tons of stuff never got published. I literally wiped off three years of my life…I've always had a personal sense that I should have hung on longer" (Cohen 2001b:126).

it harder to evaluate progress regularly through a reliable, comparative and iterative process of testing various operational trajectories[47].

8.5.2 The social framing of contaminants and populations

One group of researchers, led by Arthur, raised the possibility of a new vaccine approach. They found the surfaces of HIV and SIV had more cellular proteins than viral proteins, explaining why cellular proteins had played such a significant role in Stott's results (Arthur, Bess et al. 1992)[48]. But rather than considering them contaminants, cellular proteins could serve as a critical part of the operational principle, because HIV will contain human proteins that may stimulate an immune response in other humans[49].

Re-framing the contaminants, Arthur vaccinated two monkeys with only human cellular proteins and then challenged them with SIV grown in human cells (Arthur, Bess et al. 1992; Arthur, Bess et al. 1995). They found that monkeys did not show signs of infection. This implied that a human vaccine could be made using cellular proteins rather than just viral protein gp120.

However, the monkeys' immune systems were more likely to have been responding because the proteins were from a different species (humans). Thus, to explore the potential of this approach further, a testing regime with humans was required. Otherwise, the species difference is likely to be the cause of the immune response more than anything else. The scope for intermediate conditions is very small in this operational trajectory. Another

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[47] Stott and Cranage continued to pursue the whole-killed SIV vaccine (Almond, Kent et al. 1995) but the approach was dogged by criticism about its safety and unworthiness as a human trial candidate (Baba, Liska et al. 1995; Ruprecht, Baba et al. 1995).

[48] The number of gp120 molecules on the surface of each virus had already been estimated at 216 (Racz, Dijkistra et al. 1991 cited in Arthur, Bess et al. 1992). These proteins were viral because they were produced along with the rest of the virus inside the cell. Arthur's paper, however, asked how much cellular protein was incorporated into the surface of the virus during or after exocytosis. After purification and separation they found 'that there are between 375 and 600 molecules of β_2m and HLA DR (α and β chains) per virion' (Arthur, Bess et al. 1992:1936).

[49] Arthur's conclusion indicated that this result could be taken as the basis for the design of a new operational principle. 'cellular proteins [are] an integral functioning part of the viral envelope… which should be considered in the elucidation of steps involved in infection, design of vaccines, preparation of experimental virus-challenge stocks' (1992:1938).

alternative might have been to use proteins from a different monkey, but as already noted, instrumentalities for growing SIV in monkey cells had not been developed.

There was also a theoretical problem with this approach that involved how vaccine designers frame the broader needs of populations to be vaccinated. Organ transplants can be problematic because people's immune systems reject the transplanted tissue as foreign. Injecting people with this kind of vaccine would severely limit their options if they needed a transplant because their immune systems would be primed to attack any new substance or proteins from other humans. However, Shearer et al. (1993) pointed out that 'in some parts of the world, effective immunisation against HIV infection might take precedence over the unlikely prospect of a future organ transplant.'

Shearer et al. cited a study amongst prostitutes in Kenya who were exposed but uninfected by HIV (Fowke, Nagelkerke et al. 1996; Rowland-Jones, Dong et al. 1998). The extremely rare protein on their blood cells, Shearer et al. posited, allowed them to elicit a stronger than normal immune response when confronted with the cellular proteins on the virus of an average person. They implied that it was a target model on which they could base vaccine design.

So there existed not only animal, but human data suggesting that this idea is at least promising. But the approach succumbed to testing constraints. The idea was not integrated into a co-ordinated research programme and attempts to explore further the potential of the approach by strengthening the testing regime were not undertaken. For example by reframing safety risks (Institutions), or developing monkey grown SIV (Instrumentalities). Of course, it is possible that, even then, the idea would not have been successful. The point here is that it failed because it could not be tested and developed.

8.5.3 The live approach struggles to stay alive

One of the key protagonists for the live attenuated approach was Desrosiers. His group reported remarkable work on a weakened version of the complete virus in a landmark paper (Daniel, Kirchhoff et al. 1992). It arrived at crucial juncture, when researchers were reeling

from the Stott results, and when it was becoming clear that sleek recombinant methods were not yielding vaccines readily. This approach had always been criticised as being too dangerous, but in this article Desrosiers reported immunity which was the longest lasting, strongest protection in any HIV vaccine experiment so far.

Desrosiers was unimpressed by the whole-killed approach but he was even less so by the recombinant approach, 'The whole, inactivated virus vaccine approach has been largely unsuccessful against SIV grown in rhesus monkey lymphocytes'. This suggests that Desrosiers believed that the excitement for the approach was unjustified given that a monkey-monkey approach has not yielded protection (Daniel, Kirchhoff et al. 1992:1938). He goes on to say, 'Priming with vaccinia recombinants followed by boosting has protected rhesus monkeys against challenge by homologous cloned SIV, but little or no protection has been observed against homologous uncloned SIV. Tests of several products have shown only limited success in chimpanzee trials. What is most disappointing about these studies is that the numerous failures have occurred despite extensive efforts to maximise, in an unrealistic fashion, the likelihood of vaccine protection. The vast majority of studies have used a minimal dose of challenge virus, matched to the strain used for vaccination, at or near the peak of vaccine-induced immune response' (Daniel, Kirchhoff et al. 1992:1938).

Desrosiers' reference to lenient testing conditions highlights that early stage vaccine development involves the creation of highly artificial conditions[50], created by a range of instrumentalities, so that inferences can be made for learning. But by the same token such conditions make it highly difficult to predict whether the vaccine will be effective as a technology in the real world. Thus, Desrosiers argues not only that his results show protective effects stronger than those achieved with other approaches, but also that the conditions he achieved them in represent closer to real world conditions than tests in other approaches.

[50] Conditions range from weak challenge virus, low challenge dose, homologous strains and relaxed challenge timings etc. (See table 2 at the end of this chapter).

Desrosiers did not abandon recombinant techniques altogether though. He used the technique to remove a gene from a highly virulent SIV strain[51]. The excised gene was *nef*, and although its function was not well understood, they knew it was not required to replicate so it would not affect the vaccine's durability. He injected this constructed SIV into six monkeys and gave the control group of twelve monkeys an intact version of SIV. 2.25 years later, all of the control group were ill or dead, but all of the *nef*-deleted group were healthy with normal CD4 counts and low virus counts.

The monkeys were then challenged, along with four new controls, with complete versions of SIV. Note that 'no booster immunisations of any type were used.' By 36 weeks, the controls were dead (or killed when moribund) and the inoculated group were all healthy. Polymerase Chain Reaction analyses found no virus indicating that they resisted infection effectively. Even with a hundred times higher challenge dose, the monkeys did not show signs of infection.

The findings amazed other researchers. 'This is a significant advance' said Fauci, director of NIAID, and Schultz, chief of NIAID's vaccine branch added that 'this is three orders of magnitude better than any protection we've seen.' Bolognesi called the data 'head and shoulders above everything else' (quotes in Cohen 1992a:1880). The comments did not mean, however, that Desrosiers had their full support. It is more likely that they saw Desrosiers' work as useful in contributing to their understanding of what the different components of HIV do by removing them one by one[52].

Subunit researchers such as Bolognesi and Gallo viewed Desrosiers' live virus work as part of the journey towards understanding which immune responses could be correlated with effective protection. The rationale was that understanding what effective protection is, in

[51] Although not explicitly acknowledged in the paper, I assume that the vaccine strain was grown in human cells but unlike Stott and others, the two challenge stocks were both grown in monkey cells: 'In both cases, virus stocks were prepared in primary rhesus monkey peripheral blood mononuclear cell (PBMC) cultures' (Daniel, Kirchhoff et al. 1992:1939). PBMCs are mixtures that include CD4 cells, the cells that HIV infect.

[52] For example, Almond, Stott and Cranage defended the work against Ruprecht et al.'s (1995) criticisms by writing, 'We agree with Ruprecht and colleagues that 'it is premature to consider *nef*-deleted viruses as candidate AIDS vaccines.' Nevertheless, we believe that the study of live, attenuated SIV will provide vital clues in the development of an effective AIDS vaccine' (Almond, Cranage et al. 1995:178).

the way that Hammon did for poliomyelitis, would enable them to design their subunit vaccine better. Unfortunately Desrosiers' paper did not offer any such correlates, it merely suggested that their 'live attenuated HIV-1 may be the most potent, effective vaccine for the prevention of AIDS[53]' (Daniel, Kirchhoff et al. 1992:1941).

The high degree of protection afforded by the attenuated SIV could not be readily explained with neutralising antibodies of such low levels. Other vaccines which had triggered much higher levels of antibodies still failed to reach the kind of protection Desrosiers achieved. Attempts at making comparisons with other approaches were made explicitly, 'These are the most impressive protective effects we have seen in any vaccine experiments, including those with inactivated whole virus, recombinants expressing SIV *env*, vaccinia recombinants, and vaccinia recombinants priming followed by SIV particle boosting'[54] (Daniel, Kirchhoff et al. 1992:1940).

Desrosiers' vaccine was never taken seriously due to the safety concerns raised by the prospect of a live-attenuated vaccine[55]. Desrosiers acknowledged 'Concern for safety is likely to be the key issue for the eventual development of this approach' (Daniel, Kirchhoff et al. 1992:1941). He argued that by removing more and more components from the virus, the risk of reversion back to virulence would be minimised. 'In addition to *nef*, other genetic elements can be deleted from HIV-1 to help ensure long-term safety…The use of deletion mutations is an important part of this strategy [which] eliminates the possibility of reversion.' The use of the word strategy reflects the need to compromise for a less effective vaccine, but that was a balance that needed to be explored (see table 9)[56].

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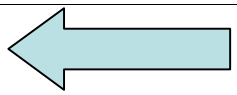
[53] 'Most viral vaccines currently in use in humans are of the live attenuated variety. It is simply difficult to match [other vaccine approaches with] live virus infection for strength, breadth, nature, and duration of the immune response that is generated' (Daniel, Kirchhoff et al. 1992:1939).

[54] The quote has been repeatedly truncated, but I do not believe I have altered its essential point.

[55] The safety concerns were, and still are, most vociferously led by Gallo (Fischinger, Robey et al. 1985; Gallo 2005). They focussed on three main areas: insertional mutagenesis, reversion to virulence and delayed onset of AIDS (see section 8.1.1).

[56] Desrosiers also countered that the link between cancer and the retrovirus family was weak, and not well understood. In addition, the attenuated virus did not replicate much making cancer less likely. The delayed onset of AIDS was merely a reason to work faster and take candidates to testing earlier, because the lead times for developing such a vaccine would be long, including 15 or so years of safety testing.

Table 9: A balance between safety and efficacy

High level of attenuation		Low level of attenuation
Safe: low probability of reverting back to virulence		*Risky*: high probability of reverting back to virulence
Less effective: at stimulating an immune response and less recognition of other strains in the field		*Effective*: elicits strong immune response

In this approach, the compromise that scientists arrived at would presumably reflect assumptions about the way they frame different populations' social needs. The evaluation and communication of desired risk/efficacy was never going to be a simple task, but the criticisms aimed at Desrosiers work seemed to lack any acknowledgment that, for some people[57], the risks of such a vaccine might be worth taking, particularly if their behaviours and lifestyle were difficult to change (drug addiction, poverty etc) resulting in high probability of HIV exposure.

Such calls for pragmatic re-framing of social assumptions bear strong resemblance to Shearer's assertion, reviewed in the earlier section, that for some people the prospect of organ transplantation is not as important as effective HIV protection. Even if attaining widespread consensus over 'objective' risk-benefit analyses were not feasible for vaccines with triple or even quadruple deletions, Desrosiers was effectively calling for a strengthening of the institutions part of the testing regime, so that the live attenuated approach could proceed purposefully to address the safety issue with as much data as possible. A more nuanced debate of needs and risks would require better governance.

Desrosiers acknowledged that the results were based on pure empiricism. 'We do not know the mechanisms that are responsible for the protective immunity observed in these experiments' (Daniel, Kirchhoff et al. 1992:1940). Desrosiers was faced with two options

[57] This was the basis for the WHO's decision to support efficacy trials of gp120 (see later chapter). See also Blower et al. (2001) who develop a theoretical framework predicting that live vaccines would *reduce* AIDS death rate in Zimbabwe (where transmission is higher), but *increase* it in Thailand (where transmission is lower). In short, different countries require different solutions, which is in keeping with evolutionary theories of technical change.

for further research directions. He could either search for other possible explanations for protection, the most obvious candidate being the cellular immune response, or he could push forward with the deletions. The former appeals to more rationalist inclinations of explaining what is needed and then designing a vaccine that works. The latter is an option that places the search for an effective vaccine as a priority over gains in theoretical understanding. Desrosiers had little faith that a rationalist approach would work on its own, and he says "I just kind of chuckle at it. It's dreaming that science can do more than it can. It's a worthy concept, but dream on" (Cohen 2001b:130). Desrosiers concentrated on the more technological exercise of engineering SIV's and HIV's with more and more deletions, and evaluating how well they worked in chimpanzee challenges.

Cohen (2001b:130) points to an experiment with monkeys that could suggest causal mechanisms. If the hypothesis were true that killer cells were responsible for protecting the monkeys, then it follows that researchers should be able to bleed the animals, separate out those killer cells (or whatever they suspect is causing immunity), and inject them into unvaccinated monkeys[58]. If the monkeys that received the transplanted killer cells could resist infection after a challenge with SIV, that would provide evidence that they were a correlate of protection.

However, there was again an instrumentality problem hindering the creation of the required experimental conditions. The monkey receiving the cells would mount an immune response against the transplanted cells because they are 'non-self'. Identical twins, which can freely share cells, offer a way around this problem. They are an important instrumentality that changes conditions, such that growth of knowledge becomes feasible.

