



Knowledge Accumulation and the Development of Poliomyelitis Vaccines

Ohid Yaqub

Vaccines



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What does it take to develop a vaccine? This paper explores the technical and institutional conditions that allow reliable knowledge to build up in a series of structured stages from the laboratory to the field. The paper highlights the role of instrumentalities (instruments, skills and organisational capabilities) in allowing iteration between these stages; and shows how instrumentalities can be influenced by their institutional context, so that the resulting knowledge grows in a cumulative rather than fragmented manner. By explaining the historical importance of instrumentalities in polio vaccine development efforts, this paper highlights key features of technological change that are missed in current policy debates focussed on addressing market failure or poorly funded science.

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1. POLICY PROBLEM: THE NEED FOR VACCINES AND THEIR UNCERTAIN SUPPLY

Vaccines have prevented more premature deaths, permanent disability and suffering than any other medical discovery or intervention (Andre 2001; Andre, Booy *et al.* 2008:2206). The WHO has estimated that poliomyelitis eradication will save governments \$1.5bn per year in treatment and rehabilitation costs (Barrett 2004), whilst the US alone saves the total of all its contributions to the smallpox eradication programme every 26 days (Rappuoli, Miller *et al.* 2002).

However vaccines are not easy to develop. Estimates of the cost of bringing a new vaccine to market range from \$600m to \$800m (Douglas 2004; Plotkin 2005), with a recent influenza vaccine costing more than \$1bn (NIH and NIAID 2007). Even when greater sums are spent, new vaccines do not necessarily emerge. Total global investment in HIV vaccine research and development increased to \$961m in 2007 (UNAIDS 2008:12); two thirds of leading scientists in the field think a vaccine will not be developed in the next ten years (Connor and Green 2008).

This hints at the heterogeneity observed in the history of vaccine innovation: some vaccines have been developed in a decade, whilst others have eluded discovery for over a century (IAVI 2008:14). Explanations of this wide variation have often focused on downstream issues related to product innovations. Economists for example have emphasised demand-side issues for vaccine products (Pauly, Robinson *et al.* 1995; Esparza, Chang *et al.* 2003; Farlow 2004) or have analysed issues around the trade-offs in vaccine efficacies, costs and development times (Tangcharoensathien, Phoolcharoen *et al.* 2001; Cropper, Haile *et al.* 2004). Sociologists on the other hand have been 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 is not as useful for explaining the non-existence of a product, even by comparing with products that do exist. A more appropriate analytical approach would involve exploring further upstream in the innovation process to trace the unpredictable turns that characterise the evolution of knowledge (Nelson 2003), the historical circumstances in which certain research paths were taken and others abandoned (Dosi 1982), and the local context in which technologies are developed (Rosenberg 1976; 1982). Economic notions of market failure and sociological notions of neglected diseases are relatively silent on why - for example HIV - vaccine innovation is difficult. HIV vaccine research is well funded, has a potential market and is supported by a coalition of prominent

social groups¹. This paper provides an alternative explanation that builds on theoretical understanding of innovation processes and the history of vaccine development.

Consequently, this paper emerges with suggestions for policy in section 4 that are intended to complement existing suggestions. Advanced market commitments (Kremer, Glennerster *et al.* 2006), intellectual property incentives (Lanjouw 2003), public-private partnerships (Chataway, Hanlin *et al.* 2007) and networking incentives (Galambos and Sewell 1995) all rest on the assumption that the disparity between vaccine need and supply represents a market failure. Advocates for boosting vaccine research funds (Archibugi and Bizzarri 2004) have done much to raise awareness of their woeful inadequacy, especially for neglected diseases, nonetheless such advocacy rests on assumptions that science can overcome the challenges of vaccine innovation largely on its own.

This paper adds to these suggestions the idea that science is not enough: vaccinologists must also be able to accumulate technology-specific knowledge. For this, policies can significantly facilitate (or hinder) the innovation of vaccines. To analyse this idea further, the paper presents a process model of vaccine innovation in section 2 and a historical case study in section 3 with which to make explicit policy recommendations.

