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By

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Abstract

This dissertation is an analysis of the strategic management of risk and uncertainty in health policy. The question I have posed is: how does the government and its scientific advisers attempt to control the future of a disease when many gaps in our knowledge persist? In particular, I focus on selected debates, discussions, and decisions surrounding the management of Transmissible Spongiform Encephalopathies (TSEs), or prion diseases, in both the US and UK over the past two decades.

Between the summer of 2001 and the spring of 2005 I conducted participant-observation research in a variety of settings. Beginning with a few nodes in the network of prion disease management, I followed the network to other nodes, or sites, where knowledge was being produced, disease management actions were being discussed, and decisions were being made. In addition, I conducted semi-structured interviews with 10 family members of patients diagnosed with prion disease, 15 past or present US and UK government employees in positions dealing with prion disease risk management, and 48 scientists from the US, UK, France, Germany, and Switzerland.

I found that risk and uncertainty were managed strategically through recourse to metaphors. These metaphors included model systems of the disease and past experiences with other diseases. Uncertainty was further marginalized, or rather disguised, by employing Future Oriented Statistical Projections, or predictions of the ensuing course of a disease based on the aforementioned metaphors. By presenting the future course of a disease as knowable through numbers, the remaining uncertainties appeared to melt away. Further, risk was often treated as though it could be bounded spatially and

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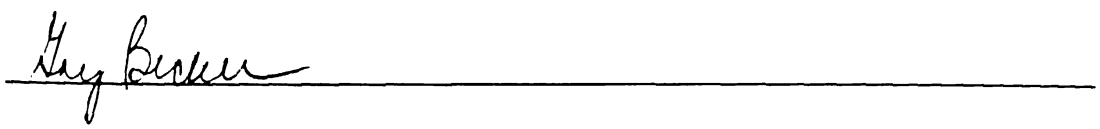
temporally through recourse to bodily, geographic, and temporal metaphors while the attendant uncertainties were bracketed to produce a momentary feeling of certainty. These strategies offered a means of cloaking risk management decisions in a guise of rationality despite the underlying uncertainties involved. In this way, governments, advisory committees, and other institutions charged with managing disease upheld their mandate to plan for the future in a "rational" manner. Such rationality was often only temporary in appearance, readily dissolving as uncertainties resurfaced.



signed by Dr. Becker, chair of committee

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Ch. 1 - Introduction

This dissertation is an analysis of the strategic management of risk and uncertainty in health policy. The question I have posed is: how does the government and its scientific advisers attempt to control the future of a disease when many gaps in our knowledge persist? In particular, I focus on selected debates, discussions, and decisions surrounding the management of Transmissible Spongiform Encephalopathies (TSEs), or prion diseases, in both the US and UK over the past two decades.

In science studies, the analysis of the management of risk and uncertainty in different circumstances has been ongoing for decades. Within the laboratory, the sources of risk and uncertainty have been viewed as multiple and interacting (Fox 2000, Star 1985), leading to interpretive complications and opportunities for creativity. Within the political arena, representations of scientific risk and uncertainty may be translated into a variety of flexible forms. Risk and uncertainty may be represented as a reason to delay action (Jasanoff 1987b), or as a reason that action must be taken immediately, as exemplified by the precautionary principle (Goklany 2001). Risk and uncertainty are sometimes minimized to the point of insignificance in the context of overshadowing institutional arrangements (Campbell 1985), interpreted strategically to discredit the results of a scientific study (Nelkin 1984) or the scientific community as a whole (Ezrahi 1980), deployed to garner support for a particular side of a debate (Martin 1996), or hyped to justify new research agendas and investment practices (Shackley & Wynne 1996).

In my examination of the debates surrounding risk management decisions involving TSEs, I found that uncertainty was managed strategically through recourse to

metaphors. These metaphors included model systems of the disease and past experiences with other diseases. Uncertainty was further marginalized, or rather disguised, by employing Future Oriented Statistical Projections, or predictions of the ensuing course of a disease based on the aforementioned metaphors. By presenting the future course of a disease as knowable through numbers, the remaining uncertainties seemed to melt away. Further, risk was often treated as though it could be bounded spatially and temporally through recourse to bodily, geographic, and temporal metaphors while the attendant uncertainties were bracketed to produce a momentary feeling of certainty. These strategies offered a means of cloaking risk management decisions in a guise of rationality despite the underlying uncertainties involved. In this way, governments, advisory committees, and other institutions charged with managing disease upheld their modernist mandate to plan for the future in a "rational" manner. Such rationality was often only temporary in appearance, readily dissolving as uncertainties, previously bracketed, resurfaced.

The methodology I applied was nominalist in nature (Rabinow 1999). I approached my objects of study, the management of TSE related risks and uncertainties, as malleable, contingent, and open to interpretation and change. The space in which this management occurs is located between high culture and the practices of everyday life. It is a space that spans time and place, over continents and across oceans, and concretizes itself at particular events – meetings, conferences, hearings, phone calls – which form the nodes of this networking, interconnected, technocratic space. As such, these nodal events have become a major focus of my dissertation, the formal sites of participant-observation where I met and interacted with the scientific and technocratic constituencies who

concern themselves with the management of prion disease. By letting the details of the story take the place of a more formalized theoretical methodology, I hope to produce an organic account of the way in which given forms of risk and uncertainty management have come into being, become stabilized and, sometimes, destabilized through multi-sited, historically-specific modes of action.

The Maginot Line as a Metaphor for Prion Disease Management

World War I was a war of attrition fought through the defense, obliteration, and capture of trenches and fortifications. After the war was over, and concerned about the prospects of a future war, the French undertook a multi-year project involving the construction of the best-equipped, strongest, most impenetrable trenches imaginable. These were not simply ditches dug in the mud, but an interconnected series of concrete and steel tunnels with heavily protected cupolas and forts from which to launch attacks and defend the country. Stretching along the German and Italian borders, the Maginot Line, as it came to be called, was believed by the purveyors of the plan, the technocrats who constructed it, and the politicians who made its funding a reality, to be an impenetrable defense. The fears embodied in the construction of the Maginot line were the fears of World War I: large numbers of armed troops, heavy tanks that functioned well only on relatively flat surfaces, and chemical weapons. To combat these fears, the heaviest fortifications of the line were focused in regions deemed at risk for attack by such threats. The line, of course, did not surround the entire country. In particular, the Forest of the Ardennes, a heavily wooded and semi-mountanous region of France, believed to be impenetrable by tanks, was excluded from fortification.

Unfortunately for the French, German warfare had evolved in the direction of lighter, more flexible tanks and smaller, more mobile regiments. In the spring of 1940, Hitler's forces swept over the Ardennes like so much kindling, an outcome which the French had not forseen and, based on World War I technology, had dismissed as impossible. Their focus on the threats and fears deemed most powerful in the previous war led them to neglect the innumerable possibilities of other forms of attack, forms which led to the swift fall of Paris in May of 1940. Only after Paris fell and France was under German control did the German army even bother returning to the Maginot line to remove the troops populating its snaking, interconnected system of underground tunnels and submerged defenses.

While the Maginot line is often used as a metaphor to denote initiatives which fail in their intent, I believe the narrative has another layer of meaning that is often overlooked: the way in which modernist attempts to control future outcomes are constrained, and sometimes thwarted, by drawing on metaphors from the past. In the effort to configure rational, logical responses to events which have not yet occurred, modernism calls for, and indeed demands, recourse to past events and outcomes as metaphorical configurations, or sensitizing frames, from which rationalist strategies may be conjectured. Such efforts apply not only in the realm of war, but in the domains of economics, urban planning, social welfare, and, the focus of this dissertation, disease management.

Fears of a world plague, a destruction of public confidence, and above all, economic and humanitarian disaster, drive the desire to manage disease. This desire is ancient, but came into its more modern form, including the tendency to rationalize and

governmentalize disease management policy, during eighteenth century European attempts to control cholera (Rabinow 1989). In effect, the aim of disease management policy is to generate, or make possible, certain future scenarios, usually the future scenarios that are more palatable to those in power.

In modern times, disease management has come to be portrayed as a rational endeavor involving "risk assessment" and "risk management," techniques based on the statistical modeling of the future course of a given disease. This modeling is in turn based on observations, or rather interpretations of observations, of the given disease and other diseases from the past. Perhaps it is most useful to conceptualize disease management in this way:

the attempt to produce a certain kind of future,

based on the modeling of different futures,

based on interpretations of the past.

Though presented as a rational, straight-forward, and dependable process, this dissertation will show that disease management is by no means any of these. Each of the steps above is colored by subjective interpretations, practical contingencies, policy prerogatives, financial concerns, and pressures from various interest groups. Each of these steps incorporates numerous uncertainties and unknowns about which assumptions are made. These assumptions, in turn, are often formulated based on past experience with other diseases or with model systems. These uncertainties and unknowns are multiplied, reworked, and adjudicated through the iterative and continuous process of seeking to

characterize and control a disease. In the course of this dissertation, the attempts to rationally and logically manage a disease, given the myriad of uncertainties, may come to appear no different, in terms of effectiveness, than taking a random stab in the dark.

Transmissible Spongiform Encephalopathy (TSE), or prion disease, is an especially appropriate disease through which to examine this process because every aspect of it unfolds at an unusually slow rate: the incubation period is long, therefore epidemics unfold in slow motion; the causative agent remains elusive, therefore research unfolds in slow motion; there is no diagnostic test to detect the disease before symptoms appear, therefore surveillance unfolds in slow motion. To put the slowness of the development of this disease and related research into context, it is useful to remember that less than a year elapsed between the discovery of SARS and the sequencing of the infectious agent which causes it. While TSEs of one form or another have been known since the 18th century, the infectious agent has yet to be definitively identified. While occurring on a collapsed timescale, SARS, bird flu, Ebola, and other rapidly evolving infectious diseases offer a compressed version of many of the same uncertainties, intractable scenarios, and strategies that are identified in the following study of prion disease.

This study has broad implications for the scientific and policy management not only of emerging infectious disease, but of other ill-defined threats to the population, such as bioterrorism and environmental degradation, that involve substantial uncertainty and yet seem to call, given our modernist urges, for preemptive action. The results generated by this dissertation will, it is hoped, complicate and yet inform our

understanding of the political, social, and scientific implications of policy formation in a climate of emergent and poorly understood risks of all types.

TSEs – A simplified background

Scrapie, a fatal wasting disease of sheep, had been rampant in Europe at least since the 18th century. A scrapie affected ewe or ram was recognized by its irresistible urge to rub up against things, scraping the wool from its body. Over a course of months, such a sheep would become increasingly incoordinated. Finally, the sheep would lose the ability to move. In all cases, the sheep then succumbed to death. Many farmers believed that the disease was inherited, a product of breeding for certain traits. But in 1937 an epidemic of scrapie in sheep that had been vaccinated for another disease, louping ill, made an infectious process seem more likely. Louping ill vaccine is made from the ground up brains of sheep with the louping ill virus. Unfortunately, several of the sheep used to make this batch of the vaccine also harbored scrapie, which primarily affects the brain. Around the same time, two French scientists, Cuelle and Chelle, infected sheep with scrapie by injecting brain material into their eyeballs. The period of time, however, between exposure and the appearance of symptoms was one and a half years.

In the 1950s, a disease nicknamed the "laughing death" in Australia, plagued a New Guinea tribe. The disease was called "kuru" within the tribe, for the shaking and wobbling it induced in its victims. Laughter was a product of the emotional lability that attended the disease in its later stages, before somnolence and paralysis set in. Kuru, too, was thought to be an inheritable disorder. Women and children who were close relatives of each other developed the disease. Then, in 1965, a chimpanzee injected with brain

material from a kuru patient developed the disease, almost two years after it had first been exposed. Gajdusek postulated that the disease was caused by a "slow virus", a previously unknown type of infectious agent with a long incubation period. In doing so, he initiated a new paradigm which led to the recognition of Subacute Sclerosing Panencephalitis, Multifocal leukoencephalopathy, and other slow viral diseases. Paradoxically, a virus was never identified in TSEs.

After Creutzfeldt-Jakob disease (CJD), a human disease with similar neuropathology to kuru, was also shown by Gajdusek and Gibbs to be transmissible to chimpanzees, they proposed a new term to encompass scrapie, CJD, and kuru: Transmissible Spongiform Encephalopathy. Over the years, the category of TSE has grown to encompass a variety of human ailments including Gerstman-Straussler-Shanker disease (GSS) and Fatal Familial Insomnia (FFI), as well as a number of animal diseases, including Transmissible Mink Encephelopathy and Chronic Wasting Disease, which affects deer and elk. These illnesses are classified as TSEs based on their transmissibility to laboratory animals through injection of brain or spinal cord, the extended incubation period (from months to years), the presence of gliosis and spongiosis in the brain, and, more recently, the presence of the prion protein. In all of these forms of TSE, the brain and the spinal cord harbor the greatest infectivity. In some forms of TSE, other parts of the body, especially the lymphoreticular system, have been shown to be infectious. Intracranial injection, through a small hole drilled in the skull, is the most efficient way of transmitting the disease in the laboratory. TSEs may also be transmitted in the laboratory by inoculation of the skin, muscle, peritoneum, intestinal tract, or the feeding of animals with infectious material. The incubation period of the disease is dependent

upon the route of inoculation, the amount of infectious material inoculated, the species of the animal inoculated, and its genetic background.

The prion hypothesis, as proposed by Stanley Prusiner in 1982, has now become the dominant narrative for contemplating TSEs. The story goes something like this. TSE is unlike any other form of disease in that it manifests itself through infectious, inherited, or, most peculiarly, spontaneous mechanisms. The disease is triggered not by a bacteria or a virus (which, Pasteur assured us, are incapable of such spontaneous production) but by a protein named "the prion". The healthy form of this protein happily goes about its own business (though exactly what this business is remains unknown), without causing any problems, in the brains of all mammals, birds, and even fish. Under unusual circumstances, which have not been characterized, this protein undergoes an irreversible transformation into its alter-ego: Dr. Jekyll becomes Mr. Hyde. The altered prion then accumulates in the brain, transforming every happy Dr. Jekyll prion that it meets into a monstrous Mr. Hyde prion. While the mechanism of propagation remains cryptic, a mysterious "protein X" has been postulated to play an important role. The monstrous prions tend to stick together, leading to clumps of protein in the brain. Eventually, severe structural damage and loss of neurons ensues. The brain, inevitably, becomes a spongy mass with little capability of processing thoughts or bodily functions. The process terminates in death.

The identity of the infectious agent, and even the ability of it to spontaneously arise, is still a point of contention among some in the field. Those skeptical of the prion hypothesis have generated an alternative narrative. These doubters propose that there is an as-yet unidentified viral component of the TSE agent. Small though it may be, it

would allow for consistency with the observation that different strains of TSE exist. How could one protein, they say, encode for so many different forms of the disease? Nucleic acid genomes, with their ability to rapidly undergo random mutations, represent a more acceptable and ready-made analogy to conceptualize this phenomena. The malformed prion protein, according to this line of thought, is merely a byproduct of the infectious process. While the search has been on for years, this putative "virino" has yet to be found, as elusive as the "protein X" that evades the scientific gaze of prion-hypothesis believers. Meanwhile, the presence of malformed prion protein has become the accepted marker of the disease in all its formations and TSEs are now often referred to as "prion diseases." I will use both terms interchangeably throughout the dissertation.

As the scientific literature rapidly alters our conception of prion disease, its mechanism of propagation, and the pathway by which it produces symptoms, the clinical illness presents an equally baffling narrative. To begin with, the presence of the disease cannot be detected without examination of central nervous system material, usually the brain. While some patients undergo biopsy of brain material to confirm the diagnosis, this is an understandably gruesome and undesirable procedure. Most cases of disease are confirmed by post-mortem autopsy. A probable diagnosis, therefore, is based on the exhibition of symptoms that fit the criteria for the disease and the ruling out of other causes.

The course of CJD is highly variable. Any two patients may present with strikingly different symptoms, creating a conundrum for physicians. Initial symptoms may include psychological disturbances (depression, insomnia, anxiety), visual abnormalites, difficulty with coordination and balance, paresis (partial or incomplete

paralysis of a limb), memory loss, rigidity, pain, difficulty speaking, or a host of other complaints. CJD is often referred to as "the great mimicker" among practitioners due to its protean character. The only uniform characteristics are its rapid progression and devastating conclusion. This variability, compounded by most physicians' lack of familiarity with the disease, explains why diagnosis often remains elusive. Additional symptoms may develop gradually at first, and then more rapidly as the disease progresses. According to Will et al. "the most striking feature of sporadic CJD is the relentless and multifocal progression of neurological deficits" (Prusiner 1999). A patient who begins with difficulty using his right hand may in short order develop difficulty in speaking, walking and swallowing his food. Seizures and/or involuntary "twitching" movements of the limbs may appear. Inevitably, cognitive difficulties become more apparent and a pronounced dementia sets in. Death usually follows within a matter of months.

10% of cases of CJD can be traced to a mutation in the prion protein gene. These cases are referred to as familial CJD. GSS and familial fatal insomnia (FFI) are classified as forms of familial CJD. The majority of cases of CJD, about 85%, are classified as sporadic CJD. These cases are thought to be due to spontaneous conversion of the prion protein into its Dr. Jeckyl form. This, however, is speculation. The remainder of cases of CJD, about 5%, can be traced back to iatrogenic transmission from sources such as pituitary derived human growth hormone, dura mater grafts, or neurosurgical procedures.

Only a few years after Stanley Prusiner developed the prion theory, a new form of TSE was detected in cattle. Termed Bovine Spongiform Encephalopathy by the scientific press and Mad Cow disease by the media, this disease, and the choices made in managing

it, would come to have serious political and economic consequences in Europe. While only a small proportion of human prion disease cases, 156 so far, are thought to be caused by the ingestion of Mad Cow disease infected cattle, most prion disease management concerns now revolve around this form.

Specific Sites and Methods

Between the summer of 2001 and the spring of 2005 I conducted participant-observation research in a variety of settings. Beginning with a few nodes in the network of prion disease management, I followed the network to other nodes, or sites, where knowledge was being produced, disease management actions were being discussed, and decisions were being made. These nodes were located in different countries (the US, England, France, Germany, and Switzerland), sometimes coalescing temporarily, sometimes existing for a longer-period of time. Participant-observation of my chosen subject of study involved discussions of patient care, of scientific studies, and disease management approaches in different settings. Many times my participation was limited to being a member of the audience at a committee meeting or a conference. As a member of the audience, however, I was by no means a non-participant. I participated by asking questions, sometimes formally, during the course of the meeting, and sometimes informally, during breaks and lunches, of the other attendees who included representatives from regulatory agencies, scientific researchers, patient advocates, and others. I conducted such participant-observation research at a hospital caring for TSE patients, two different laboratories studying prion disease, 15 different international conferences on TSE science and disease management policy, 3 meetings of the Institute

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of Medicine committee charged with advising the National Prion Research Program on research priorities, 2 meetings of the USDA's Foreign Animal and Poultry Disease Committee, 5 meetings of the FDA's TSE Advisory Committee (TSEAC), 3 hearings of the US Congress on prion disease, and 3 meetings of the UK's Spongiform Encephalopathy Advisory Committee (SEAC).

In addition, I conducted semi-structured interviews with 10 family members of patients diagnosed with prion disease, 15 past or present US and UK government employees in positions dealing with prion disease risk management, 48 scientists from the US, UK, France, Germany, and Switzerland, 40 of whom work directly with TSEs and 8 of whom serve on TSE-related advisory committees but conduct research in another subject area. In total, 25 of the scientists I interviewed serve or have served in the past on TSE advisory committees in the US and UK. 14 of these scientists have served on TSE advisory committees in the UK, including the Southwood Committee, the Tyrrell Committee, and SEAC. 11 of these scientists have served on the FDA's TSEAC.

Finally, I gathered historical data from the transcripts and minutes of dozens of TSEAC and SEAC meetings from 1995 to the present, hundreds of research publications from the 1950s to the present, and the notebooks, journals, and letters of TSE scientists.

Towards a Theory of Risk Management

What Charles Rosenberg says of disease could be said equally well of risk: the framing of disease reveals much about the structure of a society, and changing constructions of disease causation can be taken as indicators of changing social relationships (Rosenberg 1992). In this section, I will describe and critique several

different perspectives for theorizing risk in the social sciences and propose an alternative. I will begin with Beck and Giddens, two of the most popular risk theorists today.

Beck separates modernity into two eras – industrial society and risk society (1992). During the first, according to Beck, society was primarily concerned with the industrial production and distribution of goods. It was believed that hazards were calculable and could be controlled. However, the success of this period of modernity produced a variety of threats that were unforeseen. Soon "the dangers of industrial society" began to "dominate public, political, and private debates and conflicts" (Beck 1994). People now find themselves "sliding into a new society without the primeval explosion of a revolution, bypassing political debates and decisions in parliaments and governments" (1994, 2). This is the risk society, in which "more and more social conflicts are no longer treated as problems of order but as problems of risk. Such risk problems are characterized by having no unambiguous solutions; rather, they are distinguished by a fundamental ambivalence. During modernity, risks were thought to be calculable through probability and statistics. Now, the non-localized, hidden qualities of risk evade calculation. As a result, everyone in the world has become "caught up in defensive battles of various types, anticipating the hostile substances in one's manner of living and eating" (Beck 1994, 45).

While Beck suggests that the perception of risk is symbolically mediated, he propounds a realist notion of risk. This perspective is expressed in his dictum that risks are not only subjectively increasing, but also objectively increasing. Consequently, individuals have come to realize that experts no longer have control over the situation, leading to a fundamental distrust of institutional and expert claims of knowledge. This

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realization has resulted in a quiet political revolution. Politics has become reflexive, leading to the fragmentation of traditional political parties into smaller, more specialized groups, of which people would belong not to one, but to several. Doubt becomes the defining principle of risk society, doubt which would promote a regime in which: "...nothing 'goes without saying' any longer; everything must be inspected, chopped to bits, discussed and debated to death..." (1994).

For Giddens, risk arises as one of the mechanisms through which the self is biographically constructed. Biographical self-construction is necessitated by the loss of traditional "embedding" mechanisms such as kinship, which are replaced by new relationships that require new modes of trust (Giddens 1994). Simultaneously, "disembedding" mechanisms, such as expert systems and forms of standardized exchange materials, increase the individual's reliance on outside sources for developing her own internal constructions of meaning. The public's trust in expert knowledge is necessarily increasing due to the lack of traditional forms of knowledge dispensation and community. In this way, Giddens sees the public as dependent on expert systems. However, he does not share the realist conception of risk that Beck promotes. He allows much more room for social construction and the play of values in the guise of risk assessment. In general, while Beck is more critical of the role of expert systems, Giddens is more critical of their product.

Giddens posits that moderns are different from pre-moderns in that man's relationship to space and time has complexified and man is now seen as the central cause of his misfortune. Here, Giddens relies on an image of "premodern society" that is not only totalizing but blatantly incorrect and misleading. First, he posits that in pre-modern

societies, space and time always coincide because all interactions are local (Giddens 1991). This does not fit with the image of space and time in pre-modern societies as described by anthropologists. For example, both Leenhardt (1979) and Malinowski (1950) have articulated how people living in pre-modern societies often cross great distances in space and time as they speak with ancestors or tell stories around a fire. That such space-time dissonance is a property of both modern and pre-modern worlds is ignored by Giddens. Second, he posits that in pre-modern society all misfortune was blamed on supernatural forces or the force of fate. Again, this is a position that is readily discredited by anthropological research. As both Evans-Pritchard (Evans-Pritchard & Gillies 1976) and Lindenbaum (Lindenbaum 1979) have shown, man is often viewed as the "cause" of misfortune in pre-modern societies, whether mediated through another entity or not.

In the end, both Beck and Giddens construct broad, overly-simplified theories for explaining the modern preoccupation with risk. They provide top-down analyses of what are complex and multi-faceted scenarios. Their totalizing theories provide little room for the variation in perspectives on risk that exist in the real world, the dynamic properties of risk construction, or the fluidity of risk management. I believe that a more situated mechanism for coming to terms with risk is called for. An understanding of how risks come to be perceived as such, and what should be done to manage them, requires a bottom-up approach to the construction of risk, one which is contextually and historically specific. Nominalism provides such an approach.

While I agree with Giddens that constructions of space and time are important for modernist conceptualization of risk, the results of my research have led me to view them

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as operating in a different domain, not as disembedding mechanisms which have undermined our trust in society, but as rationalistic forms for making risk appear more manageable than it really is. The ability to construct risk as containable by spatial and temporal boundaries allows technocrats to satisfy their modernist tendencies for control and manipulation of the future. The management of infectious disease is indeed perceived as dependent upon such boundaries in space and time, boundaries which allow risk to be localized and therefore contained.

Spatially, risk may be constructed through a metaphor of the physical body, as the susceptibility of different organs, tissues, or cells; the social body, as the susceptibility of different individuals, families, or population; the political body, as the susceptibility of different classes, associations, and nation-states. The spatial dimensions of risk may also be constructed in geographical terms as the susceptibility of different regions, continents, or transnational flows. Temporally, risk may be constructed as varying with the age of an individual or with duration of exposure to a certain entity. In the following chapters, we will see examples of these and other spatial and temporal formulations within the realm of prion disease as strategies for creating the appearance of manageability.

A phenomenological approach to risk investigates the individual's construction of risk in relation to his or her social and cultural context. Using this approach, Gay Becker shows that individual constructions of risk are not only socially and experientially embedded, but subject to constant change (Becker & Nachtigall 1994). Rayna Rapp, through her extensive study of amniocentesis, discovers that patients respond to the statistical discourse of genetic risks by incorporating it into their unique, though culturally-patterned, understanding of the world (1988, 1997, 1998, 1999). Within what

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she terms the phenomenology of risk, "the seeming objectivity of numbers is continually undermined by their subjective interpretation. From the patient's point of view, any risk may feel like either 100 percent or zero, depending on prior experience" (1999, 69). I will argue that it is not only patients and lay-people for whom this is true, but scientists and government officials as well. In other words, an interpretation of the meaning of phenomena is embedded in an experiential context, rather than a rational one, even for those who are charged with the management of disease.

Through his writings on governmentality (1991), disciplinary practices (1995), and the development of disease nosologies (1994), Foucault has generated the impetus for a post-structuralist school of thought on "risk". This school of thought emphasizes the centrality of discourse and institutional practices in the production of power and knowledge. Expert systems, such as science and medicine, play a pivotal role in theorizing through this lens, with experts setting the standards of the discourse on risk.

According to Governmentality scholars, statistics has transformed the discourse of risk from one based on the inherent danger within an individual to one of multiple risk factors spread out over time (Castel 1991). Intervention becomes an open-ended, future-oriented project. The goal of risk management "is not to confront a concrete dangerous situation, but to anticipate all the possible forms of irruption of danger" (Castel 1991). According to Simon (1987), Ewald (1991), and Defert (1991) calculations of risk have been utilized as a means of rationalizing and justifying intervention on the part of social engineers during the liberal era of government. This is a key point which emerges in my dissertation fieldwork, one which will be discussed in subsequent chapters. In essence,

statistical tools are capable of disguising the indeterminacy of risks through a rationalistic discourse, thus making them appear more manageable and knowable than they are.

Mary Douglas postulates that people selectively perceive only certain risks via collectively-held constructs. The collectively-held constructs that govern the perception of risk are reinforced by, and in turn serve to reinforce, a particular social form that is associated with a particular world view. Douglas avoids the pitfall of totalizing risk across society by proposing that within society there is a constant struggle between rival social forms. A given social form: "is always precarious because members of a civil society try to alter it...If a social system stays stable...it is because the upholders of the present constitution were able to win the debate thus far and muster agreement to the supporting beliefs and values" (Douglas & Wildavsky 1982). Struggles between rival social forms become struggles over the understanding and management of risks. Douglas provides a way of explaining the situated and contextualized construction of risk by different groups as well as the contested, and often controversial, quality of risk perceptions.

According to Douglas, the coherence of social groups requires an outside evil to focus upon: "for this, the idea of global, irreversible damage serves well" (Douglas & Wildavsky 1982). Douglas sees a fundamental continuity between groups that believe in a vengeful God and a vengeful nature: "The border is worried about God or nature, two arbiters external to the large-scale social systems of the center. Either God will punish or nature will punish; the jeremiad is the same and the sins are the same: worldy ambition, lust after material things, large organizations" (Douglas & Wildavsky 1982). A fundamental difference between those at the border of society and those at the center is

their view of time and how it will affect the social structure. At the center, people see "the future as continuous with the present. It has numberless ways of discounting information to the contrary. It expects disturbances and setbacks in the normal course, but it also expects to weather them. In the long run it is optimistic" (Douglas & Wildavsky 1982). Such a world view tends to downplay the risks of internal harm to society. By contrast, peripheral groups tend to see discontinuity: "They expect a different future and they expect it will be bad. Established society is incorrigibly evil, being both coercive and hierarchical...They have a vested interest in bad news that shows the society outside is polluted and also shows that the sect inside is pure" (Douglas & Wildavsky 1982). This outlook guides their behavior and their perception of risk, causing them to see danger from within.

While more satisfactory than several of the aforementioned approaches to risk because it allows for and explains the existence of competing social forms of risk perception and management, I found Douglas's theory lacking in several respects. First of all, the ideal types seem over-generalizing. While she provides empirical evidence to support her claims, it is not clear that her examples serve to justify the broad assertions that she makes. Second, her theory, while positing that instability is an inherent property of the social structure, provides no mechanism for analyzing change. Third, while her theory posits an explanation for the differential construction of risk within different segments of society, it does not provide an explanation for the means by which certain phenomena come to be conceptualized as risks. Such an explanation requires a deconstruction of the properties a risk and a genealogy of its instantiation. This type of deconstruction depends on an examination of how we come to know what we think we

know about risk. In our society, the discourse of risk often references scientific and epidemiological studies. This does not mean, however, that it is rational. For technocrats, these scientific phenomena often take on an experiential quality that drives decision making. Because of this, an analysis of the construction of scientific objects and truths is essential to developing an adequate description of the construction of modern notions of risk and disease.

Science Studies and Risk

Science, in our society, comprises the taken-for-granted basis upon which public discussion and examination of risks, such as global warming, genetically modified foods, or oceanic contamination occurs. In controversies over risk, battles are often fought through reference to science and particular scientific studies (Barnes & Edge 1982, Chubin 1990, Collins & Pinch 1998, Cozzens 1990, Martin 1996, Nelkin 1977, Shapin 1995a). Each side seeks to deligitimize the other's construction of risk by revealing the uncertainties and insufficiencies in their scientific data (Campbell 1985, Ezrahi 1974, Nelkin 1975). At the same time, each side seeks to strengthen their own construction of risk by citing the claims of experts and legitimate scientific bodies, such as the National Academies of Science or the Institute of Medicine, that support their construction of risk (Ezrahi 1974, Toumey 1996).

While science, for a long time, was thought of as a completely rational endeavor, this idea began to come under scrutiny in the 1960s. With the development of the

Sociology of Scientific Knowledge[1] (SSK), science was, for the first time, subjected to a rigorous analysis of social factors. Shapin describes SSK as an attempt to demystify science by showing that "the making of scientific knowledge can be sufficiently accounted for by ordinary human cognitive capacities and ordinary forms of social interaction" (1995b). In other word, science was subject to influence by everyday social factors. Furthermore, science, because of its influence on society, was subject to political distortion.

David Bloor is regarded as a founding figure of the SSK movement for his role in enunciating the principles of the Strong Program[2] (Bloor 1976) which became the basis for the Edinburgh School project of interest analysis. Bloor's guiding principle was that social causes can explain beliefs or states of knowledge. Critically, he argued that the same social factors could account for beliefs that are held to be true and those which are later deemed to be false. The Edinburgh scholars sought to reveal the influence of larger social interests on the conduct and outcome of scientific controversies. For example, Shapin and Barnes describe how a turn-of-the-century controversy over statistics embodied a class conflict between conservatives and new professionals (Barnes & Shapin

[1] While it has come to represent many different strains of thought, SSK originated in Britain with the likes of Michael Mulkay, Harry Collins, Barry Barnes, David Bloor, David Edge, Donald MacKenzie, Karin Knorr-Cetina, and Steven Shapin.

[2] The basic tenets of the Strong Program are: 1) social causes can explain beliefs or states of knowledge, 2) SSK will be impartial with respect to dichotomies such as truth/falsity, rationality/irrationality, and success/failure, 3) symmetry: the same types of social factors will be used to explain beliefs that fall on either side of these dichotomies, and 4) reflexivity: the same explanations that apply to science will also apply to the social studies of science Hess DJ. 1997. *Science studies: an advanced introduction*. New York: New York University Press. vii, 197 pp..

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1979). Many SSK scholars have utilized Bloor's principles as a starting point for the subsequent development and articulation of their own analytic principles and theories.[3]

Beginning in and around the mid-1970s, Latour and Woolgar[4] pioneered the methodology of in-depth observational laboratory studies.[5] While their technique differed from the historical investigations typified by interest analysis, they explicitly drew on and extended the conceptual framework of Bloor. Unlike those in the Edinburgh school, Latour and Woolgar proposed that one does not need to identify an outside influence in order to appropriate social characteristics to science. They argued that science is social from its very beginnings in the laboratory (Latour & Woolgar 1986).