Desrosiers searched for identical twin monkeys in captivity but found none (Cohen 2001b:131). The next step might have been to recruit assistance from reproductive endocrinologists, who have learned much about how to manipulate multiple births. But

[58] In passive immunisation, previously made antibodies injected into a subject can provide protection or treatment (see section 5.4.3 or 6.4).

such an effort to bring together the required capabilities and resources was not made (Cohen 2001b:131).

With no correlates for protection in sight, and safety fears emphasised repeatedly, the live approach attracted little further support.

8.5.4 Summary

Perhaps the learning conditions provided by Stott's crucial control experiments would have been created earlier if monkey supply was as closely monitored as Basil O Connor's efforts. Even when Stott's results were out, efforts to strengthen the testing regime were not made. For example, monkey cell lines to facilitate monkey-monkey tests were not a priority. Some researchers such as Arthur and Shearer found promising research avenues with Stott's result, but efforts to test their approach based on cellular proteins were thwarted by a reluctance to re-frame the need for and risks of organ transplanting. Similarly, the risks of a live-attenuated approach were not re-evaluated, even when data existed showing Desrosiers' vaccine to be highly promising. Instead, the strong results were used to pursue other (recombinant) vaccine approaches.

Lack of comparability between the approaches resulted in the entrenchment of researchers into vaccine approach 'camps' where researchers like Murphy-Corb were made to 'switch camps' for lack of support. If researchers were not communicating freely, this is likely to have affected the knowledge flows that were identified as being important in chapter 2.

A way of improving the live vaccine was held back by the lack of monkey twins to test a major hypothesis in. This represented a failure in co-ordinating access to important testing instrumentalities in terms of failing to bring the skills and capabilities of an endocrinologist to bear on the problem. Monkey twins may have provided a critical set of intermediate conditions for learning.

Despite these problems of underdeveloped instrumentalities, and the comparability problems of weak R&D governance, Desrosiers was able to have his vaccine labelled as the

best effort so far. In doing so he highlighted how researchers developing other approaches had used purified - but unrealistic - laboratory conditions. This supports the notion that vaccine development progresses through an iterative process of testing ideas in incrementally tougher and more realistic testing conditions.

8.6 Conclusions

The popularity of biotechnology and the fondness for applying it, coupled with a paucity in traditional vaccine development skills and capabilities, contributed to a heavy emphasis on the subunit approach that may have had an excluding and detrimental effect on the other approaches. The subunit approach focussed on the development of hepatitis B vaccine as if it were a predecessor model and used its recent success to downplay the problem of variation in HIV. Advocates of the subunit approach were convinced that a conserved region could be found, and that separate vaccines could be developed for different geographical regions.

After the need for cellular immune responses were belatedly recognised, new approaches emerged in small biotechnology companies. However, the weak testing regime meant that preliminary tests lacked immediate commensurability to the other approaches. The companies failed to attract further investment with which to develop their ideas and the lack of commensurability probably contributed to this. The small companies were taken over by large pharmaceutical firms who had already clearly expressed their intentions to refrain from AIDS vaccine development, if not all vaccines generally. The takeovers led to tensions and intraorganisational problems in the development of these new approaches.

This left Chiron and Genentech with the subunit approach in the private sector alone, against the whole-virus approaches led, for example, by Stott and Desrosiers in the public sector. Stott's and Desrosiers' data showed how poorly deviation away from the dominant model was managed. Stott and Desrosiers produced strong vaccine candidates but found it difficult to explicitly compare with recombinant approaches, and faced a lack of testing resources (monkeys) and instrumentalities (cell lines and twins). In addition, they faced

heavy criticism about safety and a testing regime with institutions reluctant to engage in governing or mediating any risk discussions.

This chapter has shown that many potential operational principles emerged after a decade of AIDS research. However, selecting an operational trajectory was difficult (discussed in next chapter) because the wide variety of laboratory practices remained largely ungoverned (see table 10 below). As such, developments in many of the operational trajectories could not be related or compared with others. Greater standardisation would have allowed researchers to make comparisons with more confidence, identify strong vaccine candidates more easily, and focus resources. Instead, scarce resources were scattered across many new vaccine approaches, and the uncertainties permeating vaccine development were perhaps greater than they were ever before.

Table 10: Variation in vaccine development

A list of operational principles to select from	**A list of laboratory practices left unstandardised across operational trajectories**
• Whole, killed	• Use of HIV, influenza or herpes for 'proof of concept'
• Live, attenuated; with varying number of deletions	• Species of test animal; mice, chimpanzees, monkeys
• Recombinant envelope proteins; e.g. gp120, gp160	• Immunisation schedules
• Mixtures of core (e.g. p17, p27) and envelope proteins	• Route of challenge: rectal, mucosal, intravenous, foetal
• Naked DNA; with cationic liposomes	• Dose of challenge
• Live vectors to express and deliver different proteins; e.g. vaccinia, venezuelan equine encephalitis, canarypox, fowlpox	• Strains of challenge; virulent primary isolates taken from patients or weaker laboratory adapted strains
• Prime with live vector vaccine, then boost with recombinant protein	• Assessment of antibody neutralisation; neutralisation judged at 50%, 90%, 95%?
• Cellular proteins mixed with recombinant viral proteins (e.g. gp120, gp160, p17, p27)	• Assessment of protection; sterilising immunity, delayed onset of disease

Source: compiled from chapter 8.

Knowledge growth remains fragmented unless standards are set across the dimensions listed on the right hand column. In this environment it is difficult to bring new knowledge to bear on the process of selecting putative operational principles for further, focussed development because it is not stable and shared. A strong testing regime may assist in deciding when to winnow down the options in the left hand column, and when to continue developing in parallel.

Chapter 9

Testing Times for an AIDS Vaccine: Testing regimes in clinical development

The progression of a vaccine candidate from the laboratory to the market is long, and becomes increasingly complex and expensive as tests are conducted closer to their intended operating conditions. Following studies in laboratories and animals, candidates are tested in phase I clinical trials for short-term safety and immunogenicity in a small number of humans. In phase II, these attributes are examined in hundreds of people, and the trials also seek to determine the immunisation doses, routes and schedules to use (Pocock 1996; Plotkin and Orenstein 2004).

This chapter explores the role of the testing regime in the decision to move to phase III trials. These trials seek to establish the efficacy of the vaccine by testing in thousands, or tens of thousands, of people. Establishing efficacy in the field is more difficult than the other phases of testing because of the interaction of other influences (Levine, Kaper et al. 2004). Fewer variables can be controlled, so the concern for vaccine designers is much more about 'does it work?' than it is about 'how does it work?' Consequently they are the longest of the tests, lasting several years and are the most expensive, costing millions of dollars (see section 5.2.2).

With such large stakes, the decision to move to phase III can be arduous, contested and conspicuous. This chapter explores how without a strong testing regime in place, processes to legitimise the selection of operational trajectories become more difficult and less likely to be widely acceptable. This affects the take-up of knowledge generated in the trials and makes it less likely to be shared, integrated and added to previous knowledge. Cumulative technological knowledge growth is unlikely if the knowledge is not seen to have been produced through institutional processes that make it robust. This chapter therefore argues that clinical trials require a strong institutional presence with leadership, management and co-ordination.

Section 9.1 describes how the funds for testing one vaccine were politically allocated despite serious doubts in the scientific community. Section 9.2 examines how, for a different approach, scientists struggled to reach consensus on whether to move into phase III and how weaknesses in the testing regime were partly responsible. Sections 9.3 and 9.4 examine the consequences of a decision not to proceed and the implications of an alternative decision to proceed with the trial. Section 9.5 concludes the chapter by exploring the possibility of a new vaccine paradigm.

9.1 Pork-barrel science

Along with Salk's Immune Response Corporation, MicroGeneSys was the only other company whose sole activity and aim was the development of an AIDS vaccine (Batson and Ainsworth 2001).

In September 1992, the US Department of Defense annual budget appropriated $260bn, but the Senate also passed a relatively minor $20m amendment to the appropriation (Hines 1993). The amendment ordered the Army to spend the money on a 'large-scale… clinical investigation of the gp160 vaccine' referring to Microgenesys' 'VaxSyn' product (Watson 1992:94). Although medical research priorities are often set by Congress following lobbying, this allocation was significant because lawmakers had earmarked funds for a specific product without the explicit backing of federal researchers from either the NIH or FDA. Even the Army were unaware of the proposed amendment until it was passed (Hines 1993).

The decision aroused considerable anger in the AIDS research community. Martin Hirch, director of the AIDS program in Massachusetts, said that 'new money for work against AIDS is always welcome, but there are many AIDS vaccines being studied at the moment and there is nothing to suggest that this one is better than the others' (Meier 1992). Bernadine Healy, director of the NIH, called it 'a backdoor channel' and added 'there are others that may be as good if not better' (Anon 1992). She cited it as an example of 'law

pre-empting science and scientific judgement' (Watson 1992:94). David Kessler, commissioner of the FDA, had 'serious concerns about sidestepping the normal peer review process, especially on something as important as the AIDS vaccine' (Meier 1992).

Microgenesys was well connected to political power and employed highly influential lobbyists(Anon 1992; Cohen 1992d). There was little doubt about how the $20m amendment came to be after the senators proposing the amendment credited well known lobbyists for bringing VaxSyn to their attention (Cohen 1992b; Meier 1992).

The idea behind the VaxSyn product was that a vaccine could not only protect healthy people but might also serve as a form of therapy for those already infected - but few researchers felt that the product was ready for trials. Army researcher, Robert Redfield, lent the product much needed scientific credibility whilst his study, published in the New England Journal of Medicine, showed that VaxSyn was 'safe and immunogenic' in thirty volunteers (Redfield 1993:1677). But the study did not suggest the product was effective as judged by the surrogate marker, CD4 cell counts. For example, only six out of fourteen volunteers needing treatment[1] responded to the gp160.

However, the lack of evidence regarding efficacy was not enough to overturn the considerable public attention that had gathered momentum, particularly because the vaccine candidate offered hope to activists who were often already HIV infected. Many advocates argued that it would be better to take the $20m and spend it on the vaccine than lose it altogether (Kolata 1996). Healy reconciled, "we hate the process, but we're focussing on what to do with the money" (Watson 1992:94).

The Department of Defense changed its unilateral strategy, and brought itself in line with the NIH and FDA in agreeing that '[VaxSyn] should be tested only in trials that include other vaccines and that otherwise the $20m should be spent on basic AIDS vaccine research' (Meier 1993). Since VaxSyn was also a therapeutic drug, the FDA convened a

[1] 16 out of the 30 volunteers were healthy and sought protection (>600 cells per ml) and 14 were unhealthy needed treatment (<600 cells per ml) (Redfield 1993:1677).

committee of antiretroviral drugs experts. The committee found that the VaxSyn data did not merit a large scale trial and they unanimously agreed that the money would be much better spent if it went towards a more expensive trial that compared several candidates where industry contributed to the remaining costs (NYTimes 1994; Cohen 2001b).

This comparative trial seemed like a reasonable compromise for all parties concerned. However Microgenesys, resisted with a variety of reasons, claiming that a comparative trial would dilute and delay the results of a VaxSyn trial (Squires 1993b), allow its competitors[2] to 'catch up' and then finally Microgenesys claimed it could not afford to pay for the experimental vaccine (Squires 1993a). Microgenesys wanted half of the $20m to be spent on purchasing vaccine for the comparative trial whilst other companies, like Chiron and Genentech, would have to pay for their own vaccine. When Chiron and Genentech reluctantly obliged, Microgenesys still withdrew from the comparative trial anyway.

In a highly critical article in Nature, John Moore labelled VaxSyn as the worst possible choice amongst the vaccine candidates, "Obviously they fear a comparison trial. They probably prefer to play with their friends than with people of objectivity" (Moore, Lewis et al. 1993; Cohen 2001b). Microgenesys said the charge was 'preposterous' and that they withdrew from the trial because they 'disagreed with the primary and secondary end points[3]' (Macilwain 1993). The NIH was also incensed by the withdrawal, 'This was the only study giving direct comparability between rival vaccines. But put yourself in their shoes: why would you want to help generate data showing that their vaccine offers less immunogenicity than the others?' (Macilwain 1993).

The $20m was redirected to basic research projects and the Army used its own budget to run VaxSyn slowly through its original five year plan for phase III trials (Cohen 2001b). In

[2] Jonas Salk's Immune Response Corporation, for which he raised $20m very quickly, had pioneered the therapeutic vaccine approach since the late 1980s. Chiron and Genentech were also pursuing therapeutic applications of their gp120 products. The Austrian company Immuno AG was also pursuing the gp160 approach. (See chapter 7).

[3] These terms refer to the clinical symptoms or indications needed to be observed so that a trial may be considered a failure or success. See the section 8.5 for more details.

April 1996, the Army announced that it had completed the trial and the Department of Defense press release stated:

'While gp160 was hoped to slow the progression of the disease, unfortunately, results from the study show no clinical improvement that could be attributed to the vaccine used as adjunct therapy for HIV infection' (Defense 1996).

The company's press release stated that the vaccine 'did not demonstrate statistically significant benefit' (Proteinsciences 2006). The company later changed its name, its CEO and turned its attention to influenza vaccines and, lately, SARS vaccines (Kolata 1996).

9.2 After MicroGeneSys: how strong was the rationale to back its rival over other alternatives?

The Microgenesys trials with gp160 briefly diverted attention away from gp120 and possibly slowed its route to clinical efficacy trials. Just as it was for Microgenesys, a complex mix of scientific, organisational, financial and ethical factors pushed the gp120 vaccines made by Chiron and Genentech ahead of the rest. In isolation, none of these factors made a compelling case that gp120 vaccines held substantially more promise than the other ones being developed. But collectively, they managed to beat the other vaccines to being considered for the final stages of testing: the phase III efficacy trial.

The NIH was tasked with judging whether the gp120 vaccines held enough merit to warrant the expense of designing and conducting efficacy trials. They faced significant arguments for and against going ahead with Phase III trials because the testing regime was weak. It was difficult to interpret how realistic the conditions were when experimental results were being discussed, instruments and standardised conditions were not well developed by institutions, so conditions could not be changed easily and knowledge could not be shared and accumulated easily. There was an acute shortage of accumulated technological knowledge.

