Genes as drugs: the social shaping of gene therapy and the reconstruction of genetic disease

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Abstract
This paper examines the utility of using concepts from the sociology of technology to investigate how new technologies and new disease concepts are co-constructed. For researchers to introduce gene therapy into experimental clinical practice, they had to engage in a process of heterogeneous social-technical engineering. This included: the construction of local networks of regulators, genes, firms, clinicians and patients; the social shaping of gene therapy technology as a novel form of drug delivery; the creation of a new industry; and the re-conceptualisation of many common acquired diseases as being genetic in some way. These changes marked a shift from an account of genetic disease based on the inheritance of deleterious genes, to one which explained acquired conditions in terms of a ‘molecular pathology’, resulting from errors in the way genes are regulated. This process of socio-technical change has resulted in the construction of a new type of ‘genetic body’.

Keywords: gene therapy; genetic body; socio-technical networks; biotechnology

Introduction

The idea that diseases and bodies are socially and historically constructed is well established within both medical sociology and the history of medicine, and has inspired a great deal of research (Wright and Treacher 1982, Rosenberg and Golden 1997). Many different approaches have been used to examine the processes by which new medical knowledge is created, including studies of medical education, biomedical research and clinical practice. However, with some notable exceptions (Peitzman 1997, Lawrence 1997, Wailoo 1997), relatively little attention has been paid to the relationship between the development of new technologies, the formation of new medical knowledge and the way in which new disease concepts have arisen.
This omission is of particular concern in the area of modern genetics where the introduction of powerful new technologies is closely linked to the construction of new accounts about the origins of disease. In particular, the emergence of new forms of genetic determinism questions established social and environmental explanations of why people become ill and challenge existing views about the responsibility of both the individual and society. The rise of the new genetics also raises important questions within medical sociology about the role of technology and the nature of technical change within medicine, a topic that has been largely neglected until recently (Elston 1997). Studies within science and technology studies (STS) have, in contrast, started to examine some of these issues. In particular, a number of authors have investigated the ways in which new technologies and new medical knowledge are co-constructed (Saetnan 1991, Blume 1992, Clarke and Montini 1993, Koch and Stemmerding 1994, Prout 1996, Oudshoorn 1994, Berg 1997).

One of the main consequences of the introduction of new genetic technologies has been a change within medicine in the type of explanations given about the cause of many diseases. Recent research in the history and sociology of medicine has started to analyse these new accounts and the way in which new biomedical knowledge is constructing a ‘genetic body’ (Koch 1993, Turney and Balmer 1998). In this discourse a number of relatively rare inherited conditions are the result of genetic defects, while other more common pathologies, such as heart disease, are seen to have a significant genetic component. In addition, claims are also being made about the genetic basis of behaviour ‘disorders’ such as depression, schizophrenia, and alcoholism. Within this conceptual framework, environmental and social factors may play a role in the onset of disease, but it is ultimately the genetic dowry we each inherit which determines our health status. However, this notion of how genes cause disease is historically constructed and is in no sense fixed or unchanging. This article will draw on work within the sociology of technology to analyse how the perception of what constitutes a genetic disease has changed during the introduction of a new medical technology, gene therapy, into experimental clinical practice. Gene therapy involves the transfer of genes into cells for the treatment of disease. By the end of 1996 the technology was being tested experimentally in over 2,000 patients in more than 160 human clinical trials in the USA alone and was being commercially developed by over 50 American firms (Martin and Thomas 1996). However, it must be stressed that even by 1999 no gene therapy had been proven to work in humans and no product was expected to get regulatory approval for routine clinical use before 2002.

It will be argued that in the field of gene therapy there has been a shift from an account of disease based on ‘classical’ genetics and the inheritance of deleterious genes, to one which explains many common acquired pathologies in terms of errors in the way gene are regulated. At the same time, however, this shift in the meaning of genetic disease has both
depended on, and enabled, a fundamental change in the definition, applications and design of gene therapy technology itself. Over the course of 30 years it has been reshaped from being a largely surgical procedure for the treatment of rare inherited disorders to its introduction as a novel form of drug therapy for common acquired conditions.

It will also be shown that the changes in both the definition of genetic disease and the constitution of gene therapy were not just the result of new medical knowledge and discourses, or the introduction of novel forms of clinical work. They also rested on the creation of new socio-technical relations, new organisations and new artefacts, aligned into stable networks. Central to this process have been attempts by scientists to commercially exploit the technology through the creation of dedicated gene therapy firms. This paper will therefore examine the historical development of gene therapy paying particular attention to the way it has been designed, applied in experimental clinical practice, and commercially developed by industry. By presenting an account based on the analysis of these socio-technical networks it is hoped that the article will demonstrate the utility of taking established concepts from STS and applying them to the traditional concerns of medical sociology.

New knowledge, new technologies and the construction of socio-technical networks

In the last 15 years a new sociology of technology has started to be articulated, based on a critique of technological determinism (MacKenzie and Wajcman 1985, Bijker et al. 1987). Instead of innovation and technological change being driven by an innate technical logic, the development of new technologies is seen as a fundamentally social process open to sociological analysis.