As an example of how science is social from its very beginnings, Latour offers, in Laboratory Life, the story of a young scientist named Bell. Bell's ability to perceive something that other scientists had ignored, simply because he had not yet been socialized, or taught, to ignore it, led to the subsequent discovery of a new scientific phenomena. What Bell perceived as significant and began to study was radio noise, or scruff. As Latour remarks:

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[3] see Collins HM, Pinch TJ. 1998. *The golem: what you should know about science.* Cambridge: Cambridge University Press. xix, 192 pp, Latour B, Woolgar S. 1986. *Laboratory life: the construction of scientific facts.* Princeton, N.J.: Princeton University Press. 294 pp.

[4] Other early laboratory studies were conducted by Knorr-Cetina Knorr-Cetina K. 1981. *The manufacture of knowledge : an essay on the constructivist and contextual nature of science.* Oxford ; New York: Pergamon Press. xiv, 189 pp, Knorr-Cetina K, Mulkay MJ. 1983. *Science observed : perspectives on the social study of science.* London ; Beverly Hills: Sage Publications. 272 pp., Michael Lynch Lynch M. 1993. *Scientific practice and ordinary action : ethnomethodology and social studies of science.* Cambridge England ; New York: Cambridge University Press. xxi, 333 pp, Lynch ME. 1979. *Art and artifact in laboratory science : a study of shop work and shop talk in a research laboratory.* University of California, Irvine. xi, 431 leaves pp. and John Law Law J. 1987. Technology and Heterogeneous Engineering: The Case of Portuguese Expansion. In *The Social construction of technological systems : new directions in the sociology and history of technology*, ed. WE Bijker, TP Hughes, TJ Pinch, pp. 111-34. Cambridge, Mass.: MIT Press.

[5] Specifically, many of Latour's early works Latour B. 1987. *Science in action: how to follow scientists and engineers through society.* Cambridge: Harvard University Press. 274 pp, Latour B, Woolgar S. 1986. *Laboratory life: the construction of scientific facts.* Princeton, N.J.: Princeton University Press. 294 pp. begin by explicitly paying homage to Bloor's symmetry principle.

> In this particular example, it might be argued that if scrutiny of the recording had been automated or if Bell had been sufficiently socialized into realizing that the persistent recurrence of scruff was impossible and hence not noticeable, the discovery of pulsars would have been much longer in coming. Technical events, such as Bell's observations, are thus much more than mere psychological operations; the very act of perception is constituted by prevalent social forces(Latour & Woolgar 1986).

This final observation, that the very act of perception is constituted by prevalent social forces, is the basis of phenomenology as articulated by Merleau-Ponty. Merleau-Ponty argues that there is no such thing as pure perception. Perception is always preconfigured by structuring forces, usually derived from past experience with the world (Merleau-Ponty 1962).

Latour presents his study as a study of the, "socially available procedures for constructing an ordered account out of the apparent chaos of available perceptions" (Latour & Woolgar 1986). What Latour is pointing to here is the essence of narrative theory - that meaning and structure are created from disordered, underdetermined (there are always a number of alternative explanations available) events (Becker 1997, Mattingly 1998). Narrative brings form to chaotic experience, allowing for the production of meaning.

In such passages, Latour draws to mind the field of symbolic interactionism and especially the work of George Herbert Mead. Mead argues that it is useless to talk about the interaction of individual "selves" and "minds" without recognizing that the mind and the self are social emergents (Mead & Morris 1934). In this way, every individual act can be analyzed as a social act, a product of interaction amongst members of society. In other words, the meanings of phenomena arise from their embeddedness in social worlds, or universes of discourse (Clarke 2003), and multiple meanings, or readings, are always

available. As Latour describes it, the choice of a particular reading is a pragmatic choice, fitting the purposes at hand. However, the choice is always unstable and negotiable. Thus, Latour frames his study as an investigation of the production of order from alternative, competing perspectives.

> In sum, then, our discussion is informed by the conviction that a body of practices widely regarded by outsiders as well organized, logical, and coherent, in fact consists of a disordered array of observations with which scientists struggle to produce order (Latour & Woolgar 1986).

In the process of constructing order, "the observer normally adopts some kind of theme by which he hopes to be able to construct a pattern" (Latour & Woolgar 1986). The objects around which the laboratory is constituted and gravitates, according to Latour, manifest themselves in the form of a difference. To be precise, the difference he is talking about is a difference between two traces – the control and the experimental. If this difference can be shown to be a true difference, rather than an artifact, then it forms a new object of analysis and, through a series of transformations, can be written about in a scientific article.

This difference, however, requires validation: "it is not enough simply to fabricate order out of an initially chaotic collection of observations; the observer needs to be able to demonstrate that this fabrication has been done correctly, or, in short, that his method is valid" (Latour & Woolgar 1986). This validation is performed by bringing the observations and analyses before a group of peers. The group of peers, the peer reviewers, plays the role of determining whether the purported analysis matches the experimental evidence, and whether the experiment has been conducted in an appropriate fashion. In other words, peer review is concerned with two processes: an evaluation of the production of data, and an evaluation of the representation of data. Of course, peers

do not have the opportunity to view the creation of the data from within the scientist's laboratory. Rather, they must glean the context of production from the ensuing article. Thus, at the point of peer review, the production and representation of data have fused into one.

The importance of peer review in the scientific process as a means of substantiating and validating results has come about through a series of historical contingencies. As postulated by Shapin and Schafer, peer review grew out of the desire of scientists to separate themselves from religious and spiritual domains of influence and to become, in essence, an autonomous, self-regulating discipline (Shapin et al 1989). Ezrahi (Ezrahi 1980) and Jasanoff (Jasanoff 1985) argue that peer review is the main source of authority and credibility in science today and thus has extended into the regulatory realm.

The dependence on peer review fits with Luhmann's observation that modernity is characterized by the growth of second-order systems of observation in all of the major disciplines (Luhmann 1998). Second-order observation, involving the observation of observations, and therefore revealing a further removal of autopoetic systems such as science, politics, and the media from any semblance of reality, has, according to Luhmann, become the modus operandi of modernity. Throughout this dissertation we will witness the mobilization of second-order observation as the means for articulating disease management decisions and regulatory action.

Latour's formulation of the contrast between objects and artifacts as a matter of difference has enormous cultural and linguistic implications. These linguistic possibilities form an implicit undertone to his analysis, yet he does not comment on them overtly. My goal is to take this a step further, in order to form an overarching structure that is capable

of incorporating both lived experience and experimental results within a framework of the construction of risk and disease.

To do so, I will make broad use of the concept of metaphor. I will argue that attempts to govern disease, though cloaked in rationality, are, by necessity, analogical. The analogical elements reference past experiences with other diseases and model systems. These elements comprise a sensitizing frame through which the disease and its risks are constructed. The relevance of any element in the sensitizing frame is based on the strength of its metaphorical relationship, or perceived correspondence to, the matter under consideration. Because this relationship is always open to negotiation, the sensitizing frame is constantly restructured through continuous discourse and debate. Thus, a sensitizing frame is a dynamic concept that constitutes the perception of risk from moment to moment. Importantly, the sensitizing frame is interactively produced. It does not exist in any one person's mind, but is constituted through discourse, both written and spoken. Thus, it is open to investigation.

One of the most fundamental ways in which we perceive, which enables us to uptake amorphous sensory input, is through analogy to what we already have experienced (Lakoff & Johnson 1980). If we cannot say what something is, we can always ask what it is like. If we find out what it is like, then we can try to estimate how much it might be like the other thing which we have experience with. If, as Susan Sontag has argued, illness is metaphor (Sontag 1978), then uncovering an emerging disease involves coming to terms with a metaphor through a metaphor of a metaphor. One can easily discern that such a process is likely to be vague, ambiguous, and sometimes completely inscrutable. Such was the case, time after time, in attempts to manage TSEs.

By examining the way that scientists, regulators, and industry representatives discuss a disease and its risks, we can see the ways in which these concepts are transformed through metaphorical action, which involves the weighing of analogies for perceived relevance. There are two main types of metaphors that have been drawn on in the process of conceptualizing prion disease, of which I will provide detailed examples throughout the dissertation. These two types of metaphors include other diseases and model systems.

Analogies to specific diseases, like scrapie and AIDS, have at times driven the perception of prion diseases and their risks. These perceptions are consequential in that they drive reactions in the present, and plans for the future. They impact both the way that prion diseases are studied as well as the way that they are managed on an individual and population scale.

A model system on which experiments are conducted in the laboratory is another type of metaphor through which disease and risk are constructed. In disease research, a model system is taken to correspond to the disease in question but usually involves a modified form of the disease affecting a host, such as a mouse, a cell, or a monkey, which is not the usual host of the disease in nature. These hosts are chosen because they can be easily manipulated, stored, experimented on, and examined. Model systems provide a simplified version of reality in which certain variables are held stable while other variables are controlled at will in order to evaluate the effect of some action. The experimental results within an accepted model system are taken to be indicative of characteristics of the disease. However, the validity of this truth depends on the continued acceptance of a correspondence between the model system and reality

(Gaudilliere 1999). In animals, this correspondence must extend to the level of the biological process under question and all potential factors that may be involved (Clarke 1987). In this way, we see how the stabilization of a metaphor is necessary for the interpretation of experimental results. It is not surprising, then, that this correspondence, or lack thereof, often becomes the focal point of debates related to the meaning, or interpretation, of the results. In Crafting Science, Fujimura provides several excellent examples of this phenomena: 1) the argument over whether the tumerogenic viruses were natural or artifactual; 2) the debate over whether transformed cells in tissue culture were representative of real cancer cells; 3) the controversy over whether genetic mutation, as measured by the Ames test, was indicative of carcinogenesis (Fujimura 1996).

Model organisms, such as certain types of worms (Mitman & Fausto-Sterling 1992), fruit flies (Kohler 1994), and viruses (Creager 2002), while designed to solve specific problems, have come to define entire programs of research.[6] However, model organisms impose their own constraints and opportunities on a scientific field, highlighting certain factors while obscuring others. They can, and often do, yield unexpected results which incite a change in the direction of research. In Kuhn's terminology, the efficiency brought about by the focus on certain tools and research problems during the period of normal scientific activity promotes revolution (Kuhn 1962). Little's inbred mouse colonies provide a case in point (Fujimura 1996, Gaudilliere 1999). Originally, these mice with "homogenous" genetic backgrounds were designed to answer questions about the immunological response produced by tumor transplantation. However, the availability of inbred mice promoted a shift in the focus of cancer research

[6] For a review of model organism studies Clarke A. 1995. Epilogue: Studies of Research Materials (re)visited. In *Ecologies of knowledge : work and politics in science and technology*. ed. SL Star, pp. 209-17. Albany: State University of New York Press.

to genetics, and in a dramatic reversal, tumor transplantation became a mechanism for "testing" the homogeneity of mouse strains. But tools are recalcitrant and surprising actors, and in a third twist, the mice failed to follow expected patterns, becoming the basis for a new theory of cancer as contagion.

In summary, a sensitizing frame forms the basis through which each new event is perceived and evaluated. This perception and evaluation then forms the basis for action in the present. The subsequent results of that action, and the new perceptions they produce, then feedback to reconstitute a new sensitizing frame. By presenting the history of prion diseases as a series of events, I hope to reveal the interlocking nature of disease perceptions. One event becomes part of the sensitizing frame for another event, such that subsequent events may have many potential past experiences influencing their perception and evaluation. In other words, the perception of, and reaction to, new events is both made possible by and circumscribed by the past. While individuals may, and often do, recognize the ways in which past experiences form the backdrop for the consideration of potential new events, what remains unclear, and often cannot be perceived, is the contour of the boundaries this places on perception and the way this inhibits certain types of action. As Berger and Luckman phrase it:

> Although the social stock of knowledge appresents the everyday world in an integrated manner, differentiated according to zones of familiarity and remotness, it leaves the totality of that world opaque. Put differently, the reality of everyday life always appears as a zone of lucidity behind which there is a background of darkness. As some zones of reality are illuminated, others are adumbrated. I cannot know everything there is to know about reality...My knowledge of everyday life has the quality of an instrument that cuts a path through a forest and, as it does so, projects a narrow cone of light on what lies just ahead and immediately around; on all sides of the path there continues to be darkness (Berger & Luckmann 1980).

In other words, the sensitizing frame through which we perceive and manage risk is necessarily constrained. While metaphors operating through past experiences with other diseases or through model systems illuminate certain possibilities for future outcomes, they obscure others. In effect, most risk management decisions are made based on the path that is illuminated most brightly, the path which comes into view most easily when considering the experiential quality of the past and present. Like the Maginot Line, it is easier to regulate based on the past than it is to anticipate the future. The future, unlike the past, is potentially limitless in the number of possibilities it contains. While some of these possibilities may be easy to perceive, others may remain almost completely imperceptible.

Despite the fact that the past constrains the perception of future possibilities, limiting the effectiveness of disease management, disease management is enacted as though it is a completely rational, transparent matter. Future Oriented Statistical Projections (FOSPs), such as risk assessments, are generated both ad-hoc, as a means of "performing," for the public's benefit, a rationalist decision-making process despite the absence of any secure ground on which to make a decision, as well as post-hoc as a means of garnering credibility and securing political support for a given risk management decision.

Just as Cheryl Mattingly's conception of narrative emplotment, building on Aristotle's notion of emplotment, produces and requires an imaginative envisioning of the future to function (Mattingly 1998), so too do sensitizing frames. Sensitizing frames both produce the environment which allows for a certain image of the future to be conceived, and depend upon this imagined future for their existence. These imagined

futures do not need to be singular, and, in the case of novel events such as an emerging disease, are unlikely to be so. Rather, they incorporate a plethora of possibilities, some of which serve as the motivating force behind further consideration and action. This conception of the futuristic component of a sensitizing frame parallels Jerome Bruner's notion of subjunctivity. "To be in the subjunctive mode is, then, to be trafficking in human possibilities rather than settled certainties" (Bruner 1986). Byron Good utilizes Bruner's notion of subjunctivity to analyze the narratives told to him by Turkish sufferers of epilepsy. He concludes that subjunctivizing elements, such as multiple interpretations and story-lines, function to maintain hope, despite the dire straits in which patients find themselves: "healing was an open possibility, even if miracles were necessary" (Good 1994).

The other side of subjunctivity, of course, is fear of a future danger. In our modern society, this fear is often encapsulated in terms of "risk." Attempts are made to direct, manage, and control potential future dangers through the activity termed "risk management." Fears of a world plague, a destruction of public confidence, and above all, economic and humanitarian disaster, drive the desire to manage disease risk. In effect, the aim of risk management policy is to make some futures, the most desirable futures, more likely than others (or at least to decrease the likelihood of the most devastating futures).

"Hope" and "Danger", then, comprise the opposite poles of the multiplicity of possible futures that attend to each new and poorly understood disease risk. In this dissertation, I seek to peel at the levels of metaphorical transpositions through which hope and danger have been constructed throughout the history of prion diseases. I do not intend to "uncover" an underlying truth, or arrive at the "source" of this disease, or its

"inherent meaning." What I will try to do is shed some light, however dim, into the shadowy world of a disease with a multiplicity of manifestations and a multiplicity of potentials. In so doing, I hope to explore some of the ways in which the temporality of the disease and the metaphors of its incarnation have come to drive management processes, scientific discovery, and public reaction. I hope to critique and destabilize the modernist tendency to cover-up the unknown with risk assessments and other FOSPs in order to justify decision-making. I call for uncertainty in science and in life to be acknowledged, not in a perfunctory way but in a deep way, so that both the technocratic elite and the public may embrace the chaotic and uncontrollable world into which we have been thrust. I do this while acknowledging that such insight as I may provide is a result of, and also constrained by, my own positioning in the world and my own sensitizing frame. I am, in Donna Haraway's words, a situated observer, nothing more nothing less.

All-purpose Caveat

In order to comprehend the debates, discussions, constructions and assessments presented in this dissertation, there is a certain amount of taken-for-granted information that must to be conveyed. While I cannot escape the feeling that in doing so I am committing the cardinal sin of further reifying what Michel Callon calls black boxes nested within black boxes (Callon 1986), the reified versions of previous controversies that become incorporated into current controversies. Such a sin, however, is unavoidable, unless I write a dozen more dissertations, each of which would uncover further black boxes requiring even more dissertations. Since this is more than one can accomplish in a

lifetime, I am forced to treat some knowledge as taken-for-granted. In order to avoid reifying it too much, I will try to present it within a historical context that brings to light some of the contingencies and specificities of the knowledge. I will also try to highlight the hidden uncertainties of this knowledge as they come into play during the debates around the transmissibility of TSEs.

Sequence of dissertation

In the course of this dissertation, I will attempt to draw together different threads of the prion disease story. Along the way, I will seek to identify events that inform the sensitizing frame through which the disease category and the risks it represents have come to be conceived. Through examining the construction of these representations and their relationship to a sensitizing frame, I hope to illustrate the co-construction of science and society. Science and society have been reconstructed many times through the course of the prion disease story. Each time, there are implications for the way we live, think, and eat, on a personal level, and for the way we trade, manufacture, and govern, on a societal level. The management of prion diseases affects all of us in some way or another.

In Chapter 2, I will discuss the implications of the recognition of Bovine Spongiform Encephalopathy (BSE) or "mad cow" disease. I will describe how scrapie became a potent metaphor for conceptualizing BSE and imagining the possibilities for transmission. I will follow the growing concerns about transmission of BSE to humans, the failure of the feed ban to prevent the spread of BSE, and the discovery that certain risk management measures had not been implemented as expected. I will show the way in which gaps in the understanding of the disease were covered up or paved over for the

purpose of public performance. I will then describe the circumstances that led the UK government to announce that a new variant of a prion disease in humans, vCJD, was likely to have been caused by BSE.

In Chapters 3, 4, and 5 I will examine the way in which the blood transfusion transmission risk of CJD and vCJD was constructed, negotiated, and acted upon in the US. I will illustrate how metaphors with HIV, previous iatrogenic transmissions of CJD, and animal model systems formed the basis for conceptualizing this risk. I will also examine the production of future oriented statistical projections (FOSPs) as a way of performing rationality in the midst of uncertainty. By compartmentalizing risk through spatial and temporal metaphors, the uncertainties surrounding this new form of prion disease were bracketed temporarily, allowing for a seemingly rational risk management decision to be made.

In Chapter 6, I will provide a counter-example to the US construction of risk by exploring how the UK came to perceive and manage CJD and vCJD transfusion transmission risk in an alternative manner. While many of the metaphors they applied were the same, the weight they held in the sensitizing frame of the UK was different from the US. AIDS, while a major crisis in the UK, did not lead to the political fallout and public outcry that it had in the US. As a result, the UK downplayed the CJD blood transfusion risk relative to the US. After the shocking announcement of vCJD, however, following years of public pronouncements concerning the safety of beef, the UK was unable to avoid taking strict risk mitigation measures when it came to the potential for iatrogenic transmission of vCJD, including the risk of transmission through blood and blood products.

In Chapter 7, I will describe the increasing role that quantitative risk assessments and other Future Oriented Statistical Projections (FOSPs) came to play in decision-making at SEAC following the announcement of vCJD and the way this affected the committee's deliberations and choices. The increasing role of FOSPs at the committee fit with a new drive amongst members, in the wake of vCJD and the public crisis, to avoid giving direct policy advice on disease management. In their efforts to wall themselves off from potential criticism, FOSPs grew in importance, as neither the government nor the committee wanted to take responsibility for any future missteps in disease management policy. In this way, I suggest that FOSPs have become the modus operandi for making disease management decisions in a modernist trap. If the FOSP is the basis for decision making, then only it, not the governmental bodies who ordered or designed it, can take the blame for unfortunate outcomes. In this way, the FOSP has become the new "fall guy" in a society where nobody wants to bear the responsibility for mistakes. I will suggest that FOSPs serve to legitimize governmental action by bracketing and burying uncertainties within a complex numerical analysis.

In Chapter 8, I will discuss subsequent events that influenced the perception of vCJD transfusion risk and the development of concerns over risk management choices in both the US and UK, including the transmission of BSE by transfusion from sheep to sheep and the continued absence of any identifiable human to human transfusion transmissions. In terms of the sheep experiment, I will examine the ways in which metaphors through model systems function to reconfigure perceptions of risk. In terms of the continued absence of human cases, I will examine the way in which such lengthened temporalities, which one encounters in diseases with long incubation periods, serve to

extend and increase the relevant uncertainties. The lengthened temporality prevents concerns from being laid to rest and allows for the continued reemergence of uncertainty, as well as the expansion of doubt. These doubts and uncertainties are difficult to contain, and lead to explosive disagreements and heated debates at scientific meetings and conferences.

In Chapter 9, I will conclude with some thoughts on the attempts to contain uncertainty and compartmentalize risk through the modern discourse of disease management. I will analyze the role that metaphors and Future Oriented Statistical Projections, specifically quantitative risk assessments, have come to play in this process. I will also examine how FOSPs take on the appearance of rationality, masking the inherent uncertainties, though the uncertainties multiply and continue to fester all the while. I will suggest that, despite our modernist tendencies to create the appearance of rationality where there is none, it is high time to open the doors and windows to the messy world of risk management and allow the uncertainties to enter into full view.

Ch. 2 – Bovine Spongiform Encephalopathy

In this chapter I will describe some of the crucial events surrounding the discovery and management of Bovine Spongiform Encephalopathy or Mad Cow disease. The data from which these events have been reconstructed include interviews I conducted with many of the actors described, journal and newspaper articles published at the time, and the BSE Inquiry Report as well as primary evidence collected for the Report. All of the citations designated "Year Book" reference the primary evidence, including internal agency memos, reports, white papers, and so on, collected during the Inquiry and now available publicly. The BSE Inquiry was ordered by parliament in 1998 and completed in 2001. The Inquiry was prompted by the occurrence of a previously undescribed form of CJD in teenagers and young adults which was made public and ascribed to BSE in 1996. This was after the government had assured the citizenry of the country, for over a decade, that BSE would not transmit to humans.

In order to consider the possibilities which BSE presented upon its discovery, it is important here to take a step backwards in time. Now, with news of Mad Cow disease in the headlines, it is easy to forget that this disease was not viewed as a necessary or even a likely zoonosis (an infectious disease that can be transmitted between animals and people). It is important to remember that before 1996, only humans had transmitted TSEs (CJD and kuru) to other humans: through ritualized cannibalism in New Guinea and through transplants of dura mater and human growth hormone in the industrialized world. In my description of the events below, I hope to bring forth the feeling of the context in which they occurred, with all its uncertainty and indeterminacy.

In fact, what is probably the best studied form of TSE, scrapie, had been observed in sheep since at least the late 18th century. Like all other TSEs, it was known to be uniformly and unalterably fatal. While associations had been proposed between scrapie and CJD, the consensus of the time was that scrapie posed little if any threat to humans, either through ingestion or close contact.

In their attempts to rationally manage BSE, scientists, government officials, and politicians turned to scrapie as a ready analogy regarding the properties of the new disease. Many of them assumed that, like scrapie, BSE would pose little threat to humans. Some of them worried that, like scrapie, BSE would bring detriment to the British agricultural economy. The confluence of these assumptions and concerns led to the issuance of official statements about the disease which led the public to believe that BSE was not a risk. The statements provided by the government, in turn, relied on Future Oriented Statistical Projections, or FOSPs, which were constructed based on assumptions derived from the analogy with scrapie. Such FOSPs played a crucial role in shaping the perception and management of the disease, as well as a certain amount of public credibility. In the end, most of these early FOSPs were worth less than the paper they were printed on. Though cloaked in rationality and statistics, they provided mostly misleading predictions about the course of the future epidemic and the risks it presented.

Like the French in their construction of the Maginot Line, the British scientists and government officials sought to manage the future through recourse to the past. They did not expect much deviation from the paths of scrapie and other previously described prion diseases, and in turn failed to perceive the very real possibility that BSE might behave differently from any TSE they had yet encountered. While the path they chose to

take was lit brightly, and seemed like a rational solution to the problem before them, it was the darkness around the edges which would gradually engulf them.

The Identification of a New Disease in Cattle

The first case of what is now considered to be Bovine Spongiform Encephalopathy (BSE) was viewed by pathologists at the Central Veterinary Laboratory (CVL) of Britain in September of 1985. This was the seventh animal on this particular farm in Sussex to show peculiar "nervous" symptoms (Phillips Committee 2000a). While vacuoles were described by the investigating pathologist, it was decided that the most likely cause was toxicity or metabolic disorder (Phillips Committee 2000a). It was not until over a year later, in December of 1986, that something more significant was suspected. Three brains were sent from a farm in Kent, where a veterinarian had observed cattle that became "nervous, aggressive, and progressively incoordinated..." (Phillips Committee 2000a). As Martin Jeffrey, a ruminant neuropathologist, would later tell the BSE Inquiry committee "One is a novelty, two is a coincidence, three is a problem" (Phillips Committee 2000a). Indeed, these three brains were striking to Gerald Wells, the examining neuropathologist, for their "multifocal spongy transformation of the brain parencyma and a degeneration of neurons..." which most closely resembled, in his opinion at the time, scrapie (Phillips Committee 2000a). Wells believed that he may have discovered a new disease in cattle of the Transmissible Spongiform Encephalopathy (TSE) or prion disease type.

But the observation, on pathological examination, of spongiform change in the brain did not cinch the identification of the disease as a TSE. Many toxins, nutritional

deficiencies, and a number of systemic diseases were known to produce effects which manifest as vacuolation or spongy change in the central nervous system. According to Hugh Fraser, a respected scrapie researcher, designation of the new disease as a TSE would require evidence of the transmissibility of the disease, which could only be obtained through time-consuming and expensive animal experiments.

Wells's findings were shortly disseminated to selected individuals within the Ministry of Agriculture Fisheries and Food (MAFF). While a multiplicity of meanings could be assigned to these findings, and the identification of a new disease of the "scrapie type" was by no means secured, the analogy with scrapie presented two different framings of the future that would come to drive subsequent events. These images of the future, while mutually inclusive on an intellectual level, pointed to different possibilities for reacting to this discovery depending on one's position. They each had a force of their own, generating struggle, and culminating in compromise, within the organization.

Scientists, and the staff who worked closely with them, could see the potential for the discovery of a new TSE in cattle to lend credibility to their surveillance efforts and "bring deserved prestige to MAFF, ADAS, the CVL and the workers involved" (Phillips Committee 2000a). This view was not shared by the higher officials in MAFF who, identifying more closely with their role as protectors and promoters of the agricultural industry, viewed BSE as a potential economic problem. Scrapie, while present at a low level in Britain and in many other countries for centuries, had come to be viewed as a costly disease which cut into the profits of farmers. The spread of this view had led to the gradual introduction in many countries of policies and practices aimed at eradicating scrapie. Trade restrictions on sheep, especially from Britain, were beginning to damage

the industry. Extension of such restrictions to cattle would, it was suspected, be a severe blow, as cattle have a much higher market value than sheep (Phillips Committee 2000a). Most intriguingly, the frightening possibility of an association between this new bovine disease and human TSE was raised early on, even though this was considered a remote possibility due to the lack of such human/animal cross-over in scrapie. In any case, MAFF officials recommended "playing it low key because a simple explanation may be forthcoming as a result of current investigations which will allay fears" (Phillips Committee 2000a).

The position of the higher officials at MAFF was that "Irresponsible or ill-informed publicity is likely to be unhelpful since it might lead to hysterical demands for immediate, draconian government measures and could lead other countries to reject UK exports of live cattle and bovine embryos and semen" (Phillips Committee 2000a). Their fear of this potential outcome was displayed in their efforts to prevent dissemination of results outside of MAFF. As in many state run agencies, MAFF employees were required to submit manuscripts for approval from their superiors. Mr. Hancock, a MAFF veterinarian with a local service, wanted to publish his observations on a single case of this new disease in the South West of England. He was denied publication "because of possible effects on exports and political implication" (Phillips Committee 2000a). Mr. Gallagher, a senior veterinary investigation officer, suffered denial along similar lines. In response, he informed his superiors at the CVL that they were making a mistake. He argued that in order for the service, charged with disease surveillance, to maintain credibility, it must disseminate information through publication. "Our embarrassment will be considerable when, as will inevitably occur, some other source will claim the

surveillance trophy by reporting and detailing the condition first," he warned (Phillips Committee 2000a).

Not all those who saw the disease as a path toward recognition and scientific accolades were interested in publishing quickly. Gerald Wells was asked by his superiors to draft a short article detailing the clinical signs and the gross post-mortem findings of the new disease for closed circulation amongst state veterinary investigators (Phillips Committee 2000a). Wells was concerned that making their findings public at this point in time would hinder their ability to obtain samples, which were seen as necessary for validating their discovery. If veterinary schools became aware of the potential new disease, he worried, samples might be diverted to these institutions rather than funneled up the chain to the CVL. According to Wells:

> A statement about the potentially novel disease for distribution...outside of CVL is at present premature, uninformative by virtue of necessary omissions and predictably damaging to scientific achievement at this Laboratory (Phillips Committee 2000a).

When Wells eventually felt ready to publish his findings, however, he was denied permission unless he deleted any comparisons to scrapie or other TSEs (Phillips Committee 2000a). Although internal documents show MAFF was convinced of the pathological similarities between the two (Year Book 1987), they did not want to draw attention to this aspect of the new disease, which would highlight its potential transmissibility. An article written by Dr. Jeffrey on a zoo animal of the bovine family which had contracted a similar disease was also denied publication on the grounds that it emphasized the similarity to scrapie (Phillips Committee 2000a). Dr. Jeffrey had in fact titled this paper "scrapie-like Disorder in a Nyala" (Phillips Committee 2000a).

A stalemate developed between MAFF officials and senior scientists. Jeffrey and Wells refused to delete comparisons to scrapie, while their superior maintained that "It is the duty of all of us to correct such false statements or opinions which could be damaging to the cattle industry..." (Phillips Committee 2000a). As the evidence for similarities to scrapie began to build, however, a more conciliatory tone was sounded by the officials: "It will be necessary and appropriate to include references to spongiform encephalapathies of other species (including sheep) but emphasis on them and in particular to ovine scrapie should be avoided" (Phillips Committee 2000a). Officials compromised by allowing mention of other TSEs, while scientists compromised by emphasizing that the etiology remains unknown and that no connection to other TSEs has been unequivocally established (Phillips Committee 2000a).

This example is the first in a series which reveals the powerful force that tightly held images of the future potential of BSE have played on those who struggle to manage it in the present. These future images are, in turn, formulated through metaphors to past experiences with other infectious diseases, particularly TSEs such as scrapie. The scientists knew, for instance, that researchers in the past had received recognition and prestige for their discovery of new forms of TSE, and believe that the same will hold true for BSE. The MAFF officials, on the other hand, are cognizant that "importing countries already take a serious view of scrapie in sheep" leading them to believe that "the existence of BSE in GB could result in a ban on cattle exports to those countries" (Phillips Committee 2000a). Each of these views is based on present knowledge of how people, within their varied communities, have reacted to similar events in the past. But each extends this knowledge into a time frame for which certainty does not exist.

Epidemiology

John Wilesmith, a grey-haired and bespeckled epidemiologist in an underfunded and overworked department of MAFF, was given the difficult task of assessing the prevalence of this new disease, which had by then been dubbed Bovine Spongiform Encephalopathy or BSE for short. While scrapie was deemed the most likely metaphor for this new disease by scientists at MAFF, Wells instructed Wilesmith to keep his mind open to other possibilities.

Wilesmith's prerogative, to record cases, estimate the prevalence of BSE, and determine a possible common factor or cause, was hindered by difficulties in collecting data which stemmed from a variety of contingencies. First, the Ministers left him in what he describes as a Catch-22 situation regarding funding: "[they] were saying: 'well, you find out the true incidence and how big is this problem now and we'll think about giving you some money'" (Ponte 2003c), but to calculate the incidence, he would first need to do the surveillance and analysis, which required money. Shortage of funding was a concern across the government agencies, as Torries eliminated and reduced funding for various programs. In this context, John was forced to make the best of what little resources he had. He drove from farm to farm in his small car, examining cows that were reported to have unusual symptoms. This is where Wilesmith's second problem arose.