¹ Possibly to the neglect of many other important diseases.

2. A FRAMEWORK FOR ANALYSING KNOWLEDGE ACCUMULATION

The conceptualisation of technology as a multifaceted form of knowledge gathered momentum as technology theorists such as Layton (1972; 1974), Ferguson (1977; 1992) and Price (1965; 1986) tried to make sense of detailed qualitative and analytical histories of technologies, for example radios, bridges, aeroplanes, and electrical systems (Aitken 1976; Vincenti and Rosenberg 1978; Constant 1980; Hughes 1983). To differing degrees, their explanations drew on philosophies of science and knowledge (Polanyi 1958; Popper 1959; Kuhn 1962; Lakatos 1970) and tended towards the notion that technologies have their own social and cognitive processes of development centred around problem-solving (Laudan 1984). Efforts to set this process in economic and socio-political contexts yielded evolutionary (Nelson and Winter 1982; Pavitt 1999; Consoli and Ramlogan 2008) and constructivist frameworks (Winner 1985; Bijker, Hughes *et al.* 1987; Blume 1992).

These process models begin with phenomena that become 'problematized' (Blume 1992:71). In the context of vaccine innovation, problematisation involves bringing together previously unrelated symptoms to coalesce around a disease characterisation, which becomes increasingly specific so that the course of life (or death) events is more predictable (Rosenberg 2002)². Social and political factors, such as who the disease primarily affects, can draw resources initially, but identification and characterisation of a disease-causing agent retains these social resources for more persistent vaccine innovation efforts.

Pathogen elucidation and disease construction are guided by the retrospective question: 'how is the disease caused?' As a question of causality, it is amenable to scientific investigation. As causality is established, the guiding question then becomes more prospective and overtly technological: 'how can we intervene reliably?' As Vincenti (1990:209) notes, putative ideas of how the technology might work are conceived and subjected to initial testing that constitutes a proof of concept, or 'operational principle' (how a technology works). The operational principle is then developed through a series of carefully structured stages to align its characteristics with a socio-economic market (Tidd, Bessant *et al.* 2009).

The process of diagnosis (Rosenberg 2002) helps direct the development of specialised clinical knowledge and plays an important role in generating a *vision* of the technological future (Blume 1992:64-70). Shared expectations help form

² Rosenberg (2002:236) argues that disease concepts play a pivotal role in 'how we organize health care delivery, think about ourselves, debate and formulate social policy, and define and manage deviance'.

networks, which assist in the mobilisation of resources. As a consequence, 'opportunities presented as promises, get accepted and become part of an agenda; and are subsequently converted into requirements that guide search processes' (van Lente 1993:198).

Visions help change social problems into more specific technological problems. They inform the 'operational principle' such that it incorporates non-scientific features of knowledge (Polanyi 1958:328). 'The laws of physics may be used to analyse operational principles once they have been devised, and they may even help in designing it; they in no way however contain or by themselves imply the principle' (Vincenti 1990:209)³. So, science is often necessary but never sufficient for innovation.

As a consequence, the complex technological knowledge needed for vaccine innovation cannot be obtained 'as-is' from scientific knowledge. Instead, technological knowledge has to be specifically generated and accumulated through its own dedicated and deliberate steps. Because of the inherent complexity, uncertainty and weak theoretical understanding of practice, generating technological knowledge involves repeated testing and empirical learning (Pavitt 1999). 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 (Nelson 2008c). These allow a series of conditions to be created, that can mark milestones or stepping stones in the path to an innovated product.

New operational principles are built up in a series of iterative and recursive steps, whilst complex phenomena are broken down and simplified (Nightingale 2000)⁴. 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 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 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

³ Similarly, Polanyi (1958:177) states 'The [scientific] knowledge of a machine as an object tells us nothing about it as a machine.'

⁴ Mahdi (2002) refers to this breakdown of phenomena as problem parsing.

world outside the laboratory⁵ (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.

