Relocation, Realignment and Standardisation: Circuits of Translation in Huntington 's Disease

Jamie Lewis*, Jacki Hughes and Paul Atkinson

Published in Social Theory and Health 12(4): 396-415

Relocation, Realignment and Standardisation: Circuits of Translation in Huntington's Disease

Abstract

Based on complementary ethnographies of a biomedical laboratory and a clinic – both working on Huntington Disease (HD) – we discuss *the circuits of translation* evident in biomedical and clinical research. By examining a recent epistemological shift from understanding the disease as genetic to understanding the disease as a problem for neuroscience, as well as documenting the multiple framings of the disease that migrate between the laboratory and the clinic, we emphasise the complexity involved in the movement of biomedical science into clinical work. We stress that this is not a one-way flow from the colloquially known *bench to bedside,* but is dependent on a cluster of contextual activities and local actors. We also stress the extent to which global collaborations, standardisation and regulatory frameworks can facilitate such framing and migration by aligning local practices and different disciplinary outlooks. We take a sociological perspective on translational processes – or rather to an expanded understanding of translation – to capture the material flows and conceptual transformations that are involved in the complex relationships between fundamental and clinical research.

Keywords: Translation, Huntington's Disease (HD), Ethnography, Relocation, Realignment, Standardisation

Relocation, Realignment, and Standardisation: Circuits of Translation in Huntington's Disease

Introduction

Biomedical research is increasingly described and justified in terms of the metaphor of 'translation' (Martin, Brown and Kraft, 2008). This is often portrayed as the passage of laboratory-based research into clinical treatments. The linear model of basic research → applied research → clinical intervention or technological product was developed during the twentieth century as a rhetorical tool used by scientists (Godin, 2006). To quote Vannevar Bush (1945) "basic research leads to new knowledge…It creates the fund from which the practical application of knowledge must be drawn. New products and new processes…are founded on new principles and new conceptions, which in turn are painstakingly developed by research in the purest realms of science" (p19). Here we take a sociological perspective on translational processes – or rather to an expanded understanding of translation. We suggest that there are complex processes of migration and circulation that extend the notion of translation. We maintain that translation is not simply the uni-directional movement from *bench to bedside* (Bush, 1945), nor the bi-directional movement of *bench to bedside* and *bedside to bench* (Keating, 2002; Löwy, 1996; Sartor, 2003). Equally, it is not solely a rhetorical device used to promote enthusiasm for the research (Wainwright *et al.*, 2006); although precisely because it is rhetorically powerful in justifying research, it is important to take a broader perspective. We argue that 'translation' is multi-directional and multi-modal: objects, knowledge, practices and resources are circulated between multiple sites. 'Matter'

and ‘matters’ migrate – physically or virtually - from one site to another. In the process they cross a variety of boundaries and potential barriers.

In particular, we describe the relative success achieved by one research group in mobilising the promise of cellular applications for Huntington Disease (HD) to develop research collaborations. In our example, there is a process of alignment between the knowledge-systems of the laboratory and the knowledge-systems of the clinic as scientists and clinicians render HD *doable* through the careful coordination, cooperation and calibration of the laboratory with the clinical and social worlds. In the process, instruments, biomedical tests and patients are configured as well (Keating and Cambrosio, 2003). These future-based networks are communities of promise, and in this particular case of the HD research clinic they traverse between the local and the global facing at least some of the impediments discussed by Martin, Brown, and Kraft (2008), including different working practices and diverse disciplinary outlooks.

We draw on two separate ethnographic studies conducted at sites situated within the translational operation - the laboratory (known here as Headlab) and the clinic (known here as Neurotest). We argue that an ethnographically-based, sociologically informed analysis of these processes permits a more sophisticated grasp of the circuits of collaboration and implementation than does a simple one-way, or even two-way, approach to ‘translation’. Most importantly, we argue, ‘translation’ implies the multiple framings of disease entities, that in turn imply more complex epistemological work than might be understood in terms of the unproblematic ‘transfer’ of stable knowledge or practices from one site to another (Wainwright *et al.,* 2006; Wainwright *et al.,* 2009*)*. The complex and messy reality of biomedical science rests on the practical integration of many different social worlds. Furthermore, scientific and medical phenomena are themselves translated and transformed in the process.

Our research suggests that the concept of 'translation' often fails to capture the material flows and conceptual transformations that are involved in the complex relationships between fundamental and clinical research. In the case of HD, we identify three major forms of transformation. First, in order for HD to be rendered observable and measurable in the clinic, it has been *relocated*: it has been re-framed as a neurological condition, rather than as a genetic one. Consequently, clinical observations and measurements of behaviour and cognitive function can be conducted in the interests of clinical research. Such *relocation* implies a change in professional personnel, a shift in technologies of assessment, and a physical relocation from one clinical site to another within the hospital. Secondly, there has been a process of *realignment* in order to render congruent the laboratory model of HD and the manifestations of HD in the neurological clinic. Technologies of visibility (Lynch, 1990; Galison, 1997; Dumit, 2004) and processes of measurability (Keating and Cambrosio, 2003) aid such arrangement. Laboratory science is translated into a clinically applicable practice and clinical phenomena are translated into researchable laboratory topics. Thirdly, there is an imperative to *standardise* HD in the laboratory and clinic in the interests of globally distributed research collaboration. Translational research is dependent on the collaboration between scientists and clinicians, and standardisation enables multiple parties to work together across boundaries (Fujimura, 1992). Relocation, realignment and standardisation are thus among the cognitive and institutional strategies implicated in *the circuits of translation*.

Research Context

Ethnographic fieldwork was conducted in the United Kingdom at two sites of work - the laboratory and the clinic - examining the translational operation. They both work on HD, they collaborate directly, and some key personnel work in both. The first, conducted by [Author 1], was a fifteen-month ethnography of Headlab; a cell laboratory conducting foetal tissue transplantation trials for HD. Twenty-five days of laboratory observation were conducted at

both the cell laboratory and its animal house. Handwritten field notes were taken during observation days and typed up in the evenings. In addition, fifteen semi-structured interviews were conducted with laboratory researchers.