According to Wilesmith: "I think at that point in time, it was a difficult disease to diagnose in the very early stages because of the non-specific signs that the cattle show" (BSE Inquiry Oral Evidence 1998b). Slight behavioral changes or a slowing of movement may be all that is discernible at first. "Often it is only the farmer, who knows

the animal well, who can tell...Maybe he notices that the lead cow has suddenly become a follower, or a certain cow is more resistant to milking than she used to be" (Ponte 2003c). Given time and experience, however, "[there are] some characteristic signs which this definitely does bring out" such as changes in behavior and progressive incoordination (BSE Inquiry Oral Evidence 1998b). Undoubtedly, the difficulty in clinical diagnosis and the variability of symptoms attributable to BSE contributed significant uncertainty to the ascertainment of the disease, especially in the early days. Definitive diagnosis relied then and continues to rely upon neuropathological examination of the animal's brain, which could only be conducted after the animal was slaughtered

There were other factors which contributed uncertainty to the ascertainment of the disease. For one, John claims he had little control over whether he was notified of potential cases of the disease or not, as this was the prerogative of those "in the field to ensure on a day-to-day basis" (BSE Inquiry Oral Evidence 1998b). This reporting was hindered by the delay in publishing and notifying veterinarians and farmers about the clinical symptoms of the disease due to the economic concerns raised by an analogy with scrapie. By preventing early publication of the clinical symptoms, MAFF had missed an opportunity to create awareness of the disease amongst the larger veterinary and farming communities. Instead, Wilesmith had to rely on the passive surveillance system employed by MAFF in order to identify cases. This system relies on a sequence by which a farmer calls their local veterinarian to examine a sick cow. The veterinarian, if he is unable to diagnose the cow, then reports the cow to the Central Veterinary Laboratory (CVL) (Phillips Committee 2000a). While passive surveillance may identify a disease, it is a notoriously poor method for determining the prevalence of a disease. This is particularly

true for BSE, in which diseased cattle display subtle and non-specific symptoms. These changes may be attributed to other causes, such as birthing or injury. Complicating matters further, cows showing abnormal behavior are often slaughtered preemptively, to avoid loss of value due to wasting.

Early on, Wilesmith felt that he was able to eliminate the possibility that BSE was a genetic disease based on the lack of relatedness between cases. Cases seemed to be occurring almost randomly in herds across the country, but mainly in the Southwest. John Wilesmith took the liberty of classifying the cases he had identified as "index cases", or the first of their kind. This technique, of course, avoids the question of whether the disease had been around for much longer but had merely escaped detection through the passive surveillance system.

Given his predilection, Wilesmith was looking for some practice that had begun only recently to explain why this disease had appeared in multiple places at the same time. Early on, he concluded that scrapie was the most likely source of the new disease in cattle, based on the similarities between the two diseases. But even if scrapie were the source, that still did not rule out the potential for a "contributory cause" to explain the disease's sudden and recent arrival. After all, sheep and cows had co-existed for many years without cows contracting scrapie. He questioned farmers about pesticide treatments, management practices, and nutritional sources, among many things. One of his favored initial hypotheses was that a contaminated vaccine had spread BSE, just as the louping ill vaccine, made from sheep brains, had transmitted scrapie to multiple flocks in the 1920s.

Investigating these potential factors involved the very practical and by no means straightforward task of figuring out:

> ...how one could get various things out of farmers' records and out of their memories. So there were some sort of tips and so on that I could give people when they were asking questions. For example, on some occasions you may have to go through invoices to get what they actually purchase. Or it may be, as we were talking about, calving books for breeding information and so on.... (BSE Inquiry Oral Evidence 1998b).

The real-world, on-the-ground process of data collection involves the investigation of a variety of incongruous and often undependable sources. Once collected, however, the data is often analyzed in a standardized and seemingly precise manner. The cleanliness and precision of the data presentation disguises the contingent circumstances and subjective interpretation that led to their collection. Adding further layers to the potential for variations in subjective bias, Wilesmith handed off much of the data collection to colleagues in order to focus on analysis.

Eventually, Wilesmith collected enough data that he became convinced, despite the inconsistencies and the difficulty of obtaining comparable data, that most of the factors he had initially considered could be eliminated. He came to the conclusion that the only remaining common factor was the use of commercial feed. He began examining the specific components of the feeding regimes affected cattle had been subjected to.

> This is just going back to, at this point in time I was looking for new happenings and for what may be involved in feedstuffs. I mean, what I was seeing is conventional feeding regimes and not people doing anything rather peculiar or rather new. It was that aspect of the feeding that at this point I was after and not the, as it were - here the source of animal material which could contain the agent... (BSE Inquiry Oral Evidence 1998b).

In other words, Wilesmith began to suspect that meat and bone meal (MBM) derived from the carcasses of sheep, cattle and other animals might be the transmission factor.

MBM is the protein component of processed left-over animal waste after all the parts deemed inedible or inappropriate for the human food supply have been removed. The processing of this animal waste to produce tallow, the fat component, and greaves, the protein component, is called rendering. It involves the heating of the leftover animal waste until the protein component coalesces and can be removed from the tallow.

Meat and Bone Meal

One particular "origin" story of rendering credits the popularization of the feeding of rendered animal protein back to animals to a hog farmer in Berkeley, California (Franco & Swanson 1996). In the 1890s, this hog farmer, Nels Peterson was looking for a way to supplement the diet of his animals. He began collecting waste fat, bone, and muscle from butcher shops in San Francisco. He heated them in a huge iron kettle on his kitchen stove, skimmed the liquid fat off the top, and then used the protein residue on the bottom, the cracklings, to feed his hogs. He stored the tallow, which could be used to make candles and soap, in drums until he had collected enough to sell to merchants at the Oakland Port. Eventually, Nels Peterson's rendering business outgrew his kitchen and he built a plant in Emeryville, a small city next to Oakland with favorable tax laws. As the cattle trade in California grew, so did Nels's operation.

> Nels Peterson was one of a handful of men across the country who were pioneering what today can be recognized as the first full-blown recycling industry – an industry that currently converts some 50,000 tons/day of fat, bone, and muscle tissue from the meat and poultry industries into billions of pounds of products used by both industry and agriculture (Franco & Swanson 1996).

Newer and more efficient systems for rendering were developed over the next century. In the United Kingdom, where arable land was scarce, agriculturalists saw the feeding of meat and bone meal (MBM) derived from rendering as a prime source for fattening and improving the milk output of cattle. And yet many felt the industry could do even more with MBM. Dr. Bob Orskov of the Rowett Research Institute in Aberdeen proclaimed that "every beef animal in Britain could be fattened to slaughter weight using only waste products" (Year Book 1979). Three-quarters of the calories required for raising pigs, he believed, could also be produced from animal by-products. "Greater use of waste could release more arable land for growing food for direct human consumption," an article on the process concluded (Year Book 1979).

Another factor contributed to an increase in the production and utilization of MBM. Many municipalities, both in the United Kingdom and the United States, stipulate the maximum amount of fats, proteins, and other waste products that are allowed in the waste effluent from slaughter and packing plants, and levy fines if plants exceed these. As a result, several plants, such as the one in East Kilbridge, UK, found it advantageous to invest in a protein-recovery system which would allow them to capture even more of the protein from waste products of the slaughter industry, mixing it with the protein component obtained from the usual rendering process, and selling the combined product as MBM for animal feed (Year Book 1976). Such extra processing resulted in cleaner effluent and less pollution to the environment, a point which was often highlighted by the rendering industry.

Thus, while MBM had been fed to farm animals for over a century, economic pressures had steadily increased the attractiveness of utilizing MBM as an alternative to

vegetable protein. As time passed, John Wilesmith became more and more convinced that MBM in feed was the source of BSE. It was the only factor he could identify that was common to all affected cattle. There were inconsistencies in the data supporting this conclusion, however. For example, two brothers owned a herd of cattle in Southwest England in which a case of BSE had been diagnosed. One of Wilesmith's associates was sent to question the farmers about their feeding practices. This associate spoke with one of the brothers, who assured him that they had never fed their cattle any compound feed containing meat and bone meal. This result presented an anomaly in Wilesmith's data that could have potentially disproved his hypothesis. Unsatisfied with this inconsistency, however, Wilesmith went to the farm himself and questioned the other brother. The other brother recalled that he had, indeed, fed some of the calves a compound feed supplement during one of the winters. With this second layer of questioning, what was previously an anomaly was transformed into a data-point in support of the MBM hypothesis. This example illustrates the malleability of data analysis and data collection, and the contingency of obtaining results that support or fail to support a given hypothesis.

But if scrapie-infected MBM was the source of BSE, and if cattle in Britain had been fed MBM for over a century, why had the cattle not contracted BSE until now? Wilesmith sought to uncover changes in the rendering process that might have allowed more infectious material to enter MBM. Wilesmith, along with the help of a Task Force, went beyond the farm and investigated the evolution of practices in feed mills and rendering companies. This brought him into contact with another set of unknowns:

> *It was very complicated because at the time, or at the time of interest, then there had been quite a lot of takeovers of small companies and so on and those records were therefore not kept. And really it was not only until later that we had sort of computer-based records in these companies and so on. That was then*

> compounded, made worse by the fact that some farmers do keep to the same suppliers. A calf in its first six months of life can have three different types of rations, three different manufacturers. If you go into adult life it gets very complicated. To get an adequate history, and then go back to the source material, it really was not possible at all. We would be wasting our time (BSE Inquiry Oral Evidence 1998b).

Based on the information they could extract from incomplete records of a consolidating industry, different members of the team developed different interpretations of how or why MBM had suddenly become infective. For instance, Peter Smith, an epidemioligst who would later chair a TSE advisory committee, thought batch cooking might be to blame and commented that: "It is surprising the BSE problem has not arisen earlier if batch cooking is as suspect as it is particularly with the very variable standards of hygiene and operations still found in this sector of the industry" (BSE Inquiry Oral Evidence 1998b).

Wilesmith, however, came to a different conclusion based on conversations with scrapie scientists. These scientists informed him that heat was very inefficient at inactivating scrapie. This led Wilesmith to look for some other change in the rendering process that might have triggered BSE. He identified the elimination of a solvent extraction step in many rendering plants, which he believed might decrease the ability of the process to inactivate the infectious agent.

Wilesmith then constructed a computer simulation model to calculate the likely incubation period of the disease and the likely age at which cattle had been exposed. Based on this model, which, like any model, depends on the validity of the data entered into it, Wilesmith calculated that the incubation period could range anywhere from 2.5 to

8 years. Calves seemed to be 30 times more likely to develop the disease if exposed to contaminated MBM than their adult counterparts.

Wilesmith's work, like all scientific work, was beset by contingencies and uncertainties that made interpretation difficult. These contingencies and uncertainties began with the ability to identify cases of BSE in the field and extended to the potential for various manufacturing processes to increase the infectivity of scrapie in feed. The importance of these contingencies and the magnitude of the uncertainties were magnified due to practices within MAFF that stemmed from concerns over future economic and social impacts, which in turn derived from analogies to scrapie.

While seeking to navigate these uncertainties and contingencies, Wilesmith made several assumptions about the cause and scope of the epidemic that colored his efforts at constructing Future Oriented Statistical Projections of the disease. First, he assumed that the cases he observed were index cases of the disease (i.e. that he was witnessing the first wave of spread of an infectious disease, rather than the second, third, or nth wave). Second, while he felt convinced that MBM was responsible for the spread of the disease since it was the only common factor of all cases, there was no indication of what component within the MBM might be to blame. Based on the pathological similarity of BSE to scrapie, and the metaphorical fit in the clinical course of the two diseases, he assumed that BSE came from scrapie in sheep and that the effect of cattle recycling of meat and bone meal was negligible. Therefore, he did not factor the potential for the disease to transmit from cattle to cattle into his calculations. Based on these assumptions, Wilesmith projected that, at most, 60 cases per week could be expected once a ruminant

(cattle and sheep) to ruminant feed ban was imposed. It should be noted here that this pales in comparison to what actually happened.

While Wilesmith's conclusion that MBM was to blame for the spread of BSE led MAFF to propose a temporary ban on the feeding of ruminant remains to ruminants, his FOSP of the epidemic, which projected only limited growth, left MAFF feeling comfortable enough to allow a short lead-time before enactment of the ban. This lead-time was seen as necessary to allow the industry and farmers to clear already produced ruminant MBM from shelves was admissible. The feed industry association, which foresaw economic disaster for its constituents given what they viewed as insubstantial time to complete this task, begged for more time

> We would thus be grateful if you could defer the enforcement of that section of the new order suspending the use of animal proteins in ruminant rations for as long as possible. Failure to do this could, in turn, result in our having to press for compensation from the Government. [1]

In implicating the government for responsibility in any economic consequences faced by the industry, they were able to bargain for more time. As a MAFF official concluded:

> ...there are no overriding veterinary reasons why we should not permit them a two month period of grace from the date of making before this particular part of the legislation comes into force (emphasis added). [2]

This official's reference to a lack of overriding veterinary concerns as a reason to allow a grace period before implementation of the ban highlights the power which Wilesmith's FOSPs had in convincing the government that action, while necessary, need not be imminent. Wilesmith's FOSPs, in turn, were based on assumptions about BSE largely derived from analogies with scrapie.

Through Wilesmith's efforts we can see the way in which analogies to past experiences with disease become the basis, and form the boundaries of, the creation of Future Oriented Statistical Projections (FOSPs). Disguised in the rational cloak of mathematics, these FOSPs, and the analogies on which they are based, then become prominent actants in the debate over the appropriate disease management action to be taken, influencing the future outcome of the disease. In this way, FOSPs both constrain and make possible the field for present action, which then constrains and creates the possibility for the production of altered images of the future. As we will see, however, despite the prominent role played by FOSPs in influencing disease management policy, the decisions taken based on these rationalistic projections were not always effective.

The Southwood Report

Another way in which modern societies seek to rationalize and gain credibility for disease management policy decisions is by appointing expert committees, comprised of renowned and respected scientists, to analyze and make recommendations about the management of disease. Such advisory committees possess the appearance of independence because the members of the committee are not employed by the government. Most often they are academics, but sometimes derive from industry or consumer advocacy groups. Despite the outside appearance of independence, which is necessary to garner credibility in the public domain and is key to lending authority to the committee's pronouncements, we will see, in this section, how intertwined the advisory committees may become with their governmental sponsors.

The first expert advisory committee that was appointed to consult on BSE was the Southwood Committee. In many cases, government officials reviewed the committee's recommendations and made suggestions before they were solidified into their final form. In some cases, government officials succeeded in changing the substance of the committee's recommendations. The members of the committee, in turn, adjusted to their interdependent role and made many of their demands privately, whether to the government or private companies, rather than publishing them in the report.

The decision by government officials to appoint an advisory committee on the matter of BSE may also be seen as an attempt to deflect blame for any future negative outcomes of policy decisions. Advisory committees, because of their perceived independence from the government and expertise, can serve as a shield for the government. By making it appear as though the committee's recommendations were purely their own, without influence from government officials, and by deferring to the committee as professionals with expertise lacking in the government, the government seeks to insulate itself from criticism for enacting the resulting recommendations. This tendency of the government to hide behind the recommendations of advisory committees on the matter of BSE began with Southwood but only intensified in later years as further committees were appointed to advise on the matter.

The Southwood committee, for its part, continued to rely on analogies with scrapie and other TSEs to formulate predictions for the course of the epidemic and the risk of BSE to humans and other animals. This led them to conclude that it was unlikely BSE would cross the species-barrier into humans. While there was some data from rodent model systems of scrapie that called this assumption into question, this data was

dismissed due to its experimental nature and the lack of any epidemiological evidence for prior transmission of animal TSEs to humans.

The Southwood committee also served as a type of peer review committee for John Wilesmith's FOSP of the disease course. By including Wilesmith's FOSP, his calculation of the likely course of the BSE epidemic, within their final report, they, in effect, certified Wilesmith's projection and lent it further credibility. The government, in turn, disseminated the conclusions of the Southwood report widely, citing them in televised conferences and other media events. Thus, experience with TSE's from the past became the basis for projections of the future which solidified the government's position with regard to BSE disease management policy.

In 1988, Sir Richard Southwood, a zoologist at Oxford who had prior experience chairing advisory committees for the government, was asked by MAFF and the DH to head an expert group to evaluate the risk of BSE to humans and animals. John Wilesmith was selected to serve as an expert advisor to the committee and was allowed to sit in on all their meetings. None of the members of the committee, other than Wilesmith, had any direct experience working with Transmissible Spongiform Encephalopathy (TSE). The committee was designed this way because great controversy existed in the field at the time over the identity of the infectious agent. It was thought that this controversy would inhibit TSE scientists from working together efficiently and would likely result in a skewed view of the disease. Southwood was viewed by MAFF as someone who could take an unbiased approach to the disease within an ecological context.

At their first meeting, on June 20, 1988, the Southwood committee, as it came to be called, congratulated MAFF on their intention to impose a ban on feeding ruminant

remains to ruminants in July of 1988. They were, however, appalled to learn that cattle diagnosed with BSE were still entering the human food chain. This seemed, to Southwood and the other members of the committee, a blatant disregard of a potential avenue of risk. As a precautionary measure, they advised the government to destroy the carcasses of all cows diagnosed with BSE until more was known about the potential transmission properties of the disease. In response to the recommendation of the Soutwood Committtee, in July of 1988 MAFF announced a cumpolsory slaughter-with-compensation policy which would come into effect in August. The program allowed for 50% of the market value of the animal to be paid as compensation to the farmer. The rule also made notification of the disease to a government veterinarian compulsory.

Before their second meeting on November 10, 1988, the members of the committee were informed that Hugh Fraser had succeeded in transmitting BSE to mice. The committee members interpreted this result as cinching the classification of BSE as a TSE. The now-proven transmissibility of the agent prompted the Southwood Committee to recommend that the ruminant-to-ruminant feed ban be made permanent. If the disease could be transmitted from cows to mice by the transfer of infected brain material, the committee reasoned, it could likely be transmitted through the feeding of infected brain material to cows.

Still, the extent of the host range which could be infected with the agent, and whether this host range extended to humans, was unknown. They could only guess at this possibility, based largely on analogies to other TSEs. The committee considered that humans had lived near sheep with scrapie and had eaten sheep with scrapie for centuries, yet there was no good epidemiological evidence linking consumption of scapie-infected

sheep to any form of human disease. If scrapie was not a danger to man, the committee surmised, it seemed likely that, by analogy, BSE would likewise prove to be non-threatening to humans. In fact, there was no evidence at all for any human TSE ever having transmitted from an animal source. While kuru appeared to be directly transmissible between humans through potential oral or mucosal routes of exposure, and CJD had recently been shown to be transmissible through human growth hormone injections and neurosurgery, these all represented transmissions within the human species. The fact that sCJD and kuru could be transmitted easily to primates but not other animals in the laboratory reinforced this perception, creating the image that the host-range was likely to be very limited.

Richard Kimberlin, a scrapie-scientist who was called in to consult with the committee, produced data that complicated this logic. He and his co-workers had conducted several painstaking experiments in which they transmitted mouse-adapted scrapie to rats and then back to mice again. Most of the time, the disease pattern remained the same in the second generation of mice that were infected. In a small number of cases, however, the disease pattern changed in a reproducible way. Kimberlin interpreted this as showing that when transmitted to a new species, sometimes the properties of a TSE will change through an unknown process of adaptation, and sometimes they will remain the same. The question, as the committee and Kimberlin saw it was: did scrapie change when it was transmitted to cattle, adapting to its new host? If so, would this alteration permit the disease to transmit from cattle to humans?

More important from the perspective of animal health was the question of whether cattle could infect each other. Kimberlin raised the analogy of Transmissible Mink

Encephalopathy (TME), a TSE which was thought to arise in mink through the consumption of infected sheep carcasses. Because mink did not seem to transmit the disease amongst each other, epidemics of TME were self-limited events. As Kimberlin recalled during questioning by the BSE Inquiry:

> ...when BSE first came along and we recognized a spongiform encephalopathy in cattle, which had not been seen before, one of the first things one thought of is: "Ah, this could be another TME type of story."... We thought very much of scrapie as being the primary cause of TME outbreaks. Some of these TME outbreaks were very substantial, very severe; a large number of breeding female mink would die of this disease. What was interesting about TME was there was no natural transmission of infection, for example from mother to offspring, as we knew happened with scrapie in sheep. Therefore outbreaks came. They were feed-borne; they were often extremely devastating, and they then just disappeared; they were self-limiting. Providing you did not keep on feeding mink infected material, then you would not have any more problems with the infection.... If that vehicle of infection was cut off, so that new infections could be prevented, there was a good chance that BSE would then become a self-extinguishing disease if it followed the TME, kuru pattern (BSE Inquiry Oral Evidence 1998a).

After deliberation, the committee decided that BSE was unlikely to transmit to humans and unlikely to spread from one cow to another. "From present evidence," they surmised, "it is likely that cattle will prove to be a 'dead-end host' for the disease agent and most unlikely that BSE will have any implications for human health. Nevertheless," they continued, "if our assessments of these likelihoods are incorrect, the implications would be extremely serious" (Southwood Working Party 1989). Southwood made it clear, however, when presenting the committee's report to the government, that the conclusions were uncertain given the lack of knowledge regarding BSE and the reliance on analogies with scrapie.

It was no secret to the government ministers and officials involved that Southwood was not a fan of the recycling of meat and bone meal among livestock. As a

zoologist and ecologist, he tended to think broadly about infectious disease. In one draft of the report, before it was made public, he slipped in a paragraph that described his feeling toward such modern agricultural practices:

> This problem has arisen as a result of the practice of feeding animal materials to herbivores, which are thus exposed to infection/infective risks against which they have not evolved such defenses. Such practices are often a feature of modern intensive agriculture, but inevitably (as with BSE and bacterial pathogens in poultry) they open up new pathways for infection to the herbivores and potentially from them to man, via food and/or medicinal products. We note these animal meal supplements do increase the rate of growth of the animals, whilst also providing a superficially efficient way of disposing of animal waste. But we believe that the inevitable risks are such that it would be prudent to change agricultural practice so as to eliminate these novel pathways for pathogens (Phillips Committee 2000d).

MAFF and the agricultural community were incensed at this statement. Worried that all rendering would be put to a halt, a measure which they feared would cripple the animal feed industry, and perhaps the entire agricultural industry, they were intent on preventing this statement from being included in the final Southwood report. MAFF submitted a memorandum to the Southwood Committee advising them on the environmental and financial implications of excluding meat and bone meal from animal feed. They suggested a dire future in which waste would overwhelm landfills and pollute the planet.

Under pressure from MAFF, Southwood's statement was removed. The minutes of the next Southwood meeting, however, record Southwood's continuing concern:

> Sir Richard said that he was not merely concerned with cattle and goats but also with other animals such as pigs and poultry...We either had to find a rendering process capable of producing more sterile result (i.e. the destruction of all pathogens) or we should consider finding other ways to dispose of the animal products (although this last point was not something he would say in public) (Phillips Committee 2000d).

While Southwood capitulated to the demands of MAFF in terms of not making his concerns public, he continued to pressure industry and the government to change practices from behind the scenes. He followed a similar course when it came to pharmaceutical products, such as vaccines, hormones, or other products that could be made from cattle tissue. Some of these products, such as bovine insulin or heparin, were used in the treatment of humans with diabetes and clotting disorders. Southwood felt that such products were of the greatest risk, as they involved the direct injection of cattle-derived material into human beings. He wrote letters to those in the regulators and pharmaceutical companies suggesting actions which could be taken to mitigate this potential risk.

The Southwood Report recycled John Wilesmith's prediction that exposure, and therefore the incidence of the disease, would continue at a constant rate. This prediction, as mentioned above, was based on the assumption that cattle to cattle transmission would play a negligible role in the epidemic. Scrapie-contaminated sheep remains were considered the main source of infection. "If this is the case," the Southwood report read, "and given the incubation distribution, then a constant number of cases, of the order of 350-400 per month, can be expected...this rate of presentation of the disease will continue until 1993" when "a cumulative total of about 17000-20000 cases from cows currently alive and subclinically infected" will have resulted (SW-15). Further, the report predicted that "no new infections [of BSE]...will arise after 18 July 1988" (Southwood Working Party 1989). This, of course, was based on the notion that the ruminant to ruminant feed ban, recently instituted by MAFF, would be 100% effective at preventing transmission of the disease once enacted. This prediction had the effect of reassuring

MAFF that no other regulation of the cattle industry or the feed industry was necessary to prevent the spread of the disease.

The Southwood committee recognized that a certain number of BSE-infected cattle, either because their symptoms had been missed or because they were still in the incubation period, would not be detected. These animals would be ingested just as any other animals. The work of Hadlow provided evidence that the infectious agent of scrapie increases exponentially in the spleen, liver, kidney, and lymphatic organs during the early part of the incubation period, and in the brain and spinal cord throughout the later part of the incubation period (Eklund et al 1967). If BSE were like scrapie, then these tissues could be infective in cattle that were killed while incubating the disease. While the Southwood committee briefly considered regulating the entire food supply to exclude these parts, they deemed this an untenable solution given the structure of the industry. They were, however, particularly concerned about baby food. Baby food, they found out, often contained parts of cattle that were not otherwise sold for human consumption, such as kidneys. Moreover, because baby food was homogenized, it would be difficult to tell whether it contained any of the "risky" cattle parts. The committee was also concerned because Wilesmith's computation model had produced data indicating that young cattle were far more susceptible to infection with BSE than adults. If people were like cattle, then babies and children might be more susceptible to BSE than adults. Therefore, the committee suggested the banning of specific cattle parts, such as intestine, brain, kidney, and any organ from the lymphoreticular system, from baby food. Eventually, finding it politically and legalistically untenable to enact such regulation for young people but not for adults, and with further urging by consumer representatives, MAFF banned such

"specified bovine offals" from all human food at the end of 1989. The Southwood committee also recommended that the DH put in place a national surveillance system for CJD to detect an increase in cases in the "unlikely" event that it should occur.

With Southwood's report in hand, the government ministers assured the British public that cattle were a 'dead-end host' for the disease-causing agent (Phillips Committee 2000d). These same ministers cleverly neglected to mention the uncertainty inherent in the Southwood report, which Southwood himself had impressed upon them (Phillips Committee 2000d). The message that "British beef is safe to eat" was so often repeated that it became a mantra for the ministry. They not only said it, they performed it through a ritual of eating of beef in public. John Gummer, then minister of MAFF, fed his four year old daughter a hamburger on television to "perform" the safety of beef in a public venue. Officials continued to repeat the mantra of safety, even after domestic cats and exotic zoo animals began to contract what appeared to be a very similar disease. The Southwood committee's assessment, taken out of context, became the justification for almost a decade's worth of denial.

In retrospect, Wilesmith feels that it was unfortunate that the government chose to emphasize certain aspects of the report while minimizing or, in some cases, completely ignoring the uncertainties surrounding the assumptions involved:

> I think what happened is that the uncertainties were stated as certainties, because there are certain things that were taken out of context. It's like here are the results of this modeling, and forget the assumptions, where that is in fact the crucial part. ...But I don't think you can ever write a report that can't be misquoted. I think again, it's a matter of not realizing what the uncertainty was (Ponte 2003c).

What Wilesmith refers to here as uncertainties were largely blanketed over, in the course of events, by referring to previous experience with scrapie and other TSEs. In the end, it was their reliance on past experience through extended analogy that tricked them into feeling that they knew more about this new disease, BSE, than they really did. When seeking to manage a disease in a rational fashion, modern governments often fall into this trap. But it should be remembered that every instance of a new disease is just that – a new disease – and it is difficult to make such all-encompassing predictions based on past experience. In my view, it would be better if governments, in instances of emerging disease, publicly acknowledged the uncertainty inherent in their decision-making rather than caving in to their modernist urge to perform certainty and predictability when it does not exist. When dealing with so many unknowns, rationality is a mirage.

Subsequent Scientific Advisory Committees

The Southwood Committee, which had only been convened on an ad-hoc basis, recommended that another committee be appointed to advise on scientific and epidemiological studies of the new disease. David Tyrrell, a specialist in viruses, was appointed chair of this committee, and the committee he chaired became known as the Tyrell Committee. Unlike the Southwood Committee, the Tyrrell committee included two members who had expertise in the TSE field: Robert Will, who would later head the CJD Surveillance Unit, and Richard Kimberlin of the Neuropathogenesis Unit in Edinburgh. The Tyrrell committee was concerned about the increasing number of BSE cases that were being detected each month, as well as the problem of subclinical cases of BSE entering the food supply. As Kimberlin recalls:

> ...the uncertainty about how big the epidemic of BSE was going to be made one wonder to what extent Southwood's recommendations were an adequate response to the public health issues. What he did was absolutely right and fine. He did recommend that...clinically diagnosed animals did not enter the food chain. The problem always was what to do about animals that are infected but cannot be detected because they did not have clinical disease. And the degree to which one would worry about that obviously would be determined by the scale of the epidemic to come which, as I said, was regarded as uncertain (BSE Inquiry Oral Evidence 1998a).

Kimberlin reveals here that despite the government's public reassurances regarding BSE, experts knowledgeable in the field of TSE perceived many more uncertainties and concerns than were publicly acknowledged. High among these concerns was the danger from eating meat from an animal that had not yet developed symptoms of the disease, but was incubating the disease, and the infectious agent, nonetheless. This concern also reached the public through the media. Dr. Helen Grant wrote a letter to The Guardian which was published on March 2, 1989 regarding this matter and later sent Richard Southwood a personal letter complaining about "the ominous problem of the incubation period" not being "given enough emphasis" in the report. "Since it is impossible by testing to reveal which animals are infected," she warned, "the long incubation period is potentially very sinister because these animals continue to reach our food" (Phillips Committee 2000d).

It was the temporality of the disease, the extremely long "incubation period" in which infection remained invisible, that worried those involved. This made BSE and the other TSEs unusual compared to most infectious diseases, and harkened back to struggles with HIV/AIDS. As compared to AIDS, however, Tyrrell felt that they were even more in the dark, as they lacked the diagnostic tools available for HIV:

> It was interesting when talking to people who were not actually sitting on the committee, they all said: "But these days you can work out who is infected or not. Look at what you can do with AIDS, there is a blood test for it." You had to explain, patiently, that this was a very strange process. There was no method, and at the time no great likelihood there would be a method to detect infected animals. If you could, if you could use a method like culling which had been used with all sorts of other problems in agriculture, TB, brucellosis and so on. It was something which had to be thought through again towards a different solution (BSE Inquiry Oral Evidence 1998a).

Controlling BSE was considered more problematic than managing viral and bacterial infections, even AIDS, because it could not be diagnosed through a test. BSE could only be confirmed by examination of the brain post-mortem. This aspect of the temporality of the disease generated and prolonged much of the uncertainty surrounding the BSE epidemic.

In their interim report, presented to the government on June 10, 1989, the Tyrrell Committee recommended that transmission studies in pigs be carried out. Pigs and chickens, under the law, could still be fed ruminant-derived MBM. Because the committee's primary concern was detecting susceptibility, even if it was a low-level susceptibility, they recommended that the Central Veterinary Laboratory undertake these studies using large amounts of infected material injected through multiple routes. Gerald Wells, who was put in charge of the study, followed Tyrrell's advice and inoculated 10 pigs with fairly high doses of BSE-infected cattle brain intracerebrally, intravenously, and intraperitonealy.

In the conclusion of their report, the committee stressed that the research they recommended was desirable because:

> If the preliminary studies and arguments-by-analogy used to determine our present control policies turn out to be incorrect, it will be essential to have well-

> documented facts available so that current policies can be effectively advised (Phillips Committee 2000b).

In other words, if the Soutwood committee's choice of emphasizing the analogy with scrapie were wrong, and BSE did turn out to be infective for humans, it would be useful to have scientific studies to assess the damage the disease might cause and delineate better disease-management policies.

The Tyrrell committee recommended that a standing advisory committee be created to advise on questions regarding BSE and to oversee research. MAFF and DH agreed that having such a committee would be advisable, and David Tyrrell was invited to be its first chairman. Many of the original members of the Tyrrell committee were incorporated into the new committee. The new committee was announced by Mr. Gummer on April 3, 1990, and labeled the "Spongiform Encephalopathy Advisory Committee," or SEAC. The charter of the committee was quite broad, and involved advising both MAFF and DH on all "matters relating to spongiform encephalopathies" (Phillips Committee 2000b).

On June 13, 1990, the committee was asked to advise on practices in slaughter plants. These practices revolved around head-splitting, the breaking open of the skull to remove the brain, and carcass-splitting, the sawing in half of the animal, splitting the spinal column. These practices were deemed risky because, based on an analogy with scrapie, the greatest infectivity was likely to be found in the brain and spinal cord of BSE animals. In the first case, the removal of brain material was often messy and could contaminate the head meat, which could thereafter be consumed by people. In the second, there was the potential that the saw might splatter spinal cord material on the surrounding

carcass, including meat for human consumption. In addition, there was a potential for unintentional shredding of the spinal cord, resulting in the lodging of small fragments in the vertebral column. The vertebral column could then go on to be used in the production of mechanically recovered meat (MRM), which involves the removal of meat from the bone through mechanical pressure or scraping. MRM could then be added to hamburgers, hotdogs, the ever popular British meat pie, and other ground beef products.

While experts in science, the committee members were not experts in agricultural practices. The committee, unsure about how to design a recommendation regarding practices they knew nothing about, asked for further information. For the time being, they recommended only that contact between meat and brain or spinal cord be avoided. The DH and MAFF recognized the reluctance of SEAC to put themselves on the line when it came to the practicalities of risk management. In a memo between the ministries, it was noted that:

> The Committee (and particularly the Chairman) obviously feel uncomfortable about offering firm advice on specific measures and from now on may well try to avoid doing so, preferring to describe the scientific situation and explicitly leaving the policy decisions to Ministers. It was only with some difficulty, for example, that they reached a clearer conclusion in writing on the issue of the removal of head meat than that contact between meat and brain or spinal cord should if possible be avoided (Phillips Committee 2000c).