A number of different theoretical perspectives have been used to examine the creation of new technologies, including actor-network theory (ANT) (Callon 1987), the social construction of technology (SCOT) (Bijker 1995) and the analysis of large technical systems (Hughes 1987). Although each takes a distinct approach they share several common features, notably the idea that the development of a new technology involves a range of heterogeneous social, technical, economic and political processes. In addition, it is argued that new knowledge is co-produced at the same time as new technologies and new socio-technical relations, through a process of mutual shaping.

This paper will draw on the following concepts within this new sociology of technology:

The construction of socio-technical networks

In order to be successfully introduced into routine use new technologies require the alignment of a range of heterogeneous human and non-human
actors into stable socio-technical networks (Callon 1987). To achieve this, network builders, or 'heterogeneous engineers', might be involved in, for example, the creation of new social practices, new companies and new forms of state regulation, which emerge together during innovation. Network formation therefore requires the enrolment of various actors, the formation of alliances and the mobilising of different social, technical, and economic resources.

**The creation of visions and the enrolment of support**
An important process in the formation of networks is the creation of particular 'visions' or expectations for how the technology might be used in practice and sold as a commodity (van Lente 1993). Visions act as both a means of enrolling support and resources into the emerging socio-technical network and as a guide to the physical design of artefacts. They may also form part of a new set of cognitive structures that both enable and shape the development of the technology (Bijker 1995). During the early stages in the introduction of a radically new technology a number of competing visions for how it might be used may co-exist (Pinch and Bijker 1984). These are often associated with the formation of different networks and the emergence of alternative designs or technological options.

**The social shaping of technology**
As an integral part of the creation of stable socio-technical networks the emerging technology is socially shaped to reflect the activities and interests of the groups involved in the innovation process. This is mediated through the design, testing, selection and redesign of the various technological options and may result in the physical form of the technology changing dramatically over time. For example, as new groups of actors join the emerging network, they may favour particular options over others and shape the future direction of research and design (Bijker 1995). Through an examination of the competing technological options, the changing designs and applications, and the role of the various groups involved, it thus becomes possible to analyse the physical development of a new technology in sociological terms.

These theoretical tools will be used to analyse the development of gene therapy in the United States (US) between the late 1950s and 1996. The US was chosen because almost all the work in this field took place in America before 1990 and the research draws on both historical documents and interviews with scientists, clinicians and the managers of gene therapy companies (Martin 1998). I shall start with a brief history of the early development of gene therapy and the work leading to the initial clinical trial of the technology in 1989. Case studies of different strategies for the subsequent introduction of gene therapy into experimental clinical practice will then be used to examine changes in both the concept of genetic disease and the design of the technology. Finally, I shall reflect on the socio-technical processes that
have been at work, the way in which the idea of a genetic disease has been reconstituted and the manner in which gene therapy technology has been socially shaped during this period.

**The early development of gene therapy: from eugenics to therapeutics**

*The construction of different technological options*

The idea of genetic therapy has its roots in pre-World War II futurism and eugenics. The first suggestions for the genetic alteration of people for both social and medical reasons can be found in the writings of scientists such as Haldane and Muller, and the science fiction of Stapledon (Haldane 1923, Muller 1935, Stapledon 1930). Early advocates of the technology drew on Jacques Loeb’s concept of ‘biological engineering’ as a means of modifying man and combating the degeneration of the race (Pauly 1987). These ideas were also articulated in the policies and programmes of the Rockefeller Foundation, whose funding was fundamental in shaping the development of the new science of molecular biology during the 1930s and 40s (Kay 1993).

In many ways, biological engineering was implicit in the central project of molecular biology from its beginning, but it only found clear scientific expression with the advent of early gene transfer techniques after the War. The first programmatic proposal for genetic therapy was made in Edward Tatum’s 1958 Nobel Prize acceptance speech in which he anticipated molecular biology enabling ‘the improvement of all living organisms by processes which we might call biological engineering’ (Tatum 1958: 75).

The idea of biological engineering was subsequently articulated by a number of the early scientific leaders of molecular biology, many of whom had worked on gene transfer in the 1940s and 50s (Hotchkiss 1965, Szybalski 1992). However, two competing ‘visions’ of how genetic therapy might be developed emerged during these first discussions of the subject during the 1960s. The first took its inspiration from eugenics and was centred on the idea of modifying future generations to make social and intellectual ‘improvements’ and cure genetic diseases. This vision was advocated by Hermann Muller and other supporters of what Kevles has called reform eugenics (Muller 1965). The second vision was purely medical and was only concerned with genetically altering affected patients and not their offspring (Tatum 1966). It was mainly proposed by a younger generation of clinically trained investigators who largely rejected the eugenics of the 1930s.¹