The second, conducted by [Author 2], was a 36-month ethnography of Neurotest; a disease management and research clinic for Huntington's Disease. **[**Author 2] followed a series of patients through their consultation with the director of Neurotest (Professor Craven), then on to any sessions with a psychiatrist, and into any research projects being carried out by psychologists, physiotherapists and research nurses. Ethnographic observations were made of waiting-room activity, clinical routines, neurological and cognitive testing, and patient consultations. These were in the form of observational field notes for each separate activity, including snippets of conversations, actions, expressions, and negotiations. Clinic observations were conducted over twenty-nine days. Ten semi-structured interviews were conducted with patients and carers, seven semi-structured interviews with experts, and a further twenty-seven informal conversations with patients and carers. Thematic analysis of the observations and interviews from both sites was carried out during and after fieldwork. All names of the research sites and people mentioned in the article are pseudonyms.

The ethnographies were analysed separately in the first instance. This paper derives from a subsequent exercise in synthesising findings and insights from a number of studies in this field (Lewis and Atkinson, 2011; Lewis *et al.*, 2013; Stephens, Lewis and Atkinson, 2013). Given this focus and given the different styles in which the authors wrote their field notes, our approach in this paper, following authors such as Rapp (2011), is not to present the field notes as separate freestanding pieces of data. But, rather to both describe and analyse the research sites in the body of the text (see Jackson, 1990 on field notes and head notes).

Such syntheses seek to transcend the site-specific nature of the originating ethnographies, in order to trace and follow the biomedical phenomena across a number of sites of knowledge-production. Headlab and Neurotest are part of a global collaborative approach to researching HD. A collaborative approach to modern biomedicine is a trend that has been noted in earlier work when discussing stem cell science and its potential applications for diabetes (Wainwright *et al.* 2006). Indeed, at our empirical settings we see the realization of two levels of collaboration. In the first instance we are privy to a type of *local* translational collaboration. This institutional alliance is a clear intention to strengthen interactions between Headlab and Neurotest. The second involves collaboration on an *international* scale and the cooperation of multiple parties and agencies. We discuss both forms of collaboration as we follow the phenomena across various sites of work.

Relocating Huntington's Disease

Translation between the clinic and the laboratory has involved the *relocation* of the disease from one specialty to another. Conceptually speaking, 'the same' medical condition can be located in a number of different specialties, each one framing the disease in a different way (Mol, 2002). Consequently diseases can follow a trajectory of migration between specialties, and of redefinition or reclassification. Such processes have been described by Latimer (2013), who traces the migration of dysmorphology, and Keating and Cambrosio (2003) who examine the field of hematology, across time and biomedical specialties. HD is rendered visible and researchable in the clinic we describe, and consequently in its paired laboratory, by a process of *relocation* from genetics to neurology.

HD is an inherited disease of the brain (Harper, 1991). It is an incurable genetic condition in which symptoms typically develop between the ages of 35 and 50. Symptoms include chronic choreic movements, which are jerky and uncontrollable, and a gradual loss of

insight and cognition that manifests as a dementia-type condition. Death occurs approximately 15 to 25 years after onset of symptoms (Roos *et al.*, 1993). The cause has been identified as a dominantly inherited gene on chromosome 4, with an unstable protein sequence (The Huntington's Disease Collaborative Research Group, 1993). The sequence (Cytosine, Adenine, Guanine) is known as a trinucleotide repeat. These CAG repetitions occur in everyone on chromosome 4, but in people who inherit the HD-type gene there are many more repetitions of CAG at this position. The disease pathology is the attaching of 'Huntingtin' proteins to neurons in the brain in an irreversible process. The build-up of protein attachments causes loss of cells and function in particular areas of the brain. Currently there is no effective treatment for HD, which is physically, psychologically and socially debilitating.

Despite the genetic component underpinning the disease, there has been a recent shift to understand the neurological basis of HD. The epistemological relocation of HD from genetics to neurology has been mirrored by the physical relocation and recasting of the clinic. The previous incarnation of Neurotest was a permanent base in the genetics department for management and palliative care. The general recollections of families prior to the current neurological research programme were that these were always routine clinic appointments, and that no treatment was available, but that they had a support network and a point of contact to make enquiries. In addition to the clinic there was also a home visit policy, which meant specialist genetic nurses and counsellors could meet the family outside the confines and formality of the clinic, and could examine the family and home situation. This form of additional social support for discussion and advice was considered a valuable service for the families involved, enhanced by other forms of support such as social services.

Whereas the previous clinic was permanently rooted, and centred on genetics, family members and local problems; today's clinic is mobile and transferable with an emphasis on

data collection and redistribution on an international scale. Today, Neurotest is a *pop-up* – documentation and personnel are easily transported in and out of its interim location for one day a week, and researchers travel from various parts of the university to perform clinical rituals and routines. Like most outpatient clinics, it is a meeting site for various clinical and scientific actors as well as patients. However, unlike most outpatient clinics, despite being based at a hospital, it is no regular National Health Service (NHS) setting. Although maintained to a hospital grade standard, the *pop*-up is situated in a research centre. This means that there is no permanent scrimmage for appointments and no constant churning over of patients. The clinic is, in contrast to most outpatients, quiet and spacious with a conspicuous lack of hospital trolleys and other NHS paraphernalia. At the end of day, the consultation room, the equipment and research paperwork are packed up and stored away until being laid out again in the next clinic. Contrast this picture of a portable, sterile (by this we do not just mean hygienic, but also barren) space that can *pop-up* anywhere at any time with the impressions of patients who consider the clinic to be a fixed abode existing all week around. For one day a week the perception of an anchored site provides a *moment of repose* in an otherwise shifting landscape where matter and matters – such as data, equipment and personnel - move from site to site being *relocated* in the process. To this end, today's, Neurotest acts as a gateway to biomedical research as well as a place of clinical monitoring as the line between research and clinical management is muddied. The clinic is defined as a management clinic where patients can ask to be involved in research. This has meant that some patients have been referred to the clinic specifically because they know it is active in research. However, as part of its management role, patients partake in, among other things; psychological and cognitive testing where standardised data is collected (and then distributed).