Despite the recognition on the part of government officials that SEAC members were uncomfortable being thrust into the position of making recommendations on practices they knew nothing about, the government officials persisted in asking SEAC for advice on these matters. SEAC, as an expert scientific committee, was no expert in agricultural matters. Most members of the committee had never worked on a farm before, and some of them had never even visited a farm before. The persistence of the government in

shunting policy questions to a committee with little expertise on the matter, despite their designation as an "expert" advisory committee, reveals how strong this urge to avoid outright decision-making regarding disease management policy on the part of the government, policies for which it might later be blamed.

Finally, in October of 1990, SEAC was presented with the requested information from MAFF regarding the process of carcass splitting. As the report summarized:

> The spinal cord will inevitably receive some damage during this operation, although it is often surprisingly intact...The concern that has been expressed regarding carcass-splitting relates to the possible transfer of material from the damaged spinal cord onto the carcasses. The volume of material is likely to be small, in most cases no more than a few grams (Phillips Committee 2000c).

It is clear that the authors of the report intended to communicate that such a small amount of tissue, "no more than a few grams," was unlikely to present a source of transmission. At the time, the belief had become widespread that a large amount of infectious material, substantially more than a few grams, would be necessary to transmit infection. This belief found its expression in the "attack-rate study," which was designed to determine the dose-response relationship to the infectious agent of BSE. In this study, four different quantities of infectious material were fed to four different groups of cows. Gerald Wells and the other scientists who designed the study decided that, based on the belief that based on the notion, as put forth by Kimberlin, that the oral route is generally inefficient, a relatively high dose would be required to cause infection by this route. In order to ensure that infection would occur, they chose to feed one group of calves 100 grams of infectious brain material on three different occasions. The other three groups were fed 100, 10, and 1 gram of brain material on a single occasion. It was believed that the group receiving only a single gram of material would be unlikely to contract the disease,

thereby providing information on the low-end of the dose-response relationship. It would be years, however, before the results of this study were known, and the members of SEAC, as well as the government ministers, were thrust into assessing risk and designing policy without the benefit of the study results.

Before the sixth meeting of SEAC, visits were arranged to two slaughterhouses where members of the committee could witness slaughterhouse practices first-hand. While the committee recognized that these were staged events, in that the slaughterhouses were prepared for their visits ahead of time, they were impressed by their ability to adequately remove spinal cord (Year Book 1991). The slaughterhouse performances served to reassure the members of the committee who had no previous experience with such facilities, despite their lack of knowledge of practices in other such facilities.

At its sixth meeting in November of 1990, therefore, the committee concluded that: "provided all the rules were properly followed and supervised, there was no need to recommend further measures on the grounds of consumer protection (Year Book 1990). Later, in interviews with the BSE Inquiry, Tyrrell emphasized the importance placed on the caveats included in this statement. But, while the committee may not have intended to provide a stamp of approval for all slaughter processes, this is how the advice was interpreted by MAFF.

It would be several years before SEAC would come to understand that their advice was not being followed, that most slaughterhouses did not follow the procedures on display at the ones they had visited, and that the most infectious materials, brain and spinal cord, were still entering the food supply. Not until the number of cases of CJD in

young adults had climbed to levels unimaginable, for such a rare disease, and the Meat Hygiene Service, newly separated from MAFF, began its own audits and inspections, would this information come to light. Meanwhile, confident that agricultural practices were sufficient to protect the population, even if BSE proved to be transmissible to humans, SEAC continued to reassure the public, in statements released at the government's suggestion, that meat was indeed safe to eat, free, as it was, from all incriminating tissues.

A Growing Epidemic

And yet, beyond all projections, the monthly incidence of BSE continued to rise. By the beginning of 1990, over 1200 cases were diagnosed each month. Clearly, John Wilesmith and the Southwood committee had underestimated the power of BSE to spread. At the end of January, it was reported that 5 exotic antelope (kudus and nyala) held in zoos had succumbed to spongiform encephalopathy that looked peculiarly similar to BSE. Zoo animals were sometimes fed MBM as part of their feed regimen to increase protein uptake. The next month, cattle to cattle transmission of BSE by intracerebral injection and the transmission of BSE to mice through the feeding of infectious cattle brain was reported in the Veterinary Record.

In May of 1990, the media reported that Max, a cat in Bristol, had been diagnosed with a spongiform encephalopathy. Max had begun falling asleep while standing up in December of the previous year. His head leaned permanently to the right. Sudden movement or noise would cause him to jump. Max's owners had him euthanized after he

could no longer walk. Pathological examination of the brain revealed the vacuoles of spongiform change. The new disease was dubbed "Feline Spongiform Encephalopathy."

Cats had never before developed a TSE. Newspaper articles raised the question of whether Max had contracted BSE through contaminated cattle parts in pet food. It was insinuated that if cats were in danger from this new disease, humans might be as well. SEAC was asked by the government to draft a report on the safety of beef. While the first draft of the report contained the statement "if this is the start of a new cat epidemic it suggests this species could be sensitive to BSE in a way it has not been to scrapie," meaning that BSE could be different from scrapie and therefore might pose a threat to humans, officials in MAFF discouraged this wording and SEAC changed it to:

> We do not yet know if the recent description of spongiform encephalopathy in a cat indicates transfer of scrapie or BSE to a new species or whether this is a feline disorder in its own right. In our view, this cat does not increase the likelihood of BSE transmission to humans (Phillips Committee 2000c).

Satisfied by these changes, a MAFF administrator wrote "the most potentially inflammatory pieces of drafting in earlier versions have now been edited and I see no particular points that should be raised with DH about the manner of its publication" (Phillips Committee 2000c).

Tyrrell admits that by this point the committee was no longer reviewing information in an independent manner, and had come to accept their political positioning (Phillips Committee 2000c). Like Richard Southwood, the members of SEAC had become accustomed to the government making demands in terms of how they worded their recommendations and what they were to say in public. In addition, SEAC framed its advice in a manner that already anticipated the reaction which it would draw from the

media. Tyrell makes it clear in the quote below that the committee configured its advice to minimize public concern:

> Do remember that we were all under this worry about what was the outside world, what were the papers, what was the television going to make of this thing when it came out? I suppose the people in the Ministries and the politicians would have that as a stronger pressure on them, but we all had it to some extent (Phillips Committee 2000c).

This creates a sort of circularity, where the committee formulated advice with the intention of producing a certain effect rather than communicating their frank interpretation of events and results. Because of this circularity, SEAC deleted much of what their true concerns were about the safety of beef, believing that the media had already overemphasized these concerns, and instead sought to reassure the public. The tendencies of SEAC to behave in this manner were furthered by MAFF and the other government agencies, which made demands on SEAC.

Soon after, Gerald Wells obtained the first transmission of BSE to pigs. He notified his administrators at MAFF immediately. The meaning of the results, however, was difficult to interpret as the pigs had been inoculated by multiple routes, including the intracranial route. If you pump a lot of infectious material into the animal by unnatural routes, Wilesmith reasoned, you are likely to see transmission even if the animal would never contract the disease naturally. Thus, the correspondence, or metaphorical fit, between the model system and reality became a point of contention. In fact, this concern was highlighted in a memo from Donald Acheson to Mr. Dorrell:

> While this clearly is a cause for concern we should not jump to the conclusion that this means that pigs will necessarily be infected by bone and meat meal fed by the oral route as is the case with cattle (Phillips Committee 2000c).

An emergency meeting of SEAC was called to consider the pig transmission study finding, which had not yet been released to the public. Mr. Meldrum of MAFF prepared a paper for SEAC outlining the potential actions they could take. Amongst the options he listed were: do nothing, legislate to ensure that meat and bone meal derived from specified offal cannot be used in pig rations, and ban the use of ruminant-based meat and bone meal as a feed ingredient in pig rations. Of the three options listed, Meldrum reported that MAFF favored the second.

Reiterating the concern that the model system, with its extreme exposure conditions, may not mimic reality, he proposed that a ban would be an:

> Over-reaction since there is no evidence of a porcine encephalopathy under natural conditions and it is possible that pigs are not susceptible to BSE by the oral route but only when presented with a massive challenge (Phillips Committee 2000c).

After reviewing Meldrum's memo, the committee deliberated. While deciding that "it was very difficult to draw conclusions from one experimental result for what may happen in the field," the committee concluded that it would be prudent not only to exclude SBO from pig feed, but from the feed of all animal species. Despite their formal recognition that the host-range of BSE was unknown, and could include animals of any species, the committee advised that "there were no implications for human health in the fact that a pig had shown itself susceptible under laboratory conditions" (Phillips Committee 2000c).

Ministers at MAFF and SEAC members underplayed the results of the transmission of BSE to pigs because it had occurred under unnatural circumstances in a model system. This reveals the way in which analogies through model systems may be solidified or negated depending on the interpretation of the congruence between the model system and reality. Despite the fact that this was an experimental result from a

model system that had been recommended by the committee, once they had the result in hand they did not use it to transform their understanding of the potential for BSE to cross species barriers. Rather, it was more convenient at the time to relegate this result to the unlikely finding from an obscure model system with no bearing on real human or animal disease.

BSE Infected Cattle Born After the Ban

John Wilesmith had predicted that the feed ban would prevent the transmission of BSE to cattle born after it went into effect in July 1988. In March of 1991, however, the first case of BSE in a cow born after the introduction of the ruminant feed ban (Born After the Ban or BAB) was identified. If Wilesmith's projections were wrong, MAFF's entire policy response to the disease would become suspect. At first, some officials at MAFF tried to blame this case on maternal transmission, maintaining that no feed that had been manufactured after July 1988 could have contained contaminated cattle parts, and thefore feed transmission was impossible. Then, however, a second BAB was confirmed by pathological examination of the brain on September 16. This one could not be blamed on maternal transmission. Mr. Bradley of MAFF wrote that: "There was confidence that, in general, in those cases where cattle had been fed ruminant protein after the ban, this had only occurred up to three months after the ban" (Phillips Committee 2000c). In other words, Bradley suspected that there may have been leakage in enforcement of the ban in the beginning, but that this should have ceased within three months.

I asked Wilesmith where this idea originated. He told me that everyone at MAFF had been convinced that, even if farmers continued to feed their cattle ruminant-containing feed after the ban, that this feed would have to be used up or thrown away within three months of its production. As he put it, "theoretically the shelf-life of these products is about three months, because of the fat-associated vitamins. The fat goes first, as it were." By the end of 1991, however, there were 122 confirmed BABs, many of which had been born after the three month interval following the ban. As Wilesmith later conceded, "That was theoretical...we found things being used that had been manufactured a year previously. So, if anything we underestimated that actual shelf-life business" (Ponte 2003c). In other words, part of the projections as to the size and limits of the BSE epidemic were based on assumptions about the behavior of farmers and the stability of foodstuffs that turned out to be entirely incorrect.

Wilesmith's fears were confirmed when an anonymous survey conducted by UKASTA in 1992 showed that most feed compounders had continued to manufacture cattle feed containing ruminant protein right up to the deadline and had continued to distribute this feed up to three months after. The farmers who purchased this feed then continued to use it for several months longer, despite the ban. Representatives from the feed industry later told the BSE Inquiry that they had not taken the ban seriously due to the way MAFF had framed the ban: there was a grace period included, there was no recall of previously produced feed, and there was no ban on exporting the MBM to other countries. In addition, they cited the belief, which MAFF had communicated to them, that large amounts of infective feed would have been required to transmit the disease. As Wilesmith recalls, in the lead-up to the ban one official at MAFF had convinced the feed

manufacturers that it would take "buckets full of stuff for this to transmit." In fact, Wilesmith admits, everyone involved would have been more concerned if they had thought a small amount of infectious material could transmit the disease, including himself. As Wilesmith puts it, "Underneath it all, we were underestimating the dose side of things."

In other words, it slowly became obvious that cross-contamination (the adulteration of cattle feed with small amounts of cattle-derived tissue) was continuing to spread the disease amongst cattle. This could occur on the feed production line, during transportation, or on the farm. This seemed even more likely, when, in 1994, the results of the "attack-rate study", the dose-response experiment in which cattle had been fed four different amounts of infected brain material, became available. As previously described, the scientists had selected 1 gram as the lowest dose to test by the oral route. Thus, they were shocked to learn that 1 gram of material transmitted the disease with ease. Subsequently, they ran further experiments with even smaller amounts of BSE brain material in an attempt to establish the minimum dose. Within the past year, it has been revealed that as little as one milligram, or .001 g of infected brain, much less than a peppercorn's worth of material, can transmit the disease.

The implications of these experiments quickly became apparent. While the UK government had banned the use of cattle MBM in cattle feed in 1988, it had not banned the use of cattle MBM in the feed of chickens, pigs, and other livestock. A farmer using the same equipment to transport cattle feed and feed for other livestock, a mill operator using the same production line for each type of feed, or a farmer storing each type of feed in similar containers, could easily contaminate the cattle feed with a small amount of

BSE material contained in the feed for other livestock. Thus, while the ruminant feed ban decreased the rate of spread of the disease, it did not eliminate it. A small amount of cattle MBM continued to make its way into cattle feed, leading to the development of BSE in what has now amounted to over 40,000 BABs. Clearly, Wilesmith's FOSPs, Southwood's report, and SEAC's advice, which had been used for years to lend credibility to the government's disease management strategy, bore no semblance to reality. Despite their best efforts to cloak their disease management efforts in a rational guise, the irrationality of it all was quickly becoming apparent.

Marmosets

In early 1992, Gerald Wells and his coworkers at the Central Veterinary Laboratory identified spongiform encephalopathy in one of the marmosets[7] they had inoculated intracerebrally and intraperitoneally with BSE. This was the first time that a primate had been infected with BSE in the laboratory. This result was reported promptly to the relevant authorities, who asked SEAC for advice and a restatement of the safety of beef. SEAC held an informal meeting on February 27 at which they considered the result of BSE transmission to the marmoset.

On first appearance, this result might have given them pause. If a primate such as a marmoset could be infected with BSE, why not humans? However, this potential concern was balanced by another result Gerald Wells had obtained. Two marmosets inoculated with scrapie by the same routes had also contracted a spongiform encephalopathy. And yet, no one on SEAC believed that scrapie was a threat to human health, as years of epidemiological data had failed to produce a convincing association.

[7] A marmoset is a small primate.

Perhaps Sir Donald Acheson, the previous chief medical officer, summed it up best in a letter to a member of SEAC:

> Happily the potentially serious implication of the successful transmission by cerebral inoculation of BSE to primates (marmosets) in 1993 is offset by the fact that scrapie has also been transmitted to marmosets (Year Book 1996a).

The interpretation of this result was also influenced by the route of inoculation used to achieve transmission. While the intracerebral route had been chosen to enhance the sensitivity of the experiment, it had the double effect of allowing the results to be easily discounted due to their lack of perceived association to realistic circumstances. As in the pig experiment, SEAC deemed this route to be highly unnatural and not at all indicative of the potential for oral transmission. By viewing the transmission of BSE to a marmoset in the context of simultaneous transmission of scrapie to a marmoset, and in light of the "unnatural" route used to achieve this transmission, the committee was satisfied that this experiment, in and of itself, did not change the balance of risk.

Meanwhile, the government continued to cite the Southwood Report's conclusion that BSE was unlikely to be a risk for human health, minus the qualifying uncertainties stated by Southwood. They continued to do so despite the increase in BSE cases far above the level predicted in the Southwood Report and despite the transmission of BSE to an ever-increasing number of species. In fact, the Southwood Report was the only formal risk assessment the government commissioned on the threat of BSE to human health all the way through 1996. The rationalistic guise in which they had cloaked their decision-making had become a straightjacket rather than a crutch. Ignoring the building evidence to the contrary, the government and its advisory committee continued to follow the pathway that had first been illuminated by analogies with past experience. Subsequent

results from model systems and discrepancies in FOSPs were swept away like so many annoying insects.

Human cases of BSE?

Just in case, on an off-chance, BSE were transmissible to humans, the Southwood Committee had recommended that the DH put in place a national surveillance system to detect any transmission of BSE to humans, should it occur. This was formally initiated in 1989. Because no one knew what BSE would look like in humans, the Southwood committee recommended monitoring all cases of human prion disease. Because the most common human prion disease is Creutzfeldt-Jakob Disease (CJD), the division created to fulfill the Southwood committee's recommendation was named the CJD Surveillance Unit.

As luck would have it, a reputable British neurologist, Dr. Brian Williams, had conducted a national survey of CJD in the beginning of the 1980s. Like all successful scientists, Williams relied primarily on a precocious student for the nuts and bolts of his research. This student was Robert Will. During the study, Robert Will visited hundreds of patients with classical CJD in order to characterize the course of the disease.

Will and Williams found that CJD occurred in England at an incidence of 1 in a million, similar to the rate of CJD in other parts of the world. They found no evidence of a relationship with the occurrence of the disease and particular eating habits. This survey provided the CJD Surveillance Center with the necessary background information to monitor the disease and detect an increase, should it occur. It also provided the center with the perfect director, in the form of the previous student, now practicing neurologist,

Dr. Robert Will. No clinician in Great Britain was more familiar with the disease, and the symptoms it can cause, than he.

Will was paying particular attention to cases of CJD in people whose occupations might lead to greater exposure to BSE. Theoretically, such individuals would have a greater chance of "catching" the disease, should it prove to be transmissible to humans. It was through the surveillance unit's efforts that Will first identified two cases of suspected CJD in dairy farmers. While the first case had been dismissed as a chance occurrence, the second one triggered an emergency meeting of SEAC in July of 1993.

By January of 1995, a third person working in the agriculture industry was suspected of harboring CJD. He was a 54-year-old man who had worked as a laborer on the same dairy farm since 1955. Three cases of BSE had been confirmed on this dairy farm. While transmission studies utilizing brain material from the first two farmers dying of CJD had been injected into mice to check for transmission, the results were not expected for another year or two. Many on SEAC felt that transmission studies should be initiated with brain material from the third farmer, but each transmission test from humans to mice cost a quarter million pounds and the Medical Research Council (MRC) balked at paying for another.

In May of the same year, a 19-year-old boy from Wiltshire, Stephen Churchill, died of suspected CJD. Upon pathological examination of his brain, this diagnosis was confirmed. By September, a case of CJD in a 17-year-old girl had been confirmed by brain biopsy as well. These cases were highly unusual due to the age of the victims.

While SEAC found these cases concerning, Will assured the members of the committee that they were not outside of the statistical norms for the disease. Nonetheless,

he suggested that transmission studies should be done in mice, in order to detect any similarities to BSE. Given the scarcity of resources for conducting transmission studies, SEAC members debated whether priority for the next set of transmission studies should be given to the recent cases in teenagers or the recent cases in farmers (Year Book 1995f). Professor Allen felt that the emphasis should be on testing the cases in farmers, as they had greater exposure to BSE and should therefore be at greater risk of contracting the disease.

Dr. Will, on the other hand, argued that it was more important to test the samples from teenagers. His argument was based on the notion that these cases bore less resemblance to sporadic CJD than the cases in farmers. As Dr. Will knew well, most patients were at or near retirement when they developed sporadic CJD. It was highly unusual to see cases in teenagers. In addition, a lengthy period of psychological disturbance preceded the development of frank neurological symptoms in these cases. And on top of this, the clinical course was longer.

Disturbing News

At a June 1995 SEAC meeting, coincident with discussions regarding farmers and teenagers with CJD, some disturbing news came to light. All along, as SEAC had been recommending appropriate practices in the rendering and meat production industry, they had assumed that their recommendations were being put into practice. They had felt confident, after their visits to slaughterhouses and conferences with government officials, that no malicious parts, those which contained the highest infectivity, such as brain and spinal cord, were entering the human food supply.

At this particular SEAC meeting, however, committee members were told that MAFF had found inadequate removal of specified bovine offals (SBOs), including brain and spinal cord, at more than 40% of the plants they had inspected (Year Book 1995c). The committee members were outraged. Moreover, they felt like they had been severely misled. The committee had given advice that beef was safe for human consumption based on the belief that all SBOs were cleanly and efficiently removed from meat before human consumption.

In particular, they had been told that the process of mechanical meat recovery (MRM), in which meat is picked or pressurized off of bone by machines, was only conducted on the vertebral column after all of the spinal cord had been removed. What they were now learning, however, was that the vertebral column entering the MRM process often contains bits or even large sections of spinal cord. These bits of spinal cord are then included in the resulting meat. SEAC learned, to their dismay, that vertebral columns from sick and injured cows, cows which were more likely to harbor BSE, were still being used to produce MRM. In exasperation, Dr. Tyrrell noted that "the key question was once again how effectively the SBO controls were being carried out" (Year Book 1995c). And yet, the committee in its official report to the ministers concluded that "the MRM process was safe and there was no reason for the committee to change its advice" (Year Book 1995c).

In November of the same year, however, the committee received more troubling news about spinal cord removal. An administrator presented an audit of slaughterhouses. Small amounts of spinal cord had been found on dressed carcasses on 17 separate

occasions (Year Book 1995j). This led to an estimate that about 0.4% of carcasses were contaminated with spinal cord.

Bob Will was appalled by this new information (Year Book 1995j). Will advised that the uses to which vertebral columns were put must now be reexamined. Kimberlin agreed. He expressed his opinion that 0.4% incomplete removal of spinal cord was unacceptable, as the central nervous system was the major reservoir of the infectious agent. Further, he raised the point that all of the advice SEAC had offered on the safety of meat for five years now might be false in light of this new information.

The anger and resentment expressed by Will and Kimberlin illustrates the problems which can occur when scientific assessment is separated from the practicalities of risk management or implementation. Tucked away in their academic research centers, Will and Kimberlin had no idea how the real world of agriculture was operating. While they had visited two slaughterhouses to view such practices, these visits were clearly engineered to present the best side of the industry. They lacked knowledge of everyday practices at these facilities, and the holes and gaps in the rules they had designed.

At first, Bob Will demanded that a complete ban should be placed on MRM. Ray Bradley, an observer from MAFF present at the meeting, expressed his concern that such action would alarm the public. Kimberlin agreed that a ban would be tantamount to "an admission that we cannot guarantee removal of two easily removed tissues" (Year Book 1995j). But he carried this interpretation to a different level: if the industry can't even guarantee removal of these two tissues, then perhaps the entire meat trade should be suspended.

Ray Bradley talked Kimberlin and Will down from the measures they suggested, stating that the vertebral column was the only real risk when it came to MRM. If a ban were recommended, he suggested, it should be limited to the vertebral columns. Clearly feeling manipulated by MAFF and other authorities, Kimberlin wondered aloud whether there was a hidden agenda to the meeting. He was reassured by other members of committee that this was not the case.

Eventually, the committee came up with a draft opinion on the matter. The statement expressed a turnaround from their previous position that MRM was safe, and they demanded that vertebral column from older cows no longer be used to produce MRM:

> In the light of the current audit reports showing failure to remove parts of the spinal cord in a small number of cases the committee expressed its grave concern. It noted the further tightening up of controls but felt that unless and until it was clear that the removal of SBO, particularly spinal cord, was now being undertaken properly in all cases it would be prudent, as a precaution, to suspend the use of vertebrae from cattle aged over six months, in the production of MRM (Year Book 1995j).

The administration had no choice but to accept SEAC's advice. By this point in time, media concern due to the reported cases of CJD in farmers and teenagers was high. The ministers wanted to be seen as doing everything possible to prevent exposure. In addition, they had long ago framed themselves as "always" following the advice of SEAC. Not doing so now would ruin this image and put their own positions in jeopardy. In effect, the government had created an efficient mechanism for hiding behind the advice of SEAC, and now they had no choice but to continue to do so. By refusing to make any decisions or enact legislation on BSE without consulting the committee first, and by claiming to always follow their advice, the government had fashioned SEAC as a

sort of protective flack jacket. Any criticism of government actions could always be deflected towards SEAC, which would have to absorb the initial blow because they had granted the advice which the ministers followed. Of course, what was left out of this carefully fashioned image was the way in which the government, both during SEAC meetings and from the sidelines, influenced the advice given by SEAC. By providing certain assurances - such as the ones regarding the removal of spinal cord, for example – members of the government provided the basis for the perception of risk through which SEAC formed its opinions and recommendations. Only by using the information provided to them by the various government bodies, however colored, could SEAC form any advice at all. This framework of communication formed a perfectly circular feed-back loop which need not have any impingement from reality. In other words, the network containing SEAC, MAFF, the DH, and later the MHS, formed an autopoetic system. It was only when this system gained surprise contact with other systems, such as the agricultural system, through unannounced audits, that the circulation and magnification of misrepresentations became clear. As a result of this intersection, a ban on the use of vertebral column in the production of MRM was made official in December, a full decade after BSE had first been recognized.

A "New Variant" of CJD is announced

On a March 8 1996 SEAC meeting, concern over cases of CJD in young adults finally came to a head. James Ironside, a pathologist who worked with Robert Will at the CJD Surveillance Unit, had been invited to describe the pathology in the eight confirmed cases under the age of 40. All of these cases had onset dates after 1994, creating a

relatively large CJD cluster in space and time. In addition to the usual spongiform change and astrocytosis of CJD, all of these cases in young adults harbored prominent stellate plaques staining positive for prion protein. Plaques similar to these had been observed in kuru, but these plaques were slightly different, bearing an almost floral appearance, like a daisy with multiple petals protruding outwards. Dr. Will and Dr. Ironside expressed their opinion that these young cases of CJD, with their unique pathology and clinical features, represented a new form of CJD. They planned to publish their results in the Lancet as soon as possible, but preferred to keep their findings confidential until then (Year Book 1996c).

John Collinge immediately concluded that there must be a new risk factor responsible for this new form of CJD, and it was likely to be BSE. In his opinion, this indicated that the existing regulatory measures needed prompt review. Others agreed. When several members suggested that increased ascertainment might have led to the discovery of an already-existing form of CJD in the population, Bob Will discounted this potential by arguing that awareness of CJD had been growing amongst neurologists over a number of years, long before BSE. James Ironside reassured everyone that the pathology he had described was entirely different from anything else in the literature (Year Book 1996c).

Within this SEAC meeting, the tables had turned. No longer did anyone express concern about the slaughterhouse workers and farmers with CJD. Attention shifted entirely to the young cases. This was partly due to the statistical oddity of CJD occurring in young adults, and partly due to the novel pathology, the peculiar "florid" plaques which were discovered. All in all, what these young people were coming down with

looked strikingly different from classical CJD. And yet, each of these cases appeared strikingly similar to each other. The ability to differentiate the disease in young adults from sporadic CJD certainly made it easier to claim that it was not simply due to increasingly efficient ascertainment, as could easily be claimed for farmers with CJD. This turn in events, this break in perception, leads one to wonder when, if ever, CJD might have been linked to BSE had a new variant with strikingly unusual pathology and age-distribution not appeared.

As agreed to during the meeting, the public was not immediately informed of this break in perception on the part of SEAC. Will and Ironside were given time to sort out the details of their investigation. The other committee members demanded that they seek adequate peer review to validate their claims before going public.

Despite the lag-time in informing the public, the public perception regarding a link between BSE and CJD was already well down the same track. The media and public had undergone a major breaking point in the latter part of 1995, when the cases of CJD in farmers and young people were reported. In effect, what had previously been a gap between public perception and the perception of the committee members was about to close. What was not yet realized was how big the backlash on the part of the public would be, and how lasting its effects.

Meanwhile, SEAC went about its business. On March 11, they paid another prearranged visit to a slaughterhouse to view the removal of spinal cord. During a meeting afterwards, members reported that they were generally pleased with what they saw and had fewer doubts about SBO removal now. At the CJD Surveillance Unit, Bob Will and James Ironside had received feedback from three neuropathologists who agreed

that they had identified a new variant of CJD. In the interim, another case of CJD in a young person was referred to the CJD Surveillance Unit and found to have a similar clinical picture and pathology as the other cases.

Within the government, much activity was occurring in response to the change in perception on the part of SEAC and the recognition of a new form of CJD in young people. In one memo circulated amongst officials of the DH, the timing of any announcement that should be made was discussed. The author of the memo projected that not releasing the information soon would increase the probability that a leak would occur, making the government look even worse:

> Every stage will increase the number of people who know, or at least suspect, that there has been a striking development in the CJD field here. There is therefore the increasing risk, as time passes, of premature, uncontrolled disclosure (Year Book 1996d).

The memo suggested that further consultation was needed with MAFF and SEAC.

SEAC met again on March 16. Bob Will updated the other members on the developments that had occurred at the CJD Surveillance Unit, including the ninth confirmed case of the new variant of CJD in a 31-year-old. Before agreeing that an announcement should be made, the committee rehashed its concerns over potential ascertainment bias. Professor Collinge argued that there had been wide media interest in BSE and CJD all throughout the 1990s, but no cases of the new variant had been identified until 1994. To him, this indicated that the disease had not previously existed (Year Book 1996e).

In addition, genetic analysis had now been carried out on 6 of the 9 confirmed cases. In no case were there mutations in the PrP gene which were known to cause a genetic form of the disease. In other words, this mini-epidemic could not be dismissed as

a familial form of the disease. All, however, were of the MM homozygous type at codon 129 of the PrP gene. As 40% of the population of the UK was also of this genetic polymorphism, this alone could not explain the development of the disease. None of the nine conformed cases had ever received growth hormone treatment or undergone neurosurgery, making it unlikely, in the estimation of Bob Will, that they represented iatrogenic cases (Year Book 1996e).

The committee concluded that the new variant of CJD represented a distinct entity, and was a cause for great concern. As there was currently no other likely explanation, they agreed that the possibility that BSE may have been the cause must be taken seriously, although no conclusion could be drawn without more data. In particular, the committee wanted to see the results of strain-typing studies in regular and transgenic mice. Only by comparing the patterns of PrP distribution and incubation period between new variant, classical CJD, and BSE, did they believe a conclusion might be reached. This, however, would take some time.

Professor Almond suggested that the committee consider a complete ban on the use of MBM on farms. As the committee had previously determined that cross-contamination of feed, and the inadvertent feeding of BSE contaminated feed to cattle, had been the likely cause of the continuation of the epidemic, he believed it might be time to eliminate this potential avenue of transmission. In addition, he noted that the results of experiments in which the effects of different rendering processes on the scrapie agent were tested had revealed that conventional rendering methods were incapable of inactivating the agent. As Almond projected:

> A ban on the use of all meat and bone meal of mammalian origin in farm animal feed would remove the possibility of new infection of cattle in the future and so

> bring the BSE epidemic to a close as quickly as possible. This would solve the animal health problem and by doing so, reduce any risk to public health (Year Book 1996e).

SEAC agreed that action should be taken along these lines as soon as possible, and recommended that the use of mammalian MBM in the feed of farm animals be prohibited henceforth.

By the end of the day-long meeting, SEAC had drafted a statement which was circulated amongst government officials. In it, they concluded that, given a thorough review of 9 cases of CJD occurring in people under the age of 40 in the last two years, the CJD Surveillance Unit:

> ... has identified a previously unrecognized and consistent disease pattern. A review of patients' medical histories, genetic analysis to date and consideration of other possible causes, such as increased ascertainment, have failed to explain these cases adequately. This is cause for great concern (Year Book 1996f).

Most importantly, they suggestion that:

> On current data and in the absence of any credible alternative the most likely explanation at present is that these cases are linked to exposure to BSE before the introduction of the SBO ban in 1989 (Year Book 1996f).

In other words, despite evidence that the SBO ban had been ineffective, as discussed at the previous meeting, SEAC publicly maintained that the SBO ban was effective and that the public should have no concern regarding the ingestion of beef after 1989. This indicates that they were likely still in denial themselves about how thoroughly they had been misled and how important this pathway could be. With the Statement finalized, SEAC adjourned, expecting to meet again on March 23rd and 24th, when further discussion and recommendations would ensue. Most of the members of the committee were headed to a TSE meeting in Paris, which would last for the next several days.

During the interim, they agreed not to share information on the new variant of CJD with anyone.

The minister of agriculture, Douglas Hogg, drafted a letter to the Prime Minister revealing his assessment of the future course:

> So far as my responsibilities are concerned it is clear that we will face a major crisis of confidence in British beef. As a consequence, we can expect consumption to fall dramatically. The beef industry is a large one with output valued in 1995 at some 2 billion pounds. Over one hundred thousand UK farmers keep cattle and thousands are also involved in the marketing and retailing sectors (Year Book 1996g).

Despite the "significant financial implications," he foresaw no other choice than to announce SEAC's conclusions because of the fear that a leak would cause greater harm.

On the day before the announcement of a new variant of CJD and its potential link to BSE, a meeting was held between the upper officials of MAFF, the DH, the chairman of SEAC, and the Prime Minister. Douglas Hogg, the minister of agriculture, argued vehemently that a ban on the sale of beef and beef products derived from UK animals over 30 months must be included within the announcement in order to lessen the blow of the news. He believed that avoiding an all-out panic was contingent on erecting a perceived "firebreak" that would further protect the public (Year Book 1996h). Professor Pattison warned that SEAC might not agree that such a stringent measure was necessary, and once it had been proposed by the government it would be hard to go back. Douglas Hogg, however, argued that it was the minimum the government could defensibly do and was necessary to assuage concerns at such a dreadful announcement. The exchange between Hogg and Pattison illustrates the way in which disease management efforts may be strategically used to sway public opinion, rather than to actually control the disease.