9.2.1 Arguments *for* proceeding with efficacy trials

a) Antibodies offer poorly understood protection

The main argument in favour of the gp120 vaccines centred on a mechanistic perspective of the role of antibodies. The basis for injecting lots of it into a person was that the gp120 may either, by itself inhibit the binding process through competitive inhibition (also a basis for therapy), or it may stimulate the production of antibodies which could block the viral envelope glycoproteins docking with CD4 sites and prevent infection. Similar to arguments in poliomyelitis vaccine development, prior to Hammon's results, the role of the antibody in immunity was frequently argued to be unclear and, as such, its use in determining the value of a vaccine candidate was debated (Fauci 1991; Sabin 1992).

Regardless of exactly *how* antibodies might protect against HIV, evidence existed to show that antibodies alone could do it in some conditions. For example, researchers had injected chimpanzees with antibodies taken from HIV-infected humans and then showed that the animals resisted infection from challenges (Prince 1991). In addition, Genentech had published in Nature to show that their recombinant gp120 could protect chimpanzees from an HIV challenge whilst gp160 (the complete envelope protein used by MicroGeneSys and Immuno) could not (Berman, Gregory et al. 1990).

Don Francis of Genentech questioned the necessity of understanding the role of antibodies in immunity in the face of such results. But the results did not convince everyone because, although many antibodies were known to bind to HIV, only those that prevented the virus from infecting cells were deemed *neutralising* antibodies. These experiments showed immunity with antibodies, which can bind to HIV, but not necessarily immunity with neutralising antibodies, which can bind *and* prevent infection.

For Francis, a vaccine's ability to induce antibodies capable of neutralisation was not a criterion that should be used to judge the vaccine's worth. The vaccine was able to induce immunity, and it involved antibodies somehow – and that was enough. Debates over whether neutralisation had occurred were irrelevant (discussed further in part a, section

9.2.2). He highlighted the fact that sera taken from vaccinated animals failed to neutralise the virus in the laboratory, even when sera were taken from animals that were protected against a 'whopping dose' of challenge virus. "Anybody in their right mind would have known that the neutralising antibody was not predictive of protection" (Thomas 2001:201).

b) An opportunity to learn and retain industrial involvement

The purpose of the trial was also argued to be a means for learning rather than simply being a test for efficacy. This perspective emphasises that putative operational principles are not merely tested, they are corroborated through repeated testing and they evolve through incremental refinements in the testing regime. However, to do so at this stage is expensive, slow to feed back and possibly even unsafe.

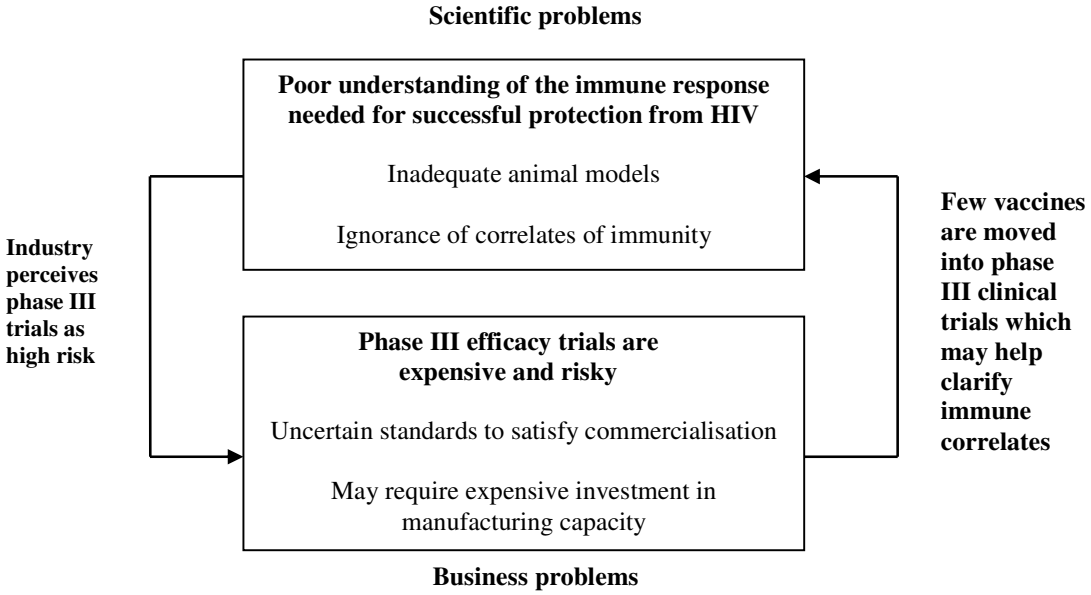
Jack Obijeski, who ran Genetech's AIDS vaccine project, argued that the efficacy trial would be a way of generating 'the next big increment of knowledge' (Thomas 2001:200). Scientists would be able to evaluate their laboratory results against what happened in the field and if the trial went well, they might know what immune response a successful vaccine would need to elicit (Ada, Koff et al. 1992). Even if the trials did not show complete success, it was argued that unsuccessful trials hold clues to improvements in vaccine design, dosing and immunisation schedules. New data acquired at government expense could stimulate industry to develop more and better products.

Clinical evidence was claimed to be ultimately more meaningful and relevant than laboratory results. However, this claim relies on whether the clinical evidence is derived from a product that has been brought reasonably close to working order through the testing regime. Complete failure would offer little information and so a reasonable chance of success is necessary in order for this 'learning' justification to be valid.

Batson and Ainsworth (2001:723) call this particular testing issue a 'vicious circle', where failure to undertake phase III trials can perpetuate the lack of knowledge that underlies industry's reluctance to invest their resources in the first instance (see figure 8). They seem

to think that frequent iterations and the ability to move back and forth between different conditions is an important factor in innovation. Chapter 2 theorised that these conditions can be more or less suited to learning on the one hand, and more or less relevant to technological use on the other. It added that these degrees of variation in conditions may be controllable through the governed use of instrumentalities.

Figure 8: The vicious circle: scientific barriers make industry reluctant to invest in the phase III trials that may be required to solve them



Source: Reproduced from Batson and Ainsworth (2001:723).

Another factor was the perceived need to protect industry involvement. Large pharmaceutical companies were avoiding AIDS vaccine research, leaving it to small biotechnology companies that lacked capabilities and money, such as MicroGeneSys, Repligen and Vical. Chiron and Genentech were different. These companies had strong scientific reputations; their scientists had integrated themselves into the AIDS vaccine network, collaborated with other scientists, published in the best journals, and even published negative data like the primary isolate study done by Chiron (see below). So NIH

and NIAID staff did not want to alienate the most attractive industrial partners they had when it came to deciding which candidates to consider for funding through efficacy trials.

Genentech's Obijeski expected public health urgency to drive candidates forward into trials and was furious when he realised that the trials may be in jeopardy, particularly as many of the necessary testing resources were already in place. For example, he complained that they had already manufactured 200,000 doses of vaccine under the impression that the NIH had made a commitment to move forward into efficacy trials. "To leave that vaccine on the shelf, something that might help someone, we think that's ridiculous… it's a monumental disincentive for Genentech…NIH [should] not dwaddle about, one step forwards, one step back. That's what makes CEO's nervous" (Cohen 1993a:981). Chiron was in a similar position needing commitment to move forward.

If the NIH did not move forward, it would discourage any further industry involvement. One scientist commented, "If they get the sense that this is not an area of fertile investment, I think you are going to see a lot of little companies disappear, and a source if potential future vaccines disappear. That's not a threat, it's just a fact. The community will react… with some fear and panic with regards to decisions made here, should they be… negative" (Cohen 2001b:235). The larger firms and more established biotechnology companies were also nervous. Genentech's Don Francis said, "If you do this to us, we're telling you that the corporate decision is going to shut us down" (Thomas 2001:204). Merck's Hilleman also offered the same warning more moderately, and added "it's not bad enough not to consider" (Thomas 2001:205).

c) Other reasons

There were other reasons, discussed in chapters 7 and 8, to proceed with efficacy trials. A recombinant Hepatitis B vaccine developed by Chiron heralded new hope for subunit vaccine researchers. Scientists also believed that the subunit approach was less risky simply because there was less of the virus in the vaccine. In addition AIDS activists had constructed considerable expertise and had established themselves as an important

stakeholder group in decision making processes (Epstein 1995). Although they focussed most of their attention on the development of new treatments, they also applied significant pressure to move forward with vaccine clinical trials because it offered a chance to 'do something,' even if the chances of success were low. For example, Pinching, an immunologist, believed that in licensing the antiretroviral AZT, the US authorities 'extrapolated' beyond the limits of legitimate scientific deduction and had been led by 'the widespread desire to see progress achieved and the wish to be seen to have made such progress' (Pinching 1991:158).

9.2.2 Arguments *against* proceeding with efficacy trials

There were strong arguments against going forward with Phase III trials.

a) Primary isolates problem

To ascertain whether a vaccine can induce neutralising antibodies, there are tests which mix HIV with blood taken from vaccinated individuals. But these tests, or assays, were much debated because there were many differences in techniques (Hanson 1994). Some used undiluted sera whilst others used various dilution factors, and there were differences in the growth media used to grow isolates in. Different investigators obtained their virus from different sources, which mattered because the kind of strain used affected results. There was no way of knowing how the strains compared to each other in terms of virulence. Furthermore, titrations differed because some considered neutralisation to have occurred if 50% of the HIV was disabled whilst others held out until 90% (Hanson 1994).

However, the high variation within the assay techniques, and resultant lack of comparability between them, was not their most significant drawback. These assays rely on HIV that is grown in immortalised laboratory cell lines and, even though antibodies may (differentially) protect against such laboratory-adapted viruses, they may be ineffective against a real-world strain of HIV. A more stringent test would be to use HIV that has been freshly harvested from patients because these 'primary field isolates' are believed to be much closer to the type of HIV that would infect a vaccinated person.

David Ho and others had gathered evidence to show that primary isolates (virus taken directly from patients) behaved very differently from laboratory adapted strains (Daar, Li et al. 1990). Many investigators, including Chiron themselves, also published studies showing antibodies capable of neutralising primary isolates of the virus could not be found in blood taken from people who had received vaccines from many different companies (Hanson 1994; Matthews 1994). Although even more variation existed in these more stringent tests, because the characteristics of the fresh blood cells would vary[4], the key finding of many independent tests was that primary isolates were not being neutralised[5] (Matthews 1994).

So whilst the tame laboratory adapted strains were being neutralised, the more virulent primary isolates taken from patients were not being neutralised. It has been suggested that this may be because proteins in the primary isolates are more tightly coiled, whilst those in laboratory strains unwind in the absence of selective pressures and lose their shape, or 'conformational integrity' (Matthews 1994). The inability to neutralise primary isolates brought into question the quality of the antibody response the vaccine might induce and stood alongside the fact that this vaccine approach cannot[6] induce a cellular response at all (Letvin 1993; Klein and Ho 2000).

b) Animal model problem

The lack of consensus over which animal models to use has meant that animal experiments have played a somewhat confusing role in AIDS vaccine development.
Genentech built its research programme around its chimpanzee results and promoted them as a success. However, closer inspection (see table 11) reveals more limited success.

[4] For example, some blood cells would be more susceptible to infection than others, or some would grow faster than others.
[5] There was only one single exception where blood from one vaccine injected person neutralised a field isolate (Matthews 1994).
[6] Because this type of vaccine antigen does not enter the MHC class I pathway after administration, so cannot induce a cellular response (Letvin 2006).

Table 11: Problems with Genentech's gp120

- Chimpanzees are better than humans at fighting off HIV infection
- The vaccine only worked in chimpanzees, failed in monkeys' SIV model
- The immunisations needed to be tightly scheduled in order to work
- They used so few chimpanzees that the study lacked statistical significance
- The route of the challenge, an intravenous injection, might not reflect what happens during sexual exposure

Source: Based on chapter 8.

Following the initial results with the chimpanzees, the logical experiment would have been to design similar conditions with monkeys or to repeat with more chimpanzees in order to reach statistical significance. However, expense and logistics make adequate chimpanzee studies too risky for a company to undertake and represent a major testing constraint. 'To really test efficacy in chimpanzees, one would have to inoculate animals at the mucosal surfaces with small amounts of virus. Given that most of them would not become infected even without a vaccine, the experiment would require approximately 100 vaccinated compared to 100 unvaccinated chimpanzees in order to reduce the infection rate in the vaccinated group to about 2 in 100 from about 8 in 100' (Grady 1995:99). At approximately $70,000 per chimpanzee this study would be a sizeable [$14m] outlay (Grady 1995:99).

The success of the experiments was also undermined because comparing them to monkey experiments conducted by other groups, which may have used different routes of challenge or immunisation schedules, was difficult. Uncertainties could have been reduced if organised groups ensured their experiments were comparable, even if they were not statistically significant.

Some members of the NIH, such as Alan Schultz, recognised the difficulty the companies were in, "If in fact this group or some decision-making group would say, 'if you did this experiment and if you got that result, we will do the trial,' then, in fact, I think maybe those experiments would get done." He went on to say that the current message being conveyed

was, “Well go ahead and spend half a million on a couple of chimpanzees, show us the results, and we’ll think about it” (Cohen 2001b:253).

c) Challenge stock issues

One of the advantages to the vaccines developed by Chiron and Genentech was that they used more common strains (HIV_{SF2} and HIV_{MN}) whilst others used laboratory adapted strains to make their vaccines (Berman, Matthews et al. 1992; Steimer, Yoshiyama et al. 1993). But Genentech’s experiments on chimpanzees, described above, was with their earlier version of the vaccine, which was made from HIV_{3B} (a less common strain). Moreover, they only challenged the HIV_{3B} vaccine with HIV_{3B} (a homologous challenge). A real-world vaccine would have to work against a variety of strains.