The ability to tinker with these conditions so that ideas work and become operational principles (and conversely, the ability to adjust our ideas for given conditions) is important for overall technological development. The impact of instrumentalities on knowledge growth has been noted by several 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). The impact of instrumentalities on technology is being explored, for example in the nano-materials sector (Meyer 2001; Olsen 2009); although, why they can have such immense impacts on the development process is not directly examined. Nelson (2008a:6) 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 1984:13) to allow the variation and selection of alternative explanations (Deutsch 1997).

Instrumentalities (instruments, skills and capabilities) 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 are an infinite number of possible explanations for a phenomenon, there are only a finite number of actual ones. Most technologies are too complex to explore

⁵ 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.' Presenting intermediate conditions as a scale adds to Nelson's (2008c) concept of offline development by indicating that conditions need not be either 'offline' or 'online'; there may, in principle, be a continuous spectrum of conditions that lie in between. 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.

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.

Local variations in experimental practice and instruments can mean that comparison is not possible; protocols or standards between tests may be different, accuracy and relevance may be checked with different instruments. With low comparability, the interpretation of testing data becomes subject to more social negotiation as interests are able to form around particular trajectories. Governance structures are often challenged with co-ordinating such instrumentalities to improve comparability. Under standardised conditions, knowledge can accumulate quickly because there is less to debate. Governance plays an important role in developing and selecting between potential operational trajectories (Nelson 2008b). It is possible to conduct development along parallel trajectories but this can become difficult if costs escalate, so choices must be made along the way.

Leadership of, and co-ordination between, research and development groups ensures that the new knowledge growth does not remain fragmented, but is accumulated, assimilated and integrated (Chataway, Brusoni *et al.* 2007). Instrumentalities are a shared utility that form an important part of the invisible research infrastructure, and becomes embedded within norms and traditions of the technological community (Constant 1980:8).

When understanding vaccine innovation, two central ideas are important: a social vision and a testing regime. The social vision becomes most significant when a disease concept and its causal agent are established. Social problems become more specific technological problems as operational principles are

devised. A testing regime develops the operational principles with three elements: intermediate conditions, instrumentalities and institutions. Intermediate conditions are points in between the simplified but unrealistic conditions that facilitate learning and the realistic but complex conditions that are most relevant to practice. Instrumentalities allow the creation of these intermediate conditions, in which knowledge can grow reliably. Institutions ensure knowledge does not remain fragmented and accumulates along intermediate conditions and cross-sectionally across different groups working at the same point.

3. THE ROAD TO POLIOMYELITIS VACCINES

This case proceeds in three parts. The introductory part 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 part describes some of the failures and barriers faced by researchers, which might otherwise be overlooked in a history of poliomyelitis successes. The third part describes the development of a testing regime, which involved developing instrumentalities to create intermediate conditions and strengthening institutions for accumulating knowledge.

THE EMERGENCE OF A PROBLEM AND THE VISION OF A SOLUTION

Poliomyelitis was eventually given its name as a specific disease in the middle of the 19th century⁶ 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 clustering of cases in single households however, suggested the disease was of an infectious nature.

⁶ 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).

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 (Paul 1971:98)⁷. 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 to be a living parasitic microorganism⁸, able to reproduce in the cells of its victims.

The search for a specific infectious agent, likely to have been informed by Koch's postulates (Paul 1971:100; Mullan 1989), allowed public health officials to be less concerned with intractable environmental tasks such as cleaning up the city, ridding it of 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 quarantine (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 to also be caused by a specific agent⁹. However, beyond having a target to take aim at, the operational principles that such a poliomyelitis vaccine might exploit remained unknown, and further knowledge about the epidemiology of the poliovirus was needed before a vaccine was a technical possibility.

⁷ 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).

⁸ 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. A contrasting example is the relationship between HIV and the onset of AIDS, where SIV infection, *not* HIV infection, is needed to bring about AIDS-like disease in monkey models.

⁹ The poliomyelitis researcher Hortsman (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.'