The Prime Minister, John Major, expressed his concern about striking the correct balance between responding appropriately and over-reacting. In this vein, the Attorney General suggested that it was important to clarify what the maximum and minimum effect of the epidemic might be. According to Pattison, however, this was a difficult task. With so many unknowns looming, the potential size of the new variant CJD epidemic could not be approximated as of yet:

> ...it was impossible to predict how many more cases there might be and it might well be eighteen months before the full extent of the problem could be ascertained...It might be that there would be no more than the existing nine to twelve cases or perhaps it might be four to five cases a year for a few years and then dropping away. Equally a large number of the population could be susceptible to infection and there could be significant numbers of exposures (Year Book 1996h).

As precedent for the first possibility, he cited FSE, which had leveled off at about 60 cases. As a precedent for the latter possibility, he cited BSE, which had risen exponentially until 1993, resulting in over a hundred thousand detected cases and perhaps ten times as many undetected cases. In other words, there were two alternative analogies which could be looked to, and the choice of which analogy was more appropriate would determine the perceived efficiency of a given action.

SEAC members were called back from the TSE conference in Paris early. They commenced an emergency meeting on the evening of March 19th to consider which policy interventions they would recommend for tomorrow's announcement. At the meeting, Dr. Will informed the committee that another case of the new variant of CJD had been confirmed, bringing the total to 10. The committee agreed that they still endorsed their previous recommendation that all mammalian MBM should be excluded from animal feed. This was required, they felt, to put an end to the BSE epidemic. The

question of which further measures to recommend, however, generated more debate. The main options that were presented to them were: 1) slaughter the entire UK beef herd and restock; 2) slaughter all cattle over the age of 30 months and ban them from the human food chain; or 3) debone beef for human consumption from cattle over 30 months (Year Book 1996k).

The first option was dismissed as unnecessary. While all of the animals in the over 30 months age group could be slaughtered, it seemed to the committee that removal of the most dangerous remaining tissue, such as the peripheral nerves and lymphatics around the bone of meat, would be adequate for removing most of the risk. Thus, they recommended the deboning of beef from cattle over 30 months of age as the most sensible protection. Kimberlin, however, stressed that the nerves and lymphatics from deboning enterprises must be treated as SBO and carefully segregated from meat for consumption.

The next day, the Secretary of State for Health, Stephen Dorrell, announced the new variant of CJD in the House of Commons. As he stated:

> There remains no scientific proof that BSE can be transmitted to man by beef, but the Committee have concluded that the most likely explanation at present is that these cases are linked to exposure to BSE before the introduction of the specified bovine offal ban in 1989 (Year Book 1996i).

The "new variant" of CJD that Will and Ironside had identified came to be called, in the press and amongst scientists, simply "new variant CJD." This, in turn, was abbreviated to nvCJD, and later simply vCJD, for variant CJD.[8]

[8] It should be noted that this nomenclature represents a sort of communicative evolution, rather than an intentional process.

With the announcement of a potential link between BSE and vCJD, the performance of beef-eating by public officials only gained momentum. As Hogg assured the public:

> ...the Government's Chief Medical Officer advises us that there is no scientific evidence that BSE can be transmitted to man by beef. Indeed he has stated that he will continue to eat beef as part of a varied and balanced diet as indeed shall I. In view of what I have announced, we believe that British beef can be eaten with confidence (Year Book 1996j).

Headlines across the country blamed the government for causing an economic and humanitarian disaster. One article began with the statement:

> For 10 years the Government has insisted that humans could not catch Mad Cow Disease. Now, at last, it has seen sense...Why has it taken so long? How many thousands – possibly millions – have been put at risk while the Government dithered? (Year Book 1996l).

For his part, Richard Lacey, who had struggled for years to bring BSE to the public's attention, penned an opinion that was published in the Daily Mirror titled "You're right to be angry." In it, he described how:

> By 1989, many scientists, including myself, thought there was no reason to think that BSE couldn't infect us...But events have now proven us right. The danger facing all of us now is clear and serious – that most of us have eaten infected beef because any precautions taken by the Government have been too late, inadequate and improperly policed. Even vegetarians may have unwittingly eaten the infectious agent expected to be in the bones of cows that are made into gelatine found in numerous products such as sweets, soups, stocks and other processed foods...I hope that anyone reading this will feel angry over the way that they've been deceived (Year Book 1996m).

Headlines like "We've already eaten 1,000,000 mad cows" insinuated that there was little that could be done to prevent exposure, as much exposure had already occurred. This, however, did not prevent meat consumption from dropping precipitously, albeit for only a few months time.

In the House of Commons, the two parties began attacking each other. The opposition Labor party spokeswoman Harriet Harman, argued that "this crisis shows that this government can no longer be trusted" (Weiss 1996). During her speech, however, a conservative member of parliament interrupted with a rude statement, which, when called to task, replied that he had indeed "called the honorable lady a stupid cow" (Weiss 1996).

If the animosity within the British government was striking, it was even more so between the British government and governments of other European countries. Almost immediately after the vCJD announcement was made, several European countries responded by closing their borders to British beef imports. One of these was France, previously Britain's biggest buyer of beef. The French Agriculture Minister said the step was needed "to provide all necessary guarantees to French consumers pending complete results of European Union scientific experts in this case" (Darnton 1996a). Belgium, the Netherlands, and Sweden followed suit. According to Margareta Winberg, the minister of agriculture in Sweden, "This is a correct decision because we are working from a principle in Sweden that if it is not possible to prove that something poses no threat to public health, then we should take no risks by importing it" (Financial Times Reporters 1996). She claimed their decision to unilaterally ban imports was legal under Article 36 of Rome in European Union law, which allows a country to take action to protect the health and safety of its citizens. Meanwhile, Douglas Hogg charged these countries with taking illegal actions that were "totally unreasonable, quite unnecessary and probably illegal" under European law.

Franz Fischler, the EU agricultural commissioner, announced an EU-wide ban on British beef and cattle in order to "ringfence the problem in the UK and recover

confidence in the EU meat market" (Southey et al 1996). Fishler's stated desire to "ringfence" the epidemic ignored the incubation period of the disease, which dictated that most transmission of the disease to other countries had already occurred. Fischler said that the ban would remain "until such time as, on the basis of scientific evidence, we feel we can say the measures can be revoked" (Southey et al 1996). The British Prime Minister, John Major, responded by arguing that the ban "goes well beyond anything justified by the scientific knowledge available to the UK" (Southey et al 1996). Stephen Dorrell, the UK health secretary, called the decision "outrageous and totally unjustified. I would invite any advocate of that policy in Brussels to produce a scintilla of evidence to prove that it is justified" (Southey et al 1996). In similar language, Douglas Hogg labeled the ban "unjustified" saying that "it does not reflect the proper assessment of the risks" (Darnton 1996b).

Under pressure from Europe to do more to protect public health, and given the lack of adequate deboning facilities Britain, the government proposed the slaughter of all cattle aged greater than 30 months that had reached the end of useful life. They estimated this would amount to about 15,000 head of cattle per week, for a total figure of 4.7 million cattle over a number of years (Wolf 1996). Such a slaughter policy, however, would require the compensation of farmers. The UK asked the EU to pay 80% of the cost, which they estimated would run to $700 million in a year (Cowell 1996). While the other members of the EU expressed a desire to help, they were not sure if they could afford to help that much. Finally, the EU offered to pay for 70% of the costs of compensating farmers for lost income(Evans 1996).

On April 3, The World Health Organization convened a meeting of scientists to review the data on vCJD . While they concluded that there was as yet no proven link between BSE and vCJD, that this seemed the most likely explanation at present (Evans 1996). As Larry Schonberger of the CDC recalls:

> I actually raised my hand, at the WHO meeting in April of 1996, and said, "Until we know more about this thing, I don't think that the developed world, at least, where we have the wealth and the liberty to take certain steps, that we should no longer feed the carcasses of cattle back to other cattle. That should be stopped." That practice, or course, was still ongoing in the United States at that time, even though it had been stopped, as I recall, in the UK, by that time. And it was going on in several other places among the developed world {Ponte, 2004 #1039}.

The WHO body recommended that nations across the world should take action to prevent the feeding of sheep and cattle remains to other animals, and that all nations should improve their and CJD surveillance systems in order to be able to detect further cases of the disease. Now that they knew how detrimental BSE could be, other countries were quick to institute measures that the UK had only put in place long after the beginning of their epidemic.

All across the world, nations came under pressure from their populace to enact precautionary measures to prevent the spread of BSE to their national herds. In the United States, state agricultural officials began ordering the slaughter of cattle that had been imported from Britain. 113 such animals were identified. "We're doing this not because these animals have any symptoms," said the New York State Agriculture Commissioner, "but because we don't want to have the disease here" (Reuters 1996a). The National Cattlemen's Beef Association, a powerful lobbying group for the cattle industry, was fully in support of this action. "We want these cattle eliminated," said Gary

Weber, an animal health expert for the organization, "the stakes are too high" (Reuters 1996a).

Consumer groups, however, demanded more. Public Voice for Food called for a ban on the feeding of cattle and sheep tissue to other cattle and sheep. "Given the lack of understanding of the disease-causing agent, the difficulties of surveillance and the severity of the disese, the federal government should err on the side of caution," argued Mark Epstein, the president of the organization. Epstein wrote a letter to David Kessler, the FDA commissioner, asking for this action to take place within 18 months (Reuters 1996b).

With the pressure from consumer's groups and the weight of a WHO recommendation, in 1997 the FDA implemented a ruminant-to-ruminant feed ban in the United States. This feed ban was similar to the original ban the UK instituted in 1988. Of course, BSE continued to spread until the ban was modified to exclude the feeding of ruminant material to all other animals. Because, however, the US had no reported cases of BSE at the time, this ban was deemed a sufficient precautionary measure.

In order to put an end to the export ban, British representatives to the EU adopted a practice of blocking all votes that required unanimous approval. This stymied EU business at a time that was considered crucial to the continued existence of the multinational institution. Eventually, after Britain had blocked more than 70 votes, the other EU member countries agreed to lift the ban (Ulbrich 1996). The fate of the European Union was deemed to be more important than the concern over mad cow disease, though this concern held sway over much of the public.

The EU lifted the ban in steps. In June of 1996, three months after the ban had been implemented, the EU agreed to allow the export of cattle embryos followed by beef from herds certified as having no BSE (Ulbrich 1996). French farmers protested by setting fire to effigies of John Major and preventing a British ferry from docking. They were worried that allowing the importation of British beef again would only worsen the beef crisis spreading across Europe.

Strain-typing of vCJD

It took more than a year after the announcement of vCJD for UK scientists to obtain the first evidence through strain-tying by mouse-bioassay that vCJD was related to BSE (Bruce et al 1997). This evidence came from the NPU in Edinburgh, where Moira Bruce had inoculated three different lines of inbred mice with brain homogenate collected from three cases of vCJD. The resulting incubation period and distribution of pathological lesions in the brain (lesion profile) were compared with those obtained from the same inbred mice inoculated with BSE and sporadic CJD. Moira found that the incubation period for vCJD and BSE in genetically identical mice was equivalent. In addition, the lesion profile, a graph of the number of pathological lesions for a given area in the brain, showed almost complete overlap between vCJD and BSE. The lesion profile and incubation period were also very similar for FSE from three domestic cats, and a greater kudu and nyala that were suspected of harboring BSE. In contrast, the lesion profile and incubation period were very different for the sporadic cases of CJD, two of which came from dairy farmers. In all of the mice that had been inoculated with brain material from sCJD cases, no clinical signs had appeared until 600 days post-inoculation,

almost double the incubation period for vCJD and BSE. The lesion profile, of sCJD showed a very different distribution pattern in the brain. Moira Bruce and her group interpreted these results as further evidence indicating that vCJD had arisen from BSE and was unrelated to sCJD.

In the same issue of Nature, Collinge's group reported on experiments in which his lab had transmitted vCJD, BSE, and sCJD to a number of transgenic and non-transgenic mice (Hill et al 1997). They claimed that the resulting glycoform patterns of the prion protein, as visualized by western blot, in both the vCJD and BSE transmissions were extremely similar, while those for sporadic CJD transmissions were quite different. Such patterns were reproducible on multiple transmissions.

"Taken together," argued Almond and Pattison, "the two new sets of results complement each other and give a consistent message" (Almond & Pattison 1997). They noted, however, that it was still almost impossible to estimate the size of a potential vCJD epidemic stemming from BSE:

> To date, there have been 21 confirmed instances in the UK...The rate of new cases is not increasing, which provides some hope that the overall number will be relatively small, but it may take several years before we can be confident that this is not a period of comparative calm before a storm. Much depends on the average incubation time of vCJD: the longer the time, the higher the final figure is likely to be. At present we cannot calculate the average incubation time of BSE in humans; nor is it possible to estimate the amount of infectivity...required to infect a human (Almond & Pattison 1997).

They noted that any estimates of the potential size of the vCJD epidemic were also colored by the observation that, so far, all of the cases of vCJD had been identified in people who bore the MM homozygous genotype at codon 129, the locus of human polymorphism in the prion protein gene. While most of the predictions that had been made regarding the future size of a vCJD epidemic rested on the assumption that only

MM homozygotes could be infected, it was impossible to say, at this stage, whether and to what extent people who were VV or MV, upwards of 60% of the population, would respond to BSE exposure. As Pattison and Almond commented:

> This raises the possibility that people who are homozygous for valine at this position or who are heterozygotes (about 11% and 51% of the UK population, respectively) may be relatively resistant to infection, may be subject to longer incubation times, or may have different symptoms (Almond & Pattison 1997).

In their conclusion, Almond and Pattison harkened back to that fateful day in March when the announcement of vCJD was made:

> The UK government's decision, in March 1996, to point publicly to a probably link between BSE and vCJD was taken on the advice of the Spongiform Encephalopathy Advisory Committee (SEAC) – of which we were and are members...At the time, the evidence connecting the two diseases was relatively slight and SEAC's advice was rightly questioned in both the scientific and popular press. Only rarely in such circumstances can science offer definitive evidence quickly, and decisions have to depend on the weighing of uncertainties. More such judgments may yet be required concerning BSE and human disease (Almond & Pattison 1997).

Given how dramatically the recognition of vCJD changed the landscape of risk perception with relation to BSE, one wonders how contingent this observation was. Might it have been missed, had not a system been in place with the purpose of detecting it. I asked John Wilesmith whether he believed that the vCJD cases would have been recognized as early as 1996 if the CJD surveillance system had not existed:

> No, that was an absolute key, and it was a really good thing. They were working on a shoestring. Their project was embarrassingly underfunded. Although it probably hasn't resulted in a lack of studies, I think one year they had 15,000 pounds to do the epidemiology, and I'm sitting there with probably 100,000 or something all told. But, it worked, and they got it and extended it to the Europeans and others. But I think to have spotted it beforehand, without that, the probability must be pretty low {Ponte, 2003 #1001}.

But, after all, what is now termed "vCJD" and viewed as a separate entity from CJD was first viewed as CJD occurring in young people, perhaps with an atypical type of

pathology. Whether one differentiates vCJD from CJD, or whether one classifies them together, depends partly on one's purposes and one's point of view. The contingency of this designation is illustrated most clearly in the way Clarence Gibbs describes his choice in nomenclature:

> I prefer to call it an atypical form of Creutzfeldt-Jakob disease, which to my way of thinking is more descriptive. I don't know a single human disease that doesn't vary in clinical presentation and pathological response to that infection. I'm open to being educated, but I don't know one, and so I always tell my students learn to diagnose the atypical and you'll never miss a typical (Blood Safety Advisory Committee 1998).

Conclusion

The uncertainty surrounding the future course of BSE stemmed from several sources. First of all, it was a newly described disease. In the beginning, it was unclear whether it was even caused by an infectious agent. As this understanding settled, the insidiousness of early symptoms, the novelty of the infectious agent, and the inability to detect infection without sacrificing the animal impeded the study of the disease. Most of all, the temporality of the disease, with its incredibly long and largely unknown incubation period, dictated the impossibility of securing an estimate of its magnitude. The incubation period also ensured that measures taken in the present would not have an effect until months or even years in the future, making it difficult to determine the effectiveness of disease management policies in a timely manner.

In this context of uncertainty, certain metaphors provided the raw material for imagining future potentials for BSE. The metaphor with scrapie, and concern for similar economic repercussions, at first led MAFF officials to withhold information on the disease. As scrapie had generated economic hardship for the British sheep industry,

MAFF officals worried that BSE would trigger an economic backlash against British cattle. These early actions inhibited John Wilesmith's ability to identify and count the number of BSE cases, leading him to underestimate the size of the epidemic in his efforts to construct Future Oriented Statistical Projections (FOSPs).

Scientists and veterinarians within MAFF, however, insisted on pursuing the scrapie metaphor and providing information about the potential analogy between scrapie and BSE to their professional colleagues and eventually farmers. While it was the metaphor with scrapie that led John Wilesmith in the direction of examining meat and bone meal as a potential vehicle for BSE, it was also the metaphor with scrapie which prevented him from seeing the potential for BSE to have arisen from another source. It also led him to believe that BSE was primarily spread by the ingestion of scrapie-contaminated feed, rather than BSE-contaminated feed. The neglect of this potential, in turn, led Wilesmith to fashion a Future Oriented Statistical Projection (FOSP) that represented the future of the BSE epidemic as manageable. This FOSP became a major actant in the debate between MAFF and industry officials over whether a grace period should be allowed for the implementation of the ruminant-to-ruminant feed ban. With "no overriding veterinary concern" to demand immediate implementation, a grace period was granted.

When the Southwood Committee met to assess the risk of BSE spreading further amongst cattle, metaphors with other TSEs provided the raw material for assuaging concerns about both of these potentials. First of all, John Wilesmith's projection of the future course of the epidemic, which showed the disease continuing at a constant rate rather than increasing, which was based in turn on the metaphor with scrapie, convinced

the committee that there was little risk of BSE becoming a scourge to cattle. Second, a metaphor with Transmissible Mink Encephalopathy, a TSE of mink suspected to be contracted through the eating of scrapie-contaminated sheep, and which rarely transmits from mink to mink, convinced the committee that BSE was unlikely to spread from cattle to cattle, limiting the size of the epidemic. This was the basis for the Southwood Report's statement that it was likely for cattle to be a "dead-end host."

When the Southwood Committee met to assess the risk of BSE transmitting to humans, the dominant metaphor with scrapie provided further reassurance. Despite the co-existence of humans and sheep with scrapie for over two centuries, there was no indication that scrapie could be transmitted to humans. Likewise, no human had ever become infected with Transmissible Mink Encephalopathy, a putatively scrapie-derived TSE of animals. With these metaphors in mind, the committee deemed it unlikely that BSE would transmit to humans, though they did add that the implications would be dire if they proved to be wrong.

In presenting the Southwood Report to the officials in MAFF, Southwood was careful to communicate the uncertainties and the dependence on analogies, especially with scrapie, that their conclusions involved. Despite these caveats, government scientists and officials continued to cite the conclusions of the Southwood Report for well over a decade after the BSE epidemic began. Even more amazingly, they continued to cite them with an aura of certainty and dependability. The ability of governmental scientists and officials to overlook the uncertainties inherent in Southwood's conclusions reveals an ability to marginalize uncertainty that has previously been remarked upon by Brian Campbell (1985). In his study of a debate over whether to drill for oil in a certain region,

Campbell found that while uncertainty was acknowledge by both sides of the debate, one's view of the ease with which such uncertainty could be managed, and therefore marginalized, depended on whether one trusted the relevant institutions to do so appropriately. To the side which opposed drilling, the potential uncertainties were viewed as unmanageable. For the side which favored drilling, the uncertainties were viewed as manageable by the institutions involved. Because the relevant government scientists and officials were all operating within the structure that was charged with managing the BSE risk, they tended to view the uncertainties as manageable. This allowed them to overlook effect such uncertainties might have on the outcome of the BSE epidemic and to present Southwood's Report and Wilesmith's projections as more certain than they really were.

Through this mechanism of marginalizing uncertainty, the projections provided by Southwood and Wilesmith become major actants in the government's efforts to present the epidemic of BSE as manageable and its risk to humans as negligible. It even allowed them to persist in their performance of manageability and recourse to FOSPs despite the continued growth in the BSE epidemic and transmission of BSE to other animal species.

Even more than the Southwood Committee, SEAC maintained close ties of communication with the government agencies which they advised. Hardly anything was published by these committees without first being reviewed and commented on by government officials. The committees often caved into suggestions made by government officials as to the wording of statements and always tailored their statements with the media response in mind. In this way, the putative independence of SEAC disintegrated. As Daine Vaughan has previously shown, the institutional structure of such committees

can have a profound effect on the role that science plays and the way in which it plays it (Vaughan 1990). For example, in the Challanger launch decision, there was a strong incentive, based on the necessity of good communication, for the regulatory body to maintain good relations with the regulated and thus overlook errors (Vaughan 1990). Such interdependence, which exists between the UK government and its advisory committees, links the success of the two bodies, making disagreement almost impossible.

The transmission of BSE to other animals through experimental means, such as intracerebral inoculation, is a good example of the effects of the interdependence that developed between SEAC and the UK government. While some members of SEAC initially interpreted the results of the experiments as indicating that BSE could have a greater host-range than scrapie, and thus might be a concern to human health, government officials persisted in arguing that the model system employed was not a good analogy for reality. These technocrats maintained that on the farm or in the field, animals such as pigs would never be injected with infectious material directly into their brain. By questioning the metaphorical fit between the model systems employed and the actual transmission systems of concern, they were able to downplay the results of such experiments at SEAC meetings. This highlights the negotiability of the correspondence between model systems and reality, and the ease with which model systems, if the metaphorical fit is deemed weak, may be discounted. It also illustrates the important effects of political interdependence on the evaluation of scientific results by putatively "independent" advisory committees.

Variant CJD (vCJD) was first recognized by the CJD Surveillance Unit due to its resemblance to CJD – the spongiform change, astrocytosis, and staining with antibodies

to PrP. Without these similarities to other members of the TSE class, it is unlikely that vCJD would have come to the attention of the Surveillance Unit at all. In other words, it was the metaphorical fit between vCJD and other TSEs which allowed it to be perceived at all. If vCJD had appeared in some entirely unique form, devoid of spongiform change, it might have been missed altogether.

It was the notable differences between vCJD and CJD, however, which finally led the CJD Surveillance Unit, SEAC, and the government to admit that there could be a connection between vCJD and BSE. Variant CJD affects much younger individuals and it produces striking floral plaques in the brains of its victims. The differences between CJD and vCJD, which could only be recognized as differences given the acceptance of an underlying similarity, drove SEAC to conclude that vCJD represented something new. A connection between vCJD and BSE was postulated even though the pathology of BSE and vCJD were far from identical. BSE animals did not harbor the floral plaques of vCJD victims.

Because of the differences between the pathology of BSE and vCJD, and the fact that no animal TSE had been known to transmit to humans before, scientists eagerly awaited the results of strain-typing studies to decipher the relationship between the two. The idea behind strain-typing studies is to look for similarities in the pathology between the two diseases on the same genetic and physiological background. When both diseases where transmitted to the same lines of inbred mice, similar patterns of pathology were noted by Moira Bruce. It was this metaphorical similarity in the patterns upon the same canvass, so to speak, that led to the eventual acceptance in the scientific community of a connection between vCJD and BSE.

Thus, we can see the way in which the perception of BSE risk was driven by the negotiated application of certain metaphors and not others. These metaphors, in turn, became the basis for projections, both positive and negative, that might attend to the future of BSE. Many of these projections, such as Wilesmith's initial prediction of the course of the epidemic, later ratified by the Southwood Committee's Report, took the form of Future Oriented Statistical Projections (FOSPs). These projections took on an agency and power far beyond what was merited, given the uncertainty surrounding BSE at the time, and became a major force in the management of BSE risk. The FOSPs, which had been constructed through metaphors with scrapie and other diseases, both constrained and made possible action in the present, action which then partially produced the future of BSE. In this way, a circular loop of temporal determination, circumscribed by metaphors, bounded the potential for action in the present.

The way in which the contours of possible action are bounded by our experiences with the past, despite the cloak of rationality provided by FOSPs, has implications for the way our society manages all sorts of uncertainties and risks. The story of the British government's reaction to BSE and its ill-fated efforts, at least in the early days, to stem the tide of this epidemic illustrate the false sense of security that can be induced by reliance on a cadre of rationalistic systems for managing risk. These include not only the production and reliance on FOSPs, but also the dependence on putative "expert" advisory committees for decision-making capabilities, the issuance of official evaluations and recommendations from these committees, and reports such as those produced by the Southwood committee. The effect of all these apparently rationalistic endeavors is to make risk management appear more formal and logical than it really is. Thus, the public

is surprised and upset when they find out that the government and its advisors are wrong, that the risk has not been contained, and that the future is uncertain. Like the French, surprised that their rationally designed Maginot line failed to protect them, the British were shocked when BSE failed to listen to reason, the advice of SEAC, and the government ministers, deciding it would ignore the species barrier after all.

Ch. 3 – The construction of a CJD blood risk

Even before vCJD appeared, concerns were raised by the public health and hemophilia communities in the United States about the prospects of CJD transmitting through the blood supply, and particularly plasma products. The hemophilia community was still reeling from the deaths of over half of its ranks from inadvertent transmission of HIV through Factor VIII and other clotting products produced from human plasma. These products, when they first appeared, had been viewed by the community as a modernist dream come true. They allowed hemophiliacs to live almost normal lives, completely untethered from the hospital. It took a relatively large number of HIV transmissions through blood and plasma products to convince the FDA, the plasma products industry, and relevant members of the hemophilia advocacy community that the products from which they derived their pleasure were, indeed, a terrible threat.

The response to CJD, with AIDS as the most relevant metaphor to turn to, was almost the mirror image of the public health and hemophilia community's response to AIDS. Having endured a previously unfathomable tragedy, any infectious agent present in the blood was now viewed as a grave danger. With the analogy to AIDS in mind, hemophilia advocacy groups pressured the FDA and other agencies for strict risk management measures in regards to CJD. But with no cases of CJD transmission by blood ever detected, the relevant agencies had little evidence on which to base such risk management measures. In an effort to maintain the guise of rationality, they turned to their advisory committee on Transmissible Spongiform Encephalopathies (TSEs). This advisory committee, also at a loss as to how the risk of transfusion transmission should be

regulated, advised excluding and withdrawing donations from individuals deemed to be at a greater risk of developing CJD.

A year passed by, however, and there was still no evidence of CJD transmission by blood. When vCJD appeared in the UK, the newness of the disease, its apparent difference from CJD, and its unknown properties allowed vCJD to eclipse any concerns regarding CJD transmission by blood. As a result, the US Department of Health rescinded its previous CJD blood transfusion management policies, in place for only a year, and sought to replace them with vCJD risk reduction measures. With little evidence on which to rationally base such measures, the FDA, once again, turned to their TSE Advisory Committee. The committee, recognizing the bind it was in and the darkness that surrounded this disease, sought to procure rationality in the only form that seemed possible – by developing a Future Oriented Statistical Projection. This FOSP, based on the statistics from a survey on the travel habits of blood donors, but little or no actual data about the disease in question, became the only basis for decision making. While the actual meaning of the FOSP was almost uninterpretable, the numerical terminology of the FOSP allowed the committee to compartmentalize their uncertainties and to feel reassured that they were making decisions in the most rational way possible. The reality is, though, most committee members realized there was absolutely no way to rationally design such risk mitigation measures and that, in effect, they were merely taking a stab at limiting the exposure of certain groups to a potentially harmful disease. Nonetheless, this FOSP remains the standard rational given by the FDA and other DH bodies for the current disease management strategies.

A Brief Introduction to Blood Transfusion

In order to comprehend the series of events and debates surrounding the risk management measures taken to prevent the transmission of CJD and later vCJD through blood, there is a certain amount of taken-for-granted information about blood transfusion that must to be conveyed. In order to avoid reifying it too much, I will try to present it within a historical context that brings to light some of the contingencies and specificities of the knowledge.

If whole blood is left sitting for several hours, it separates into a red clump at the bottom of the jar, a clear amber liquid, or plasma on top, and a thin, whitish layer in the middle. While John Elliot was not the first to suggest plasma as a treatment for shock, he became one of the most vocal, and effective, spokespersons for it (Starr 2000). Through his promotional efforts, he initiated the establishment of nodes for the production of plasma and networks of supporters and distributors. John's entrance into the field illustrates the contingency of science. He was directing the laboratory section at Rowan Hospital in North Carolina, when a man who had been stabbed in the heart was brought to the emergency room. The hospital's blood bank did not have a match for the patient, who was almost sure to die from shock. John had several bottles of plasma which had been sitting on the shelf for over a month. Given the circumstances, Elliot took the liberty of infusing the patient with the plasma. Three weeks later, the man went home. There had been no immune reaction, and he seemed to have been miraculously brought back to life.

Edwin Cohn, a protein chemist, was convinced that if he could isolate the protein that was associated with the anti-shock characteristics of plasma, he could cut down on

contamination and increase the effectiveness of the treatment (Starr 2000). Beginning with plasma, Cohn searched for methods to separate and stabilize various proteins. Through much tinkering, Cohn's team discovered that after a series of five 'fractionations' - in each one adding ethyl alcohol, centrifuging, and then removing the pellet at the bottom of the test tube - they were able to obtain a relatively purified protein with immense osmotic strength (ability to absorb fluid), the property they were looking for. The protein that they had purified, albumin, was much more effective at preventing shock than plasma. Because it could be stored as a liquid in a small vial, it was much less prone to contamination than plasma. Albumin became a staple for the treatment of shock throughout the rest of the war.

Before the war was over, Cohn and his team discovered that an early fraction harbored concentrated immunoglobulins, or antibodies, against infectious diseases (Starr 2000). These became useful in treating outbreaks of measles and mumps in military camps during the remainder of the war. After the war was over, certain immunoglobulins that were active against polio were purified. These were used to treat and prevent polio up until the development of the Salk and Sabin vaccines. Nowadays, immunoglubulins, in the from of an intravenous infusion (IVIG), are widely distributed. They are used to treat immunodeficiency syndromes as well as a variety of auto-immune disorders, including Guillain-Barré Syndrome, Myasthenia Gravis, and Multiple Sclerosis. Specialized antibodies to treat and prevent disease are fractioned from people with known immunity to tetanus, rabies, herpes zoster, and hepatitis B.

After the war, Cohn turned his attention from plasma to the other two layers that settle out in blood - the clump at the bottom, which was discovered to contain primarily

red cells, and the thin white layer in the middle, often referred to as the "buffy coat," made up mostly of platelets and white cells (Starr 2000). He figured blood could be used more efficiently if each unit collected could be separated into its individual components. Then, these components could be used to treat the conditions to which they are most suited. Working with centrifugation, a physical process by which a mixture is spun and the components of the mixture settle at different levels depending on their density, he developed a continuous flow apparatus that was able to separate these layers efficiently.

"Component therapy" soon became a staple of blood transfusion services. Whole blood was collected and then centrifuged and separated into units of red cells, packed platelets, and plasma. Red cells, the oxygen carrying component of blood, are the treatment of choice for acute blood loss, whether due to trauma, surgery, or hemorrhage, or to correct anemia. Platelets form clots when there is tissue damage, preventing blood loss. Patients with leukemia or other malignancies, as well as other conditions which lead to a deficiency in platelets, are treated preemptively with platelets to prevent severe bleeding episodes. Fresh frozen plasma, or unfractionated plasma, has many uses. These include restoring blood volume in burn victims, supplementation of clotting factors following massive red cell transfusion, and replacement therapy for rare clotting conditions. Very little blood is transfused as whole blood anymore. Whole blood does not last as long as the separated and treated components, limiting its flexibility and utility

Following the war, new uses were found for fractionated plasma as well. The clotting cascade that initiates the formation of platelet clots involves a number of proteins, all of which are found in the plasma. The absence of any of these proteins can disrupt the clotting process, as in hemophilia. There are many different types of

hemophilia, depending on which protein in the clotting cascade is missing. The most common is Hemophilia A, caused by an absence of Factor VIII.

In Cohn's laboratory, it was discovered that the first fraction, the one enriched for fibrinogen, contained many of these clotting factors. However, it was not pure enough to be effective in therapy for hemophilia. Then, in 1965, a researcher at Stanford, Judith Graham Pool, found that she could produce a substance rich in Factor VIII by freezing plasma and slowly thawing it. She called this substance cryoprecipitate (Resnik 1999). It had ten times the clotting power of plasma. It could be produced cheaply and easily through the processing of pools of plasma from five or ten donations. With it, the lifestyles of hemophiliacs changed forever (Resnik 1999). They were able to store cryoprecipitate in their freezers, decreasing the time between bleeding episode and injection.