The epistemological relocation of HD as a set of neurological signs and symptoms has therefore seen a transformation in the function of Neurotest, both for those working there and for the patients that attend the clinic. Viewed in this manner, interest in the disease is less about its genetic causation, and less about the personality of the patient or departure from normal life, and more about what happens in the patient's brain. Drug developments that focus on brain functions, and the potential renewal of brain cells via technologies such as stem-cell or foetal tissue implantation, have relocated HD from the backwaters of genetic incurable disease, to the forefront of a new biotechnology based on research on brain-function. This has an effect on the general thoughts surrounding HD within families at risk or those affected – it is regarded less as a social and family problem and more as a biological condition. In turn, this facilitates understanding of the effects on different parts of the brain in different patients, allowing the individual patient to be better understood in terms of their specific difficulties. Patients at Neurotest are inquisitive about developments in stem cells and are aware of the research at Headlab (Neurotest's paired laboratory) and some of the clinical trials conducted by the laboratory's collaborators in France. *Relocation* of the disease to the forefront of neuroscience therefore stimulates interest in scientific developments enabling laboratory products such as stem cells to travel – whether discursively or physically - between the laboratory and the clinic. Such bio-objects (Vermeulen, Tamminen and Webster, 2012) are the material reification of communication, functioning as boundary objects that connect different worlds (Star and Griesemer, 1989).

Due to the paucity of any therapeutic alternatives for HD via medication, stem cells are capturing the imagination of Neurotest patients. That patients *have* heard of developments in stem cell research at Headlab, even though *no* trials were currently being conducted, consolidates a 'community of promise' (Martin, Brown and Kraft, 2008). This community helps foster relations between the laboratory where trials are expected to be conducted (Lewis

and Atkinson, 2011; Stephens, Lewis and Atkinson, 2013) and the clinic. Patients and families who attend today's Neurotest therefore obtain tangible benefits in terms of time to discuss the disease, disease comprehension, and a sense of partnership with scientists and clinicians. Relocating the disorder from genetics into neuroscience has therefore also provided the opportunity for patients and patient groups to become a more active group in the biomedical process (Novas and Rose, 2000; van den Hoonard, 2009).

The Collection, Standardisation and Distribution of Huntington's Disease

The relocation of the condition from genetics to neurology created the opportunity to intensively study the behavioural and cognitive trajectory of the condition in individuals and record the results. The course of increasing impairment could be traced and measured through standardised neurological assessments. This was, in turn, grounded in a global process of standardisation, through a major research collaboration. A global effort to address HD is pursued by mobilising the combined efforts of scientists and clinicians in an international project. The Huntington Project began in the USA, and encompasses most of Europe, parts of Asia, and extends into South America (Huntington's Study Group, 2010). This type of large-scale multi-national collaboration involves the recruitment of large numbers of patients as participants in a longitudinal study on several heterogeneous projects and online research discussions. It also enrols different types of clinicians, biomedical scientists and health workers, working together in different laboratories, clinics and countries. The data collected from these projects is brought together in an integrated approach, stored in databases, and made available for future HD researchers. Indeed, databases have become central instruments of scientific work and their development and maintenance is integral to the success of ongoing research (Hine, 2006; Millerand and Bowker, 2009). In particular, the European Huntington Disease Network (EHDN) is taking part in Registry, a large multinational study that is 'dedicated to finding treatments that make a difference for HD' **(**EHDN, 2010**)**. In

practice, this means that routine data collected and anonymised from HD patients at neurological clinics throughout the UK such as Neurotest is collated together with the same data from HD patients all over Europe, and then fed into a mass storage system to be retrieved by researchers all over the world. The collaborations and the practices of research are therefore both global and circular: the data collected is linked, accessible (both now and in the future), and all patients are contactable and re-contactable. Such distributions form part of *the circuits of translation.* To borrow words from Keating and Cambrosio (2003) "unlike laboratory research, research at this level concerns less the production of local and unprecedented "epistemic things" than the constitution and circulation of protocols, instruments and substances between laboratories and the establishment of conventions that allow them to be used in the generation of biomedical facts" (p3).

Clinical and cognitive HD tests carried out in participating clinics continue to be refined and standardised across the globe so that the resulting datasets can be shared and compared between laboratories. Data of this kind are heavily focussed on recording the actions of patients, linking the growing knowledge of brain-function to the observation of its embodied performance (Dumit, 2004; Rapp, 2011). This surveillance has resulted in a battery of testing procedures, through which HD patients are enrolled in the research process. As Petryna (2009) has demonstrated, the global dispersion of biomedical research places a premium on the reliability and standardisation of clinical trials. Local interventions must always be translated into global data. This results in a further process of *relocation* – from patients to records and then on to shared-databases that form the basis of major research syntheses. Data such as this are mobile and can travel across various physical and virtual borders. In other words, the re-classification of HD as a neurological topic, for research purposes, is shaped by the demands for data that can be gathered and pooled on a trans-national basis.

Standardisation results in documentary records that can migrate between one research centre and another, and measurements that can be pooled. Documents have a way of traversing boundaries and aligning practices, whilst the standards themselves are vehicles that help transport scientific fields from one domain to another (Eriksson and Webster, 2008). The expectation is that using a single, uniformed file, research groups around the globe can create an agreed ideal-type of HD making it easier to share research findings, obtain large samples of suitable patients and push the boundaries of the research faster without recourse to local protocols and ethical procedures. For example, the normal informed consent procedure would usually apply to just one particular study. However, the ongoing informed consent procedure for Registry allows patients to be re-contacted for other drug or treatment trials as and when they are available. This prevents lengthy delays in attempting to find a 'suitable patient population' since patients have already been identified. It also means researchers do not need to apply for new protocol approvals before contacting these patients. Indeed, this feature of recontactability is part of the 'community of promise', which has spiked the curiosity of the HD patients and families.