By 1910 it was demonstrated that monkeys surviving poliomyelitis often resisted re-infection, and their blood contained a substance that neutralised the virus in a test tube (Paul 1971:108). This served to reinforce the vision by offering further hints about the possibility of a vaccine. In 1911 Flexner issued a press release declaring that within six months¹⁰ 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, 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 impossibility¹¹.

There were several early obstacles to establishing operational principles. 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 dependent on skilled people (Paul 1971; Rogers 1992). 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 (Ohka and Nomoto 2001; Racaniello 2006). 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 (in 1-2% of infected people) the virus travels through the blood and into the central nervous system, causing meningitis. Paralysis occurs only if the virus then enters nerve cells (Ohka and Nomoto 2001; Racaniello 2006).

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 the spread of disease because children were less exposed to mild forms making them more

¹⁰ 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 (Panem 1988:25; Shilts 1987:451).

¹¹ The eminent polio researcher John Paul concedes, '[Flexner] can be forgiven for making mistakes about poliomyelitis' (1971:125).

susceptible to severe infection (and also because mothers did not pass immunity to foetuses¹²).

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) the 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 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).

FINDING WIDER SUPPORT FOR THE VISION

By 1916, the annual incidence of paralytic poliomyelitis in the US was over 27,000, killing more than 7,000. New York, in particular, was badly hit with about a third of the disease burden (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 windows and refused to let children play outside (Oshinsky 2005). By 1953, poliomyelitis

¹² However, Immunoglobulin A, which contains antibodies, is passed on to newborns in the colostrums in their mothers' milk (Chase 1982).

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 Roosevelt¹³ was struck by poliomyelitis (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 to poliomyelitis victims and those with other disabilities, at a time when physical handicaps were judged harshly. Many afflicted individuals were hidden by families (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 more like a triumphant hero despite being burdened with physical limitations; this significantly contributed to the transforming structure of disabled identity (Gallagher 1985). Even so, no photographs of Roosevelt in a wheelchair were made public and what Gallagher (1985) calls 'FDR's magnificent deception' was kept secret. 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 reinforced after his daughter died from poliomyelitis (Oshinsky 2005:271).

In 1934 Roosevelt staged nationwide charity balls on his birthday 'to dance so others may walk' (Carter 1965:14) to relieve the debts accruing at Warm Springs (Rose 2003). Given the stock market crash of 1929, the campaign achieved extra-

¹³ 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).

ordinary success (Rose 2003). It raised \$1m that year¹⁴, \$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).

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 lives¹⁵. 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... [it] displayed no power whatever to inhibit the action of the virus' (cited in Chase 1982:302). Poliovirus could not be grown in horses, or any other non-primate animals¹⁶. Further research and development would have to involve either humans or monkeys.

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 envisaged rudimentary operational principles and wanted to refine them into a vaccine by testing them promptly. In 1936, they independently conducted field trials of ill-conceived vaccines prepared from spinal cords of infected monkeys (Chase 1982; Robbins 2004). 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).

¹⁴ All dollar figures have not been adjusted for inflation.

¹⁵ For example, the United States' death rate for diphtheria halved between 1900 and 1909 (Chase 1982:302).

¹⁶ Although, in 1939, a poliovirus strain was adapted for certain rodents, its growth was limited and rare (Robbins 2004:19; Paul 1971:276). Humans and monkeys seemed the only alternatives.

Using what Paul (1971) 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)¹⁷. These childhood deaths stifled vaccine development¹⁸. The impact of the experience traumatised researchers, sapped enthusiasm, and sparked 'a wave of revulsion against human vaccination attempts in poliomyelitis' that lasted for two decades (Paul 1971:260).

LEARNING FROM FAILURE WITH A TESTING REGIME

The failed efforts are indicative of the norms and traditions of those testers (Constant 1980:8). Vaccinology was seen largely as an empirical art of producing effects without necessarily knowing why those effects are caused (Nightingale 2004:1272). For example, smallpox and rabies vaccines 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 to the purpose of the operational principle.

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 impeded by three sets of difficulties. 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 easily, because monkeys were so difficult and expensive. 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). Thirdly, the community did not establish the types of poliomyelitis virus they were working with before trialling.