The number of strains a vaccine is effective against can be considered a secondary performance criterion which might be incrementally improved as it is tested against more and more strains. But there were hurdles in broadening the reach of gp120 vaccines to other strains because of limited challenge stocks (Cohen 1991). Challenge stock is a batch of virus that scientists have characterised by determining the precise dose needed to infect an animal (Cohen 1991).

Although challenge stock existed for HIV_{3B}, Genentech did not want to test this against its HIV_{MN} vaccine because the result might be misleading: even if the vaccine failed to protect against the distantly related HIV_{3B}, the preparation still might have an impact in parts of the world where HIV_{MN} – and other similar strains – predominated. So ideally the company wanted to test against an HIV_{MN} challenge stock, but HIV_{MN} had not been characterised in chimpanzees (Cohen 1991; Palca 1992).

Challenge stock is a crucially important aspect of the testing regime, a shared resource which allows others to accumulate knowledge by testing prototype vaccines in conditions that can be related to the tests of other groups. It is an example of the knowledge infrastructure flagged in chapter 3. However, this knowledge infrastructure was not

provided for a range of HIV strains by government. One possible reason is that developing challenge stock is expensive and of little scientific interest.

To make challenge stock, scientists must test various doses of the virus in several chimpanzees to determine the amount needed to cause an infection, an experiment that in the early 1990s could cost up to $0.5m (Cohen 1991). In addition to expense, companies that needed challenge stock had to find someone with chimpanzees who would run the experiment. Jorg Eichberg, a veterinarian who managed one of the largest private chimpanzee colonies in the US, turned down several requests to make challenge stocks, describing it as "scientifically unexciting work and you're really burning up animals" (quoted in Cohen 1991:519). Eichberg, who had performed more chimpanzee challenges than any researcher in the world, agreed with many of his colleagues that government should do this type of work. Government, however, was not forthcoming on this (Palca 1992).

The problem of challenge stock has been identified more recently by Johnston, who goes on to suggest, in the manner of chapter 8, that this characteristic of the testing regime may affect the choice of operational principle. '[Disadvantages to using the chimpanzee model]…include the difficulty and expense of developing reproducible mucosal challenge stocks, particularly those that address clade [genetic subtypes] issues, and the expense, which limits the number of animals that can reasonably be employed. Thus, the use of chimpanzees to evaluate HIV vaccines will probably remain limited to those experiments that cannot be adequately carried out in the macaque model. These might include, for example, evaluating the safety of a live-attenuated HIV candidate…' (Johnston 2000:268).

d) Virus typing

The way in which virus typing for HIV was done stands in stark contrast to the way it was done for poliomyelitis. The classifying method involved studying commonalities of amino acid structure in 245 different HIV isolates. This put HIV_{MN} as the most prevalent, HIV_{SF2} as the next most, and HIV_{3B} as less prevalent[7] (LaRosa, Davide et al. 1990:935).

However, there were two major limitations. Firstly, the study was conducted with isolates that were not 'fresh' primary isolates, they had 14 days in which to become more 'tame' laboratory-adapted isolates. 'To obtain the PND[8] sequences, we collected PBMCs[9] from 133 HIV-1-infected donors and co-cultured these cells for 14 days with uninfected PBMCs (113 donors) or with H9 or CEM cell lines (20 donors)' (LaRosa, Davide et al. 1990:932). Consequently, the ranking of strains by prevalence is open to some question since primary isolates could look completely different. In other words, a vaccine made with HIV_{MN} may not necessarily elicit antibodies with the anticipated breadth of efficacy.

Secondly, the typology relied on a view that reduced the potency of the entire HIV virus to a small part of its structure, the V3 loop, introduced earlier in section 8.3. It was hoped that antibodies directed to this short segment might neutralise the virus, so only those 35 amino acids were sequenced and classified in the sample of 245 isolates. The rest of the HIV structure was completely disregarded from the typology.

Such was the belief that the V3 loop would be decisive in immunity that the study proposed a theoretical structure of the consensus sequence, 'C-β strand-type II turn-β strand-α helix-C' (LaRosa, Davide et al. 1990:933), analysed the character of the conserved amino acids 'nonpolar, polar or charged' (LaRosa, Davide et al. 1990:935), and whittled the binding site down to just six amino acids 'this suggests that, for example, an antibody that binds

[7] The study's authors included influential authors such as Bolognesi, Emini, Putney, and Matthews.
[8] LaRosa et al (1990:932) refer to the V3 loop as a primary neutralising determinant, or PND. (See section 8.3 for further details of V3 loop).
[9] Peripheral blood mononuclear cells (PBMC's) are a fraction of the blood that contains T cells, the cellular targets of HIV infection.

GPGRAF as contained in the gpl20 glycoprotein will neutralize roughly 60% of randomly selected virus isolates' (LaRosa, Davide et al. 1990:934).

Moreover, the typology was not tested using animals. In contrast, the poliovirus typing project centred on the observed immunological responses of lots of monkeys, and consequently the typology was based on the whole virus. There are testing regime barriers to typing HIV in an analogous way. As noted in chapter 7, monkeys are not infectable by HIV. Chimpanzees can be infected by HIV, but, when they are infected, do not neutralise the virus or develop AIDS readily. Furthermore, they are, compared to monkeys, very expensive.

A practical alternative could have been to analyse the genetic and amino acid structure similar to the LaRosa et al study. Instead of restricting it to the V3 loop of laboratory adapted isolates, typing could have encompassed the whole virus in primary isolates. This would have been an enormous project, perhaps 80 times larger than the V3 loop approach[10]. But this scale has been reached before in that the virus typing project for poliovirus was a multi-university, multi-year and multimillion dollar project. Such projects need institutional leadership and co-ordination to recognise and exploit strategic opportunities for strengthening knowledge infrastructure.

e) Path-dependency problems

One of the arguments put forward was that the phase III trial in question could be used as a learning experience specifically to improve a low efficacy vaccine candidate. However there are several path-dependent risks with going ahead on a candidate vaccine that is expected to be of low efficacy.

Any efficacy trial requires many volunteers, but if the vaccine is of a low level of efficacy then only very large studies are statistically sensitive enough to detect such vaccines. This

[10] This would be a larger project but not impossible because the HIV genome is only 9749 nucleotides long (Alberts, Johnson et al. 2002), about 80 times larger than its V3 loop.

meant that there was a need to consider if the gp120 trial would use up most of the potential volunteers in the US, a valuable testing resource. As a result, there may not be enough volunteers left for future studies of products that might be more effective.

The future of the AIDS vaccine 'pipeline' was considered important because, as discussed in section 8.4, the gp120 vaccines barely stimulated cell-mediated immunity at all. Vaccine research shifted to a focus on cellular responses suggesting that this was suspected to be where the problems lay. New vaccine approaches developed at the time all aimed to address this directly, so phase III testing resources might have been better saved and deployed later in the testing of these newer operational principles.

One such candidate was the vaccinia vector based vaccine known as the prime boost approach (discussed in section 8.4.2) which had encouraging results but was not ready to be considered for efficacy trials. Using volunteers for the gp120 trials could ruin the chances for later candidates such as the prime boost. This is because those volunteers would be primed to respond to gp120, so if they are given gp120 again as part of the prime boost approach, it would cross react with those pre-existing antibodies. Furthermore, the vaccinia vector caused problems because it could only be used on people who were not smallpox vaccinated (section 8.4.2), since they too would cross-react with pre existing antibodies induced by smallpox vaccine.

Lastly, introducing low efficacy products means that future products will be compared to this standard. Evaluating the efficacy of future products is likely to be more complicated when the controls are people vaccinated with an older vaccine. It would require an inordinately large number of volunteers (or years) in order to detect any incremental improvements in efficacy. Therefore deciding to move to efficacy trials is not simply a question of the available of volunteers without pre-existing immunity, but also the opportunity costs of testing one concept over another.

f) Ethical restrictions

In accordance with ethical guidelines dictating that current best preparations be made available to all participants, the control is often not an inert placebo (Grady 1995). The implications of contending with a low efficacy control vaccine were considered above to be a complicating factor. But there were other ethical concerns as well.

Administering an injection, whether a placebo or a vaccine of low efficacy, may influence the participants towards higher risk behaviour. This may well be countered by educating participants about risk reductive behaviours. However, the tone and strength of the education programme would add another layer of statistical complication in examining vaccine efficacy. The underlying issue was inescapable: in order for efficacy to be shown, some people (in the control arm) needed to get infected and die.

In addition, it was becoming apparent that cocktail drugs were extremely effective in reducing viral loads (to undetectable levels[11]) and allowing patients to resume normal lives. Ethical restrictions meant that participants who became infected during a trial would need to be offered antiviral therapy. But these therapies were expensive and would add to the cost of trials.

There were important analytical consequences to such provision too. If everyone who became infected during a vaccine trial quickly began taking antiretroviral drugs, it would be impossible to tell whether the vaccine had delayed the disease. In such a setting, some of the vaccine's potential benefits may go undetected. Even increasing the length or size of the trail may not clear up that kind of analytical problem. Thus, the licensing of antiviral drugs like AZT, in one fell swoop, had completely invalidated existing testing procedures and protocols, and served to increase the difference between ethical treatment conditions and effective learning conditions.

[11] Less than 50 RNA copies per millimetre (Johnston and Fauci 2007).

9.2.3 A Phase 2½ trial

Given the difficulty of choosing whether to go ahead or not, one option considered by NIH Committees was the possibility of an intermediate clinical trial in between phase II and phase III to indicate whether the expense of a full efficacy trial was justified. This midsize trial would bear the advantage of being less risky, and initially cheaper and quicker; but since a full efficacy trial would be needed to clear FDA regulations, collectively the trials would be dearer and longer. Furthermore, the initial midsize trial would lack the statistical power to detect low efficacy rates, and so moderately effective vaccines might go undetected.

9.3 The NIH's decision to not proceed to Phase III

In June 1994, the NIH decided not to go ahead with trials in the US (Moore and Anderson 1994). As predicted, the NIH's negative decision triggered an industry withdrawal. By 1997, Bristol Myers Squib, British Biotech and Immuno AG were no longer conducting research into AIDS vaccines and no new companies expressed interest in the field (AVAC 1998).

Chiron stock price dropped and became 49.9% owned by Novartis, a large pharmaceutical company. It scaled back its vaccine programme and shifted its priorities to less problematic and more lucrative pathogens (AVAC 1998; Batson and Ainsworth 2001). To make matters worse, Chiron's head of HIV vaccines, Kathy Steimer, died in 1996 (Thomas 2001). The NIH brokered a deal that brought together Pasteur Merieux Connaught and Chiron in a bid to develop the prime boost approach discussed in section 8.4 (Excler, Duliege et al. 1996).

Genentech responded by taking its case to Congress and the Executive branch in an effort to override the NIH decision (Cohen 1994a) but, after the MicroGeneSys affair, few were willing to take their case up. Genentech's management withdrew completely from HIV vaccines, shutting down the division and reallocating its staff to other projects (Thomas

2001). Only Don Francis remained, saying "we've got a vaccine that deserves to be tested" (Cohen 1994a:1839).

VaxGen was spun off solely to stage efficacy trials for Genentech's product, with 'epidemiologist Don Francis [as] president and sole employee of Genenvax[12]' (Holden 1996:1237). Genentech offered VaxGen $1m starting capital and would offer another $1m and exclusive rights to the vaccine if the company could raise $18m on its own (Gershon 1996). With biotech start-up expert Robert Nowinski[13], Francis promoted VaxGen across the country to private investors saying "it's a social experiment [that directly asks the public whether it is] willing to invest" in a vaccine (Holden 1996:1237). They succeeded in raising $27m by March 1997 (Thomas 2001:361).

In October 1994, only four months after the NIH decision, the world's public health officials and scientists met in Geneva to discuss whether the WHO should approve of efficacy trials being undertaken generally. The WHO Committee came to a different decision. It recommended that 'any decision to go ahead with a trial of any product must be made by the government of the country hosting a trial and… the governments concerned will have the full support of the WHO when they make a decision that is most suitable for their populations taking into account the benefits and chances of success, and the consequences of failure' (Moore and Anderson 1994:314).

Public health officials and epidemiologists emphasized that AIDS is different across the world in its burden, its HIV genetic subtypes, and its most common transmission modes. In some parts of the world the public health need to try something was dominant and gp120 was seen as the best candidate. The WHO recommendation gave VaxGen confidence and credibility in fundraising. The NIH's rejection together with WHO's recommendations forced manufacturers to consider other subtypes that affected poorer countries (Moore and Anderson 1994).

[12] VaxGen was initially known as Genenvax. Genenvax was required to change its name because it was too similar to the naked DNA vaccine's trade name Genevax (Thomas 2001). Incidentally, a Nature Medicine article (Gershon 1996) made this very mistake when it misspelled Genenvax as Genevax.

[13] Nowinski was known as a man with 'a Midas touch who has helped bring in hundreds of millions of dollars for other start ups, earning him the nickname 'No-lose-ski'' (Holden 1996:1237).

Thailand had favourable characteristics for staging efficacy trials. Foremost was its high infection rate. After the first cases of AIDS were reported in Thailand in 1985, rates of new HIV infections were relatively low (Phanuphak, Locharernkul et al. 1985). But between 1988 and 1989, HIV prevalence amongst injecting drug users and sex workers rose dramatically, from almost zero to 40% (Weniger, Limpakarnjanarat et al. 1991). These were amongst the highest infection rates in the world (UNDP 2004; WHO/UNAIDS 2006). There are many studies showing benefits of a low efficacy vaccine to countries that have high infection rates (see for example Farlow 2006). There was also a history of Thai collaboration with Chiron, the US Army, and Genentech (Barker 2004).