Both these visions found expression in scientific research programmes aimed at inserting foreign genes into mammalian cells and drew on the recently developed techniques of recombinant DNA and funding from the National Institutes of Health (NIH). The realisation of the neo-eugenic vision depended on being able to transfer genes into sperm or eggs, the so-called germ cells, so that changes might be inherited by future generations. Several investigators attempted to develop techniques to alter germ cells during the
late 1960s and early 70s, culminating in 1982 in the creation of the world’s first ‘transgenic’ mouse which contained a growth hormone gene from the rat (Palmiter et al. 1982). In contrast, attempts to realise the medical vision rested on inserting genes into cells other than the sperm and eggs (the somatic tissues). In particular, research focused on the treatment of blood disorders such as thalassemia, where cells might be removed, genetically modified and returned to the patient using conventional blood transfusion. The alteration of cells outside the body became known as ex vivo therapy. This was in contrast to the direct injection of genes into the patient, so called in vivo therapy. Despite their different aims the neo-eugenic vision and the medical alternative were constructed around the central concept of classical genetics in which the inheritance of deleterious genes cause particular diseases. Both options continued to be actively investigated by a small number of scientists until the early 1980s when a major new debate about the ethics of gene therapy started to fundamentally influence the direction of research.

Opposition, ethics and the development of ‘classical gene therapy’

During the 1960s, scientific progress in molecular biology and reproductive technology prompted discussion in the media of a forthcoming ‘biological revolution’ (Turney 1998). At the time many of these new developments were couched in positive futuristic terms, but by the 70s concern grew about the social and ethical consequences of ‘playing god’. These included fears of creating a super race using genetic engineering and several prominent molecular biologists voiced their misgivings about the direction of research (Luria 1969). This unease coincided with a growing sense of environmental crisis, concern about the abuse of science and the anti-Vietnam War movement, and led to the formation of groups such as the Committee for Responsible Genetics. Public fears about genetic engineering were crystallised in 1980 when Martin Cline, a prominent American clinician, attempted the world’s first human experiment using recombinant DNA techniques: an event which prompted the first organised opposition to the development of gene therapy (Cook-Deegan 1990).

Cline made international headlines for not only trying to cure thalassemia by genetically modifying the bone marrow of two patients, but also because he deliberately proceeded after being refused prior ethical approval for the research. The storm of protest that followed his experiment culminated in an inquiry into the ethics of gene therapy by the recently created President’s Commission for the Study of Ethical Problems in Medicine, and Biomedical and Behavioral Research (the President’s Commission) (Cook-Deegan 1990). The Commission findings were published in 1982 in the landmark report Splicing Life, coinciding with increasing political pressure for an outright ban on research into gene therapy from religious groups, environmental activists and a number of prominent scientists.

The Commission’s report was important in making a distinction between the neo-eugenic idea of altering future generations, which it called germ line...
therapy, and the medical use of gene transfer directed solely at treating the non-reproductive cells of an individual patient, which it labelled somatic gene therapy. The Commission believed that germ line therapy was unethical and should not be allowed, but it felt it was acceptable to proceed with the development of somatic therapy for life threatening genetic diseases (President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research 1982). This distinction subsequently played a key role in helping legitimise somatic therapy as little more than a conventional medical intervention and has shaped all subsequent debates about the ethics of gene therapy (Capron 1990). Furthermore, it also distanced the technology from eugenics and the idea of human genetic engineering and strengthened the association with therapy.

*Splicing Life*, and a subsequent study by the Congressional Office of Science and Technology, were then deliberately used by the advocates of gene therapy to enrol support amongst bioethicists, theologians and scientists around the idea of somatic therapy (Cook-Deegan 1990). In particular, politicians and government policy makers played a key role in the process of winning consent. As part of this process a de facto moratorium was placed on clinical research into gene therapy and in 1984 the National Institutes of Health Recombinant Advisory Committee (‘the RAC’) was given responsibility for establishing a regulatory framework for clinical research in this area which would attract broad public support.

The RAC was composed of a majority of scientists as well as clinicians, lawyers, policy makers and lay members, and as such brought together the key groups whose support had to be enrolled. It subsequently acted as the locus of an attempt by the scientific advocates of gene therapy to build a national consensus about what sort of research would be socially acceptable. This was not an easy process and it was only in 1986 that the Committee finalised its guidelines. Furthermore, the RAC’s criteria for an experiment were demanding, and a trial would only be approved for ex vivo somatic therapy targeting a life threatening genetic disease for which there was no alternative cure (National Institutes of Health 1985).

Following *Splicing Life* all serious work on germ line therapy ceased and the field’s sole attention rested on developing ways of transferring genes into blood stem cells, the immortal precursors of the entire blood and immune system. If this could be achieved it would then be possible to provide a permanent cure for a number of rare enzyme deficiencies and genetic disorders. This approach to gene therapy drew heavily on classical genetics and the concept of genetic diseases caused by single gene defects and simply aimed to replace or correct the gene that caused the condition. For this reason it became known as ‘classical’ gene therapy and dominated the field until 1984, with the prime disease target continuing to be thalassemia (Anderson 1984). However, around this time it became apparent that the efficient transfer of the globin gene, which caused the disease, was still a long way from being technically feasible. This was a major setback to the field and
brought all plans for immediate clinical development to a halt (Martin 1998).