All of this travelling – the transportation of standardised data, documents and procedures – can be performed whilst scientists, clinicians and, importantly, patients remain firmly rooted in their own locale. Standards and regulation therefore play a fundamental role in stabilising a field, bringing momentary clarity to an often shifting landscape. In this process, patients become calibrated, displaying key features of HD as manifested in the standardised research protocols and measurement instruments. As a consequence, it is not merely the biomedical science that is translated *into* patients: patients are themselves translated into ideal-typical displays of neurological impairment.

Calibrating the Laboratory and Clinic

The processes of re-framing and re-locating are by no means one way. There is no single passage of ideas, materials or treatments from the laboratory to the clinic as the metaphor of *bench to bedside* would suggest. Rather, both the clinic and the laboratory need to be *realigned*. We have already discussed the way in which 'the clinic' is itself formulated as a site of research, and to that end the condition itself is re-framed in terms of neurological testing. Moreover, HD itself must be relocated *back* into the laboratory in order to render clinically observed signs and symptoms into researchable laboratory phenomena. In a process of *relocation* that parallels the clinical re-framing of HD, the disease is translated into a series of 'doable' phenomena (Fujimura, 1987). The neurological signs and symptoms are therefore reformulated into behavioural traits that can be observed and measured in laboratory models (mice and rats).

We have described the process of modelling in more detail elsewhere (Lewis *et al.* 2013). Here we stress the significance of such modelling within *the circuits of translation*. There is a reflexive relationship between the laboratory and the clinic. The clinic frames the disease in ways that are susceptible to observation and measurement. The laboratory models the observable behaviours, and in turn provides a model *of* the disease that feeds directly back into clinical observations and interpretations. The disease entity (HD) is thus resolved into a number of different behaviours (such as gait or manifestations of memory) that can be induced and observed in laboratory animals. Knock-out mice or mice that have been given lesions can be induced to behave in a way that mirrors the observable behaviours of patients with HD; while laboratory rats, similarly treated, can be used to study more complex behavioural traits.

If HD is to be studied in the laboratory, embodied in animal models, then there is a fundamental act of translation to be performed. HD has to be re-framed in terms of one or more animal models. The translation of the disease from human patients into laboratory

animals is, of course, one of the most significant of the multiple relocations and translocations that are required in order to make HD itself tractable. While it is conventional to discuss these issues in terms of animal 'models', this can readily gloss over the complex interpretative and judgmental processes whereby biomedical scientists have to decide collectively and locally what 'counts' as an adequate representation of HD in the laboratory animal. Consequently, the translation process calls for a series of equivalences to be established; both metaphoric and metonymic (see Lewis *et al.* 2013).

Laboratory models need to be established with sufficient fidelity to the human condition as to permit experimental interventions to assess the possible efficacy of cellular implants into human patients with HD. Headlab had previous success with animal models that suggested transplanting cellular material into the brains of HD patients could have positive therapeutic effects. Based on the success of these experimental studies, the group planned to transplant embryonic striatal cell grafts collected from donated aborted foetuses into HD patients. The clinical trials were part of wider European research collaborations. Headlab hoped to assess the effectiveness of the trial by conducting transplant procedures with 10 patients and then assessing them for a further two years. The team had demonstrated some success with this approach in earlier years, but had been forced to suspend that work when regulatory directives required that laboratories be up-graded to clinical Good Manufacturing Practice standard (Lewis and Atkinson, 2011; Stephens, Lewis and Atkinson, 2013). Having up-graded the laboratory facility, they were at the time of the fieldwork in a position to resume the work of translating laboratory experiments into preliminary trials on HD patients. The relationship between Headlab and Neurotest is vital for the success of such a venture. The implantation of cells into human patients will once more relocate the experimental intervention from the laboratory to the clinic and from the model to the human patient. There is thus a dialectical relationship of modelling and calibration that shuttles back

and forth between laboratory modelling and clinical observation and measurement, which even extends to the type of care afforded to the animals and patients (see Friese, 2013). Just as the laboratory models the disease, so patients in turn are fashioned into models of neurological presentations. This process of *realignment* renders congruent the laboratory model of HD in the neurological clinic and helps secure coherence for the classification of HD as neurological.

As discussed, patients and carers of Neurotest had a very sketchy idea of the term 'research', often describing their visit to the clinic as 'just a check up', or 'a chat to see how things are progressing'. The movement, psychological and cognitive tests were all perceived as ways to monitor the disease, and ways of calculating the health of the patient, rather than any specific investigative research exercise aimed at standardising cognitive tests and shaping HD categories. There is, and has been, an intimate dialectic between research and the clinic. Historically, this has been reflected in what has been described as the implicit 'contract' between the patient population and senior medical practitioners (Fox, 1959; Löwy 1996). The former receive treatment in the major teaching hospitals while the latter use them as 'clinical material' on which to base their clinical careers, experience and research. The original form of this relationship was based on the translation of *treatment* in one direction in return for greater *knowledge* of human ailments in the other: in return for medical care, clinicians gathered in-depth, local knowledge of the body. Here, we see a contemporary version of this intimate relationship, based in part on a renewed version of that tacit contract. In return for routine monitoring, clinicians and researchers at Neurotest are gathering in-depth, local knowledge of the body on a global scale. Similar to previous arrangements within medical history, there is a form of exchange within the translational process: this time it is the potential for clinical research and 'check ups' in exchange for standardised medical and

biomedical knowledge of the patient.[1] The knowledge gleaned from HD patients is circulated back to the laboratory and forms part of the laboratory models of HD. Calibration between the laboratory and the clinic is therefore an institutional strategy implicated in the *circuits of* translation. We return to this is the next section.