There were several disadvantages to holding the trial in Thailand. Physical trial infrastructure would need to be set up in Thailand in order to recruit and track volunteers, costing over $100m. VaxGen also needed to modify their vaccine to include the clade E strain prevalent in Thailand (Batson and Ainsworth 2001:724; Thomas 2001:362). Some claimed that it was exploitative to go to the developing world to run trials of a vaccine that was previously rejected in the US (Lurie and Wolfe 1997). Others questioned whether clinical trial participants should have access only to the best *local* treatment rather than the best treatment available *universally* (Bloom 1998). The latter would imply the provision of cocktail drugs, which would dramatically increase the costs of the trial and impact on the interpretation of the results as discussed above (Varmus and Satcher 1997). Medical ethicists were sharply divided on these questions. For example, one author in the New England Journal Medicine even compared the trials to the Tuskegee study of untreated syphilis[14] (Thomas and Quinn 1991; Angell 1997).

The Thai government approved the trial of VaxGen's modified vaccine, called AIDSVAX. Their decision, along with the WHO recommendations, contrasted with the NIH's decision. Risks were judged more in their social and economic context. This recognition was what

[14] The Tuskegee study was sponsored by the US Public Health Service from 1932 to 1972 and is the longest non therapeutic experiment on humans in medical history. It observed poor African-American men with syphilis to determine the 'natural history' of the disease, even after penicillin had proved effective and had become widely available (Thomas and Quinn 1991; Angell 1997).

Desrosiers was implicitly calling for within the NIH about the development of his live attenuated vaccines (discussed in section 8.5.3). Not only was risk judged differently but the Thai government was also deciding whether to allow somebody else to spend their money running trials as opposed to justifying the expenditure of government funds. This latter factor seems crucial because, later, a trial of AIDSVAX was also approved in the US.

9.4 The results of the trial

The trial of gp120 vaccine went ahead in 1999 and the results were released in 2003. The vaccines failed to protect healthy subjects from HIV infection (Johnston and Fauci 2007:2076). 'The complete lack of efficacy of antibody responses raised by monomeric gp120 vaccines in protection against HIV infection has been proven beyond any doubt in the world's first Phase III clinical trials of AIDS vaccines' (Girard, Osmanov et al. 2006:4064)[15].

Many scientists expressed their lack of surprise at the results. 'The vaccine did not provide any protection against infection and did not lower viral loads… it is no surprise that the VaxGen gp120 vaccine failed' (Desrosiers 2004:222). 'Most investigators involved in HIV vaccine development were not surprised by the outcome of this trial' (Letvin 1993:932).

The only success left to celebrate was simply that VaxGen managed to mount and complete a Phase III trial. 'Regardless of the ultimate results, just completing the study marks a significant achievement' (Cohen 2003c:1663). Some recognised this but it did not change the result. 'Although these studies were successfully mounted, they both very clearly showed the complete lack of efficacy of the recombinant monomeric HIV-1 envelope gp120 vaccine (AIDSVAX; VaxGen Inc, Brisbane, CA, USA) tested… Given the difficult, and as yet unresolved, challenge to elicit antibodies by vaccination that are capable of

[15] Initially, VaxGen thought there was a mistake because they admitted to finding 'absolutely no difference between the vaccine and placebo groups' (Cohen 2003b). The use of placebos made interpreting the results quite clear. But VaxGen tried to salvage something from the trial by splitting the participants into ethnic subgroups in order to find statistical significance in the results. Statisticians subsequently showed that applying more accurate techniques of analysis made the results lose their significance (Cohen 2003a).

neutralizing primary HIV-1 isolates, these negative results were expected by many investigators in the field' (Garber, Silvestri et al. 2004:397).

9.5 What can be gained by trialling ineffective vaccines?

The decisions to move gp160 and gp120 into phase III trials were the result of a mix of political, financial, ethical and historical factors. In the case of gp160, the lack of legitimacy and credibility emerged principally because it was felt that the candidate had not been put through a progressive programme of testing and iterative improvement. It had unfairly queue-jumped.

In the absence of a co-ordinating organisation, Microgenesys was able to bypass earlier phases of the testing regime. It failed to do the proper learning needed to move itself towards increasingly realistic, and expensive test, conditions. Ultimately, the entire gp160 operational trajectory failed to acquire legitimacy and credibility because, as the theory chapter suggested, vaccine development is necessarily cumulative and the knowledge acquired by undertaking a phase III trial on gp160 did not have an adequate base to build on. Trail and error is a learning tool only as long as the research process can incorporate the lessons of the error in a repeated game (otherwise it is just failure); and for this, sound governance of the testing regime is needed.

The case of gp120 displayed some differences however. The companies involved in this operational trajectory had progressed through the testing regime, but its problems highlighted weaknesses in different parts of the testing regime. It meant that whilst they had observed efficacy in some conditions and not in others, they were not able to interpret the significance of those changes for real-world use. The lack of knowledge infrastructure, such as standardised challenge stocks, virus types and antibody neutralisation protocols, served to exacerbate uncertainty.

The combination of uncertainty and inability to readily access instruments and testing resources such as tissues, primary isolates, monkeys, chimpanzees created a 'vicious

circle'. It introduced an element of gambling when one thought one had a good enough hand. Costs increased further when the development of antiviral treatments, such as AZT, emerged. Non-pecuniary, but path-dependent, costs such as the consumption of available human test subjects also needed to be considered in the decision to gamble forwards.

The NIH's decision meant that the vicious circle was not broken, and private investments in the AIDS vaccine dried up. However, VaxGen managed to attract some new investment following the WHO's encouragement and declaration of support for phase III trials. The contrasting decisions of the NIH and WHO reflect some similarity to the decisions taken by USA and USSR regarding choice of poliomyelitis vaccines discussed in section 6.6.3.

As decisions were increasingly made in the context of the vaccines' planned use, broader public health issues, such as safety, needs and costs, were likely to have had a more subjective bearing, resulting in more heterogeneous outcomes. As Jasanoff (in Epstein 1996:277) notes, the experts on these sorts of panels 'seem at times painfully aware that what they are doing is not 'science' in any ordinary sense, but a hybrid activity that combines elements of scientific evidence and reasoning with large doses of social and political judgement.' This indicates that the institutional aspects of the testing regime become increasingly important towards the innovation end of the development process. In this sense, social visions return to the fore.

But there are important differences between the poliomyelitis and HIV cases. The USA/USSR divergence occurred after standards of clinical efficacy had been established in trials whilst the NIH/WHO divergence occurred before phase III trials had been undertaken. The fact that such divergences occurred in both instances, when there was low *and* high uncertainty about the vaccine efficacy, before and after innovation one might say, suggests that socio-economic forces do not act on vaccines only after they have been innovated. Sociological and economic enquiries into vaccine choice, and vaccine product demand are therefore likely to be missing important dynamics that explain heterogeneity in vaccines.

The divergent decisions also indicate that phase III trials do not answer questions of how to proceed in the face of the vast diversity of operating conditions around the world. It suggests that there can be no one single testing regime capable of encompassing all possible technological needs, requirements and values in its evaluation. Consequently, there is little point in trying to find a technology that is 'best' or 'optimal' for everyone in every situation.

Because the gp120 vaccine candidate fared so poorly, the results of the phase III clinical trial seem to have been largely free from debates about its success, which would typically have asked questions such as 'on what basis do we choose a significance level?' and 'exactly how successful was it?' These questions dogged the Salk and Sabin vaccines long after their respective clinical efficacy trials, well after they were introduced, and the debates continued long after data started to be collected about their real-world use (Carter 1965).

Similar to the Hammon trials (see section 6.4), these trials may be forgotten in future historical accounts of the development of an HIV vaccine. Whilst Hammon demonstrated that a 'low concentration of antibodies will protect man' (Hammon, Corriel et al. 1953:1283), the HIV phase III trials did the opposite. They confirmed that an antibody response was not enough to confer protection against HIV infection. This affected future decisions about which operational trajectory to pursue. At the recent International AIDS Conference, the global health director of the Gates Foundation said, 'The road to success is littered with failure, we have to be unafraid to fail' (Picard 2008).

In addition, the clinical trials helped to establish field-based testing capabilities. For example, they prepared activists and patients for placebo controlled trials. As was the case in the Salk trials, many objected to the use of 'sacrificial lambs' or 'death by placebo' (Epstein 1996:214)[16]. Without their co-operation and the compliance of trial subjects, test results could not be shared, related and interpreted.

[16] One subject who had discovered he was in the placebo arm commented, "Fuck them. I didn't agree to donate my body to science, if that is what they are doing, just sitting back doing nothing with me waiting until I get PCP [*Pneumocystis carinii* pneumonia] or something" (quoted in Epstein 1996:214).

For HIV/AIDS, clinical trial designers and activists were brought together to negotiate aspects of the trials and learn from each other. For example, such discussions yielded grounded and tacit knowledge about the conduct of clinical trials. Fauci said that activists often had 'an extraordinary instinct… about what would work in the community and probably a better feel for what a workable trial was than the investigators [had]' (quoted in Epstein 1996:249).

For activists and participants, trials represented a means of early access to new technologies. However, their position began to shift to one where they acknowledged that placebos were sometimes in the participants' individual and collective long-term interest, 'whether they realise it or not, and no matter how many signs they paint and march around with' (Byar in Epstein 1996:250).

Clinical trial designers exclude certain population groups to remove extraneous variables and yield 'clean data' (Epstein 1996:253). Activists often objected, seeing the exclusions as arbitrary. The trade off was one where 'strict entry criteria promised an efficient trial, but one that might lack generalisability; and broad criteria meant that findings would be generalisable but that the trial would be less efficient in the short run' (Volderberg in Epstein 1996:256). In the terms set out in chapter 3, the conditions of the trial could be institutionally set to either facilitate learning more, or represent real-world conditions more[17].

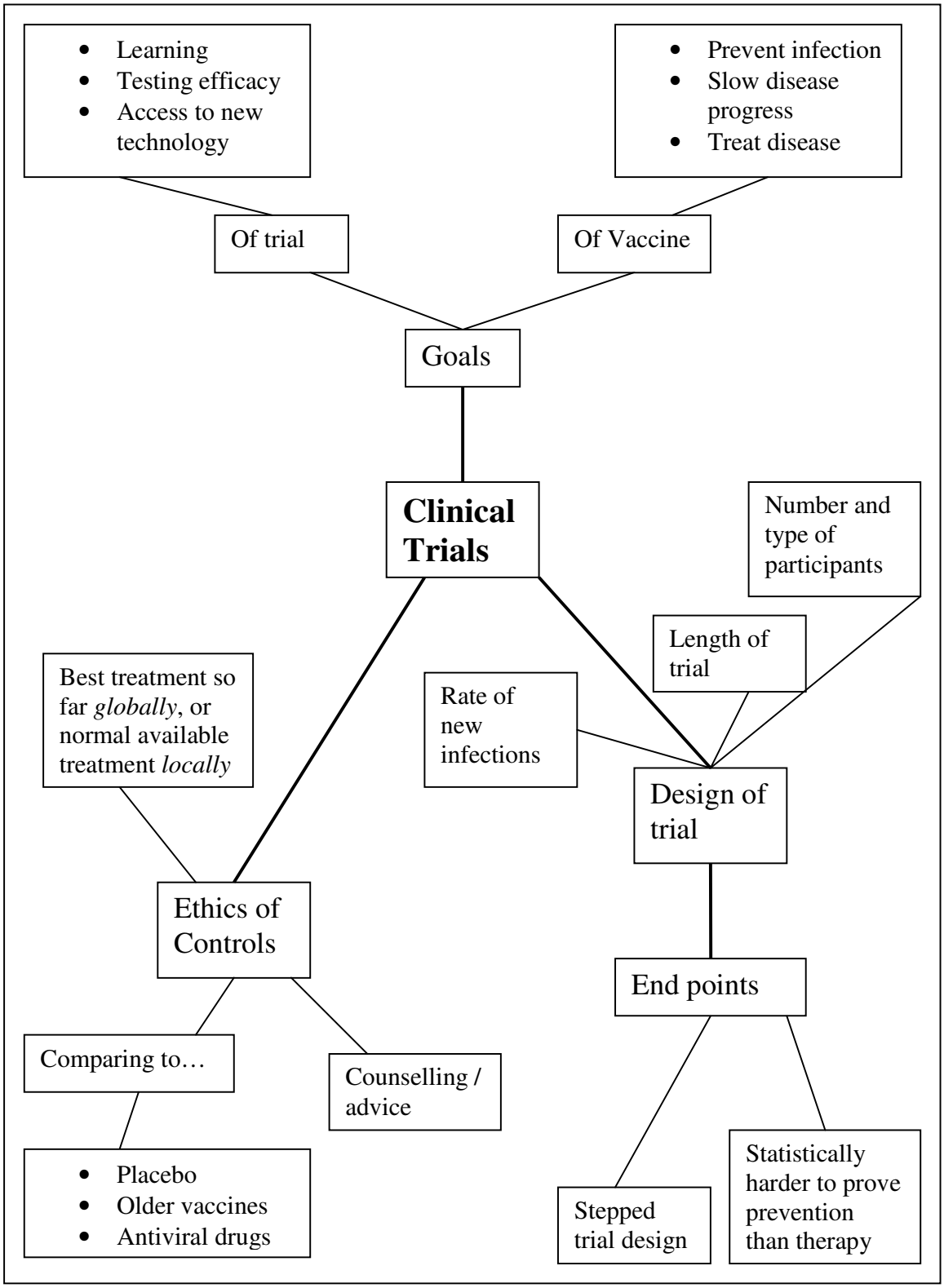
Building field test capabilities is a large, but necessary, undertaking which requires considerable co-ordination and institutional guidance (see figure 9 below). It ensures that clinical trials are feasible and can be conducted where participants conform to expected behaviour. The prescribed and constrained behaviour during clinical trials are a legacy of the last set of 'relevant' conditions in the testing regime where technological knowledge was accumulated, typically characterised by phase I or II safety trials.

[17] Contaminants could be re-framed as virtues and warrants of validity. They were difficult real-world conditions, not artificially pristine laboratory ones.