These technical difficulties severely limited the possibility of progress. During the mid-1980s gene therapy was still highly controversial, pursued by fewer than 10 laboratories in the USA. Furthermore, research was focused on a small number of very rare genetic diseases and commanded little interest amongst clinicians more generally. Despite this, the sanctioning of somatic therapy as ethical, the enrolment of support from theologians, bioethicists and politicians, and the formation of a socially acceptable regulatory framework to govern clinical research, enabled research to continue. Opposition to the technology had been overcome through an active process of enrolment and heterogeneous engineering by scientists and public policy makers and the first elements of a socio-technical network around gene therapy had been put in place. During this process gene therapy had been redefined as an experimental medical procedure for the treatment of rare genetic diseases and the direct link with eugenics had been broken. These first elements would later be used by the leading scientific figure in the field, W. French Anderson, to construct a stable network around the development of classical gene therapy. To achieve this, however, he would have to mobilise a wide range of actors and resources to overcome further technical, clinical and political obstacles.

**French Anderson and the organisation of the first clinical trial**

French Anderson was one of the earliest advocates of gene therapy. He suggested the possibility of using gene transfer to cure genetic diseases as far back as 1968 (Anonymous 1968) and established the first dedicated gene therapy laboratory in the world in 1974. After spending nearly a decade working on classical gene therapy for thalassemia at NIH, Anderson decided to abandon this line of investigation as a result of technical difficulties, and started a search for a new disease target during 1984 (Anderson 1984).

To achieve this he had to construct what Fujimura has called a ‘do-able’ research problem (Fujimura 1987), that would be scientifically feasible and at the same time might meet the rigorous criteria being established by the RAC. Anderson wrote a major review of the field and argued that only one disease, adenosine deaminase (ADA) deficiency, might realistically meet these two demands (Anderson 1984). ADA deficiency is a very rare genetic enzyme disorder of the blood that causes a fatal immune deficiency in children. Although less than 30 patients in the US were living with this genetic disease at the time, it had the great advantage that the gene for ADA had recently been isolated.

When he started his work to establish a clinical trial for ADA gene therapy Anderson had few of the resources he needed for a trial: he didn’t have
a copy of the ADA gene, which was closely guarded by other researchers; and he lacked efficient gene transfer ‘vectors’ and a means of manufacturing them to the standard required by the Food and Drugs Administration (FDA). Furthermore, he had no access to patients, no experience of managing the disease and was faced by a largely sceptical RAC.

In order to bring together the disparate elements of the network needed to allow his research to proceed Anderson undertook a process of enrolment and heterogeneous engineering. Through the creation of professional alliances he managed to get access to the ADA gene and the gene transfer vectors he needed (Lyon and Gorner 1995). He also teamed-up with Michael Blaese, a clinical researcher specialising in rare immune deficiencies, who provided two ADA patients. The main outstanding problem facing Anderson was the need for manufacturing facilities, the sort of technical support normally provided by industry. However, the production of gene therapy vectors had not been attempted before and no existing firm had either the interest or facilities to undertake this task.

As a consequence, during 1986 Anderson worked with venture capitalists to found the world’s first gene therapy firm, Genetic Therapy Inc, with the explicit aim of manufacturing vectors to support a clinical trial of ADA deficiency (Lyon and Gorner 1995). In creating a company Anderson was drawing on the increasingly close association between industry and academia which had arisen during the late 1970s and had become the cornerstone of the emerging biopharmaceutical industry (Wright 1994). It was a mutually beneficial relationship which provided companies with new sources of innovation and scientists with both research funding and potentially lucrative share options and consultancy fees. These academic-industry links were actively encouraged by government policy as a means of increasing industrial competitiveness and a series of legislative initiatives were taken to stimulate technology transfer during this period. In 1986 Congress passed the Federal Technology Transfer Act which enabled government employees to benefit from collaboration with industry, and Anderson established the very first Collaborative Research and Development Agreement (CRADA) under the new law between the NIH and Genetic Therapy Inc.

By 1987 Anderson had put in place almost all the heterogeneous elements of the network, but he still had to win regulatory approval from the RAC. During 1988 he submitted a protocol for the trial and supporting preclinical data, but was refused permission to proceed on the grounds that there was still not enough scientific evidence that the experiment could work. After several months of continuing technical criticism from his scientific peers on the Committee, Anderson made a radical change of tactic and switched to a non-therapeutic gene marking study of cancer using the same basic techniques (Anderson 1993).

The idea of introducing genetic markers to track cells in cancer patients was based on the work of Steven Rosenberg, the President’s cancer physician at the time. Blaese and Anderson teamed up with Rosenberg and in
1989 they submitted a protocol to the RAC for an experiment involving the transfer of genetic markers into the white blood cells of patients who had bone marrow transplants to treat leukaemia. After a carefully orchestrated campaign of persuasion and much controversy, the three researchers won the support of a majority of the RAC to vote in favour of this cancer experiment, and in May 1989 the world’s first human clinical trial using gene transfer commenced (Lyon and Gorner 1995).