The Realignment of the Lab and the Clinic: the importance of boundary personnel

Translation, in its various forms, implies border-crossings and the transcending of boundaries. Such boundaries can be soft or hard, visible or invisible, rigid or elastic. Boundaries, whether physical – as in the walls of a laboratory or clinic – or social and epistemological – as between disciplinary fields and territories - frame and legitimate the activities conducted within them. Translation is often accomplished in terms of the movement of objects, ideas and instruments across such terrains. Boundaries are crossed, bio-objects such as animal models (Vermeulen, Tamminen and Webster, 2012; Lewis *et al.*, 2013), stem cells, standards and experiments travel (Petryna, 2009). But, the vectors for such movement and boundary-work also include personnel, who may move organizationally between the clinic and the laboratory.

As illustrated, the processes of translation are not based simply on local collaborations, or the physical proximity of laboratory and clinic, but such arrangements *do* facilitate the practical conduct of research and the everyday work of clinician-scientists. Headlab and Neurotest are based in the same city and some of the patients selected for Headlab's foetal tissue transplant trial will likely be filtered from those who attend Neurotest. The positioning of a Clinical Professor (Professor Craven) who is able to navigate both sites is critical here. Building an infrastructure where the two institutions draw from one another

[1] On a broader front, of course, this historical relationship finds its modern counterpart in the more explicit form of contract enshrined in the processes of informed consent and enrolment into clinical trials.

and where boundary people can work from varying points of the translational operation creates an environment that promotes smooth translational and reverse translational research. This multidisciplinary approach to treating a disease may determine the success of transplantation and therefore researchers from both sites require a broader perspective than that which they study. The make-up of the Headlab group thus has a mixture of disciplinary hinterlands, comprised of a lattice of behavioural scientists, psychologists, cellular scientists and clinicians. According to Rapp (2011) 'under new interdisciplinary umbrellas, the migration of researchers and their shared topics, tools, grants, and regulatory ethos, becomes a practical possibility' (p673). Indeed, the Clinical Professor epitomises the notion of multiple identities and interdisciplinary research (see Calvert, 2012; Lewis and Bartlett, 2013 on individual interdisciplinarity). Professor Craven combines clinical duties at Neurotest with her laboratory research at Headlab, including physical attendance at both sites. She identifies herself as both a clinician and a neurologist interested in neurodegeneration. Working as a clinician-scientist for 20 years, her interests extend to both developments in cell replacement therapy in the laboratory and the manifestations of HD in patients in the clinic. This has resulted in her travelling between her clinical duties at Neurotest and her laboratory research at Headlab.

According to Horig, Marincola and Marincola (2005) 'dual-trained physician-scientists are too few if for no other reason than the years required to fully train in both medicine and research' (p707). They highlight the lack of such boundary people as a barrier to translational success. However, the clinician-scientist is a central actor in the translational work of contemporary biomedicine (Wilson-Kovacs and Hauskeller, 2012). Therefore Professor Craven is in a rather unusual but fundamental position as someone who has the skills to work comfortably at the bench and in the clinic. Over the years she has worked simultaneously with sets of ideas from both clinical practices with patients and from cellular

work in the scientific laboratory. Llewellyn (2001) uses the metaphor of the two-way window to describe a similar relationship that clinical medical directors have with clinical practice on the one hand and management on the other. As the clinical neurologist Professor Craven has the knowledge to align work conducted in the laboratory with work done in the clinic. The close ties between the two settings further enable Professor Craven to push the translational agenda.

The intimate relationship between Headlab and Neurotest is fundamental to the success of translational research. As an example of how the laboratory is calibrated, basic research into animals measuring behavioural deficits of HD travels from Headlab to Neurotest, and findings showing that the cells they are looking at have a positive functional effect in good models are used to generate greater knowledge of the human disease. This is the traditional translational research model: the movement of basic research from the laboratory *bench* to the clinical *bedside*. Working together the two sites serve as discovery devices, pioneering medical practices by translating knowledge crafted in the laboratory into real-world practices in the clinic (Zerhouni, 2007). This is achieved on the back of a close working relationship between the two co-directors of the sites and the transfer of knowledge – through personnel, standards and objects - between the laboratory and the clinic.

However, the two groups also perform what is traditionally called reverse translation too. Headlab attempt to model the knowledge gleaned from the clinic on very early cognitive behavioural changes (often determined from clinical 'management' tests) into laboratory animals, before attempting to develop parallel tests on the animals back into patients. This illustrates how both the laboratory and the clinic require *realignment* as knowledge, materials and personnel flow in both directions between the two settings. In the same way that the disease is translated from the lab in to the human patient, so the disease is translated from the human patient to the laboratory (see Lewis *et al.*, 2013). The disease therefore goes through

a series of relocations and translocations. Traditional boundaries between basic research and clinical research have softened as bridging devices such as animal models or 'stem cells are used to transfer knowledge bi-directionally between the two sites. Behavioural animal experimentation is the essential basis for clinical cellular work, but knowledge collated in the clinic is also being built into the construction of animal models of the disease. Therefore a feedback loop is created: the bench informs the clinic, the clinic informs the bench, and the bench will eventually inform the clinic once more. Here the *circuits of translation* between the two institutions are evident.

At the local level, it is clear that translational research is an inherently collaborative enterprise (Marincola, 2003). At our empirical settings, close institutional collaboration of this type is made possible because of some core operational alignments: similar instrumental interests, a common and co-dependent goal, boundary personnel and institutional proximity. Against this backdrop, it is the role of Professor Craven and Neurotest to link novel scientific advancements performed on rodents in the laboratory with the real-world experiences of living with the illness. Accordingly, Neurotest can be seen to perform the role of bringing together scientific and technical knowledge with patient-disease led knowledge. In discussing 'translation' it is all too easy to assume that 'the clinic' is merely the site at which biomedical innovations (produced at Headlab) are applied. Clearly this is not the case as the HD neurological clinic is itself a site where patients are enrolled as participants in trans-national research collaborations. Clinical observation and research-oriented data-collection are sometimes indistinguishable in the clinic. Indeed, it is in the clinic that research and clinical work are most closely intertwined, and where the boundaries are most obscured. Subsequently, some of the participating patients could not tell the difference between research and clinical management. This ambiguity has been illustrated previously by authors examining fields such as Cancer Genetics (Hallowell *et al.*, 2009; Ponder *et al.*, 2008). In a

similar vein, some patients in our study could not decipher whether they were part of a research project or not, particularly given that the research involved the collection of vast amounts of exploratory cognitive data that did not take the more typical form of a drug trial.