In the cases of the gp160 and gp120, it fell on the shoulders of industrial scientists to negotiate with the governments of the US and Thailand, and to build the needed capabilities for clinical trials. However the activity yields little theoretical or scientific knowledge, and may be less attractive for academic scientists. It then effectively becomes a market-driven process, with consequent limitations in the way that the field trial can inform the overall research challenge.

Therefore, poor candidates, such as gp120, and even weaker candidates, such as gp160, may reach expensive clinical trials when the testing regime is weak. It struggles to differentiate between other candidates tested in cheaper learning conditions, and to accurately predict effectiveness of the operational principle. The testing regime influences field trials and the subsequent capacity of the research community to learn from them because, as summarised in figure 9, there may be constraints the design of trials, changing ethical and social norms, and the goals of the vaccine being tested. The relationship between the testing regime and the goals of vaccine design is discussed further in the next section.

Figure 9: Clinical trials require coordination



9.6 From HIV vaccine to AIDS vaccine: admitting defeat?

9.6.1 A new vision

Since the late 1990s, expectations of a vaccine against HIV shifted to a new perspective. 'It is not time to give up on HIV vaccines but to change the way we pursue them' (Gallo 2005:1898). Scientists had known that, 'the window of opportunity to clear HIV and prevent long term, established infection may close permanently once a pool of latently infected cells is in place' (Johnston and Fauci 2007:2074). Aiming to prevent the 'latent infection' that Johnston and Fauci refer to, sets the standard for an effective HIV vaccine very high. It not only needs to provide high levels of protection, it needs to do it very quickly. Achieving such a standard is unprecedented as Johnston and Fauci (2007:2074) explain. 'This aspect of HIV infection puts it in sharp contrast with almost all other viral infections, in which the initial rounds of viral replication do not establish a permanent reservoir of infection. For this reason, HIV poses a greater challenge to the classic vaccination paradigm in which prevention of clinically relevant infection ultimately leads to the eradication of the microbe, even though initial rounds of viral replication may occur.'

Graham makes a similar point but suggests that we need to aim for other, lower, goals. 'It is unlikely that vaccine-induced immune responses will be able to prevent the establishment of [HIV] latency… A more realistic initial goal for HIV vaccine development is to dampen the initial viremia in an infected individual, maintain a low virus load, and prevent progression to AIDS' (Graham 2002:208).

Desrosier's inability to explain his finding of live vaccine protection (section 8.5.3), and Stott's (section 8.5.1) explanation of killed vaccine protection in his controls, together with the phase III results of the subunit vaccine all ushered in a new mood that protective efficacy simply could not be achieved. The question of aiming for a lower standard of delaying or preventing disease became more pertinent.

I refer to the shift in emphasis away from infection and onto disease progression as a shift away from hoping for an HIV vaccine to developing an AIDS vaccine. Smith crystallises

such a shift in a short sentence, 'vaccination, which may not affect the infection rate, may prevent disease' (Smith 2002:107). Preventing progression to disease, however, was not the only reason for a shift towards an AIDS vaccine. Other benefits of an AIDS vaccine which lowers virus load are that it could also reduce transmission within the population[18], diminishing the spread of the epidemic. These side-benefits had now become re-framed as more central virtues.

The technological vision outlined in section 7.1 was re-shaped into a new, more modest but more complex, form[19]. The new vision implied that whilst HIV infection may not be prevented, the onset of AIDS could be prevented or delayed, symptoms made less severe, and the prospect of HIV transmission to another person could be vastly reduced. Vaccines need no longer be seen as the traditional injection that provided complete invulnerability to a disease environment. They were a substance that exploited the immune system for some kind of perceived or actual benefit that blurred the lines between a preventative prophylactic and a therapeutic treatment[20]. The prospect of an AIDS vaccine gave rise to a new choice between normal treatment drugs for an infected population, and a vaccine-drug for a healthy population to slow disease progression *should* they become infected.

Thus the testing regime worked to some extent in that it forced researchers to confront more honestly the formidable biology of HIV. The testing regime helped recognise that any vaccine that might appear soon would not act fast enough to protect the body from infection. The lesson was that complete protective efficacy would have to wait; perhaps until a low efficacy vaccine could be used as a stepping stone to accumulate further technological knowledge. As IAVI's vaccine blueprint notes, 'The next major advance on the way to the *ultimate goal* will be the first demonstration that a candidate benefits humans, by delaying the onset of disease… This *intermediate achievement*, even if it does not lead directly to a licensed vaccine, would help solve key riddles that have impeded

[18] Efficiency of transmission is directly related to plasma virus levels (Johnston and Fauci 2007).
[19] Pondering a question as fundamental as whether we are developing an HIV vaccine or and AIDS vaccine after a decade of effort reflected the fading overconfidence with which scientists began the vaccine search when Margaret Heckler famously predicted it would take only two years (see section 7.1.1).
[20] This has given rise to the exciting concept of cancer vaccines, where the immune system is primed to identify and kill only cancer cells and not healthy cells.

advances, give researchers a platform on which to improve, and attract investment and creative energy to the field' (IAVI 2008a:1).

9.6.2 Rigidities in and around the testing regime

With respect to the new vision outlined above, there were several rigidities in the testing regime that had formed around the original HIV vaccine vision and the notion of a traditional vaccine. Firstly, the MicroGeneSys debacle most likely damaged the credibility of any vaccine approaches focussing on disease expression for the foreseeable future. Such effects indicate that the testing regime is part of a path-dependent search, where altering entrenched goals and mismanaged tests of the past may incur additional costs in the present or future.

Secondly, other findings in the 1990s also prompted concern over the goal of the vaccine. Vaccinated monkeys who had failed to resist challenges and became infected often fared better than the unvaccinated controls in terms of suffering fewer opportunistic infections, less pervasive SIV infections (for example lymph nodes only and not blood infected), lower viral loads, and generally staying alive for longer (Shafferman, Lewis et al. 1992; Shafferman, Lewis et al. 1993).

This new emphasis called for a lot of old data to be reanalysed, but in many cases the monkeys had died, or the surviving 'failed' monkeys had been killed off. Even for the monkeys that were still alive, researchers would need more resources such as laboratory space, extra cages, and more personnel to care for the monkeys. These are practical issues one might call 'research infrastructure' and they are critical in making a testing regime strong. A scientist-led funding environment that calls for new and more research is likely to overlook this by favouring requests that detail new research ideas rather than proposals that ask for more resources to strengthen infrastructure.

Thirdly, if an AIDS vaccine candidate (rather than an HIV vaccine) were to reach clinical efficacy trials, there would be difficulties in setting an end point to the trial. The often long incubation period (decades) between infection and disease means that staging a trial with

disease as the clinical endpoint would require many more years and many more people to reach a statistically significant answer[21]. Participant retention may be challenging and costly. In cases where disease does occur, examining whether symptoms are more or less severe would require considerable re-conceptualisation of what is and what is not feasible in clinical efficacy trials. Few tests exist to detect subtle but important changes in patients that may occur. All of these issues suggest that new ways of looking at the virus also demand new ways of looking at the testing regime.

This shows how the complexities of the testing regime shapes the characteristics of the technology being tested, the characteristics in this case being prevention of or delayed onset of disease or symptom alleviation. The rigidities of the clinical trial design had a direct influence on the goals and aims of HIV (or AIDS) vaccine research and development. Constructing a testing regime that is sensitive enough to detect a non-traditional vaccine may be prohibitively expensive.

These deductions arrive at a peculiar conclusion: aiming for a vaccine of lower efficacy could cost more to develop due to testing requirements. This finding is likely to be generalisable to developing vaccines against other pathogens too. Thus, the move from laboratory idea to clinical efficacy trials and use in public health is a multifaceted and complex transition that begins from the early evolving technological vision of the vaccine and its testing regime.

Fourthly, even if such an AIDS vaccine was accepted through clinical trials, Johnston and Fauci contemplate further implications of disseminating such a vaccine. '[These] vaccines represent uncharted territory, and their use may have outcomes that challenge researchers and regulators alike. If proven successful, a disease-modifying [AIDS] vaccine would also present new challenges for the entire public health community, since it would not be a stand-alone preventive measure, as are most classic preventive vaccines. Instead, it would

[21] This assumes that the rate of new infections is constant. The length of the trial, the clinical end point chosen, the rate of new infections and the number of participants are four variables which are all closely inter-related. Changing one directly impacts on the others (interdependencies are depicted in figure 9).

need to be delivered in the context of a comprehensive HIV-prevention program' (Johnston and Fauci 2007:2073).

A low efficacy AIDS vaccine runs the possibility of misleading some people into a false sense of security, and influencing them to employ other means of protection less often or less consistently. Practicing more risk behaviour, rather than less, could limit the impact of the vaccine somewhat. Also, the existence of a moderately effective vaccine could make future testing of other, possibly more effective vaccines much more difficult and less of a priority.

Many scientists now believe that an HIV vaccine in its traditional sense is impossible or unlikely (Connor and Green 2008). Some retain hope that an imperfect or low efficacy vaccine is possible. These kinds of vaccines are likely to be of significant value to public health in contexts where infection rates are high and 'herd immunity' may be achieved (Mclean and Blower 1993; Garnett 2005; Farlow 2006). However, this section has suggested that the possibility of a new paradigm of vaccination, led by a putative AIDS vaccine with treatment and prevention blurred, also needs attention to the development of a relevant testing regime, as have previous vaccine paradigms.

Chapter 10

Conclusions

This chapter summarises the main outcomes of the research and discusses implications for theory and policy. It also makes some recommendations for future research and discusses limitations of the study.

10.1 Summary

This thesis has been concerned with the rate and direction of vaccine innovation. Technical change in vaccines is widely recognised as requiring urgent policy attention. The analysis in chapter 2 found that current policies towards this are implicitly based on what may be termed as 'demand-pull and science-push' models of innovation. It was argued that these approaches, whilst beneficial in thinking of an overall policy set, are likely to understate the inherent uncertainty involved in vaccine innovation. An implication of this, is the importance of infrastructure that allows researchers to learn. The chapter located the idea of 'testing regimes' within theoretical perspectives on science and technology policy.

The thesis introduced and developed concepts of the testing regime, operational principle, and social vision. As discussed in chapter 3, they draw on evolutionary theories of technical change, engineering studies, and social theories of technology respectively. It is argued that these concepts, by providing greater insight into the knowledge and innovation process, may help develop better policies in conjunction with prevailing sociological, political and industrial perspectives.

The testing regime is argued to be a set of governed instrumentalities that create intermediate conditions central for learning and technical development. The thesis shows how testing regimes, when set in the context of social visions, can be a useful lens for tracking and exploring the development of operational principles in the innovation process.

It suggests that the emergence of certain vaccines is dependent on the ability to test and learn, and on an infrastructure that facilitates cumulative knowledge growth. It argues that these are important issues about the production of technological knowledge, as distinct from scientific knowledge, that need to be addressed for innovation to proceed.

Chapters 4 and 5 emphasised the importance of analysing these issues in sufficient detail, and in cases of failure as well as those of success. As such, the study undertook a survey of historical and scientific literature about a case where multiple vaccines were developed and another case where a vaccine was not developed, despite significant investments.

The concepts of testing regimes, social visions and operational principles were applied in the empirical chapters of the thesis (6, 7, 8 and 9). They show that vaccine research into poliomyelitis and HIV have been led by contrasting social visions, features of the testing regime and development of operational principles. These points are elaborated below.

10.1.1 Poliomyelitis vaccine innovation

Chapter 6 argued that a strong and inclusive social vision was necessary before a significant technological effort could begin. Crucial to initiating the innovation process was an increasingly specific *characterisation* of the condition as a disease, eventually named as poliomyelitis, after a series of previous names which reflected different characterisations. As Rosenberg (2002) suggested, once a predictable life course was outlined for the disease, it organised social and economic resources around the particular phenomenon of poliomyelitis.

By identifying an infectious agent, Landsteiner's *cause specification* allowed the technical community to rally around a vision for a vaccine. Flexner's optimism about the possibility or *expectation* of a vaccine was publicised to the wider community just as a major poliomyelitis epidemic was taking hold. The affliction of Roosevelt added to the perceived importance of conquering the disease. Together, these factors helped to mobilise resources and attention to poliomyelitis. However, Roosevelt's involvement in setting up an organising foundation was perhaps more significant in the development of a testing regime.

As a result, the search for a poliomyelitis vaccine was uniquely led by non-private administration – this is likely to have affected the norms and values of the vaccine developers.

The Brodie-Kolmer failures were perhaps indicative of these norms, which valued urgency and immediacy of testing. But the failed trials indicated that the testing regime was initially weak. Researchers had not learnt enough about the virus, instrumentalities were poorly developed and efforts were not well co-ordinated.

In order to accumulate technological knowledge, the National Foundation for Infantile Paralysis adopted a leading role to ensure certain features of the testing regime were developed. The need for virus and monkeys was met by supporting the development of tissue culturing and the establishment of a monkey farm. This allowed more tests to be done in intermediate conditions and their results to be fed back quickly. A large project to type polioviruses was also undertaken to provide crucial knowledge about which strains the vaccine would need to provide protection against.

The Hammon trials strengthened the testing regime by continuing the effort to turn subjective design aims into objective specifications. Thus qualities such as strength and durability of immunity were translated into measures of antibody concentration. The trials also improved field-based capabilities for more scale-intensive testing. Various indices were developed[1], and these scales formed an important part of the standardised knowledge infrastructure against which field tests could be evaluated. The Foundation strengthened its administrative capacity for coping with the logistics of large scale immunisation and co-ordinating the supply of testing resources. Fostering public support was important for ensuring that there were enough volunteers and gamma globulin to test with. The trials provided all vaccine designers with an important correlate for immunity, a design standard, by showing that relatively little antibody was needed for efficacy.