This first trial marked the creation of a stable socio-technical network around somatic gene therapy. Its formation was built on the support won during the ethical debate and the regulatory framework established around the RAC. Two other events were also critical. The first was the link Anderson established with industry, which provided research funding and manufacturing facilities. The second was the switch to cancer which marked a critical turning point in the entire field, as it was the first time that anyone had made a serious proposal for how gene therapy might be applied outside the realm of classical genetic diseases. It was also vital in winning the support of the RAC, cementing the final pieces of the network, and ensuring that all the scientific, social and political resources required for a trial were present. Through this process of enrolment Anderson and Rosenberg articulated a fundamentally new vision for the use of gene therapy and transformed the scope and meaning of gene therapy.

The gene therapy bandwagon

In the five years following Anderson’s landmark trial there was a rapid expansion of the field, both in the USA and internationally, with the number of trials organised in America increasing to over 160 by the end of 1996 (Martin and Thomas 1996). This was accompanied by a dramatic increase in related scientific publications, which rose from under 50 a year in 1989 to over 1,200 in 1996. A large part of this growth was accounted for by the work of other pioneer investigators as they started to organise local socio-technical networks around their own plans for gene therapy trials. As they did this, there was a marked shift in the focus of research away from the classical genetic diseases, which had dominated the field until the eve of the first trial, and towards a range of acquired disorders, most notably cancer. By the end of 1996 over 70 per cent of US trials were for some form of cancer, with less than 10 per cent for genetic diseases (Martin and Thomas 1996).

The construction of local socio-technical networks in many of the leading US medical centres between 1989–93 essentially replicated the structure of the one built around Anderson’s trial. Each of these new networks was created by either a clinical researcher or a molecular biologist working in concert with a clinician. In particular, they were constructed around different visions of how gene therapy might be used for the treatment of a given disease and often centred on an attempt to organise a clinical trial. In nearly all
cases this also involved starting a new company as a means of getting access to key resources. In the following sections I briefly describe case studies of some of the first attempts to build networks around new applications of the technology. In particular, I pay attention to the way in which the very notion of genetic disease was reconstituted during this process, and how the design for gene therapy technology was fundamentally reshaped as a consequence.

**Gene therapy for genetic diseases**

Following Anderson’s first trial a number of different investigators tried to use ‘classical’ gene therapy as a means of curing a range of very rare genetic disorders. In all cases these trials were based on transferring genes into blood stem cells in order to replace the inherited lack of a particular enzyme. By the end of 1996 a total of seven American trials had been organised and one new firm, Theragen, founded to exploit this technology (Martin and Thomas 1996). However, no stable or long-lasting networks were built around the idea of using classical gene therapy to treat genetic diseases, as it continued to prove impossible to get genes efficiently into blood stem cells. Although all the heterogeneous elements had been configured into local networks to support these trials, they ultimately fell apart due to the recalcitrance of nature. As a consequence, most researchers abandoned the classical approach that had provided the basis for the first trial and dominated the field until 1990, and started looking for ways of delivering genes to other cell types.

Despite the failure of classical gene therapy, the possibility of treating other genetic diseases attracted scientific and commercial interest during the 1990s. In 1989 Ron Crystal, a leading chest physician at the NIH, suggested that it might be possible to transfer genes into the lungs (Rosenfeld et al. 1991) and within two years the main clinical target for this strategy was established as cystic fibrosis (CF), the most common genetic disorder in Caucasians. However, it was felt that a permanent cure for CF would not be possible because of the difficulty in transplanting cells into the lining of the lung. Instead, the therapy would have to be applied in vivo, and involved spraying vectors containing the therapeutic gene directly into the lung airway. It would therefore need to be repeated every few months and would act in a similar manner to a conventional drug.

Three different groups of researchers were successful in getting RAC approval for human trials of this strategy in 1992. To help organise their trials, each either started a new gene therapy firm or collaborated with an established company: Ron Crystal founded GenVec, Jim Wilson started Genovo and Michael Welsh formed a close working relationship with Genzyme, a large biotechnology firm (Martin 1998). By the end of 1996 a total of 13 clinical trials for CF had been approved by the RAC, each network embodying the idea of using gene therapy as a form of drug delivery to treat a lung disease.
Gene therapy for cancer
The first gene marking study organised by Rosenberg, Blaese and Anderson established the principle of using human gene transfer to treat cancer and this prospect was quickly explored by a number of other investigators. By the end of 1996 over 25 gene marking and 88 gene therapy trials for the disease had been approved by the RAC (Martin and Thomas 1996). The majority of these trials simply integrated gene transfer techniques into existing strategies for immunotherapy and chemotherapy, enabling the rapid diffusion of the technology throughout the already well established networks supporting cancer research.