Global Circuits and International Collaborations

Clinical research, as well as basic research, often transcends national and cultural boundaries to become global partnerships and international collaborations. Headlab has working relationships with other laboratories in Europe, particularly in France. This collaborative approach is not unintentional. It is accepted within the HD community that transplantation projects can do some good and alleviate symptoms, although recent results have begun to appear from France and the USA which show limited and regressive results over time (Cichetti *et al.*, 2009; Keene *et al*., 2009). With no alternative treatments, the moral mission of treating a debilitating disease has compelled laboratories to collaborate[2].

Others have made us aware of the inherent problems and obstacles of translation (Wainwright *et* al., 2006). Boundaries are places of conflict. It is clear therefore that the various scientific laboratories, clinical groups and other interested parties must have a shared goal. Their interests need to be aligned from the beginning. This collaborative attitude has moved translational research from the lips of lab directors (a rhetorical device) to the benches of respected laboratories. For example, despite clinical trials having been halted at Headlab, clinical trials are within sight (and referred to in clinics by patients and clinicians). Moreover the trials continue to proceed in France. The corporeality of the procedure and the hope

[2] Of course there may be additional economic and social rewards for collaborating as well as any moral responsibility.

invested in such a technique stimulates interest in the patient population. Joining forces to reach an agreed end goal of cellular transplantation, the triumvirate of laboratory, clinic and patient population also mobilises funding agencies and charities to support this type of research. Of course, this is not to suggest that there is not genuine competition between laboratories. Collaboration is a process of cooperation and competition (Atkinson, Batchelor and Parsons, 1998). However, we follow Fujimura (1987), in suggesting that the problem is *doable* when scientists can align tasks to three levels of organization – in this case, the laboratory, the clinic and the social world, which includes promissory futures. HD transplantation then becomes more than conceptual. It becomes tangible and viewed as dutiful across the globe.

The processes of circulation between the laboratory, the clinic and patients/families draws attention to a more nuanced version of 'translation' than the mere transfer of knowledge and technique from one context to another. Such collaborations are only possible when there is a degree of international standardisation across and between groups that enable multiple parties to work together. As described, processes of alignment require data to be gathered, pooled and analysed in accordance with agreed protocols that extend across national boundaries, as well as bringing laboratory and clinical knowledge closer together. Central to the Huntington Project is the idea that using uniform files, research groups around the globe can construct one or more ideal-types of HD and rid the research field of its untidiness. Hacking (1983) argues laboratory work is not merely about representation, but also intervention: researchers are actively engaged in dexterously manipulating materials. The messiness of observational studies of HD that collect multiple sets of data finds its counterpart in the intervention of laboratory life. Standardising the types of data collected turns HD into a doable problem (see Fujimura, 1987; Stephens, Atkinson and Glasner, 2011). Standardisation of practical testing, and of recording results is an area of expansion at

Neurotest. It was known that some clinicians carried out physical and cognitive testing in ways that had slight variation. In order to counter this (and to obtain 'standardised data'), video training was given to formalise and create uniform tests. In addition, specific forms and methods of registering clinical test results were developed, unified and used throughout all the research sites. Standard documentation was produced for recording the results, which form part of the global database. It is important to note that standardisation has not been carried out for the direct benefit of the patient. It has been developed to allow portable data to be easily recorded, manipulated and transferred between Neurotest, Headlab and their global partners. Data-types are identical enabling easier migration between sites and success is built-in to their construction reflecting the actions and work of the researchers[3].

Clinic portals such as these databases provide common recording standards that enable meaningful local and national comparisons – that is, patients can be compared against one another and laboratories can collate findings. Each site of clinic data collection has access to its own data immediately, whilst access to comparative sites may also be applied for. Comparison of this kind also extends informally to the 'competition' between sites' successful levels of data collection. The Huntington Project and Registry are therefore examples of global standardisation (and regulation) that strive for global certainty by beginning to eradicate local practices, local interpretations and local contingency (see Leigh-Star, 1985).

Discussion

The metaphors of translation and translational research have become prominent terms in describing biomedical research and its applications. While there have been long-standing

[3] Of course, there may be aspects of interpretive flexibility (see Stephens, Atkinson and Glasner, 2011) in terms of the ways in which different sites understand the data.

interactions between the laboratory and the clinic, the two have been recognised not merely as contrasting locales of biomedical practice, but also sites of contrasting modes of knowledge. This was the main message of Canguilhem's (1978) pioneering work on the history and philosophy of medicine. Canguilhem suggests that 'the clinic' (as a mode of knowledge) is never explained solely from laboratory measurements and values. The pathological is never describable solely by extrapolating extreme differences from a norm or base. In that sense, 'the clinic' and its distinctive modes of perception is an autonomous realm. By the same token, the laboratory is also a relatively autonomous intellectual domain. The point of contrast is not to imply that these domains of knowledge-production and application are entirely independent, and that there is no possible epistemological interaction between them. Indeed Keating and Cambrosio have shown us how 'biomedical platforms' help bridge the gap between biology and clinical medicine (Cambrosio *et al.*, 2009; Keating and Cambrosio, 2003). Rather, the paper demonstrates how biomedicalisation (Clarke *et al.*, 2010), biomedical platforms (Keating and Cambrosio, 2003) and bio-objects (Vermeulen, Tamminen and Webster, 2012) get produced. Translation is not a given – it needs to be made to happen. The synthesis between the laboratory and the clinic has to be achieved through a process of mutual adjustment. The paper documents precisely the ways in which biomedicine is made: translation does not just create new applications as Vannevar Bush proclaimed, it also sees new entities and new knowledges produced in the process.