In the late 1960s, further tinkering at the Hyland laboratories led to the development of a method for producing a more effective, highly concentrated form of Factor VIII (Starr 2000). This method began with the production of cryoprecipitate from hundreds, and later tens of thousands, of plasma donations. This cryoprecipitate was then redissolved, chemically treated, filtered, and centrifuged to produce a concentrated product that could be carried in a small, insulated ice bag. The lives of hemophiliacs were revolutionized again. They could now travel with their treatment, enabling them to live almost normal lives. Hemophiliacs were encouraged to inject themselves with the new treatment "early and often" in order to avoid bleeding episodes (Starr 2000).

Now for a word on short-hand terminology. In the following section, I will use "blood components" to refer to the units of red cells, plasma, and platelets that result

from the initial separation of whole blood. I will use "Plasma products" or "plasma derivatives" to refer to the clotting factors, immunoglobulins, albumin, and other proteins that result from the plasma fractionation process. "Blood products" will refer to both blood components and plasma products. This usage largely parallels that of the blood banking and plasma fractionation industry, though I am trying to be slightly more specific to prevent confusion.

While whole blood donations can be used to produce all of the aforementioned blood products, certain products can be preferentially collected and separated simultaneously. Recall that the "buffy coat," the thin white layer in separated blood, is composed of mainly platelets and white cells. While the platelets have a use in preventing and treating bleeding episodes, the white cells have no practical use in transfusion therapy. Moreover, they have been blamed for a variety of ill-effects, including febrile reactions, discomfort, and extended hospital stays. While white cells are largely removed in the processing of blood, some of them remain in all of the components mentioned. It is important to realize that while "red cells" is the name given to a unit which contains mostly red cells, a unit of "red cells" may also contain white cells, plasma, platelets, and bits of other blood components. As Peter Bennett, who conducted an assessment of the TSE risk in blood for the department of health, once said at a conference: "What actually does a unit of red cells, or platelets, or plasma, or whatever, actually contain? That actually turns out to be less straightforward than one at first imagines."

White cells, or leukocytes, form part of the immune system. Leukocytes are actually made up of multiple different cell-types, mostly lymphocytes and monocytes. The lymphocytes are commonly subdivided into two classes - those which produce

anitbodies are referred to as B-cells, and those which kill infected cells or activate other parts of the immune system are called T-cells. Monocytes are responsible for phagocytosing, or ingesting, bits of cells and cellular debris. On their cell surface, they present regurgitated bits of this debris to the B and T cells. If the material presented is recognized as "foreign," it triggers an immune response. By triggering an immune response, white cells can lead to unpleasant, and sometimes harmful, effects when transfused.

Because of the side-effects caused by the transfusion of white blood cells, methods have been developed to further remove them from blood components. The process of "leukodepletion" generally involves simple filtration. A variety of companies produce filters which can be used for this process. Some of these filters can be used at the bedside, while transfusing the components. Others can be used during the collection process or immediately afterward. If too much time goes by between the collection of blood and leukodepletion, many of the white cells will have broken into smaller fragments, making the process of filtration less effective at removing them.

The AIDS Metaphor

In many countries, the event of HIV/AIDS formed an import component of the sensitizing frame for considering both CJD and vCJD in terms of the possibility that they might transmit via blood transufusion. The response to HIV/AIDS was, in turn, shaped by a sensitizing frame that included experiences with hepatitis B and swine fever.

The way in which HIV/AIDS contributed to the sensitizing frame differed from country to country. This is because each nation had a unique experience with HIV/AIDS,

and the contours of this experience became the important factor in shaping the sensitizing frame for CJD and vCJD. To illustrate this, I will provide a description of the consideration of CJD and vCJD as transmission risks to the blood supply in both Britain and France.

Events other than HIV/AIDS, of course, form part of the sensitizing frame through which iatrogenic exposure of CJD and vCJD are considered. One of these is Britain's recent experience with BSE, and the handling of this disease by the British government and the European Union. Previous events involving CJD iatrogenic transmission, such as the highly publicized case involving EEG electrodes in Switzerland, as well as the mini-epidemics of CJD transmission by pituitary derived human growth hormone (Hgh) and dura mater transplant. In addition, the epidemic of kuru in New Guinea was incorporated into this metaphorical frame.

AIDS and blood transfusion in the United States

Dr. Bruce Evatt was in charge of the CDC's surveillance of hemophiliacs when, one afternoon in January of 1982, he received a worrisome phone call (Starr 2000). It was a hematologist whose patient, a man who had suffered from hemophilia for decades, had died of pneumocystis carinii pneumonia (PCP). PCP was a rare disease in the U.S., affecting less than 100 people each year. It tended to attack those with severe depression of the immune system, such as cancer patients receiving chemotherapy. Recently, however, there had been a spike in PCP cases, mostly occurring in gay men (MMWR). Kaposi's Sarcoma, another ailment that affects primarily immunocompromised patients, was also on the rise in this population (MMWR). There seemed to be some sort of

underlying immune deficiency present, but as to what was causing it, controversy flourished. Some believed it was due to the ingestion of drugs such as "poppers" which were popular among certain segments of the homosexual population. Others said it was a weakening of the immune system brought on by anal intercourse. Still others believed it was due to the synergistic effects of gonnorrhea and syphilis, two sexually transmitted diseases (Epstein 1996). The CDC had first published on this strange immunodeficiency syndrome only seven months prior in MMWR, when they noted the occurrence of pneumocystis in 5 previously healthy homosexual men. Since then, the number had grown to almost 100, and there was still no good explanation.

When Dr. Evatt learned of the first case in a hemophiliac, he strongly suspected an infectious agent. He had witnessed the spread of hepatitis through the hemophilia population, which was still continuing at an alarming rate, so he knew how easily an infectious agent, one that was blood borne, could affect the community. With only one case, however, it was difficult to convince his superiors at the CDC of this hypothesis. Half a year later, however, two more hemophiliacs developed PCP. He quickly set to work. First, he published a report in the MMWR (July 16, 1982) describing the 3 hemophiliacs with the syndrome, noting that this "suggests the possible transmission of an agent through blood products." Next, he convened a meeting of the Public Health Service.

July 27, 1982, members of the various relevant branches of the PHS (NIH, FDA, CDC), representatives from the National Hemophilia Federation (NHF) and gay rights groups, as well as the New York Department of Health and the blood industry, met to discuss "the significance of the occurrence of opportunistic infections with pneumocystis

carinii pneumonia in three patients with hemophilia (1982). Evatt explained to those present why he believed this immunedeficiency syndrome was caused by a virus and why he believed it could be spread by the blood. While those present agreed that, "The occurrence of PCP in three patients with hemophilia is disturbing" (1982), they, and especially the representatives from NHF, wanted to emphasize the value of treatment. It was noted that:

> Almost all patients regularly receiving Factor VIII or cryoprecipitate develop hepatitis B and non-A non-B infections. These products have been shown to transmit these infections. Because of the freedom and reduction of suffering permitted hemophilia patients by Factor VIII concentrate, the products' benefits are perceived by patients to vastly outweigh currently known risks (1982).

In other words, the NHF represented hemophiliacs as willing to take risks in order to enjoy the benefits of therapy.

While the cause remained unknown, there was an agreement to term the new disease Acquired Immune Deficiency Syndrome (AIDS) (1982). Conference participants concluded that there was a need to determine if certain blood products, particularly Factor VIII, were indeed risk factors for AIDS. To do so, they recommended active surveillance, laboratory studies to determine the cause, and the development of practical interim techniques to decrease or eliminate any infectious risk. What was interpreted as consensus by the CDC, and represented as such in the minutes, would prove to be short-lived.

By September 1982, 60% of those who had shown symptoms of AIDS only a year earlier had died. Whether AIDS was caused by an infectious process or not, however, was still a matter of debate. Cases of immunodeficiency in hemophiliacs were ascribed by many, including a few high-profile physicians, to an "AHF concentrate effect"

(Leveton et al 1995). The number of cases, at least early on, compared to the number exposed to blood products was relatively small. With little in hand, an attitude of skepticism and complacency prevailed on the part of many scientists and medical professionals regarding a potential threat to the blood supply.

In December, a 20-month old infant, who had received multiple transfusions after birth, mostly of platelets, developed the disease. This case triggered national headlines due to the age of the victim. The other parameters of the case, however, are what jolted the CDC. To begin with, this child was the first to have developed the disease after the transfusion of blood components, rather than plasma products. Second, if the disease were an infectious agent, then the incubation period could be quite long (almost two years). This was an ominous sign, because a disease with a long incubation period can spread far and wide before anyone recognizes it has done so. By that time, the original three hemophiliacs with AIDS had succumbed to death. Shortly thereafter, several children of parents who were either prostitutes or IV drug users developed the disease. When evidence of heterosexual transmission first appeared in January of 1983, CDC was ready to lay the infectious hypothesis on the line, stating that, "epidemiological observations increasingly suggest that AIDS is caused by an infectious agent." Above all, it was the similarity in the patterns of transmission of AIDS and hepatitis B and the common latency period of both diseases that led to this conclusion. As Hepatitis became a guiding metaphor for AIDS, this enabled the gradual transference of a paradigm – the paradigm of long-incubation period infectious disease – from Hepatitis to AIDS.

The use of the hepatitis metaphor had implications for how hemophiliacs and hemophilia advocacy groups viewed the potential threat of AIDS. Hemophiliacs had been

celebrating the "golden days", their first opportunity to enjoy a fairly normal lifestyle, since the advent of Factor VIII fractionation in the 1965 (Resnik 1999). According to Susan Resnik:

> Resignation to the possibility of contracting heptatitis as 'a necessary evil,' albeit rarely life-threatening, seems to have become part of the mindset shared by both the provider and the consumer. The dramatic changes in lifestyle and life span offered by the use of pooled plasma concentrates made the risk of hepatitis seem a small price to pay in the minds of most of the physicians and patients who had experience the 'bad old days' (Resnik 1999).

Perhaps this is why the National Hemophilia Foundation, upon learning of AIDS, advised hemophiliacs to continue using Factor VIII as before:

> The NHF has recently recognized, and is concerned about, the fact that public media coverage of AIDS is causing some patients to abandon appropriate use of blood products because they fear contracting AIDS. The NHF AIDS task force considers this to be an inappropriate response and urges hemophiliacs to maintain the use of clotting factor in their treatment of hemorrhagic episodes (NHF 1983).

A public meeting on the disease was held at the CDC headquarters in Atlanta on January 4, 1983. Representatives from many of the same organizations which had attended the meeting in July of 1982, as well as additional representatives from the blood and plasma products industry, city health departments, and members of the public, packed the room (1983c). Dr. Evatt presented the statistics for AIDS in hemophiliacs. He talked about how the shape of the curve was looking more and more like the one in homosexuals (Starr 2000). The growth rate of cases in homosexuals had already reached a point where it was doubling every month. The curve for hemophiliacs seemed to be gathering momentum in a similar manner. He explained that a disease with these trends, that appears suddenly and spreads rapidly, usually indicates the beginning of an epidemic. He suggested that, to stem further transmission to hemophiliacs, gays and other "at risk" groups be deferred from donating blood. He framed the importance of acting

quickly in terms of the long incubation period, which could mask the disease while allowing for its spread. Dr. Tom Spira, also of the CDC presented on the relationship between AIDS and hepatitis B (Starr 2000). He explained that nearly 90% of AIDS sufferers tested positive for exposure to hepatitis B. With this correlation, he suggested hepatitis B could be used as a surrogate marker for screening out potential AIDS donors.

Uproar followed. The blood bankers argued against the use of a surrogate Hepatitis test to defer donors. First, they worried that such a measure would impact the supply of blood, leading to shortages. Secondly, they argued it would be difficult to explain such exclusions to donors. In the context of growing AIDS hysteria, they maintained that the psychological effect on such donors could be devastating (Starr 2000). Dr. Oscar Ratnoff, a hemophilia specialist, suggested that in the light of the uncertain danger AIDS represented, the use of Factor VIII should be curtailed or perhaps suspended (Starr 2000). The NHF argued vehemently against this suggestion, as it would impede the ability of hemophiliacs to lead a normal lifestyle.

Some attacked the proposed measures by disputing the underlying theory that AIDS was caused by an infectious agent. Immune deficiencies, they contended, could have many causes. Dr. Aledort of the NHF explained that it "could be doing something through transfusion that causes it...or something in the patients' immune complex" (Starr 2000). He believed that in another 6 months, the idea of an infectious agent would be thrown out the window. At this suggestion, Dr. Francis of the CDC's hepatitis lab, pounded his fist on the table and shouted: "How many people have to die? Is three enough? Is six? Is ten? Is a hundred enough? Just give us the numbers so we can set the threshold!" (Starr 2000).

While the meeting in Atlanta certainly did not lead to consensus, it did stimulate many of the nation's blood banking organizations, the AABB, CCBC and the ARC, normally at odds with each other, to band together and initiate a "Joint Task Force On AIDS." They issued a statement on January 13, 1983, meant to guide the industry in their approach to AIDS. Their opening statement, while lending credence to the potential transfusion risk of this new disease, represented this potential in uncertain and vague language.

> The predominant mode of transmission seems to be from person to person, probably involving intimate contact. The possibility of blood borne transmission, still unproven, has been raised. This latter impression is reinforced by eight confirmed cases in hemophiliacs treated with AHF concentrate, by a case in a newborn infant who received 19 units of blood components, one of which was from a donor who later died of AIDS, and by fewer than 10 unconfirmed case-reports in other transfusion recipients. No agent has been isolated and there is no test for the disease or for potential carriers (1983b).

Both the idea of an infectious etiology and the potential for transfusion transmission were presented as uncertain. Based on the "insufficient data" at hand, however, they recommended extending educational campaigns to physicians to balance the decision to use each blood component against the risks of transfusion, emphasizing autologous blood transfusions as an alternative, donor screening for symptoms of AIDS, and the discontinuation of recruiting efforts amongst high-risk groups. These efforts were framed as precautionary measures. The task force stopped short, however, of recommending any kind of screening or questioning based on sexual preferences, deeming it "an invasion of privacy" which "can be justified only if it demonstrates clear-cut benefit." As they had already framed the potential of a transfusion risk and the characteristics of the disease itself as shrouded in uncertainty, this statement effectively delineated the boundaries of action: for if there is no clear-cut risk, there can be no clear-cut benefit. In addition, the

task force warned bankers and fractionators: "We do not advise routine implementation of any laboratory screening program for AIDS by blood banks at this time" based on the potential detriment to the blood supply. Their concluding statement that "until more information is available, we believe that the measures outlined above are prudent and appropriate" reinforced the boundaries they had already drawn around acceptable action. Uncertainty, therefore, became both a means of legitimizing action as well as constraining action.

Upon consideration of whether the deferral of high risk donor groups would decrease the transmission of AIDS, the Dr. Cumming, the author of an ARC internal memo, reasons:

> Scientifically, we don't know since the transmission mechanism is unknown at present. In the future, however, it is likely to be shown that such will be the case. In the interim it will be largely an ethical/political/marketing/legal issue. From the standpoint of product marketing we will be better off making direct and visible attempts at elimination of such groups. Ethically, I don't think sexual preference is the proper business of anyone (or an institution) other than the individuals involved in the sexual act. Legally it would seem we are open to suit in any event, i.e. by the gays if we attempt to exclude them, by patients who might contract AIDS if we don't make every attempt to exclude gays. Haitians and any other group associated with AIDS... (Cumming 1983).

His reasoning is based on the potential future ramifications (legal, political, and public relations) that could attend to certain choices. The potential impact on the availability of blood, of course, is one of these. As Cumming writes, "...eliminating all gay males...would only increase the percentage of the population required to donate once per year from about 9% to about 11%..." (Cumming 1983). Here, the future effect on the blood supply becomes something calculable and tangible. In this particular instance, it is also presented as manageable.

Cumming invokes the trend of the unfolding disease as an important component of the future-oriented basis for decision-making. He writes that, "historically the incidence of AIDS has been doubling about every six months." This forms a troubling base-line, the cited cause of the CDC's concern over the public health risk the disease portends. The CDC, in both public presentations and private meetings, had represented AIDS as a risk through projecting this trend into the future, and showing how many people could potentially be affected. Based on this trend, Dr. Cumming projects that:

> As time goes on we are liable to get more and more pressure to utilize these means also [direct questioning and laboratory testing]. If AIDS continues to double every 6 months, the concentration in gay males continues, and absent evidence to the contrary, this pressure is likely to be overwhelming in 6 to 12 months (Cumming 1983).

Through Dr. Cumming's words, we can see a complicated dance being performed, a dance between two temporalities, the trend of the disease course and the reactive trend of public perception. He presents himself as able to pinpoint a window, from 6 to 12 months, when he believes a threshold will have been reached and the organization will no longer be able to withstand external pressure.

If the ARC fails to act, according to Dr. Cumming, "it will appear to some segments of the public at least that we have a self interest which is in conflict with the public interest, unless," he notes, "we can clearly demonstrate that CDC is wrong." Because the CDC had framed its call to action in terms of a continuing trend in cases, along with the parallels to Hepatitis B, any deviation could provide a potential opening for the ARC to assert a different representation of the future. Such a deviation is noted in that the doubling "trend is not reflected in figures for November and December 1982." It is clear to Dr. Cumming that the best possible future outcome for the ARC would be if

the January 1983 incidence figure were consistent with November and December 1982 "and inconsistent with CDC's hypothesis of doubling every 6 months." This, however, would not be the case.

On June 22, 1983, the industry joint task-force issued another joint statement saying that, "it appears at this time that the risk of possible transfusion-associated AIDS is on the order of one case per million patients transfused" (Leveton et al 1995). According to Douglass Starr,

> This number became a mantra for the blood bankers, who used it whenever the question of safety came up. They based it on a back-of-the-envelope calculation comparing the number of suspected transfusion-AIDS cases at the time – fewer than twenty- to the more than thirty million units of blood collected and distributed since the epidemic began (Starr 2000).

What is not reflected in such calculations is the way in which a long incubation period can mask transfusion transmissions. Once calculated, however, such numbers develop a life of their own. They appear concrete and knowable despite the flimsy basis upon which they are derived and gain momentum through the echo chambers of the media and the law. The putative "one in a million" risk of transmitting AIDS by transfusion became such a number, reified and magnified through propagation and repetition.

The FDA's Blood Products Advisory Committee (BPAC) meeting of July 19, 1983, was devoted almost entirely to the discussion of what was known about AIDS and its transmissibility through blood and blood products (Leveton et al 1995). Specifically, the committee was asked whether or not there should be an automatic recall of AHF if a donor to the pool from which it was derived was later found to have AIDS or had symptoms suggestive of AIDS. This item was put on the agenda at the urging of the NHF

Medical and Scientific Advisory Council (MASAC), which had come out with a statement favoring automatic recall at one of their previous meetings.

Before the medical director of NHF could present on MASAC's position and reasoning, Dr. Michael Rodell of PHARMA presented a risk assessment on the effects of potential recalls. This example clearly illustrates the power of such Future Oriented Statistical Projections (FOSPs) to capture a debate and drive decision-making. Dr. Rodell projected that the withdrawal of AHF from a single donor suspected of having AIDS, if he contributed to 50 plasma pools in a year, could result in the elimination of 250 million units of AHF concentrate per year. Thus, the identification of 3 or 4 suspect donors could completely wipe out a year's production of AHF, which at the time was approximately 800 million units. This projection was so stark and influential that when it did come time for the medical director of the NHF to present his organization's position, he completely back-tracked, arguing that the view of the NHF had been established without the insight of PHARMA's calculations. He concluded that given this calculated future potential, such recalls should not automatically occur, but should be subject to considerations of availability of product.

In contrast to the FOSP projecting shortages, which took on the aura of almost absolute certainty to the members of BPAC, the question of whether AIDS could be transmitted by blood generated disagreement. In fact, the chairman of BPAC, Dr. Joseph Bove of the Yale Blood Bank, had recently testified in front of Congress that the transfusion transmission status of AIDS was unknown, and, if it did exist, the risk was likely to be less than one in one million per transfusion (1983a). Given the representation of blood supply shortage as a "real" and "big" risk, contrasted with the representation of

AIDS transmission as "hypothetical" and "small" risk, it is not surprising that the committee members overwhelmingly indicated that automatic recalls of AIDS contaminated factor VIII would be a mistake. Instead, they recommended that each case be reviewed by the FDA Office of Biologics on an individual basis. BPAC advised that in making such decisions, the Office of Biologics consider the impact on the overall supply.

Despite the putative "1 in a million" risk of transmitting AIDS by transfusion, it became apparent over the next several years that tens of thousands of hemophiliacs, other plasma product recipients, and transfusion recipients had been infected with the AIDS virus. Many went on to die of full-blown AIDS. Anger over large-scale transfusion-transmitted of AIDS led to enormous fall-out. Hemophiliacs and other transfusion recipients blamed the blood industry for not recognizing and acting upon the risk more quickly. They blamed the government for not forcing the industry to do so. And they blamed scientists and medical professionals for not warning them of the impending danger. They even blamed their own advocacy organization, the NHF, for advising continued use of Factor VIII despite the risk, which led to the formation of several new organizations to represent hemophiliacs. The Committee of Ten Thousand, or COTT, became one of the most prominent of these (Resnik 1999).

COTT and other newly-formed hemophilia advocacy groups were successful in lobbying for a public inquiry. In April of 1993, Senators Edward Kennedy (D-Ma), Robert Graham (D-FL), and Representative Porter J. Goss (R-FL) requested then Secretary of Health and Human Services, Donna Shalala, to open an investigation into the events leading to the transmission of AIDS to hemophiliacs through contaminated blood products (Leveton et al 1995). The Secretary asked the Institute of Medicine (IOM)

to investigate. Importantly, the Secretary asked the IOM to recommend a framework that could prepare the nation to deal more effectively with future threats to the blood supply (Leveton et al 1995). The idea was not to distribute blame for what had happened in the past, but rather to use insights from the past to improve future decision-making and public health policy, or to deal with future challenges by anticipating them ahead of time.

The IOM established a committee to study HIV transmission through blood and blood products. The committee arrived at several conclusions regarding what-went-wrong during the handling of HIV and blood transfusion, and established concrete recommendations. Importantly, the IOM recommended that in the future, a precautionary stance be taken with regard to potential threats to the blood supply. They advised that uncertainty should not be an excuse for inaction. "The perfect," they remarked, "should not be the enemy of the good."

> Where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the FDA should encourage, and where necessary require, the blood industry to implement partial solutions that have little risk of causing harm (Leveton et al 1995).

As a caveat, they advised that the implementation of partial solutions, and the basis on which they were implemented, should be reexamined at intervals. This was an acknowledgement that uncertainty requires continual reassessment.

While hepatitis B, as a metaphor for AIDS, was highlighted by CDC in the beginning of the epidemic, according to the IOM there was another disease metaphor that proved decisive in the broader governmental and public reaction to CDC's warnings about AIDS. Through their review of events, the IOM discovered that individuals and organizations responded to CDC's warnings about an impending epidemic of AIDS through the lens of the swine flue scare. The swine flu scare of 1976, which commenced

only four years prior to the recognition of HIV, involved dire warnings from the CDC, the president, and the entire federal government that a dread epidemic was coming to the United States. Attempts were made to immunize every American against a disease that failed to materialize. While the epidemic never came, several individuals died of side-effects from vaccination. The swine flue experience, forming an important part of the sensitizing frame from which agencies approached AIDS, led CDC to doubt itself in the beginning of the AIDS epidemic, demanding more evidence before alerting other PHS agencies. With the same metaphor in mind, other PHS agencies, in turn, responded with skepticism. They worried this might be a repeat of the 1976 swine flue scare. In their report, the IOM committee concludes that, "the HIV case constitutes one clear example in which the experience and its lessons, however they were applied, led to disastrous results" (Leveton et al 1995)

Within the AIDS narrative, we see the development, disassembly, and reconstruction of various social worlds. Each social world is comprised of individuals with a shared world view capable of acting collectively to pursue a goal. The CDC scientists and physicians are charged with warning the nation of epidemics and determining their cause. Their shared activities involve surveillance, interaction with the medical community and the rest of the government, research, and notification.

The blood industry, from non-profit blood collection facilities to for-profit plasma manufacturers, produce a number of products that have life-saving and/or life-enhancing properties. The collective activity of the blood industry involves manufacturing these products, distributing them to users, and collecting payment. Events and concerns which inhibit this activity become obstacles which must be managed or eliminated.

Unfortunately, the concern over HIV/AIDS was viewed largely as such an obstacle. When the blood industry finally did act to prevent transmission, it was too late. A deep wound in the public image of the industry had been sustained. They were left in the position of struggling to rebuild their image, while at the same time conducting their primary activity, the collection and distribution of blood products and money.

The hemophilia community, bound together by the collective requirement of clotting factors, underwent a substantial shift through the course of this narrative. In the 1960s, the introduction of Factor VIII and other purified clotting components ushered in an era in which availability and utility were emphasized over the potential for infectious transmission. Infectious disease risks, such as hepatitis B, were down-played whereas free movement and a normal life were seen as the ultimate goals. With mounting death tolls, HIV/AIDS changed this perception in the hemophilia community. Inner turmoil and blame generated a split in the community, with some demanding more militant action to protect against HIV/AIDS. This resulted in the generation of several new advocacy groups, such as COTT and the Hemophilia Federation. While the NHF survived, it was weakened and fragmented.

The FDA, as the agency charged with oversight of the blood products industry, bore much of blame from the perspective of hemophilia organizations as well as other government entities. The IOM singled them out for criticism, offering suggestions on how they might improve performance of their collective activity, ensuring the safety of the blood supply, in the future. The CDC, on the other hand, was lauded by the IOM committee for their foresight and efforts to intervene in the looming AIDS crisis. If other agencies had taken the CDC's projections seriously, the IOM committee stated, the AIDS

epidemic might not have reached the proportions it had, especially among the recipients of blood products and transfusions.

CJD - A New Threat to the Blood Supply?

Against the backdrop of AIDS, the perception of CJD as potentially transmissible by blood was slowly emerging. While there was no, and never had been, any case of CJD that could be traced to a blood transfusion, new laboratory data, based largely on animal models of the disease, produced the image of a potential risk.

The reaction to CJD as a potential transfusion transmission risk is almost a negative mirror image of the reaction to HIV as a potential transfusion transmission risk, as recounted in the previous chapter. First of all, while the perception of a possible transfusion risk for HIV arose from epidemiological data, and was in fact overlooked until the numbers were quite large, there was no epidemiological data linking CJD and blood transfusion. While laboratory data for HIV transmission characteristics did not exist in the early days of the CDC's warnings about HIV, laboratory data formed the sole basis for the concern over CJD transfusion transmission. And while AIDS was a new disease, an emerging threat undergoing continual redefinition during the early meetings about its potential as a risk to the blood supply, CJD had been known since the 1920s. In addition, while many of the players involved in HIV decision-making carry over into the CJD arena, new players, especially those with expertise in TSEs and consumer representatives that were given a greater role in decision-making vis-à-vis the IOM recommendations, entered the discussion.

In 1985, the first cases of CJD in a young adult who had received cadaveric pituitary growth hormone treatment (Hgh) for short stature was reported. Since then, there have been over 150 cases of CJD in recipients of Hgh. Hgh is injected intramuscularly, and if such a route could spread the disease, many worried that intravenous administration might also. Such a route of transmission would only be of concern, however, if the blood actually harbored infectivity.

For a long time, most of the TSE research community had agreed that blood was unlikely to harbor the infectious agent. While a few scientists had reported finding infectivity in the blood of animal models of scrapie in the past (Clarke & Haig 1967), their research had been largely overshadowed by more respected and elaborate negative results (Eklund et al 1967, Hadlow et al 1980, Pattison & Millson 1962). In Gajdusek's lab, chimpanzees were inoculated with the blood of patients who died of CJD and kuru. No infection occurred. Because these experiments were conducted with human blood, rather than animal blood, the results were believed to be highly significant, indicating the relatively low possibility that blood transfusion would transmit the disease. The one interpretive problem, however, is that transferring infection from humans to chimpanzees involves a hypothetical species barrier. The species barrier is an indication of the difficulty in infecting one species with a TSE from another species. It is denoted as a ratio of the efficiency of infecting one species to the efficiency of infecting the original species. As the efficiency of infecting a human cannot be measured directly, due to obvious ethical concerns, it is often estimated by reasoning through the species barrier measurements of laboratory animals. These can vary from as low as 1/10 to as high as 1/10,000, depending on the strain of agent and the species involved. If the infectivity in

human blood were low, such a species barrier could potentially prevent detection. Despite this caveat to interpretation, the results were perceived as reinforcing the overwhelming perspective of scientists in the field that TSE spreads along neuronal pathways, like rabies (Kimberlin). The conviction that TSE agent could not be present in blood was held so strongly that few scientists even bothered to look for it, and those who did, and happened to find it, explained it away as artifact. Even Alan Dickinson, upon detecting scrapie agent in the blood of a small percentage of infected mice, proclaimed that it was most likely due to contamination (Dickinson et al 1969). His willingness to indict the cleanliness of his own laboratory and his own procedures indicates the strength of the conviction that TSE could not be carried by blood.

This perception began to change in the midst of the AIDS epidemic. Just before AIDS was first recognized, Elisa and Laura Manuelidis, a husband and wife research team at Yale University, published on the transmission of CJD through the transfer of blood between infected guinea pigs (Manuelidis et al 1978). The Manuelidises drew blood from the heart, attempting to keep it sterile. They centrifuged it, froze it, and kept the frozen buffy coat layer, and minor amounts of the surrounding plasma and red blood cell layers, to use for inoculation. White blood cells circulate through lymphoreticular tissues, which Hadlow had shown to be infectious during his pathogenesis studies of scrapie (Eklund et al 1967). The Manuelidises packed a walloping dose, both temporally and spatially, inoculating each recipient guinea pig on a weekly basis through intracerebral, subcutaneous, intramuscular, and intraperitoneal routes. They wanted to maximize their ability to detect what might be a low level of infectivity in the blood stream. Remarkably, they reported finding infectivity in blood in the first week after

infection. The incubation period of the assay animals inoculated with blood from animals in their first week of infection was an incredibly long 443 days, which the Manuelidises interpreted as indicating that the level of infectivity in blood was low at this point. The incubation period of assay animals shortened as the time course of the infection of the donor animals wore on. The Manuelidises warned that, "there may well be a danger of transmitting [CJD] via blood transfusions from humans harboring the agent during the incubation period, when the clinical disease is not readily apparent," planting the seed for future concerns over the transmission of CJD through the blood supply. The Manuelidises' results, through analogy to human beings, began to transform the sensitizing frame for responding the CJD concerns.

The second worrying scientific result appeared in the early 1980s, just as AIDS was coming to national awareness. Yasuo Kuroda, now a prominent Japanese TSE researcher in his own right, visited the National Institutes of Health (NIH) to conduct transmission studies in Gajdusek's lab. He brought with him a mouse-adapted strain of GSS, a familial form of TSE in humans (Tateishi et al 1979).[9] Kuroda collected tissues from infected mice at one week intervals after inoculation. He then inoculated the blood intracerebrally into recipient mice in order to bioassay the presence of infectivity.

Kuroda assayed brain, spleen, lung, liver, kidney, thymus, blood, and urine (Kuroda et al 1983). Blood was collected by cardiac puncture in an attempt to avoid cross-contamination with other tissue, similar to the method used by the Manuelidises. The blood was centrifuged, frozen, and the buffy coat layer was inoculaed intracerebrally into mice. By a third of the way through the incubation period, or 6 weeks, the buffy coat

[9] Subsequent discovery that the donor patient had actually been suffering from GSS, a genetic variant of CJD caused by a mutation in the prion protein gene, would later lead to the re-classification of this strain as GSS rather than CJD derived.

was found to transmit infection to 100% of recipients. The blood continued to test positive throughout the remainder of the incubation period. Kuroda's results contributed to changes in the sensitizing frame through which regulators, hemophiliacs, and industry representatives considered CJD.

The next results came from Germany, where a researcher who had developed a method for substantially purifying the infectious agent repeated the findings in hamsters with scrapie (Diringer 1984). Now there were three model systems (CJD in guinea pigs, GSS in mice, and scrapie in hamsters) that supported the finding of infectivity in blood. Diringer also speculated that his detection of infectivity in the brain of an intraperitoneally infected animal five days after inoculation supported the theory of hematogenous spread. There was no way, he believed, that the agent could move from the gut to the brain through neural pathways that quickly. And such speed was certainly not supported by Kimberlin's experiments, which formed much of the basis for the neuronal pathogenesis argument (Kimberlin). Extending his findings to the human realm, he postulated that, "Cell-bound infectivity as found in Creutzfeldt-Jakob disease could be released continuously into the blood stream from these tissues thereby enabling a steady flow of agent from these to other organs" (Diringer 1984).