In addition to the ease with which it fitted into existing patterns of experimental practice, a major factor enabling the development of gene therapy in this area was the changing conception of cancer. Increasingly, the disease was being constructed as essentially genetic in origin (Fujimura 1996). By the early 1990s scientists believed that tumours were often formed by the inactivation of tumour suppressor genes which regulated the normal growth of a cell. If these genes were turned off, as a result of damage caused by say smoking, the cell would divide in an uncontrolled fashion leading to a tumour. Although such an explanation did not evoke a genetic explanation based on heredity, this new molecular pathology offered the possibility of describing cancer in terms of the regulation and control of particular genes. For the advocates of gene therapy, if a diagnosis could be made in molecular terms, then it might also be possible to intervene therapeutically at this level using gene transfer.

This approach to gene therapy was in essence a form of in vivo gene replacement and was first advocated by Friedmann and Lee who envisaged delivering tumour suppressor genes to cancers as a means of inhibiting their growth (Huang et al. 1988). Impetus was given to this strategy in the late 1980s by work in gene sequencing which led to the identification of a number of tumour suppressor genes. However, the strategy was only put into practice in 1992 by Jack Roth, a cancer surgeon, when he gained RAC approval for a clinical trial involving the direct administration of the P53 tumour suppressor gene in patients suffering from lung cancer (Roth et al. 1994). In order to get access to both the financial resources and vector technology required to start a trial, Roth founded the firm Introgen with the aim of commercially developing P53 therapy (Jack Roth, personal communication). In organising this trial and founding his company Roth embodied the notion that cancer was a genetic disease in both the local socio-technical network and the very design of the therapy itself. Without the central idea that cancer could be thought of as a genetic disease this therapy would not have come about.

Cell implants—gene therapy to deliver drugs
In the light of the problems of getting genes into blood stem cells, by the late 1980s researchers were starting to investigate the possibility of transferring

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genes into a wide range of other tissues, including the skin, the liver, the brain and the heart. At the same time a new therapeutic concept started to emerge whereby genes might be used as a means of locally producing therapeutic proteins. For example, if a patient’s cells could be removed, genetically modified ex vivo to contain the gene for Factor VIII, and then reimplanted at a suitable location, they might be able to secrete this missing blood clotting protein into the blood stream as a means of treating haemophilia. In principle, these cell implants would function like mechanical drug delivery devices. This new vision for gene therapy was a radical break with the previously dominant idea of treating relatively rare genetic diseases, as it reconceptualised the technology so that it might be used to treat other more common acquired conditions.

One of the first researchers to pursue this strategy was Richard Selden, who suggested that a patient’s own skin cells could be genetically modified to secrete insulin as a cure for diabetes (Selden et al. 1987). In a related proposal, Fred Gage and Theodore Friedmann, planned to genetically modify skin cells to secrete a protein, Nerve Growth Factor (NGF), and then reimplant them in the brain as a way of treating Alzheimer’s disease (Gage et al. 1987). Other proposals were made for the use of a range of different cell types: Woo and Ledley suggested using modified liver cells as a means treating haemophilia (Ledley et al. 1987); and Mulligan and Nabel independently envisaged using cell implants to reduce cholesterol levels in chronic heart disease (Wilson et al. 1989, Nabel et al. 1989).

In each of these cases the development of novel therapeutic strategies was only possible as a result of the researchers being able to describe the pathology terms of molecular genetics. In some cases, such as haemophilia, the primary cause of the disease was clearly inherited, but as with cancer, it was also possible to construct a model of these other acquired conditions in terms of problems in the way the gene was regulated in the body. For example, Alzheimer’s might be caused by the production of too little nerve growth factor (NGF) in the brain as a result of damage to the NGF gene. The role of gene therapy in these cases was therefore to restore the level of the missing protein coded by the damaged gene. This shift to a ‘molecular pathology’ was enabled by progress in many areas of biology, in particular, the information coming from gene sequencing and the recently formed Human Genome Project. By the early 1990s it was becoming possible to describe many diseases in purely molecular terms, with the prospect of all pathologies eventually being categorised in this way.

The three main groups of researchers working on cell implants led by Mulligan, Selden, and Friedmann and Gage each set about creating socio-technical networks around their particular visions of the technology in order to get access to the resources required to sustain their research. In particular, they all formed companies with the intention of moving their therapies into human trials (Martin 1998). See Table 1 for details.