Fundamentally, translation implies movement between at least two different modes of perception, modes of interpretation and modes of practice, often referred to as the movement between *bench to bedside* and *bedside to bench*. These metaphorical obstacles all require some hurdling to cross what some writers, using another metaphor, have called the *Valley of Death* (Butler, 2008). In the paper we demonstrate some of the ways in which these obstacles are negotiated or brought into alignment within Huntington's disease research. We put

forward that rather than a linear relationship between the clinic and the laboratory, there are multiple processes of relocation and translocation within *the circuits of translation.* In particular, HD has been relocated to neurology from genetics. This switch has been supplemented by promises of technical advances in the manipulation of tissue that mobilise communities of promise, the realignment and reconfiguration of the laboratory and the clinic, and the development of stable scientific infrastructures including the global standardisation of local practices and products. Indeed, regulation and standardisation play a central role in shaping and stabilising biomedical practices. Such processes can encourage, if not necessarily permit, the movement of ideas, artefacts and bio-objects between various local and international sites.

References

Atkinson, P., Batchelor, C. and Parsons, E. (1998) Trajectories of Collaboration and Competition in a Medical Discovery. *Science, Technology and Human Values* 23(3): 259-284.

Butler, D. (2008) Crossing the Valley of Death. *Nature* 453(7197): 840-842.

Bush, V. (1945) Science The Endless Frontier: A Report to the President by Vannevar Bush, Director of the Office of Scientific Research and Development. Washington: United States Government Printing Office.

Calvert, J. (2010) Systems Biology, Interdisciplinarity and Disciplinary Identity. In J.N. Parker, N. Vermeulen and B. Penders (eds.) *Collaboration in the New Life Sciences.* Farnham: Ashgate, pp. 201-219.

Cambrosio, A.. Keating, P., Bourret, P., Mustar, P. and Rogers, S. (2009). Genomic

Platforms and Hybrid Formations. In P. Atkinson, P. Glasner, and M. Lock (eds.) *Handbook of Genetics and Society: Mapping the New Genomic Era*. London: Routledge, pp. 502-520.

Canguilhem, G. (1978) *The Normal and the Pathological.* R.S. Cohen and C.R.Fawcett (trans). Dodrecht: Reidel.

Cicchetti, F., Saporta, S., Hauser, R.A., Parent, M., Saint-Pierre, M., Sanberg, P.R., Li, X.J., Parker, J.R., Chu, Y., Mufson, E.J., Kordower, J.H. and Freeman, T.B. (2009) Neural Transplants in Patients with Huntington's Undergo Disease-like Neuronal Degeneration. *Proc Nat Acad Sci* 106(30): 12483-12488.

Clarke, A., Mamo, L, Foskett, J.R., Fishman, J.R. and Shim, J.K. (eds.) (2010) *Biomedicalization: Technoscience, Health and Illness in the US.* Durham, NC: Duke University Press.

Dumit, J. (2004) *Picturing Personhood: Brain Scans and Biomedical Identity*. Princeton, NJ: Princeton University Press.

European Huntington's Disease Network (2010] European HD Registry, www.euro-hd.net/html/registry, accessed 1 August 2008.

Eriksson, L. and Webster, A. (2008) Standardizing the Unknown: Practicable Pluripotency as Double Futures. *Science as Culture* 17(1): 57-69.

Fox, R.C. (1959) *Experiment Perilious: Physicians and Patients Facing the Unknown.* Glencoe, IL: Free Press.

Friese, C. (2013) Realising Potential in Translational Medicine: the Uncanny Emergence of Care as Science. *Current Anthropology* 54(S7): 129-138.

Fujimura, J. (1987) Constructing 'do-able' problems in Cancer Research: Articulating Alignment. *Social Studies of Science* 17(2): 257-293.

Fujimura, J. (1992) Crafting science: Standardized packages, Boundary objects, and "Translation." In A. Pickering (ed) *Science as Culture and Practice* Chicago: University of Chicago Press, p. 168-211.

Galison, P. (1997) *Image and Logic: A Material Culture of Microphysics*. Chicago, IL: University of Chicago Press.

Godin, B. (2006) The Linear Model of Innovation: The Historical Construction of an Analytical Framework. *Science, Technology and Human Values* 31: 639-667.

Hacking, I. (2003) *Representing and Intervening: Introductory Topics in the Philosophy of Natural Science*. Cambridge: Cambridge University Press.

Hallowell, N., Cooke, S., Crawford, G., Lucassen, A., Parker, M. (2009) Distinguishing Research from Clinical Care in Cancer Genetics: Theoretical Justifications and Practical Strategies. *Social Science and Medicine* 68(11): 2010-2017.

Harper, P.S. (Ed) (1991) Huntington's Disease. Major Problems in Neurology 22. London: W.B. Saunders.

Hine, C. (2006) Databases as Scientific Instruments and their Role in the Ordering of Scientific Work. *Social Studies of Science* 36(2): 269-298.

Horig, H., Marincola, E. and Marincola, F.M. (2005) Obstacles and Opportunities in Translational Research. *Nature Medicine* 11: 705-708.

Huntington's Study Group (2010) Unified Huntington's disease Rating Scale & Database. www.huntington-study-group.org/Resources/UHDRS/tabid/67/Default.aspx, accessed 3 August 2010.

Jackson, J.E. (1990) "I am a Fieldnote": Fieldnotes as a Symbol of Professional Identity. In: Sanjek, R. (ed.) *Fieldnotes: The Makings of Anthropology*. Cornell University Press: Ithaca, NY p. 3-33.

Keating, P. (2002) From Screening to Clinical Research: the Cure of Leukemia and the Early Development of the Cooperative Oncology Groups, 1955–1966. *Bulletin of the History of Medicine* 76(2): 299– 334.

Keating, P., and Cambrosio, A. (2003) *Biomedical Platforms: Realigning the Normal and the Pathological in Late-Twentieth Century Medicine.* Cambridge: MIT Press.

Keene, C.D., Chang, R.C., Leverenz, J.B., Kopyov, O., Perlman, S., Hevner, R..F., Born, DE., Bird, T.D. and Montine, T.J. (2009) A Patient with Huntington's Disease and Long-surviving Fetal Neural Transplants that Developed Mass Lesions. *Acta Neuropathologica* 117(3): 329-338.