While the detection of infectivity in the blood of animal models was startling, new studies were about to push the envelope further. In 1985, two researchers on opposite sides of the world independently reported the presence of infectivity in the blood of humans with CJD as measured by rodent bioassay. The Manuelidises had collected blood from two patients while they were still alive but terminally ill with CJD (Manuelidis et al 1985). In one case, they reported that the patient's buffy coat transmitted disease to

guinea pigs, and in the other, to hamsters.[10] In Japan, Tateishi collected a blood clot from a patient with CJD at necropsy. The crushed clot transmitted disease upon intracerebral inoculation into mice (Tateishi 1985).

These studies were concerning enough that, when combined with the rescent fiasco of the transfusion-borne HIV epidemic, they formed a sensitizing frame that convinced the FDA to issue a memorandum to blood collection centers warning them to defer, or exclude blood donors who might be at risk of contracting CJD because they had received human pituitary-derived growth hormone. According to Jo Fratantoni, then of the FDA, "the decision was made at a time of extreme concern about blood safety as a result of recently acquired data on the role of HIV in transfusion-transmitted AIDS" (Fratantoni 1998). The American Association of Blood Banks (AABB) followed suit by issuing a new standard barring individuals who had received growth hormone from donating blood, tissue, or organs. Paul Holland of the Sacramento Medical Blood Center commented that, "Because of long-lasting 'viremia' in infected individuals, many of whom remain asymptomatic, an attempt to reduce the risk of transmitting CJD through blood transfusions was deemed prudent. Without a mechanism to identify individuals who might be carrying the agent of CJD...the most pragmatic way to reduce the risk of transmission of CJD via blood and its components appeared to be a new AABB standard that would apply to individuals at risk of being infected with the CJD prion" (Holland 1988).

In 1993, the FDA strengthened the management of potentially CJD-contaminated blood by requiring that blood collection centers inform the agency of any donors who,

[10] But interestingly, case # 2, which transmitted to hamsters, did not transmit to guinea pigs as case #1 had, raising the issue of differential transmissibility of different strains of sCJD.

post-donation, were found to have risk factors that should have barred them from donation. In the 15-month period from October 1994 to December 1995, at least six donors were reported to have developed CJD post-donation, in contrast to only four donors in the previous 10-year period (Menache & O'Malley 1996).

In October of 1994, a donor was reported as having developed CJD. According to Larry Shonberger of the CDC, this was no ordinary donor, this man:

> ...was a member of the American Red Cross's Ten Gallon Club. And then the community there started saying, 'Wait a minute! This guy has CJD. It's a transmissible disease, and he's famous in the community for giving blood on a regular basis. He's a member of the Ten Gallon Club. Is that a danger?' And people started getting concerned (Ponte 2004c).

This donor, aged 64, had indeed donated 93 times over the 35 years prior to his diagnosis with CJD (Brown 1995). Further, plasma from his donations had been pooled to make plasma derivatives, which had then been distributed amongst the hemophilia community. The American Red Cross (ARC) recalled 164 lots of AHF (Anti-Hemophilia Factor VIII) and albumin due to potential contamination with the CJD agent. Other pharmaceutical companies which had manufactured plasma products from plasma donated by the same donor, Miles Inc. and Sandoz Pharmaceuticals, also recalled product. Jonathan Wadleigh, President of the Committeee of Ten Thousand (COTT), a hemophilia advocacy organization, commented that, "these product withdrawals once again throw into question the safety of the nation's blood supply" (Colvin et al 1995).

On December 14, shortly after the untoward donor was identified, the FDA presented the relevant data to their Blood Product Advisory Committee (BPAC). The committee was asked to consider whether such post-donation information merits withdrawal of labile components or plasma products from the market. Based on available

information, the committee voted overwhelmingly to recommend the withdrawal of labile components in such situations, but not plasma pools or derivatives (Menache & O'Malley 1996). They viewed plasma derivates as less of a risk due to the processing involved and the likelihood that the low amount of infectious agent would be diluted by pooling. Rich Colvin of COTT expressed concern to the committee that "fractionators are once again gambling with our lives that a potentially dangerous infectious agent will not be transmitted through the blood products we use." An editorial in the Common Factor, a publication written by and for hemophiliacs, warned that "For a community already decimated by AIDS, the possibility of new diseases transmitted through the blood supply is always a real threat. As CJD shows, we cannot assure the safety from transmissible agents in the factor products we use" (Colvin et al 1995).

Not satisfied that BPAC was fully equipped to deal with the threat of such a novel infectious agent, and perhaps influenced by the recent indictment of this committee over the AIDS blood scandal, the FDA decided to appoint a Special Advisory Committee on CJD to review the same questions. Given the recent experience with HIV, there was a sense of urgency over the review of questions concerning the hypothetical threat of CJD to the blood supply, and this sense of urgency precluded taking the time to go through official channels to set up a permanent committee before considering the question. In addition to the studies mentioned earlier (Manuelidis et al 1985, Tateishi 1985), researchers in Japan, by this time, had reported the transmission of CJD to mice from the concentrated plasma of a pregnant woman infected with the disease (Tamai et al 1992), and researchers in France had published the transmission of CJD to hamsters from the blood of an affected hGH recipient (Deslys et al 1994). In contrast to these alarming

results, Paul Brown of the NIH maintained that none of his nine attempts to transmit CJD to primates at the NIH in the past several years had been successful (Brown et al 1994). Brown argued that his results should be given more weight because, "in the case of CJD, the most sensitive animals are nonhuman primates" (Brown 1995).

Despite the fact that four labs had now produced reports stating that the CJD agent could be found in human blood, Brown found fault with them all. Further, he made his critiques public by publishing them, as well as announcing them at the ad-hoc committee meeting. To begin with, he could not understand how any of these labs had managed to detect CJD agent in blood through the use of rodent bioassays when he had failed to do so with primates. While the species barrier could not be directly measured, he reasoned that the species barrier should be the lowest for human to chimpanzee transmission because chimpanzees are most closely related to humans. In contrast, he argued, that for transmission between humans and rodents should be much greater. In addition to being physiologically more like humans, chimpanzees had always proven to be more susceptible to CJD than any other type of animal in Gajdusek's lab.

Paul Brown found additional inconsistencies and anomalies in all four of the papers which claimed detection of infectivity in the blood of CJD patients, faults which he believed could, and should, invalidate their results. He argued that Tateishi's landmark paper in 1985 was problematic because not only did Tateishi find infectivity in the blood, but he also detected it in the urine. "The finding of infectivity in urine is unique," wrote Brown, "despite repeated attempts in both humans and experimentally infected animals." In addition, "a comparison of incubation times in the animals inoculated with the different specimens suggests that the urine contained a higher level of infectivity than

either the blood or cornea, and not too much lower than that of brain, which is surprising" since, as he argued, in almost every other experimental report, brain is found to harbor substantially greater levels of infectivity than any other organ or tissue (Brown 1995). Based on similar reasoning, he dismissed Tamai's study because Tamai found similar incubation periods in mice inoculated with brain and with plasma, "which," he commented, "is virtually impossible" (Brown 1995).

He saved the harshest criticism for Deslys and Manuelidis, whose results, he suggested, may have been the result of "artifact" or "laboratory cross-contamination". His reasoning was based, in Deslys's case, on the finding that only one of five inoculated hamsters became ill and the incubation period was extremely long. A long incubation period is often cited by scientists making accusations of cross-contamination in the TSE field. It is argued that a small amount of inadvertently introduced infectious agent, perhaps from a contaminated benchtop or an incompletely disinfected instrument, could produce such a result.

The Manuelidises had significantly greater difficulty making their case for infectivity in CJD blood after they published on the transmission of a brain-wasting disease to hamsters from the blood of patients with Alzheimer's disease, as well as healthy relatives (Manuelidis et al 1988) and subsequently, even unrelated, healthy subjects (Manuelidis & Manuelidis 1991). Upon microscopic examination, the lesions in the hamster brains in all cases "were indistinguishable from histological findings in experimental CJD. No neurofibrillary tangles, plaques, or AD-like amyloid deposits were detected." They interpretation these results as indicating that "many humans carry a putative CJD-like transmissible agent and are infected in utero or early in life" (1991).

Many other researchers, however, were convinced that cross-contamination was a more likely explanation. As Manuelidis notes, "the unusual and totally unexpected findings of our initial pilot study were received, with very few exceptions, with skepticism, disbelief, and on occasion ridicule and/or hostility" from colleagues, especially in the Alzheimer's research field. Manuelidis tried to dispel this criticism by, in the second experiment, purchasing new homogenizers and brand new instruments to minimize the possibility for cross-contamination.

In their own attempts to replicate Manuelidis's results, researchers in Gajdusek's laboratory were unable to detect any infectivity in the blood of Alzheimer's disease patients (Godec et al 1994, Godec et al 1991). In a scathing indictment of the Manuelidises' research, Brown proposed an alternative explanation for the findings, "CJD was mistaken in the inoculated hamsters for an endemic late-onset disease caused by Clostridium difficile, coupled with laboratory cross-contamination by the agent of spongiform encephalopathy..." (Brown 1995). Thus, Brown cast doubt, by indicting the researchers for discrepancies and potential contamination, on each of the experiments which claimed transmission of CJD to rodents.

In short, Brown pointed to illogical inconsistencies in the results of all of the model systems through which investigators purported to have detected infectivity in the blood of humans with CJD. In this way, he sought to minimize the effects of these results on the sensitizing frame from which the committee would consider CJD. His efforts, however, were in vain, as the committee, as well as the FDA, the agency which it served, was already in a heightened state of concern due to the recent experience with HIV. Both were determined not to make the same mistake twice.

While the laboratory search for infectivity in the blood of patients with CJD was one side of the coin, epidemiological surveillance for cases of transfusion transmission of CJD was the other. While it was commonly accepted that no case of CJD had ever been linked to transfusion transmission, the question remained of what sort of epidemiological study would be necessary to detect such a case. Three case-control studies conducted during the 1980s in Japan (Kondo & Kuroiwa 1982), the United Kingdom (Esmonde et al 1993), and the United States (Davanipour et al 1985) failed to uncover any link between blood transfusion and the later development of the disease. Several researchers at a German transfusion center, however, argued that such an approach was inadequate for ruling out transmission of a disease in which the incubation period is long and highly variable and (Heye et al 1994). They admonished researchers to conduct more studies like their own, in which they followed the recipients of blood from a donor who had died of CJD for a long period of time. Such studies, they argued, were necessary to rule out transmission of the disease by blood.

In addition to the aforementioned epidemiological studies, preliminary findings of a transfusion safety study at the University of Southern California were presented to the committee. The researchers found no excess dementia among hemophiliacs as compared to the normal population, which they interpreted as indicating that CJD was unlikely to be transmitted by plasma products. As Paul Brown notes, however, "population-based studies can never prove or disprove the possibility that rare cases might result from blood transfusions but be numerically insufficient to produce a statistically significant difference from case control groups" (Brown 1995).

So while some, at least, of the laboratory studies suggested the potential for infectivity in the blood of CJD patients, there was a general lack of epidemiological data to support this premise. For the regulators and their scientific advisors, what it came down to is how to weigh the scant laboratory data, with all of its concomitant uncertainties and unknowns, against the scant epidemiological data, likewise with its gaps and discrepancies. As Dr. Schonberger described the situation:

> ....there really was no clear-cut answer from FDA's perspective. And from our perspective, we had been doing surveillance of CJD and not really seeing evidence that this was a problem...And one of our basic reasons for thinking that way, in part, was that we were not getting younger cases. It was extremely rare for us to get a case that was 30 years of age or younger...We recognize that surveillance was not 100 percent, and that's always a problem, so you can't be 100 percent certain. But there was general agreement that young cases were really rare. And yet, lots of kids, particularly under the age of five, were getting all sorts of blood transfusions...There was just no way to stop people who may have been incubating the disease but who were not sick from contributing to the pool of blood that was being used to make all these products. And yet, there were no cases. So from our perspective, the risk was minimal, or practically zero (Ponte 2004c).

Unlike in the early days of AIDs, when the CDC was the only federal agency raising concern about blood borne transmission of the disease, the CDC perceived no such threat based on their epidemiological surveillance of CJD. While this, alone, might have proved convincing to skeptics, this was not the only evidence that supported a lack of transmission risk of CJD through blood. Brown's inability to detect infectivity in the blood of CJD patients by inoculation in primates, what should be the most closely related of species, also proved convincing to Schonberger:

> One of the key things that had been done at NIH is that they had actually taken blood transfusions from humans, who were actually sick with CJD, and inoculated them in the most sensitive animal there is – primates...and it did not transmit. And yet, here were a couple labs reporting that they took some blood and inoculated in a rodent where there would be some species barrier and so on. The data was just not inconsistent. And when Paul started talking about there

being problems with it, we were more willing to dismiss that type of data (Ponte 2004c).

The FDA and the rest of the TSE advisory committee, however, in the climate of heightened awareness generated by AIDS, was not so willing to dismiss the other results. So afraid of another attack from a blood-borne infectious agent, they were unwilling to leave that route of attack unguarded, despite the lack of evidence that it would ever be used. Like the French with their Maginot line, the FDA, the hemophilia community, and the majority of the committee members based their policy recommendations on past experience with AIDS. Although CJD was an entirely different species, with different modes of transmission and different pathology, this did not stop them from wanting to protect the front on which they had previously been attacked.

In addition, several scientists had concerns about Paul Brown's dismissal of the other data in favor of his primate data. While Brown tended to present his work in primates as the closest one could get to a human-to-human transmission model, Rohwer maintains that the species barrier between humans and primates is significant and could potentially inhibit his ability to detect infectivity in blood:

> ...he keeps making the point that that's as close as you can get to humans. Well, it may be as close as you can get, but it's not humans. And there's a very significant barrier between mice and hamsters which are also very closely related. So I don't buy those arguments, and I don't think we really know what the titer is of human blood {Ponte, 2004 #1077}.

Larry Schonberger admits that he, like every one else on the committee, came to the table with a disciplinary bias. How one interprets the data, as Larry saw it,

> ...depended on your background... Well, I'm an epidemiologist, and when I was looking at it, I tended to see that it just wasn't happening in the human population. But I could never tell somebody with certainty. I would always tell them, I said, "I

> can't be 100 percent sure, you know. But I can say that the risk is extremely small. If it's there, it's not gonna be like AIDS (Ponte 2004c).

Despite Schonberger's conviction that CJD could never turn into the blood transfusion crisis that AIDS became, representatives from several advocacy groups, including hemophiliacs, raised the specter of the AIDS crisis during the meeting. They urged the FDA not to stand quietly by as another transfusion-transmitted epidemic began. They begged the committee to advise withdrawal of plasma retrieved from donors later diagnosed with CJD. At the very least, they argued that recipients should be notified if such plasma were used to prepare a product.

Representatives of the AABB and the Council of Community Blood Centers, on the other hand, were wary of providing such information. They argued, in turn, that notifying the recipient of such information does not carry any recognizable benefit. There is no cure for the disease and no way of knowing who is a carrier. In addition, they reminded the committee that the risk they were discussing remained hypothetical. There was no actual case of transfusion transmission of CJD to support it.

In the end, unlike BPAC, the committee voted to withdraw plasma derivatives as well as blood components if a donor was later found to have CJD or to be at risk of CJD. Those considered at risk for CJD were those who had received Hgh treatment, had a dura mater transplant, or had family members with CJD. They reasoned that while the chance of CJD transmission was theoretical at most, it could not be excluded, and no one wanted the weight of another AIDS crisis on their shoulders, not the advisory committee members, and not the FDA.

By December of 1996 the FDA had released guidance recommending immediate withdrawal of any products deemed to contain plasma from a donor later found to be at

risk of CJD. The FDA, however, in deference to those concerned about shortages, allowed for release of such withdrawn products in the event of a "documented market shortage." In such cases, however, the FDA requested notification and the labeling of products disclosing the "risks and benefits."

Given the FDA's guidance, however, companies were unwilling to release implicated material even in the event of a shortage. They did not want to label their products as at risk, for fear of liability concerns, and chose to dump the theoretically contaminated blood instead. In essence, Fratantoni remarks, "industry has legal concerns regarding release of product that has been recalled" (Fratantoni 1998). Discontent within the plasma industry grew as shortages, and what they perceived as wastages, continued. The resentment on the part of the industry was compounded by the FDA's admission that the interim policy was "primarily in response to consumer concerns and the need to maintain public confidence in the safety of the blood supply" rather than a real transfusion risk (Menache & O'Malley 1996).

Despite the FDA's best efforts to design a balanced, rational disease management strategy for CJD in relation to the blood supply, they had failed to provide an adequate mechanism for balance. The supposedly rational decision of the FDA to withdraw potentially CJD-contaminated blood products from the market was, in turn, based on advice from an expert committee on TSEs. This committee, while recognizing the lack of epidemiological evidence supporting any association between transfusion and CJD, under the weight of a previous HIV epidemic transmitted through transfusion, caved in to demands for the strictest risk regulations imaginable. In essence, their decision, while cloaked in rationality through a debate over animal experiments, model systems, and

inoculation data, was not rational at all. It was experiential in nature, deriving from the emotional stigma that had become attached to blood as a purveyor of infectious disease in the AIDS crisis. According to the new FDA regulations, not only would donors deemed at risk of developing CJD be deferred from donating, but their blood products, if they were found to be at risk for the disease, would be withdrawn. This led to incredible disruption in the industry, where blood from a single donor could enter a pool of 10,000, resulting in the withdrawal of all the pooled products.

Ch. 4 – Out with the old, in with the new

While CJD, for the moment, consumed the FDA's attention when it came to regulating the blood supply, having become the focus of attempts to make up for the previous AIDS epidemic, further problems developed in relation to the policy. Questions were raised about the secondary contamination of products that may have only briefly come into contact with potentially CJD-contaminated materials. In the meeting at which these concerns were considered, the detrimental effects of the CJD withdrawal policy on the industry and patient communities were made palpable through the construction of statistical graphs of the shortages produced, and the costs incurred. In this way, the shortages came to feel more real to many of the committee members than the blood risk which they were seeking to mitigate. While a few committee members, based on past experience, contested the industry's representation of shortages, there is not doubt that the numerical presentations had their effect on the committee.

In contrast, the concerns over CJD transmission through blood were further problematized. Epidemiological evidence had continued to reveal an absence of documented CJD transmissions by blood. While arguments ensued over the meaning of the data and how long it would take, when considering a disease with such a long incubation period, to be convinced it was not a threat, the continued lack of an epidemiological association raised concern about the effectiveness of the policy.

In particular, a numerical analysis CJD contamination of plasma pools conducted by Donald Tankersley, a representative of the blood industry, took its toll on committee members. Based on an assumption of a very long incubation period for CJD, 25 years, he calculated that, based on the incidence of CJD, at least half of the plasma pools produced

would contain at least one donation from a CJD patient. Given this high level of "contamination," Tankersley presented the continuing lack of evidence of transmission through epidemiological data as doubly convincing. Meanwhile, some committee members built on Tankersley's analysis to claim that the current withdrawal policy was providing a false sense of security, because CJD-contaminated donations would occur during the incubation period of the disease. This caused committee members to question what they were really accomplishing with this disease management policy? Were they managing risk, or were they simply creating shortages?

As the sensitizing frame shifted and the appearance of risk from CJD began to fade, the FDA and its advisory committees were confronted with a new concern. The UK's official announcement of variant CJD was made in March of 1996. Compared to CJD, which had been around for hundreds of years, much less was known about the properties of vCJD. While guesses could be made based on analogies with CJD, these analogies were deemed suspect due to the surprising characteristics which had arisen from BSE. It did not take long for concerns over vCJD to completely eclipse concerns over CJD. As a result, after delving into the minutia of CJD regulation, and realizing the negative effects such regulations could have on the blood products supply, a high-level advisory committee suggested rescinding the withdrawal of blood products for CJD-risk. At the same time, they demanded a new withdrawal policy should someone with vCJD be found to have donated blood. Thus, in one meeting, the most demanding regulations around CJD were wiped clean, despite the lack of any significant new data on the topic, and all eyes turned toward vCJD. The rapidity with which the gaze of committee members, and of the FDA, was transferred to vCJD reveals the reactionary quality of

disease management policy. While it may appear rational on its surface, most measures are the result of experiential reactions to frightening visions of the future. It is much easier to relinquish regulation in one area if it is tightened in another, lending an imaginary feeling of balance to the disease management enterprise.

The following narrative and analysis are based on transcripts from two meetings, a meeting of the FDA TSE Advisory Committee, and a meeting of the Blood Safety and Availability Committee, a committee which reports directly to the deputy secretary of health, giving it authority broader than that of the TSE Advisory Committee. It will be revealed that while these two committees met in separate places and at separate times, there was a significant continuation in the debates within them. The exchange of influential numerical analyses and interpretations occurred through the presence of the same scientists at both meetings, where they were able to rearticulate their arguments. Despite the exchange and the continuation of certain lines of reasoning, the meetings developed in two different directions. In the TSE Advisory Committee meeting, the members of the committee stayed within their purview of providing advice only on the management of the blood supply with respect to the disease. Perceiving wider concerns, the Blood Safety and Availability Committee sought to make recommendations extending into the realm of food and animal surveillance. Their efforts were derailed by agency officials, who demanded that they stick to their given charge of advising on blood.

Changing representations of the CJD blood risk

Within the plasma products industry, some plasma derivatives are used in the production of other plasma derivatives. This can compound the potential for contamination because such derivates are exposed not only to contamination from the donor pool from which they were derived but also to contamination from the pool from which the additive, or "excipient," was produced. While the FDA had laid out clear guidelines for the withdrawal of plasma products, they had not advised on how to manage these "secondary products" if one of the ingredients used in the process was deemed to have come from a potentially contaminated pool.

An early example of this secondary form of contamination was the so-called "Transferrin Case." Factor VIII is often purified by running it through a column that contains beads that are coated with monoclonal antibodies. These antibodies recognize the Factor VIII protein, and bind to it selectively, allowing for the Factor VIII to be separated from the other remaining components in the mixture. Preparing the monoclonal antibodies, however, involves growing cells that produce the antibodies is tissue culture. Cells require certain growth factors and other nutrients in order to survive, and some of these are difficult or expensive to synthesize. Transferrin is one such growth factor. It, in turn, is purified from plasma. In the "Transferrin case," one donor who later went on to develop CJD had donated to a pool from which transferrin was extracted. This transferrin had long since been used in tissue culture production of monoclonal antibodies, which had then been used to purify Factor VIII. While the FDA's guidelines clearly stated that the remaining transferrin from the implicated pool should be removed from the market, what of the CJD-tranferrin-implicated Factor VIII?

Theoretically, all of the implicated transferrin would have been removed from the monoclonal antibodies before they were attached to the column, and the monoclonal antibodies as well would have been removed before the final product, Factor VIII was packaged. The question was, could some slight amount of TSE infectivity have been introduced to the cell culture through the addition of transferrin, and could that infectivity then have co-purified with the monoclonal antibodies, and subsequently with the Factor VIII? As Dr. Siegel phrased it: "the issue arises do we know that the TSE agent hasn't jumped from the transferrin to the producing cells and from it to the monoclonal antibody, and then bound to the column and then jumped off that monoclonal antibody onto the final product." Such a scenario involves a number of steps about which suppositions must be made. One crucial input would be whether such infectivity could somehow replicate in the cells grown in tissue culture. If that were the case, even a slight amount of infectivity might be able to multiply, building to significant levels. Without replication in tissue culture, the numerous purification steps would likely reduce the infectivity below meaningful levels. Granted, such a scenario would be moot if CJD infectivity did not exist in the blood of affected humans, a point which was still surrounded by much controversy. This was the complicated set of parameters - knowns, unknowns, uncertainties, and gaps - that the FDA faced in the context of what was reportedly a tight supply of Factor VIII.

The FDA conducted a risk assessment. While the risk of transmitting CJD through secondarily contaminated products was estimated to be too low to calculate properly, the risk of shortages was presented as calculable and knowable. This example shows how attempts to evaluate risk reduction responses in a rational manner will always

favor the more easily calculable side of the equation. With little or no data to go on, the unknown side of the equation becomes overshadowed by that which can be numerically manipulated with ease. According to Dr. Mark Weinstein, chief of the Division of Hematology at the Center for Biologics Evaluation Research at the FDA, the risk assessment indicated that: "the AHF exposure was very indirect and that a shortage was likely to occur if the AHF was withdrawn." The product was released and consumer organizations were "notified" of the decision-making process (Blood Safety Advisory Committee 1998).

In light of the transferrin case, the FDA turned to the CJD advisory committee, which had now been chartered as the TSE advisory committee, in October of 1997 for advice on how to handle future cases of secondary product contamination. This meeting provided an opportunity for committee members, regulators, the blood industry, and concerned members of the community to rehash the debate over whether withdrawals for CJD-risk should exist at all. These individuals from varied social worlds came to the table with different sensitizing frames, derived from contrasting interests and experiences.

The discussion oscillated between two negative potential future outcomes: the outcome of CJD transmission by blood transfusion setting in place a silent epidemic, and the outcome of CJD withdrawals leading to mass shortages of blood and plasma products. The first negative outcome was represented as distant and hypothetical. It was based on the idea that a silent chain of intraspecies transmission could be set in place perhaps years, or even decades before detection. Robert Rohwer frames this potential through reference to metaphors with BSE and kuru:

> In those instances in which we've had epidemics of TSE disease, they were always caused by this phenomenon. We had this vaccine back in the '40s which killed thousands of sheep. Kuru....endocannibalism in Papua New Guinea--was transmitting the disease. And most dramatically the bovine spongiform encephalopathy or mad cow epidemic in Europe where it's clearly a case of cow meat and bone product being fed in feed supplements back to cows and the

> disease was being recycled in that way, and in these cases, the danger was and continues to be silent subclinical amplification over many cycles of passages through the host before you see it and become aware of what's going on...If CJD blood contains infectivity, if CJD can be transmitted by transfusion, the disease could be amplified through transfusion from previous transfusion recipients or blood product recipients. It could take many incubation times to materialize. We're talking about decades, maybe even centuries (Blood Safety Advisory Committee 1998).

While this potential future is represented as distant and unknowable, the potential for creating shortages, at least in the beginning of the meeting, is represented as tangible and calculable.

Dr. Peter Page of the American Red Cross, which collects and distributes half of the blood used for transfusion in the U.S. each year, argues that the CJD withdrawals have had a detrimental impact on the supply of plasma products:

> the total amount of product withdrawn by Red Cross or quarantined and destroyed, or in-process and not further processed up through April of 1997, showing almost 50,000 equivalent units of albumin, over 100,000 grams of gamma globulin and almost 100 million units of AHF. In the subsequent 6 months of this year, which is a half year, the numbers show over 9000 equivalent units of albumin, 13,000 grams of gamma globulin and almost 300 million units of AHF. Currently on hold pending further investigation of diagnosis or medical history, we have some additional product on hold right now. So the totals show 80,000 equivalent units of albumin, almost 200,000 gams of gamma globulin and over 100 million units of AHF (TSE Advisory Committee 1997).

To put these numbers into context, Page notified the committee that:

> An average hemophiliac may receive between 50,000 and 100,000 units per year in developed countries. So that amount of AHF alone would be enough to treat 100 to 200 hemophiliac patients for 10 years (TSE Advisory Committee 1997).

According to Page, the CJD withdrawals led to an inability to fill the orders of customers including large hospitals and community medical centers, as well as $106 million in lost revenue. Through his presentation of statistics, Page made the effects of shortages due to the CJD withdrawal policy palpable and knowable to

committee members in a way that they had not been at the meeting in which the withdrawal policy was recommended. The tangibility of these numerical representations began to displace the concern over CJD risk to blood, a risk which, as yet, had not been substantiated.

The FDA policy to allow release of potentially CJD contaminated products in the event of a shortage, but only if labeled, was not being utilized. Industry balked at releasing product labeled as carrying a potential CJD transmission risk. According to the PHARMA representative:

> I think you can all understand the legal issues involved. If we were to redistribute a product that has knowingly been withdrawn for reasons that this Committee and other august bodies have decided represents an increased risk, there is a serious liability issue involved. So we need some way to resolve that issue I think (TSE Advisory Committee 1997).

From the FDA's perspective, the labeling of risk was designed to avoid an impact on supply, allowing patients to make their own informed decision about whether to use a product. But from the plasma industry's perspective, this was seen as a dangerous option, one which entails liability and financial risk. Dr. Schonberger argues that the failure of this "safety valve" means that the withdrawal policy must be reevaluated.

While the threat of shortages is represented by the American Red Cross and the pharmaceutical industry as a "real" risk, one that can be quantified through the collection of statistics, the solidity of this representation is called into question by others. Dr. Wolfe argues that from his own experience, industry will often claim shortages, or the potential for shortages, where none exist:

> I will tell you a quick story since you gave us a story. My transition back 26 years ago from NIH, where I was happily working, to starting the group I did was occasioned by a company claiming that there was a short supply of intravenous

> fluids. It was Abbott Laboratories who were then supplying half the intravenous fluids in the country, and it turned out that due to some change in manufacturing there was a contamination in Abbott fluids. They convinced the Centers for Disease Control and the FDA that were there to be a recall, which there was -- there should have been and ultimately was of these products, the nation would be in a crisis because of not having adequate supplies of intravenous products. I called the other manufacturers and it was easily determined that no such crisis would occur.
>
> So I think that there needs to be some verification by the FDA, independent of the claims made by companies that are in some cases accurate but in some cases may be self-serving to avoid the losses, whatever they are and, you know, making it appear as if there is no other way people with hemophilia, or whatever else disease, can do it (TSE Advisory Committee 1997).

Verification of shortages by the FDA, however, may be more difficult than one would imagine. As Dr. Epstein explains:

> I would support that statement, however, I would add that these determinations are very difficult and that they come with a very high degree of uncertainty. We, of course, have had a lot of experience trying to do this in the face of the CJD risk-related withdrawals and we have been faced with situations in which we have been told that major suppliers have no inventory, or that half of all inventory is impacted, or that all product made for the next four to six months will be impacted. Routinely, we do not know how much of the product which is on the market has already been consumed. We can learn easily what percent of lots on the market are affected but we don't necessarily know what part of supply that is either for that particular manufacturer, let alone for the entire nation's supply.
>
> There are also kinetic factors that are close to impossible to work out, such as how much inventory is distributed, how much is in hospitals how much is in major warehouses, how much is in the pipeline that could quickly be released etc. We have found that one of the impacts of a consistent withdrawal policy is never knowing how close to the brink we push the system in terms of the availability of these needed products. So the answer is we always try and the answer is we don't generally know (TSE Advisory Committee 1997).

Thus, the tangibility of supply shortages is called into question by a representative of the FDA. Dr. Epstein's description of the variety of factors and uncertainties that enter into the determination of a supply shortage makes this risk appear almost as hypothetical, or as constructed, as that of transmitting CJD by blood.

Adding to this complexity, Dr. Lessin suggests that even if a shortage does occur, this is not as scary as it might seem. Shortages need not entail hardship for patients, but may merely require a rationing of the product to meet demands in the most efficient way possible:

> My experience with the shortage of IVIG a couple of years ago when there was a big withdrawal was that, yes, the product was somewhat hard to obtain. I had about six patients on it at the time. Instead of treating them every three weeks I lengthened the interval to every four weeks. The other companies were able to fill in the gap, where one company was short just exactly the same story that you mentioned earlier. In fact, there was no real effect of shortage. I am sure there are exceptions to those exceptions but at present, with those caveats in mind, I will vote in the affirmative (TSE Advisory Committee 1997).

Meanwhile, Patricia Ewanitz, whose husband died of CJD maintains that the withdrawal of CJD-implicated products is not even occurring as it should:

> I told the doctor he was a blood donor. The doctor told me there was nothing I could do about it now. It was not until a couple of months after his death, after I learned more about the disease, I was advised to contact the blood center so they could trace the donated blood. They haven't gotten back to me yet. They are still tracing it (TSE Advisory Committee 1997).

Patricia's testimony illustrates the potential disjunction between intended management and actual implementation. The FDA's guidance on the topic of CJD and blood does not carry the force of law, and violations may not be punished directly. While the FDA can cite cases when a blood organization contacted them regarding a donation by a CJD-implicated donor, the FDA cannot know whether, by mistake or intention, certain cases do not get reported to them.

As for the hypothetical risk of transmitting CJD through blood transfusion, the committee encountered a continuing barrage of epidemiological evidence which indicated no link between blood transfusion and CJD. Dr. Marian Sullivan of the National Blood Data Resource Center presented the interim results of the CJD

investigational look-back study, which began in 1994 and tracks the recipients of blood from donors who have later been diagnosed with CJD. While the results so far indicated "no cases of CJD...in 179 recipients of blood components from 14 donors who subsequently developed CJD," this statistic was difficult to interpret given the fact that well over half of the recipients of blood die shortly after transfusion

Dr. Mike Souci of the hemophilia study division of The Centers for Disease Control reported that neither continuous monitoring of the 140 or so federally funded hemophilia treatment centers in the United States, an annual review of data from the National Death Index, nor a study of brain tissue obtained from hemophilia patients who died from dementia had resulted in the detection of any cases of CJD in the hemophilia community.