[1] Firstly, an index was developed to gauge how much antibody was needed for immunity in monkeys. Secondly, the trials allowed a similar index to be constructed for humans, which addressed crucial questions about the longevity and efficacy of neutralising antibodies for human immunity. Thirdly, graded scales were developed to measure varying degrees of severity in the symptoms of poliomyelitis.

The availability of disabled children and prisoners (and lower ethical standards than apply today) helped Salk and Sabin to test early versions of their vaccines. The operational trajectory forged by Salk went against scientific orthodoxy, and the Foundation mediated differences of opinion about efficacy, safety and when to test. One principal means for doing this was to strengthen the test by insisting on an unprecedented placebo arm, against the wishes of the main vaccine developer[2].

Sabin developed a different operational trajectory, but faced a scarcity in testing resources in the wake of the Salk trials. Although Sabin found significant sums of money to fund research, the number of remaining vaccine volunteers in the US were limited and he had to conduct tests of his vaccine in the Soviet Union. Testing in a different country emphasised the relative components of successful innovation because the conditions in, and the requirements of, the Soviet Union were significantly different.

As technological knowledge accumulated, the testing regime needed to adapt to ensure that test-results remained stable and conclusive. However, this was not the case, and there was a weakening of the testing regime in the face of technical advance. As tests became less conclusive, different researchers began to promote their respective vaccines. At this stage, the institutions in the testing regime played more dominant roles because conditions of use are less shared than they were in the development stages. The USA and USSR are different, but their laboratories were probably less so.

10.1.2 HIV/AIDS vaccine innovation efforts

Chapter 7 argued that the initial rate of technical change in HIV vaccine development was slow because there were competing social visions about how the disease should be addressed. Its association with drug users and homosexuals led to the absence of co-ordinating visions. Even for the technical community who wanted to pursue a vaccine, there remained competing visions about which approach should be used, despite a wide-

[2] Salk described the placebo arm as a 'fetish of orthodoxy' (Carter 1965:192).

scale dominance of the reductionist sub unit approach using molecular biology (chapter 8). The scope for multiple competing visions remained large well into the development process, and mechanisms for resolving them suffered from difficulties in characterisation and causes of the disease, resulting in widely varying expectations of what a vaccine could or should do.

Characterisation of the illness was difficult because deaths were due to indirect causes[3], and all that was initially known was that the immune system was somehow weakened. The disease was originally overshadowed by its social interpretation and the illness was connected to homosexuality (GRID). The deaths were subsequently connected to a broader pattern and renamed as a less specifiable syndrome (AIDS). Thereafter, the origins and *cause* of AIDS remained unclear for a decade, and many contested the identification of HIV as the cause of AIDS. For those in the technical community who felt that AIDS was adequately characterised and HIV was sufficient as its causal explanation, the *expectations* of a preventative vaccine were publicly optimistic, as they were for poliomyelitis. But for many in the wider community, there was apathy for those most at risk to AIDS. Many felt little or no imperative to act, despite optimistic forecasts.

Part of the shift to a broader and more stable perspective of the syndrome was facilitated by the development of HIV diagnostic tests and surrogate markers. The use of diagnostic tests strengthened the case for HIV as the cause for AIDS, whilst prompting stronger concerns about its spread through to the 'general population'. However, the vast range of surrogate markers indicated that AIDS remained poorly characterised and required shared knowledge growth. Visions for what a vaccine should achieve struggled to find common ground beyond the basic premise that a diagnostic blood test should remain negative after a vaccinated person has been exposed to the virus. Nevertheless, it was an instrument that provided a crude but tangible goal for vaccine designers.

Strengthening the testing regime was hindered by two salient characteristics of the virus. Firstly, the virus exhibits extreme variation. This placed great pressure to design a vaccine

[3] Patients succumbed to a variety of opportunistic infections.

that gets to work quickly before the virus has time to change. After an individual is infected, the window of opportunity is very small within which an effective immune response must be mounted before the virus becomes too varied and sequestered. Rapid evolution of the pathogen also introduced a strategic element in vaccine design that centred on the question of how many targets represent 'enough' to overcome the possibility of viral resistance.

Secondly, humans lack sterilising immunity for HIV and cannot clear the virus after infection. Natural sterilising immunity would provide research clues from the body's immune response to the virus. This means that researchers lacked a natural mechanism to mimic for vaccine design. It also made testing prototypes in humans dangerous and precluded a lot of early stage trial and error learning. These two characteristics of the virus have imposed difficult vaccine design constraints.

Chapter 7 described the representation of animals as intermediate conditions, a part of the testing regime that allows changes to the operational principle to be tested for reliability and relevance. Animal models were described as stepping stones to vaccine trials in humans. In this way, they have provided a solution to the problem of trialling vaccines against pathogens to which humans do not have any natural sterilising immunity. For other diseases[4], where animal models have not provided adequate intermediate conditions, it was still possible to forge ahead with a 'guts and judgement' approach for those viruses because natural sterilising immunity existed in humans.

The problem in the case of HIV was that both hurdles need to be crossed: a lack of natural sterilising immunity *and* a lack of animal models. This combination, the thesis argues, is a key element in explaining the lack of success in HIV vaccine innovation that has been overlooked in previous studies of vaccine innovation (for example Archibugi and Bizzarri 2004; Blume and Lindner 2006; Chataway, Brusoni et al. 2007).

[4] For example, measles, mumps, rubella, and varicella (see section 8.1.2).

However, chapter 7 noted that focusing solely on these hurdles is an over-simplification. Whilst natural sterilising immunity is an exogenous constraint, the lack of animal models is not necessarily so. Animal models did not simply appear ready-made to be taken 'off the shelf' to provide intermediate conditions. Their use as 'models' was dependent on a considerable body of knowledge. Animals were used in conjunction with techniques, skills and instruments and were thus moulded into standardised conditions from which shared interpretations and inferences could be made about realistic operating conditions.

Animals were, in this sense, fabricated through the use of techniques such as genetic engineering. They needed to be supplied, fed, observed and looked after. They needed to be selected for their appropriateness because, for example, monkeys offer different possibilities than those offered by chimpanzees. In short, there was considerable scope for variation in the use and manipulation of animals for the purposes of technological development.

This variation in experimental conditions was a key reason why institutional guidance was required to co-ordinate and standardise R&D efforts towards technological, rather than solely scientific, goals. Such an instrumental perspective of animals meant that governance was also required to mediate concerns about animal rights with those of technological development.

10.1.3 The direction of inventive efforts in HIV/AIDS vaccine innovation

Chapter 8 showed that a weak testing regime could impact on the selection and development of operational trajectories. The combination of both a lack of suitable animal models and a lack of natural sterilising immunity impacted on not only the rate but also the direction of innovation because the combination had differing implications for differing vaccine approaches.

For whole-virus approaches, the inability of humans to clear HIV infection accentuated safety concerns and emphasised the need to develop a vaccine through intermediate conditions provided by animals. However the lack of animals, or instrumentalities for

developing them into good models, meant that such intermediate conditions were not forthcoming. In the laboratory, conditions were too artificial to develop efficacy by trial-and-error; whilst in humans, there was too little room for error in order to learn safely. This favoured operational trajectories that were seen as more rational, less dependent on intermediate conditions, and altogether safer regardless of how tried and tested other approaches proved to be in the past.

The subunit approach suffered from a lack of vaccine knowledge for other viruses. All vaccines in the past have used whole viruses, with only a single exception where a subunit was used. Scientists and companies pursuing this approach lacked skills and acquired capabilities. Most private actors adopted the subunit approach as part of a broader effort to develop a platform of biotechnology competences from which they could launch into other markets.

Viral diversity and the lack of natural sterilising immunity also affected the various approaches differently. Whilst the lack of natural sterilising immunity undermined the safety of whole vaccines, it drew attention to the increased safety of an approach that relied on only small antigenic parts of the virus. However, the efficacy of such an approach was most susceptible to viral diversity precisely because it only relied on small antigenic parts of the virus. Viral diversity meant the subunit approach needed highly specific instruments and techniques to facilitate efforts to find conserved non-variable regions, such as the V3 loop. This places greater pressure on policy to support the development of a different set of instruments than in other approaches.

The trajectory also raised the possibility of having to find different conserved regions for strains of viruses in different parts of the world. This exacerbated concerns about global inequities in the development of, and access to, new health technologies. This also raised additional policy questions about the testing regime and its impact on the direction of innovation for certain groups of people compared to others.

Later, the importance of another approach came to the fore. In addition to requiring antibodies to protect cells from being infected, it became clear that a cellular immune response would also be needed to deal with cells that were infected. This implied that researchers thought that a vaccine may not be able to prevent infection completely and vaccine efforts were increasingly viewed in terms of 'damage limitation'. The issue was that the subunit approach was not very good at stimulating a cellular immune response, especially when compared to the live vaccine approach. Rather than defer to the development of live vaccines, private sector researchers attempted to develop new approaches.

Private sector efforts were lacklustre and narrowly focussed on biotechnological approaches. They suffered from takeovers from large pharmaceutical firms, faced intra-firm competition for resources and an overall lack of finance. The problem of designing an effective vaccine was perceived as being extremely difficult, and any solutions to be a long way off. Market rewards were thus heavily discounted and most likely played little role in firms' investment decisions. Firms faced a scarcity of testing resources, in terms of animals and virus, their work was fragmented due to a lack of organised comparability, and there were testing constraints due to the effects of prior smallpox vaccination.

The subunit approach remained dominant, as live and killed vaccine approaches were stalled due to weaknesses in the testing regime. Problems in the killed vaccine approach, when Stott used monkeys as intermediate conditions, may have been identified earlier if more monkeys were made available. The opportunity to improve learning conditions with better instrumentalities seems not to have been taken. Monkey cell lines were not developed to allow monkey-monkey tests, where SIV grown in monkeys (rather than humans) is used both for vaccination and subsequent challenge. Attempts to re-frame the problem as the basis for a new operational trajectory were thwarted by limited scope for creating intermediate conditions. Furthermore, central to the approach was a relativistic and differentiated view of the need for, and risks of, organ transplanting around the world.

The live vaccine approach seemed promising, even in conditions that were more stringent and realistic than those of subunit approach tests. But, again, there was a reluctance to consider risks in relative terms. And the skills of endocrinology were not called upon to develop the instrumentality of monkey twins. Technological development thereafter evolved along a path-dependent 'subunit-approach' trajectory.

10.1.4 HIV vaccines in clinical efficacy trials

Chapter 9 discussed the role of the testing regime in deciding at which point in a trajectory its operational principle should be subjected to large scale efficacy testing. The case of MicroGeneSys showed that a poor vaccine candidate could not be easily eliminated from others for phase III testing because the testing regime was weak. MicroGeneSys's vaccine performed poorly and the trial indicated how urgently institutional leadership and guidance was needed to mediate conflicting interests over the terms of the test. For example, MicroGeneSys resisted comparisons to other vaccines, and contested the controls and the end points of the trial.

Chapter 9 argued that the way in which phase III trials were staged showed that the subunit vaccine was selected and developed in a weak testing regime. The move to large scale field-tests of poliomyelitis vaccines was also difficult, but the uncertainties about the subunit HIV vaccine seems to have been more problematic.

There were arguments to proceed with the trials. Antibodies were thought to provide protection, but their mechanism was poorly understood. Industrial actors stressed a 'vicious circle' in which most, if not all, of their commitment to HIV vaccine development was staked on their ideas thus far being tested in phase III trials. The subunit approach was not thought to pose a significant safety risk to volunteers and past experience with hepatitis B had been positive. The trials were an opportunity to be seen 'doing something'.

There were arguments against going ahead with the trials. Antibody titrations were often not conducted in a standardised and comparable way, and test conditions were too varied. Crucially, the titrations relied on laboratory-adapted viruses rather than primary isolates.

Laboratory-adapted viruses represented artificial conditions, whilst primary isolates represented more realistic conditions. Results of tests with monkeys were difficult to interpret because they dealt with SIV rather than HIV. Tests on chimpanzees were done with HIV but, owing to their expense, such tests were few and far from systematic.

Such tests also suffered from two examples of weak knowledge infrastructure. Firstly, challenge stock was poorly developed. Researchers inferred that it took more HIV to infect a chimpanzee than humans, but they were not certain how much more. They were not certain how critical HIV infection dose varied by animal species and virus type. Secondly, virus type was not catalogued systematically by observing different immune responses in animals (as was done for poliovirus), but rather proxied by deviation from the V3 loop, an extremely small fragment of HIV. Such extrapolation undoubtedly saved animals and expense, but added considerable uncertainty.

The NIH decided not to proceed with the trials. But public health officials at the WHO made a contrasting recommendation. The WHO committee emphasised that risks and benefits can be different for different countries around the world. They endorsed trials in Thailand, but did not offer further guidance on the tests' difficult ethical and analytical issues regarding access to cocktail drugs for trial participants. The vaccine was unanimously accepted as ineffective.

The trials served to strengthen the field-based testing regime, playing a similar role to Hammon's trials of poliomyelitis vaccine. The HIV trials confirmed that antibodies on their own cannot confer immunity (Hammon confirmed that they could for poliovirus). The early trials were similarly useful for capability-building. The need for placebo trials was affirmed, and the chance to renew and build skills for designing, administering and executing a large scale test was taken.

The differing decisions taken by the US and Soviet Union, and the NIH and WHO, suggest that a single phase III trial is not capable of accommodating the vast diversity of technological needs and values around the world. There can be no best or optimal

technology for all people in all situations and vaccine choice in the latter stages needs to be a more socially inclusive process that is likely to stress institutions more.

Chapter 9 also suggested that the testing regime had locked researchers into aiming for a standard of vaccine that is higher than widely desired or expected. This refers to the lower goal of an AIDS vaccine that slows down disease through an immune response, and to the higher goal of an HIV vaccine that triggers an immune response which completely prevents infection. The chapter argued that testing constraints and rigidities make it more expensive to focus vaccine development efforts on an AIDS vaccine. The chapter suggested that this may be a potentially new paradigm of vaccine innovation and deployment, but it is unlikely to emerge in the current testing regime.