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<td>1991</td>
<td>Gaucher’s disease</td>
<td>ex vivo</td>
<td>transfer to blood stem cells</td>
</tr>
<tr>
<td>Genovo</td>
<td>Wilson</td>
<td>1992</td>
<td>Cystic fibrosis</td>
<td>ex vivo</td>
<td>transfer to lung</td>
</tr>
<tr>
<td>GeneMedicine</td>
<td>Ledley Woo</td>
<td>1993</td>
<td>Emphysema</td>
<td>in vivo</td>
<td>transfer to lung</td>
</tr>
<tr>
<td>Introgen</td>
<td>Roth</td>
<td>1993</td>
<td>Cancer</td>
<td>in vivo</td>
<td>tumour suppressor</td>
</tr>
<tr>
<td>GenVec</td>
<td>Crystal</td>
<td>1993</td>
<td>Cystic fibrosis</td>
<td>in vivo</td>
<td>transfer to lung</td>
</tr>
</tbody>
</table>
However, by the mid 1990s the notion of using cell implants was starting to be abandoned by the field in favour of direct in vivo therapeutic strategies which could be more easily incorporated into existing patterns of clinical practice, were less technically demanding and, above all, more commercially attractive. As with gene therapy for cystic fibrosis, many of these approaches were conceptualised in a similar fashion to conventional drugs. In this vision, gene therapies would be designed to act over relatively short periods of time rather than providing a permanent cure, would be mass-produced and administered by conventional means such as a simple injection. By 1992 George Wu had established TargeTech to pursue the idea of developing ‘gene Drugs’ for haemophilia and heart disease. In the following year Fred Ledley and Savio Woo founded GeneMedicine to investigate in vivo therapies for liver disorders and emphysema (Martin 1998).

A significant factor in the development of gene therapy as a form of in vivo drug delivery was the entry of the pharmaceutical industry into the emerging socio-technical network. In the early history of the technology the major pharmaceutical companies had been largely uninvolved, but in 1993–94 a wave of alliances and acquisitions was created with the nascent gene therapy industry. By 1996 over $1 billion of investment had been committed by the pharmaceutical industry to small gene therapy firms, most of it going to support the further development of these in vivo therapies (Martin 1998). A major reason for this interest was that the construction of gene therapy as a drug fitted easily into the dominant pharmaceutical product paradigm and was much more attractive to large firms than therapies based on classical gene therapy or ex vivo cell implants. The very heavy investment made in this area fundamentally shifted the locus of power in the network and the focus of research, reinforcing the shift to using genes as drugs.

Although the pioneers of cell implants were ultimately unsuccessful in attracting enough support to form long-lasting socio-technical networks, the strategy marked a decisive break from classical gene therapy. In particular, it opened up the possibility of using gene transfer technology for the treatment of many common acquired conditions. It also paved the way for the subsequent shift to direct in vivo therapies and the move from permanent to transient cures.

In the years following the initial trials described above, gene transfer was applied to virtually every tissue and organ in the body, and therapeutic strategies were developed for a wide range of other common acquired diseases including AIDS, arthritis and heart disease (Martin and Thomas 1996). Table 2 shows the full range of human diseases which gene therapy was being experimentally applied to, in either model systems or human trials, by 1996, and includes many major chronic conditions. A series of other socio-technical networks and companies were created during the 1990s to support these new applications and details of the most important ones are
given in Table 1. However, it must be stressed that despite this rapid expansion in clinical interest, the field remained essentially experimental, with no working therapy at the end of 1999.

The application of gene therapy to such a broad range of diseases prompted some advocates to see it as a potential new therapeutic modality, which could in principle be used to tackle virtually any pathology (Crystal 1995). Furthermore, the development of the technology by this stage was no longer wedded to the ideas of classical genetics, but was instead guided by the new therapeutic opportunities created by describing common acquired diseases in the language of molecular genetics.

**Conclusion**

The case studies described above illustrate the utility of using concepts from the sociology of technology to investigate the way in which new knowledge, and new disease concepts are co-constructed during the process of technological innovation. This paper has also shown that the development of gene therapy simultaneously required a series of technical, cognitive and social changes. For pioneering investigators to apply gene therapy to research problems in specific clinical niches, they had to engage in a process of heterogeneous socio-technical engineering (Callon 1987). This included, the re-conceptualisation of particular diseases as being genetic in some way; the reshaping of the technology itself; the construction of local socio-technical networks of regulators, genes, firms, clinicians and patients; and the creation of a new industry. The hybrid theoretical framework outlined in the introduction has provided a useful means for analysing these events and demonstrates that it is possible to describe the process of innovation and technical change in sociological terms.

It has been shown that the application of gene therapy to a broad range of common acquired conditions has reconceptualised them within the language of molecular genetics. At the same time, the very idea of a genetic disease was itself reconstructed so that it was no longer restricted to inherited disorders, but included cancer, heart disease and many other acquired conditions. Through this process it became possible to describe a given pathology as being acquired and operating at a genetic level. The point is well illustrated by the example of cancer, where the dominant model of this acquired disease started to become genetic in the early 1990s. This led to the introduction of novel anti-cancer strategies based on gene replacement and the development of these new gene therapies in turn further strengthened the notion that cancer was caused by errors in the way genes worked.