¹⁷ 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).

¹⁸ It is interesting that in 1971 Paul considers this 'blown out of proportion'.

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 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 promotion¹⁹, which 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 totalled \$67m (Carter 1965:26). Thus, a major source of funding was established for the research and development of vaccines. 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 research and development (Paul 1971:312).

THE CONSTRUCTION OF A MORE SOPHISTICATED TESTING 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 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 to educate himself about poliomyelitis and to 'encourage communication and intellectual cross-fertilisation in a field notable for its lack of both' (Carter 1965:57).

¹⁹ 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).

Weaver therefore played an important co-ordinating role between different groups of scientists, and with O'Connor, he acted as an intermediary between the scientific community and the wider public. 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 door-to-door collections. The Foundation mediated between scientific concerns for incremental advances of certainty and public demand for quick tangible advances.

The tensions between these two aims 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; Boddington 2008). 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 their resistance, Rivers and Weaver led the enterprise 'by seeking out men and institutions' to undertake an 11 point research plan (listed in Benison 1967:229). Three of the impediments to vaccine development were tackled directly. Firstly, Weaver felt that a monkey shortage had delayed poliomyelitis research. Secondly, it was not possible to grow viruses successfully in the laboratory; they had to be grown in the brains of monkeys. This was time consuming, expensive and of low yield. Thirdly, it was not known how many wild types of poliovirus existed against which a prospective poliomyelitis vaccine would need to protect.

'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 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 in conferring poliomyelitis to mice, rats, rabbits and other small, inexpensive and readily available laboratory animals (Ren, Costantini *et al.* 1990). It was possible to infect monkeys²⁰, but working with them was not easy (Robbins 2004). Monkeys required special animal quarters, rather than the usual cages or bins for smaller laboratory animals, and an entirely different kind of care from that of smaller animals (Paul 1971:101). '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). Skilled technicians were needed to clean, feed and look after monkeys. Technicians needed to be skilled in handling, exercising and observing their behaviour whilst contending with the constant threat of bites and thumps, and risks of disease²¹.

Despite these difficulties, laboratory demand for monkeys outstripped supply. Capture of wild monkeys was not always simple. Cynomolgous monkeys suffered from poliomyelitis in ways that were close to human and their temperament made them easier to work with, but their scarcity meant they were expensive to import

²⁰ The ethics of using primates were probably less considered than would be today.

²¹ The possibility of contracting disease from monkeys 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' (Carter 1965:75). 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.

from the Philippines and Indonesia (Time 1954; Smith 1990). Rhesus monkeys were more 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. 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). Many researchers complained to their suppliers about these monkeys arriving dead or diseased. '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' (Salk correspondence quoted in 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 and recuperate from any diseases before being 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 centre 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).

TISSUE CULTURING: A NEW TECHNIQUE FOR GROWING VIRUS

The effort to develop better methods for propagating the virus by various investigators continued 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; Paul 1971:373). Robbins (2004) 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 (Abe, Ota *et al.* 1995). Thus it was thought that a poliomyelitis vaccine was 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 implied that a vaccine would be very dangerous because injections of foreign nervous tissue can cause encephalitis (fatal allergic inflammations of the brain) (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 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 culturing²². It helped overcome difficulties in sourcing the embryonic tissue by keeping laboratories in close contact with local maternity hospitals²³.

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 (Chase 1982:292). In this attempt, Enders, Weller and Robbins succeeded in making the breakthrough most eagerly sought by the Foundation by 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).

²² 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).

²³ Embryonic tissue grows much faster than that of adults, and is less prone to disease, so it is the preferred tissue for culturing with. Given the contentious nature of acquiring such tissue, the Foundation often could only acquire small quantities of foreskins from circumcisions of newborn boys. Placentas, miscarriages and still-born tissue were also used but their supply was even less predictable (Smith 1990).

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 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 plenty of virus supply, 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.

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 existed²⁴ 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 speech marks).

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

²⁴ 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).