Latimer, J. (2013) *The Gene, the Clinic and the Family: Diagnosing Dysmorphology, Reviving Medical Dominance*. London: Routledge.

Leigh-Star, S. (1985) Scientific Work and Uncertainty. *Social Studies of Science* 15(3): 391-427.

Leigh-Star, S. and Griesemer, J.R. (1989) Institutional Ecology, `Translations' and Boundary Objects: Amateurs and Professionals in Berkeley's Museum of Vertebrate Zoology, 1907-39. *Social Studies of Science* 19(3): 387-420.

Lewis, J. and Atkinson, P. (2011) The Surveillance of Cellular Scientists' Practice. *BioSocieties* 6: 381-400.

Lewis, J. and Bartlett A. (2013) Inscribing a Discipline: Tensions in the Field of Bioinformatics. *New Genetics and Society* 32(3): 243-263.

Lewis, J., Atkinson, P., Harrington, J. and Featherstone, K. (2013) When is an Animal Model Good-Enough? Representation and Embodiment in the Laboratory. *Sociology* 47(4): 776-792.

Llewellyn, S. (2001) Two-way Windows: Clinicians as Medical Managers. *Organization Studies* 22 (4): 593-623.

Löwy, I. (1996) *Between Bench and Bedside: Science, Healing, and Interleukin-2 in a Cancer Ward*. Cambridge/MA & London: Harvard University Press.

Lynch, M. (1990) The Externalised retina: Selection and Mathematization in the Visual Documentation of Objects in the Life Sciences. In: M. Lynch and S. Woolgar (eds.) Representation in Scientific Practice. Cambridge, MA: MIT Press, pp. 153–186.

Marincola, F.M. (2003) Translational mMedicine: A Two-way Road. *Journal of Translational Medicine* 1: 1.

Martin, P.A., Brown, N. and Kraft, A. (2008) From Bedside to Bench? Communities of Promise, Translational Research and the Making of Blood Stem Cells. *Science as Culture* 17(1): 29-42.

Millerand F. and Bowker, GC (2009) Metadata Standards. Trajectories and Enactment in the Life of an Ontology. In S.L. Star and M. Lampland (eds.) Formalizing Practices: Reckoning with Standards, Numbers and Models in Science and Everyday Life. Ithica: Cornell University Press, p. 149-167.

Mol, A. (2002) *The Body Multiple: Ontology in Medical Practice*. Durham and London: Duke University Press

Novas, C. and Rose, N. (2000) Genetic Risk and the Birth of the Somatic. *Economy and Society* 29(4): 485-513.

Petryna A. (2009) *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects*. Princeton: Princeton University Press.

Ponder, M., Statham, H., Hallowell, N., Moon, J., Richards, M and Raymond, F.L. (2008) Genetic Research on Rare Familal Disorders: Consent and Blurred Boundaires between Clinical Service and Research. *Journal of Medical Ethics* 34: 690-694.

Punnett, R.C. (1908) Mendelian Inheritance in Man. *Proceedings of the Royal Society of Medicine,* 1:135-168.

Rapp, R. (2011) Chasing Science: Children's Brains, Scientific Inquiries and Family Labors. *Science, Technology and Human Values* 36(5): 662-684.

Roos, R.A., Hermans, J., Vegter-van der Vlis, M., van Ommen, G.J. and Bruyn, G.W. (1993) Duration of Illness in Huntington's Disease is Not Related to Age at Onset. *Journal of Neurology, Neurosurgery and Psychiatry* 56: 98-100

Sartor, R.B. (2003) Translational Research: Bridging the Widening Gap between Basic and Clinical Research. *Gastroenterology* 124(5): 1178.

Stephens, N., Atkinson, P. and Glasner, P. (2011) Documenting the Doable and Doing the Documented: Bridging Strategies at the UK Stem Cell Bank. *Social Studies of Science* 41(6): 791-813.

Stephens, N., Lewis, J. and Atkinson, P. (2013) Closing the Regulatory Regress: GMP Accreditation in Stem Cell Laboratories. *Sociology of Health and Illness* 35(3): 345-360.

The Huntington's Disease Collaborative Research Group. (1993) A Novel Gene Containing a Trinucleotide Repeat that is Expanded and Unstable on Huntington's Disease Chromosomes. *Cell* 72: 971-983.

van den Hoonard, D.K. (2009) Moving Toward a Three-Way Intersection in Translational Research: A Sociological Perspective. *Qualitative Health Research* 19(12): 1783-1787.

Vermeulen, N., Tamminen, S. and Webster, A. (eds) (2012) *Bio-objects: Life in the 21st Century*. Farnham: Ashgate.

Wainwright, S.P., Williams, C., Michael, M. and Cribb, A. (2009) Stem cells, Translational Research and the Sociology of Science. In P. Atkinson, P. Glasner and M. Lock (eds) *Handbook of Genetics and Society*. London: Routledge, pp. 41-58.

Wainwright, S.P., Williams, C., Michael, M., Farsides, B. and Cribb, A. (2006) From Bench to Bedside? Biomedical Scientists' Expectations of Stem Cell Science as Future Therapy for Diabetes. *Social Science and Medicine* 63(8): 2052-2064.

Williams, C., Wainwright, S.P., Ehrich, K. and Michael, M. (2008) Human Embryos as a boundary objects? Some Reflections on the Biomedical Worlds of Embryonic Stem Cells and Pre-implantation Genetic Diagnosis. *New Genetics and Society* 27(1): 7-18.

Wilson-Kovacs, D.M. and Hauskeller, C. (2012) The Clinician-Scientist: Professional Dynamics in Clinical Stem Cell Research. *Sociology of Health and Illness* 34(4): 497-512.

Zerhouni, E. A. (2007) Translational Research: Moving Discovery to Practice. *Clinical Pharmacology and* Therapeutics 81(1): 126-128.

Word Count =. 8455 10th July, 2014.