Through the development of this molecular pathology a new type of genetic body has been constructed in which all biological functions can be described in the language of genetics (Turney and Balmer 1998).
Table 2: *Diseases Targeted by Research into Human Gene Therapy in 1996*

<table>
<thead>
<tr>
<th>Genetic diseases</th>
<th>Cancers</th>
<th>Cardiovascular disease</th>
<th>Viral diseases</th>
<th>Neurological disorders</th>
<th>Other chronic conditions</th>
<th>Other conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA/SCID</td>
<td>Many types of cancer, including:</td>
<td>Atherosclerosis</td>
<td>HIV</td>
<td>Parkinson’s</td>
<td>Arthritis</td>
<td>Wound healing</td>
</tr>
<tr>
<td>Gaucher’s disease</td>
<td>– leukaemia</td>
<td>Peripheral vascular</td>
<td>CMV</td>
<td>Alzheimer’s</td>
<td>Lupus</td>
<td>Burns</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td>– breast</td>
<td>disease</td>
<td>Immunisation</td>
<td></td>
<td>Diabetes</td>
<td>Dental problems</td>
</tr>
<tr>
<td>PKU deficiency</td>
<td>– ovarian</td>
<td>Restenosis</td>
<td>others</td>
<td></td>
<td>Liver diseases</td>
<td></td>
</tr>
<tr>
<td>Pituitary dwarfism</td>
<td>– skin</td>
<td></td>
<td>including:</td>
<td></td>
<td>Emphysema</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>– lung</td>
<td></td>
<td>– hepatitis</td>
<td></td>
<td>Skin ulcers</td>
<td></td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>– kidney</td>
<td></td>
<td>– herpes</td>
<td></td>
<td>Kidney disease</td>
<td></td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>– brain</td>
<td></td>
<td>– influenza</td>
<td></td>
<td>Eye diseases</td>
<td></td>
</tr>
<tr>
<td>Thalassemia</td>
<td>– colon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilia A &amp; B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
cognitive change has been embodied in new therapeutic technologies, new forms of clinical practice and a new industry, and was enabled by the new knowledge flowing from the Human Genome Project.

The paper has also demonstrated that this reconception of genetic disease has both depended on, and enabled, a major change in the definition, applications and design of gene therapy technology itself. During the 30 years between the first proposal for genetic therapy and the growth of clinical applications in the 1990s, gene therapy technology was fundamentally reshaped as attempts were made to design a technology around which stable networks might be built. It moved from being a largely surgical procedure for the treatment of rare inherited disorders to a novel form of drug therapy for cancer and other acquired diseases.

In particular, four major changes in the design of the technology occurred as it moved from being a scientific idea to a clinical reality. Firstly, the link to eugenics was broken when germ line therapy was ruled unethical, paving the way for the legitimate development of somatic therapy. The second change was the break with classical genetics that occurred when the first cancer trial was approved and classical gene therapy, for technical reasons, was abandoned as a serious option. This opened up the possibility of treating a wide range of acquired diseases through the development of cell implants. Following this, the next major transition was marked by the shift from gene therapy as an ex vivo surgical procedure to it becoming a form of in vivo drug delivery. Simultaneously, the technology was reconfigured to provide a temporary rather than a permanent cure.

Each of these transformations in the application and physical design of gene therapy occurred as investigators struggled to build stable networks and each involved the reconstitution of the concept of genetic disease. Only by reshaping the technology and redefining genetic disease in this manner was it ultimately possible to enrol all the groups and resources required to introduce gene therapy into the clinic. In this sense the technology, the process of network formation and the changing concept of what a genetic disease was, mutually shaped each other. Central to this process of network building was the creation of particular visions for how gene therapy might be applied to treat a given disease and these were used as a means of both enrolling support and guiding research (van Lente 1993).

Finally, a key issue this paper has highlighted was the role of corporate firms in both enabling the development of gene therapy and in shaping the direction of research. In particular, the formation of the biotechnology industry during the 1980s, and the common financial interests amongst scientists and companies resulting from this, was fundamental to the growth of the field. Dedicated gene therapy firms were created by researchers as both a means of exploiting research for profit and a mechanism for gaining access to a range of heterogeneous financial, technical and managerial resources. The entry of pharmaceutical companies into the network in 1993 increased the power of firms to influence the technology and helped transform gene
therapy into an experimental form of drug therapy for the treatment of a wide range of acquired diseases.

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Notes

1 It should be noted that the distinction between these two options was not always clearcut, with scientists such as W. French Anderson advocating the genetic modification of future generations for purely medical purposes, a position he continued to maintain during the 1990s. However, a clear distinction was made between these two concepts during the 1960s by scientific advocates of genetic therapy (Tatum 1966, see Martin 1998 for discussion).

2 The ideas of classical genetics were first applied to medicine by the British physician Archibald Garrod, who in his book Inborn Factors of Disease published in 1931, suggested a simple correlation between inherited factors and particular familial conditions (Schriger and Childs 1989).

3 The term vector refers to the mechanism by which genes are transferred into the target cell. Prior to 1990 this mainly involved the use of genetically modified viruses which were engineered to incorporate the therapeutic gene.

4 The terms therapeutic protein or protein drug simply refer to the protein which is produced in the body by the introduction of the therapeutic gene.

References