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 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 influenza²⁵ vaccine with his mentor, Thomas Francis, for the US Armed Forces (Carter 1965:35; 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).

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

²⁵ The Army were interested in influenza vaccines because more people died from the influenza epidemic of 1918 than were killed in combat (Crosby 1976).

\$1.37m and used up 30,000 monkeys²⁶ imported at great expense (Chase 1982). It showed conclusively that there were three, and only three²⁷, 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 that 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).

²⁶ 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 *all* R&D <http://www.aphis.usda.gov/ac/ar2002.html>

²⁷ The three strains were named Lansing, Prunhilde and Leon strains (Time, 1953).

4. CONCLUSIONS AND POLICY RECOMMENDATIONS

The development of poliomyelitis vaccines was dependent on a vision that needed to be convincing not just for the community of technological practitioners, but also for wider society. Expectations (van Lente 1993) were 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 reshaped by President Roosevelt. The relationship between scientists as technological-producers, and the public as 'science' consumers, was not forged until Roosevelt established a specific and dedicated mediating organisation, the National Foundation for Infantile Paralysis.

A series of names reflecting different syndromes and symptoms became increasingly specific and characterised as a distinctive disease, poliomyelitis. This initiated an innovation process as Rosenberg (2002) suggested, where 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 allowed the technical community to rally around a vision for a vaccine. The technical community had its own set of norms and traditions (Constant 1980:8) that were highly focussed on public health innovation and establishing operational principles promptly (Polanyi 1958:328; Vincenti 1990:209). Flexner's optimism about the possibility of a timely 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 and effectively 'problematized' it (Blume 1992).

However, Roosevelt's involvement is perhaps most pertinent to contemporary vaccine innovation issues because the Foundation ensured the cumulative growth of technological knowledge through the development of a testing regime. The Brodie-Kolmer failures 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. Knowledge growth was either slow or fragmented or both.

In order to accumulate technological knowledge, the Foundation adopted a leading role to ensure certain features of the testing regime were developed. 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. It actively fostered knowledge integration across research groups and in doing so gained an overview of what was needed for innovation. It then directed technological research, sometimes in areas seen by scientists as unstimulating. The Foundation's scientific advisors, led by Rivers, commissioned the development of instrumentalities such as

tissue culturing, and important epidemiological studies such as identifying and classifying the three strains of virus.

The Foundation facilitated such research by finding specific researchers to do the work and provided them with funds, virus, tissue and reagents. 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. The large project to type polioviruses provided helpful knowledge about which strains the vaccine would need to provide protection against.

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 even more intense than it was before²⁸. 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. 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 would then turn its attention to transforming subjective issues of vaccine design into more specifiable criteria for vaccine use in human conditions rather than in laboratory monkeys. It would also go on to mediate personal agendas, conflicts of interests, and manage differences of opinion. It would even display the leadership to make the risky and unpopular decision to enter clinical trials (Yaqub 2009).

The community was well prepared to appreciate and exploit new ideas and, following these key advances, was well positioned to start thinking about how it might test and assess them in people. With the chances of making a poliomyelitis vaccine much improved, a number of groups were able to work towards that goal (Yaqub 2009).

Some significant policy levers can be identified from components of the testing regime framework presented in this paper. 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 and developing technologies that are reliable. Institutions, which govern vaccine research and development, are needed to configure those instrumentalities so that knowledge does not remain fragmented, but accumulates towards innovation. This may take the form of ensuring the plentiful supply of reagents, consistent animal models, test-subjects, and instruments. The work will require skilled personnel and

²⁸ The Virus typing program alone used 30,000 monkeys – whereas before the program, only 17,500 monkeys had been used in total (Carter 1965; Chase 1982).

experienced vaccinologists, who are allowed to transfer tacit knowledge through training for younger researchers.

Policy makers may also consider offering contracted research grants as a complement to investigator-initiated research. The development of new instrumentalities may require targeted strategic attention. Well funded investigator-initiated research may yield exquisite science, but contracted grants will ensure mundane research is undertaken systematically. The lesson from poliomyelitis vaccine development is that both are needed.

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