10.2 Theory and policy implications

There is a strong and urgent need for an AIDS vaccine and substantial investments have been made to encourage its innovation. However, there is large variance in vaccine innovation, and various explanations and policy recommendations have been forwarded by sociologists, economists, and scientists.

This thesis has focused more squarely on the knowledge production stage and identified a missing dimension in existing explanations. This draws on the idea that innovation requires technological knowledge, taken from literature on technological change, histories of technology and studies in engineering.

The empirical chapters supported the idea that vaccine design cannot be simply deduced from scientific principles. It supported the notion that the design of operational principles can follow different technological trajectories, such as the subunit vaccine approach, and that these trajectories can then be refined into yet more technological sub-paradigms, such as vector-based subunit approaches.

The thesis used the testing regime lens to argue that vaccine innovation has become increasingly indirect and iterative. This resonates with recent evolutionary theories about the increasing prevalence of 'offline' testing (Nelson 2008a; Nelson 2008b). The thesis has added to theory by showing how the testing regime is an environment in which the manipulation of intermediate conditions (rather than offline or online), with well-developed instruments and tacitly acquired skills, is a governed process that leads to the accumulation of technological knowledge.

The thesis has suggested that in testing regimes, deadlocks in the growth of knowledge may be released with the development[5] of instruments and skills because they can help make critical changes in testing conditions. However, the thesis has also emphasised that the inter-relationships between newly acquired findings are as important as the findings themselves. Findings in monkeys, need to be related to findings in chimpanzees, which both in turn need to be related to humans. The thesis concludes that the production of technological knowledge requires institutional guidance in order to encourage cumulative growth and limit fragmented growth.

The thesis has suggested that the growth of robust knowledge is scaffolded through projects such as virus typing and developing challenge stock. Although the validity of knowledge is enhanced through testing in varied conditions, governance is also needed to set standards that make the findings of one research group more relevant to another. It is in these institutionally standardised conditions that reliability is then established through repetitive and intensive tests, such as phase III clinical trials. In this sense, socially produced knowledge becomes stabilised technological knowledge when it is true, shared and integrated.

The empirical chapters also suggested that as products emerge from testing regimes, and are anticipated to enter the real world, competing social visions return to the fore. In this phase of product development, the way in which a number of features are socially framed becomes important.

[5] Development may simply mean making old instrumentalities more widely available.

These findings can be generalised across fields such as biopharmaceuticals (defined in section 2.5), where contexts of technological application are highly systemic, and the systems (such as human bodies) are non-linear, non-decomposable and non-scalable. The generalisations are limited however when one ventures into fields where technical experts play a less central role, and users are more prominent in shaping technical change. Sectors where users play important roles extend beyond craftwork, to increasingly lucrative industries such as computer video games, music and fashion tailoring (von Hippel 2005; NESTA 2008). In such contexts, users may be subject to more varied modes of governance and institutional norms than required in a testing regime. Moreover, the indirect environment afforded by a testing regime becomes a disadvantage, in that it is more likely to result in innovations that users are dissatisfied with. The findings of this thesis do not generalise to such fields where users play more active inventing roles and, at the very least, conclusions derived in this thesis should be extended with extreme caution with respect to how instrumentalities are employed in less institutionalised environments.

Some critical policy steps can be identified from the testing regime framework presented in the thesis. Instrumentalities, which are made up of instruments, skills and capabilities, need to be nurtured and developed because they are essential to the manipulation of conditions for learning. Institutions, which govern vaccine research and development, are needed to accumulate knowledge for innovation.

This may take the form of ensuring the plentiful supply of reagents, monkeys, chimpanzees, test-subjects, and instruments. The work will require highly skilled personnel, so HIV vaccine development needs to attract experienced vaccinologists, who can also offer technological training to younger researchers well-versed in scientific methods. This is likely to require stable, consistent and non-contingent institutional funding.

Policy makers should also consider offering contracted research grants as a complement to investigator-initiated research. This is because the development of new instruments, techniques and knowledge infrastructure may require targeted strategic attention. Well

funded investigator-initiated research may yield exquisite science, but contracted grants will ensure mundane research is undertaken systematically. It is likely that both will be essential for innovation.

Strengthening the overall testing regime by undertaking these steps is likely to accelerate vaccine innovation. However, strengthening different elements of the testing regime may have uneven effects on the rate of innovation, the direction of innovation, and the decision to test in clinical efficacy trials (suggested by chapters 7-9 respectively). So improving the supply of animal models may have stronger effects on the rate of innovation, developing instrumentalities may have a stronger effect on the direction of innovation, whilst improving governance, co-ordination and leadership may exert its strongest effects in clinical trials and the later stages of vaccine development. It should be noted however, that these are merely differences in emphases of various policy options. Each policy option is likely to have overlapping and helpful outcomes.

10.3 False dichotomies and technological knowledge

A number of policy dichotomies misrepresent the role of technological knowledge accumulation as examined in this thesis. Economists argue that well funded market policies will induce vaccine innovation whilst scientists assert that laissez-faire science push policies will eventually deliver a vaccine. Both neglect the role of technological knowledge in innovation. Market policies may play a more important role later in the innovation process, but they are less relevant at this stage because many companies perceive innovation to be so far away, or even impossible (Batson and Ainsworth 2001). Thus, market rewards become heavily discounted or even irrelevant.

This thesis has contributed by showing that focussing on examples of centralised research successes or failures, such as the Manhattan Project or the Virus Cancer Program, misses a very significant issue for innovation. Wilson et al.'s (2007:35,36) conclusion that 'mission mode is appropriate only when the path to success is relatively clear' and that 'what matters is whether rapid progress in following up on existing ideas is more important than

generating new ideas' implies the important question is *when* should research be co-ordinated or decentralised. This thesis has suggested that certain kinds of research activities generate technological knowledge needed for innovation. These activities require governance to set up and maintain *throughout* the innovation process.

Similarly, attempting to distinguish between basic and applied science (see Calvert 2001), neglects the role of technological knowledge in innovation. Stokes' (1997:73) influential framework attempts to reduce the tendency of policy makers to pit basic and applied research against each other. He suggests that the spectrum be orthogonally split into a two dimensional grid where the motivation to improve understanding lies on one axis and the motivation to improve use lies on the other. This gives rise to four quadrants, one of which accommodates concerns for both use *and* understanding (labelled as 'Pasteur's quadrant'). This thesis provides examples of research that might fall into Pasteur's quadrant with its detailing of cases such as the virus typing project and development of challenge stock.

However, Stokes' reconciliation does not seem to be borne out by HIV/AIDS vaccine scientists, many of whom find notions of use an encroachment on academic freedom. For example, a renowned biochemist working on HIV wrote 'We do not need an 'AIDS Manhattan Project', the centralisation of the atomic bomb had more to do with national security reasons than with scientific ones. What we do need is an emphasis on small basic research projects aimed at better understanding HIV's interactions with the human body; such projects are already underway…' (Moore 1993).

Moore also wrote, 'This approach is contrary to the way in which all great scientific discoveries have been made – free spirited questioning of the unknown in investigator-initiated research projects. To apply office-management techniques to the utterly different discipline of the laboratory displays a profound ignorance of scientific research' (Moore, quoted in Cohen 2001b).

In defending academic freedom, Moore neglects the ultimate issue, which is one of *technological* innovation and not 'scientific research'. A linear model appears to underlie

his comments, where technological innovation is believed to inevitably follow scientific progress. Issues such as testing resources, instrumentation, animal models, and knowledge infrastructure do not feature in his policy prescriptions. The HIV/AIDS vaccine problem for Moore, and those who share his view, is clearly one of not enough 'free-spirited' science[6].

Vaccines have been critical to the elimination of disease at global and local levels. But what emerges clearly from this thesis is that they are difficult to develop, and they need to keep up with evolving disease ecology and changing social contexts. A system is needed that can not only develop vaccines for an array of diseases, but can achieve this again and again. This thesis has argued that vaccine innovation should be examined as a process of accumulating knowledge, one that is embedded in a social system.

However, these contemporary debates tend to view vaccine innovation as a one-off event that is framed by dichotomous explanations. So vaccine innovation may be induced by market forces or deduced from scientific understanding, or it can be leveraged by altering the balance of basic or applied science, or it may be brought about by encouraging free-spirited investigation or establishing strategic targets. Focusing on the accumulation of technological knowledge, this thesis reveals not only how arbitrary these segregations can seem, but it also shows that establishing a sustainable vaccine innovation system is - more importantly - what is at stake.

The testing regime lens highlights parts of the public infrastructure needing investment and maintenance if we are to create a vaccine system that is responsive, adaptable and prepared for infectious disease outbreaks such as 'swine flu' or 'bird-flu'[7]. Preparedness for such contingencies is likely to be affected by the provision of stable funding for building a skilled workforce that can use instruments in a variety of ways, alongside effective

[6] See the Myth of Unfettered Research (Sarewitz 1996).

[7] I am aware that investments to mitigate infectious disease outbreaks outside the vaccine system altogether may be just as effective and equitable for public health (if not, more so). For example, investing in more sustainable agricultural systems in developing countries, or in countries such as China and Mexico where 'swine flu' and 'bird flu' are thought to have originated, may prevent or reduce the frequency of such outbreaks. Preventative strategies mean that everyone benefits, without having to consider who might have access to newly developed vaccine technologies.

governance mechanisms that are capable of coordinating and identifying strategic priority research areas.

10.4 Final Conclusions

This thesis has used evolutionary theories of innovation to show that vaccine development is a highly uncertain and groping process. It has contributed to theory by showing how these uncertainties are reduced incrementally, purposefully, and indirectly within well-developed testing regimes. Policy makers should acknowledge that investing in a dedicated testing regime, alongside science investments, is an expensive and long-term endeavour[8].

This thesis has indicated that policy makers should be sceptical about the idea that vaccine development is very different from other complex technological processes, and should not assume that scientific knowledge from academic institutions will lead to a clear, certain and costless path to a vaccine. If potential problems in the accumulation of technological knowledge are not understood, anticipated and addressed, then progress towards sustained innovation will stall, whether one is considering vaccines or any other complex technology that requires multiple scientific advances. This thesis concludes that the social imperative for an HIV vaccine could be more quickly met through carefully designed science and technology policies to address current barriers in the accumulation of technological knowledge.

[8] Suggesting that the process of accumulating technological knowledge is long and expensive is consistent with the fact that two thirds of R&D costs are spent on the D part (Rosenberg 1994:13).

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Appendix

THE WHITE HOUSE

Office of the Press Secretary

PRESS BRIEFING BY LARRY SPEAKES

October 15, 1982, 12:45pm EST

The Briefing Room

Q: Larry, does the President have any reaction to the announcement - the Centers for Disease Control in Atlanta, that AIDS is now an epidemic and have over 600 cases?

MR. SPEAKES: What's AIDS?

Q: Over a third of them have died. It's known as "gay plague." (Laughter.) No, it is. I mean it's a pretty serious thing that one in every three people that get this have died. And I wondered if the President is aware of it?

MR. SPEAKES: I don't have it. Do you? (Laughter.)

Q: No, I don't.

MR. SPEAKES: You didn't answer my question.

Q: Well, I just wondered, does the President -

MR. SPEAKES: How do you know? (Laughter.)

Q: In other words, the White House looks on this as a great joke?

MR. SPEAKES: No, I don't know anything about it, Lester.

Q: Does the President, does anyone in the White House know about this epidemic, Larry?

MR. SPEAKES: I don't think so. I don't think there's been any -

Q: Nobody knows?

MR. SPEAKES: There has been no personal experience here, Lester.

Q: No, I mean, I thought you were keeping –

MR. SPEAKES: I checked thoroughly with Dr. Ruge this morning and he's had no - (laughter) - no patients suffering from AIDS or whatever it is.

Q: The President doesn't have gay plague, is that what you're saying or what?

MR. SPEAKES: No, I didn't say that.

Q: Didn't say that?

MR. SPEAKES: I thought I heard you on the State Department over there. Why didn't you stay there? (Laughter.)

Q: Because I love you Larry, that's why (Laughter.)

MR. SPEAKES: Oh I see. Just don't put it in those terms, Lester. (Laughter.)

Q: Oh, I retract that.

MR. SPEAKES: I hope so.

Q: It's too late.

THE WHITE HOUSE

Office of the Press Secretary

PRESS BRIEFING BY LARRY SPEAKES

December 11, 1984,12:03 p.m. EST

The Briefing Room

MR. SPEAKES: Lester's beginning to circle now. He's moving in front. (Laughter.) Go ahead.

Q: Since the Center for Disease Control in Atlanta (laughter) reports...

MR. SPEAKES: This is going to be an AIDS question.

Q: that an estimated

MR. SPEAKES: You were close.

Q: Well, look, could I ask the question, Larry?

MR. SPEAKES: You were close.

Q: An estimated 300,000 people have been exposed to AIDS, which can be transmitted through saliva. Will the President, as Commander-in-Chief, take steps to protect Armed Forces food and medical services from AIDS patients or those who run the risk of spreading AIDS in the same manner that they forbid typhoid fever people from being involved in the health or food services?

MR. SPEAKES: I don't know.

Q: Could you - Is the President concerned about this subject, Larry

MR. SPEAKES: I haven't heard him express...

Q: ...that seems to have evoked so much jocular

MR. SPEAKES: ...concern.

Q: reaction here? I - you know –

MR. SPEAKES:: It isn't only the jocks, Lester. Has he sworn off water faucets?

Q: No, but, I mean, is he going to do anything, Larry?

MR. SPEAKES: Lester, I have not heard him express anything on it. Sorry.

Q: You mean he has expressed no opinion about this epidemic?

MR. SPEAKES: No, but I must confess I haven't asked him about it. (Laughter.)

Q: Would you ask him Larry?

MR. SPEAKES: Have you been checked? (Laughter.)

(Source: Cohen 2001; taken from The Reagan Library, Press Office Transcripts).