Dr. Robert Will added to the representation of negligible risk by presenting data from a case-control study in Great Britain in which no association between CJD and blood transfusion had been identified. While Dr. Will represented the negative results of the British case-control studies as significant and conclusive, Dr. Ricketts of Canada drew out interpretive problems. First, she pointed out that Will's use of hospital patients as controls presents a problem because they are more likely to have received a transfusions than the average person.

> the weakness of using hospital controls...is an important weakness and you have to be very cautious in interpreting those studies. We know from Canadian data that in one year about 6% of hospitalized patients will receive blood and only 1% of the population will receive blood in that same time period. So hospitalized controls are not appropriate controls for these studies...It systematically makes it unlikely that you will find a difference between the two populations and it must be avoided (TSE Advisory Committee 1997).

Dr. Will, however, maintained that efforts were made to control this bias:

> In all these studies we have used hospital-based controls which does introduce the potential of bias. In the United Kingdom study we have excluded any history of blood transfusion related to the diagnosis of the control case when it was identified (TSE Advisory Committee 1997).

Will did not feel that the potential effect of such bias was enough to invalidate the results of the case-control studies.

Ricketts also took issue with the studies presented by Sullivan and Souci. She argued that the lack of detection does not indicate a lack of underlying transmission. As for Sullivan's look-back study, Ricketts stated that,

> We know that about half of blood recipients die within about 5 years...From the perspective of an epidemiologist, all my population that I want to study is disappearing" and the ones who live are difficult to follow, especially if they move or change hospitals (TSE Advisory Committee 1997).

Even the failure to detect CJD in the hemophilia population, a population with life-long exposure to plasma products, did not convince Dr. Ricketts: "If the incubation period exceeded 30 or 40 years it might be actually impossible to find it inside hemophiliac populations." She explained that other diseases that affect the hemophilia population at significant rates, such as HIV and hepatitis C, decrease the lifespan of hemophiliacs and increase the risk that they will die of something else before they have an opportunity to develop CJD. Souci responded:

> ...your point about AIDS having a shorter incubation period is a good point. These people may be being exposed to HIV and CJD at the same time and, of course, the AIDS will cause their demise before the CJD can express itself. But as we continue on, and there are individuals with hemophilia who have escaped becoming infected with HIV but, nonetheless, have had many years of exposure to these factor concentrates and by continued surveillance we are hoping to pick that up if it is the case (TSE Advisory Committee 1997).

An evaluation of the likely temporal relationship between the time of exposure and the appearance of disease was viewed as important in evaluating the epidemiological data. If CJD were transmissible through blood, how long after someone received a transfusion of CJD-contaminated blood products would symptoms be expected to appear? In other words, what were the temporal boundaries on the potential risk, and when could the committee feel reassured? The sensitizing frame through which this relationship was represented consisted of past experiences with TSE transmission events. Paul Brown proposed three potential metaphors from which estimates of the likely incubation period of transfusion-transmitted CJD could be drawn:

> One is the growth hormone story, peripheral route, intramuscular or subcutaneous, with incubation periods ranging from a few years to 30 years. The second relevant piece of information comes from the story of Kuru, also an environmentally acquired form of these diseases, and the incubation periods there can range up to 30-40 years. They can also be as short as 4 years...The third piece of information is the presumed BSE origin of nvCJD in which the incubation period is likely to be around 10 years because the exposure would have occurred in the mid to late '80s and now we are seeing cases in the mid to late '90s (TSE Advisory Committee 1997).

Brown surmised that on the basis of these metaphors, it was reasonable to expect that the incubation period for blood transfusion transmission would be somewhere in this range. Thus, he derives what he believes to be plausible boundaries for the temporality of CJD blood transfusion transmission risk from analogies with other TSE and other routes of transmission. While any of these numbers may have little to do with the risk now under discussion, it is the most rational way he can think of to try to delimit and contain the risk under discussion.

Schonberger used similar reasoning to suggest that the CDC would have identified a blood product recipient with CJD by this time if blood were infectious:

> at least with the incubation periods that we have observed to date, say, with the growth hormone situation which is probably one of the very lowest contaminations that we can observe...There, we see cases, you know, certainly within the 18-year period. Although it is true we may see cases going on for many more years, we still get those early cases (TSE Advisory Committee 1997).

Dr. Ricketts argued that human growth hormone transmission of CJD may not be an appropriate metaphor through which to interpret the lack of apparent cases of transfusion transmitted CJD. In order to apply this metaphor, Ricketts maintains:

> You simply need to satisfy yourself that blood and human growth hormone are equivalent. If you can do that, then you can use the incubation period and you can make all your models based on that incubation period. But until you can do that -- and maybe someone wants to say that they are satisfied they have that information now, you have to ask the question if it is missed because of a longer one, because of dose, not route (TSE Advisory Committee 1997).

As she suggests, one's interpretation of the epidemiological data comes down to how one weighs the metaphorical fit between potential CJD transfusion transmission and other TSE transmission events. She seeks to call Schonberger's attempts to build a sensitizing frame with reference to these events into question by disqualifying the perceived congruence between the metaphors.

Dr. Schonberger stressed that even if most of the cases have longer incubation periods, he would expect to see at least a few with shorter ones, in keeping with the sensitizing frame of previous experience with TSEs:

> It is true that we get long incubation periods for kuru and other diseases, but not without some of the short incubation cases showing up as well...Secondly, the hemophilia patients, and I assume you accept the statistics we heard today that, given all the lots that a severe hemophilia patient would be exposed to at a very early age, statistically, even though we haven't pinned down where they have been exposed, a substantial proportion of hemophilia patients would be exposed, say, before five years of age or something. Is that fair (TSE Advisory Committee 1997)?

Dr. Ricketts maintained that the lack of evidence of any transmission so far is not reassuring. In this way, she argued, CJD may be different from HIV. For HIV, there were always a few cases which occurred over a short incubation period, even if most of them occurred after a decade. With CJD transmission by blood, however, even a "short" incubation period could be extremely long, perhaps over a decade.

> ...if you used HIV as an example, 2% in 2 years, 50% in 11 years, you will see the 2% cases. That is how you find HIV transmission from a dentist. You count on the short incubation period cases to give you that. In this case, I am not confident that we know what the incubation period would be in blood, and a short incubation case may be 10 or 15 years. It only makes it more difficult. It is extraordinarily reassuring that none have been found, but it does make it much more difficult and in asking yourself the question could we have missed the cases, the answer has to be yes (TSE Advisory Committee 1997).

By playing on the metaphor with HIV, Ricketts calls into question the committee's attempts to delimit the temporal boundaries of risk through analogical reasoning to other TSEs. She suggests that despite such rationalistic efforts to numerically establish the limits at which no risk may be said to exist, such efforts may, in the end, have nothing to do with the properties of the disease, which remain unknown.

Donald Tankersley, a consultant for the plasma products industry, proposed "an alternative way of looking at the risk of exposure to CJD by recipients of plasma derivatives." His alternative was statistical in nature, and relied on an estimate of the incubation period of sCJD through an anlogy with Hgh transmitted CJD.

> Now, we don't know the extent of the incubation period [for sCJD], but in recipients of pituitary-derived growth hormone it may be as long as 25 years... If we assume that plasma may be infectious for 25 years before disease symptoms appear, then one in 40,000 individuals with no other risk factors for CJD will be incubating the disease at any given time (TSE Advisory Committee 1997).

Because there is no way of measuring the incubation period of sporadic CJD directly, Tankersley can only estimate it based on a metaphor with Hgh transmitted CJD.

Application of this metaphor results in a 1 in 40,000 estimate for prevalence of individuals incubating CJD. Tankersley extrapolates this estimate to determine the probability that a plasma pool would contain a donation from someone incubating CJD:

> the probability that a pool of 30,000 plasma donations from normal donors, without known risk factors for CJD -- the probability that this pool will contain at least one unit from a donor incubating the disease is 0.527638 or slightly more than one half.
>
> Now...consider the dura mater graft recipient as representing a risk equivalent to that of two normal donors. That is, that individual contributes his own inherent risk as well as that of the dura donor. Looked at in this way, the risk of exposure incurred by a recipient of a derivative produced from the plasma of 30,000 donors, one of whom who had a dura mater graft, is exactly the same as that of a product produced from 30,001 donors who are without this additional risk (TSE Advisory Committee 1997).

Despite the fact that the incubation period of sCJD remains unknown, and thus his entire numerical analysis may be no more solid than a puff of smoke, his use of statistics makes the conclusion appear concrete and knowable. And despite the fact that he acknowledges the central uncertainty at the heart of his analysis, the assumption that the incubation of sCJD will not only mimic that for the hGH transmitted form of the disease, but will be on the high end of this range, several committee members grasp onto his analysis as if it were the only lifeboat floating in the sea after the sinking of the Titanic. Building on the numbers presented by Donald Tankersley, Detwiler argues that the CJD withdrawal policy would be expected to have a negligible effect on risk:

> I guess I am getting more and more uncomfortable here that I guess the majority of the Committee does feel that there is potential risk. Yet, we sit here and we know that what would be taken out may only be the tip of the iceberg. Is that really being responsible? I mean, if there are unreported cases going into the blood supply; if there are incubating cases -- I mean yesterday we sat and we said dura mater is okay, but you could get dura mater from an incubating CJD patient. Right? But, yet, we said it is okay and there is no way to screen that out right now. We can't screen out. And I am uncomfortable. Are we doing this just because there is no other way out of it, that there is no way to screen the

> population and this is the only way to go? So it is a "feel good." We are making the public feel like we are doing something (TSE Advisory Committee 1997).

Thus, for some of the committee members at least, the representation of CJD as a blood transfusion risk had begun to fade. The epidemiological data showing a lack of transmission seemed more secure, and a statistical analysis of the likely exposure of individuals to contaminated blood seemed to indicate that the withdrawal policy was completely ineffectual.

Dr. Sidney Wolfe, however, takes issue with Detwiler's argument as well as Tankersley's numerical analysis. He argues that in deriving his estimate, Tankersley made the assumption that the infectivity of blood would be the same throughout the incubation period of CJD. Wolfe argues that this is probably an incorrect assumption because "it is most plausible that the amount of infective units in the blood are going to be higher as one approaches or actually gets to the point of having clinical disease." If a person with CJD does not harbor infectivity in their blood until the end of the incubation period, this would invalidate Tankersley's assumption that the blood of CJD victims is infectious for 25 years before symptoms begin. This, in turn, would lead to a smaller estimate of the number of pools which donors harboring CJD had donated thus changing the perception of safety.

Dr. Rohwer, who, like Detwiler, took a liking to Tankersley's numerical analysis, argues that on the basis of his experiments in hamsters, it appears that the amount of infectivity in the blood may be constant over time, lending weight to Tankersley's methodology:

> ...we didn't see any difference in titer in animals taken 40 days after inoculation and taken at clinical disease, 140 days later. And that is consistent with

> experiments that Heino Diringer has done in the past...(TSE Advisory Committee 1997).

Dr. Wolfe is not satisfied, however, that Rohwer's experimentally infected animal model provides an adequate representation of the risk: "These are in animals whose disease arises from inoculation as opposed to what we are mainly talking about, the human disease." Rohwer concedes: "There you have identified a major difference." Thus, the validity of rodent model systems as representative of human disease, once again, is called into question.

Despite his recognition that rodent models can never completely mimic human blood transfusion, Robert Rohwer presents several attempts that he and Paul Brown have made to do so. They designed three different model systems to answer three different sets of questions:

1) Whether and where infectivity resides in the blood of TSE-infected animals
2) Whether the manufacturing process of plasma products is capable of removing infectivity
3) Whether this infectivity can be transmitted by transfusion

To answer the first question, Brown and Rohwer removed blood from GSS infected mice. Because the veins of mice are too small to draw blood from, cardiac puncture was utilized to obtain blood from the animals. The blood was then mixed with blood from other infected animals and separated into components. From the plasma, cryoprecipitate was produced and initial fractionation was conducted in a scaled-down manner to give fractions I+II+III, IV, and V. In order to answer the question at hand, of whether infectivity was even present in these components, Brown and Rohwer wanted to use the most sensitive method available for detecting infectivity, intracerebral inoculation. While Rohwer and Brown tried injecting undiluted blood samples into the

brains of mice in order to enhance the sensitivity of this assay, they quickly found that this was toxic. Thus, they tinkered with dilutions until they identified the minimum dilution which they could inject into the animals without killing them. They then followed the assay animals for over a year to count how many infections took place. Figure 3.1 shows the results of this experiment, as expressed in the number of animals that became infected out of the total number inoculated by the intracerebral route with the given blood component or plasma product.

No infectivity was detected in whole blood or red cells using this method. Because infectivity was detected in platelets, buffy coat, and plasma, which are components of whole blood, Brown and Rohwer suggested that despite their failure to detect it, whole blood must contain infectivity. They hypothesized that they had not inoculated enough material into enough animals to detect the low amount of infectivity present. Brown and Rohwer further postulated that the infectivity in blood may not be homogeneously distributed. They suggested that the lack of detection of infectivity in red blood cells could be accounted for by similar reasoning. Thus, they described away this anomalous result by maintained that if they had inoculated more animals with whole blood or red cells they would have detected infectivity.

The finding of infectivity in plasma was wholly unexpected. At the time, most TSE-researchers hypothesized that if there was infectivity in blood, it would be cell-associated. This hypothesis was based on the results of previous studies which had detected infectivity primarily in the buffy coat, a blood component full of white cells. Plasma, on the other hand, is largely a proteinacious liquid. The detection of infectivity in

plasma, said Rohwer, was "a big surprise for us." He admitted that they "had expected all of the infectivity to be in the white blood cell fraction."

Dr. Prusiner demanded an accounting from Dr. Rohwer of these surprising results. Rohwer responded that: "What it suggests to me is that we have been mistaken, and certainly I was mistaken" about the location of infectivity in blood. It also troubled the committee members that Brown and Rohwer were able to detect infectivity in cryoprecipitate, from which Factor VIII is made, and Fractions I+II+III, from which immunoglobulins are produced.

Because it is difficult to follow the partitioning of infectivity in the model system due to the low levels of infectivity in the blood of TSE animals, Brown and Rohwer created a different model system in order to track the partitioning of infectivity more carefully. The system they developed was designed to "mimic" high levels of infectivity in blood by "spiking" it with infectious brain material. They started with human blood and added trypsinized material from the brain of a hamster dying of scrapie. After mixing well, they separated and fractionated the blood.

In order to get as precise a measurement as possible of the concentration of infectivity in each level, they titrated the infectivity:

> Each one of these components and fractions was then serially diluted 8 times. These are 10-fold serial dilutions. Each dilution was inoculated intracerebrally into 4 recipient hamsters, or a cage full of hamsters. These animals were then put on the shelf and watched until they came down with the disease (TSE Advisory Committee 1997).

Such an experiment is expensive and time and space intensive. If there are 10 measurements to be made and each requires 8 dilutions, and then each of these 8 dilutions is injected into 4 hamsters, that's 10x8x4 hamsters = 320 hamsters. Without funding from

the Red Cross, who were eager to have this experiment done, such an experiment would have been difficult to conduct.

While red cells, plasma, and buffy coat seemed to harbor equal amounts of infectivity, they saw, "some dramatic changes" when it came to the plasma fractionation process. "We got vast reductions in going from plasma to cryo" and progressively greater reduction as they went through the Cohn fractionation process. The first pellet that is precipitated from the supernatent of the cryoprecipitate, fraction I+II+III, contained 100-fold less infectivity than plasma, while the next pellet, fraction IV, contained 100-fold less than fraction I+II+III, and fraction V contained about 100-fold less again. That's a reduction of 1,000,000-fold in going from plasma to fraction V, from which albumin is made. According to Rohwer, "the point I want to make is that such infectivity as we did recover from plasma was mostly in this cryo fraction and in I plus II plus III...Recovery from albumin was extremely low, 0.00008."

While Brown and Rohwer's results were the first to quantitate the removal of infectivity during blood and plasma processing, Rohwer notes that: "the relevance is unknown" because they had relied on an artificial system of "spiking" the blood with highly infectious brain material to get these results. "We don't know whether we are just simply looking at the way in which brain homogenate in this case fractionates by these same procedures" (TSE Advisory Committee 1997). It was possible, Rohwer admitted, that the infectious agent could adopt a very different form in blood, making the "spiking" results inapplicable.

All in all, Rohwer expressed the sentiment that the two experiments they had conducted, one with mice infected with GSS, and the other with human blood spiked with

hamster scrapie brain, led to consistent results concerning the ability of the plasma fractionation process to remove infectivity:

> ...what infectivity we found in the plasma fractions was in the cryo and in I plus II plus III. This is exactly what you would find for non-envelope viruses as well in these same types of fractionations. There was, however, a big overall reduction in total infectivity recovered from plasma fractions compared to the infectivity in whole blood (TSE Advisory Committee 1997).

For both of the experimental models described above, however, infectivity was measured by inoculation directly into the brains of rodents. This is a fairly artificial route, as people do not receive blood transfusions via the cerebral cavity. This left Rohwer wondering if he could do a better job of modeling the actual blood transfusion process. Rohwer struggled to create a model system using a small rodent which could sufficiently mimic blood transfusion. Although it is impossible to mimic exactly, in an animal that harbors 5 ml of blood in its entire body, a process done in humans with 5000 ml of blood, Rohwer tinkered with alternatives. After many pitfalls and tribulations, he finally settled on a model involving the collection of blood from an infected hamster by cardiac puncture and transmission of this blood to another hamster by cannulation of the carotid artery. Using this method, Rohwer observed one transmission out of 22 attempts. He framed this result as statistically uninterpretable:

> ...right now we don't know whether this represents 1 in 22 transfusions would do or 1 in 22 million. There is no statistic that we can attach to this number. Was this a fluke or is it something that would happen regularly if we had a large enough cohort?" and it occurred after a long time, 261 days (TSE Advisory Committee 1997).

While this was the most realistic model system of blood transfusion to date, albeit using hamsters, the result remained obscure and difficult to utilize for decision-making. Rohwer assured the audience that, "we have another 100 transfusions under way, which I

hope will give us some sort of [interpretable] statistic." And so, despite the entrance of ever-more animal data into the debate, the relevance of this data remained an issue, limiting its effect on the debate. The only result which was deemed to be convincing enough to merit a change in policy was the extreme reduction in infectivity in going from whole blood to the fraction from which albumin is produced. As the chair of the committee, Paul would push for, and succeed in getting, an exception to the withdrawal policy for albumin.

While in theory unnecessary to consider the issues at hand, a working model of the infectious agent in blood – a visual image of where it might be located, a rationalization for its presence, and a concept of its state – becomes a point of contention among committee members. Bob Rohwer, in describing the impetus for his experiments, says that he never perceived a reason why the agent should necessarily be present in blood. Metaphorically, he perceives the spread of CJD as akin to the spread of polio, which occurs along nerve tracts. Dr. White, however, takes issue with Rohwer's image of the spread of CJD. Drawing on metaphors with kuru and BSE, he argues that it must be able to pass through the blood to get to the brain.

> I don't seem to have a problem with something being in blood. I mean, that doesn't mean I think it is there but Kuru, BSE, they all have to get from the stomach to the brain. The only way that I can think of that they can get from the stomach to the brain is through the blood (TSE Advisory Committee 1997).

Given the new evidence submitted to the committee, Dr. White complains that the situation is less clear than it had been before the meeting started:

> Well, for a guy who has been educated all day, I feel more confused than ever on this topic. When we last visited this I guess we didn't have a lot of epidemiological data and we had some experimental data that said that these agents were probably not transmitted by blood. Now we have a relative lot of epidemiological data which says it isn't transmitted, but we now have some

> experimental data that says it is. So I am kind of left in the middle and don't feel like we have necessarily progressed a whole lot from where we were the last time we visited it (TSE Advisory Committee 1997).

Despite the worrying laboratory data, several participants downplay the metaphorical fit between the rodent model systems and human transfusion, choosing to weigh the epidemiological evidence more heavily. Meanwhile, Dr. Michael Hansen of the Consumer Association of America, during the public hearing, urges them to continue and extend the withdrawal policy based on the laboratory results.

On the basis of the complementary laboratory results from the spiking experiment and the GSS infected mice, Paul Brown proposes that the committee recommend excluding albumin from withdrawals. Albumin is derived from fraction V of the Cohn process, and according to Brown and Rohwer's spiking experiments, it contains only .00008 of the infectivity introduced into the original sample. Brown surmises that albumin "is so close to being zero risk and it is such an important element as an excipient that I would propose a blanket exception for albumin." He represents this proposal as a win-win situation which would have major benefits for the availability of products, given that albumin is so commonly added as an excipient.

Some of the committee members express exasperation at imposing a hierarchy on a risk that is hypothetical to begin with. To parse the level of risk even further, two suggestions are made for exceptions to the exclusion of albumin from withdrawal protocols. Dr. Asher of the FDA reminds the committee that albumin is used in certain childhood vaccines, and that failure to withdraw a CJD-implicated batch of vaccine may lead to a parental uproar. Dr. White suggests that from the perspective of the hemophilia community, all plasma derived factor VIII carries the inherent risk of CJD transmission,

since it is produced from plasma pools that are likely to contain at least one donation from someone with the disease, as previously estimated by Donald Tankersley. On the other hand, recombinant factor VIII has no inherent risk, since it is produced from bacteria. In this case, the addition of CJD-implicated albumin adds a hypothetical risk where previously there was none. Brown responds by incorporating the suggested exceptions into his proposal.

In the end, the committee votes unanimously to endorse Brown's proposal to exclude albumin from withdrawal, provided neither of the two exceptions applies. The committee also voted to recommend that secondary products in which the CJD implicated plasma product is added as an excipient should be treated the same as primary implicated products (i.e. they should be withdrawn unless there is a shortage, in which case they can only be released with proper labeling of the risk). Three committee members dissented to this recommendation: Detwiler, Houston, and Tramont. All three of them based their dissenting vote on their evaluation of the numerical analysis provided by Tankersley, which estimated that over half the pools from which plasma products are produced contain at least one donation from someone incubating CJD. This provides another example of the power of numerical analyses to influence the perception of risk despite the extensive assumptions required. By producing a statistic, a representative number, Tankersley to some extent, and for some committee members, succeeded in masking all of the unknowns regarding the length of the incubation period and the time at which the blood becomes infective. With these unknowns fading into the background behind the solidity of the statistic he had produced, it is no wonder that support for the CJD withdrawal policy began to fade. Based on the same sort of numerical analysis, this time

conveyed by Robert Rohwer, it would fade even more at the next Blood Safety and Availability Committee meeting.

A New Metaphor?

Importantly, this was the first TSEAC meeting where the issue of nvCJD and its possible transmissibility through blood was raised. It was brought up by Dr. Will:

> I would just like to finish with something that may be regarded as slightly irrelevant to this meeting but I felt I should put it up for the sake of completeness, in the United Kingdom a new type of Creutzfeldt-Jakob disease has been identified, which has been designated nvCJD which is believed to be related causally to contamination with the BSE agent.
>
> This is the biopsy of a tonsil from one of these cases that was obtained at postmortem and shows PrP immunostaining. It was within the tonsilar tissue. We believe that in a number of cases of classical CJD where the tonsil has been looked at, for example, from Japan, there is no such staining in the tonsilar tissue. We believe that this, amongst other things, does raise the possibility, at least a theoretical possibility, that although the risks from blood in classical CJD we regard probably as very small indeed, with really no good evidence of transmission in blood from the epidemiological data, such as it is, there is a theoretical possibility that in nvCJD the relative risks may be different (TSE Advisory Committee 1997).

Even though the UK has no withdrawal policy for CJD-implicated blood products, Will pointed out that the UK was more concerned about nvCJD. This heightened concern, he suggested, was due to the differential distribution of infectious material in the body, especially the large quantities detectable in lymphoreticular tissue, which is in a functional relationship with the blood stream.

Mr. Faitek, a hemophiliac on the committee, asked if there were any evidence that nvCJD might be more infectious. Will replied that:

> ...there is no direct evidence at all. This is a theoretical possibility.

> But what I did put up was a slide of a tonsil which does contain lymphoreticular tissue, which is apparently important in many of these diseases and replication of agent. It is also associated quite closely with the blood system. What I was suggesting was that at least in the very small numbers of cases in which we have information it looks as though the amount of staining in the tonsils of nvCJD is significantly higher than on current evidence in classical CJD. The implication of that could be that there might be more infectivity in blood in nvCJD. But there are a number of steps to this argument and I think it is still a hypothetical argument, but I think it is an important issue for us (TSE Advisory Committee 1997).

Rohwer argued that nvCJD is a more important risk to worry about with respect to blood transfusion because while CJD is rare, the size of the nvCJD epidemic is not yet known:

> ...we have no idea where it is going to go epidemiologically. We have only seen 20-some cases so far but the projections are that we might see another 20 or 100 or we might see another 100,000. If it moves in the direction of 100,000, this would have a major impact on the total number of people bearing infectivity in their blood, and I think this would all have to be reconsidered in that light (TSE Advisory Committee 1997).

In a way, Rohwer suggest, the similarities between HIV may be a better metaphor for nvCJD than for CJD. nvCJD was a new disease with unknown properties, much like HIV was before the transfusion transmission occurred.

Meanwhile, throughout the meeting, the metaphorical fit between HIV and CJD was increasingly called into question. As one committee member comments:

> There are immense differences between these two diseases which must be taken into account in our considerations here. AIDS was a newly emergent disease in the '80s. Everything changed with the emergence of AIDS. It is a high titer blood-borne disease. In comparison, Creutzfeldt-Jakob disease is probably an ancient disease. It has certainly been around for at least 100 years. The titers in blood are very low titer. It is principally a CNS disease. The main advantage that we have with AIDS is that we can effectively screen for it; with CJD we can't (TSE Advisory Committee 1997).

Dr. Schonberger of CDC worries that the history of AIDS is leading to overreaction with respect to CJD:

> I understand from what was said before that a lot of this policy and this problem stems from mistakes made in the past with regard to the AIDS epidemic. I was personally involved with the AIDS epidemic and was involved in making the decision that blood was, indeed, transmitting disease to patients. We did an analysis on that, and I do feel, and I do agree that we were slow in our response. That is, the government was slow in its response to that issue. But I don't want our slowness in response to that issue to create a second mistake now by overreacting to a theoretical risk without it having an easy kind of solution to reduce that risk (TSE Advisory Committee 1997).

By calling the metaphorical fit between HIV and CJD with respect to transfusion transmission into question, the committee members were beginning to weaken the argument for CJD withdrawals. At the same time, a new metaphor, that between HIV and vCJD, began to take shape.

BSAC considers CJD and vCJD

In October of 1996, as recommended by the IOM report, Donna Shalala had established an advisory committee that would report to the deputy DHHS secretary, David Satcher, on matters pertaining to blood safety. The Blood Safety and Availability Committee (BSAC) would be comprised of representatives of the blood industry, hematologists, ethicists, and representatives from various implicated patient organizations. Importantly, the committee's purview was designed explicitly to address availability, cost, and the concerns of patients' groups, as well as safety.

When BSAC first discussed the CJD withdrawal policy, albeit briefly, in April of 1997, the history of transfusion transmission of HIV was brought to bear through presentations as well as commentary and questions by hemophilia activist members of the committee, such as Dana Kuhn. Dr. Glen Pierce of the NHF contextualized current concerns about CJD through the metaphor of AIDS.

> We need to know the risk before we use these products. No more can we treat until we find out after a period of scientific study whether or not the products are safe, and of course, this principle applies not only to the coagulation factor products but to all blood products (TSE Advisory Committee 1997).

Dr. Pierce commended the CJD withdrawal policy.

During the public hearing, Angie Hendrickson introduced herself as "one of those untrusting people" who has a son with hemophilia and AIDS. She expressed concern not about CJD, but vCJD, and urged the committee to prevent human mad-cow disease from entering the blood supply. "My son has been exposed to a lot of diseases. I have him on videotape sticking an IV needle into his arm looking into a camera saying, "You mean now I might get mad cow disease?" There was no time, however, to discuss this issue, as other items dominated the agenda.

When BSAC met again on January 29th and 30th, 1998, it was with the sole purpose of discussing the CJD withdrawal policy. Rohwer presented the results of the spiking, endogenous, and transfusion rodent model systems. In addition, he built on the risk analysis Donald Tankersley had presented at the TSEAC meeting, presenting a statistical representation of the risk of CJD inherent in every plasma pool. He maintained that the current policy of withdrawals for CJD implicated products is at best futile and at worst deceptive:

> What is our exposure to CJD infection? The incidence of clinical CJD in our population, in the population worldwide, is about one case per million persons per year. That means that in the United States we should expect about 250 cases in our population of 240 million people. This, however, isn't the whole story because CJD has a long incubation period that can range from a minimum of two years in iatrogenic transmissions where it's inoculated directly by accident, by medical accident, into the brain of a person, to we know from one of the human growth hormone transmissions and also from Kuru, which is a long story, that the infection can take up to 40 years or more.

> So the true prevalence in our population must be this incidence times the incubation time, whatever it is...If we had a 40 year incubation period, then we would have one carrier per 24,000 donors. If we had a 20 year incubation period, it would be one carrier per 48,000 donors. Ten year incubation period, one per 96,000 donors. We don't know what this number really is, but we're in the ball park of having a donor for practically every pool of 60,000 donors. Well, knowing this, does it make sense to withdraw product on the basis of the few Creutzfeldt-Jakob Disease cases that we have identified?
>
> We can't differentiate, I don't feel we can differentiate pools on the basis of these occasionally identified cases. The great bulk of the exposure is from the undiagnosed cases, the carriers that are out there in the population. And as a consequence, virtually all pools must be exposed to this stuff. And just picking on a pool because we happen to know that a CJD donor contributed to it really gives us a false sense of security. It's misleading (Blood Safety Advisory Committee 1998).

Here we see the transference of a numerical argument from one meeting to another, though through a different medium. Rohwer has adopted Tankersley's technique and made it his own. As Rohwer represents it, the current CJD withdrawal policy is accomplishing little in terms of risk reduction. It is, rather, providing a false sense of security. The longer the incubation period, the higher the number of people who would be walking around with the disease, and the higher the number of people who would have donated to a plasma pool while incubating. This choice of input assumptions gives him the result, along with another set of assumptions about how many of these people would be donating blood and how many donations are included in a single pool, that almost every pool would contain at least one unit of plasma from a CJD donor. More and more, this type of calculation is beginning to take on the character of a significant argument against the possibility that CJD blood is infectious. Just as Tankersley's calculation convinced some TSEAC committee members that CJD withdrawals were providing a "false sense of security", Rohwer's calculation would become a determining factor in BSAC's decision to recommend a relaxation of the CJD withdrawal policy.

Rohwer points out that if CJD were transmissible by blood transfusion, the real fear would be the production of a silent chain of subclinical amplification, which could grow the disease to epidemic proportions without anybody knowing it. But how real is this possibility? While it may seem very real to some, such as those who were just affected by the HIV/AIDS epidemic, Rohwer indicates that this fear is overblown. In this vein, he steers the discussion toward nvCJD, which he perceives as a much greater risk.

> The big question in everybody's mind, the big fear, is that this will follow the same course that cattle took after 1985 and turn into something like this. If we have a big subclinically affected population of New Variant Creutzfeldt-Jakob Disease, one, the number of people, the level of exposure may be far greater to these diseases than we are currently considering, and also there is something different about this disease. I am not at all confident about extrapolating the work that we have done using classical Creutzfeldt-Jakob Disease and sheep scrapie to this particular disease (Blood Safety Advisory Committee 1998).

Because vCJD is a newly emergent disease, the size of the epidemic is unknown, and the transmission factors are unpredictable, Rohwer sees vCJD as more of a concern to blood transfusion based on the HIV metaphor than CJD. HIV, like vCJD, was newly emergent, possessed unknown transmission properties, and would generate an epidemic of an unpredictable size, when it was first discovered in the 1980s. By addressing vCJD in the opening presentation, Rohwer sets the tone of the meeting. Unlike the TSEAC meeting, where vCJD was mentioned but the discussion centered squarely on CJD, the BSAC meeting, from the very beginning, establishes a course that shifts back and forth between the two.

Following Rohwer's presentation, Schonberger presents the recent surveillance data for CJD in the hemophilia population. Once again, however, the counfounding variable of intercurrent AIDS deaths in the hemophilia population is brought to bear. This

time, the topic is introduced by Dana Kuhn, a hemophilia activist infected with HIV who sits on the BSAC committee.

> It seems my perception that the reason that there was no CJD evidence of cause of deaths in hemophilia between 1979 and 1995 in your slides is more than likely they were AIDS deaths, and so that number might be a little bit skewed with statistics there. Also, I think there probably hadn't been autopsies or clinical autopsies done on those AIDS death. I know you've done 29, but I understand from Bruce Evatt that there is approximately 1500 AIDS dementia deaths in hemophilia. Now, I know they haven't had clinical autopsies either. I know you're starting studies on that. So I think that, I mean I feel like it's kind of inclusive, you know, whether or not those were CJD deaths at that point (Blood Safety Advisory Committee 1998).

Schonberger defends the data by pointing out that some hemophiliacs live into their 50s and 60s, "So even though AIDS did devastate the population, there's no question--it's a terrible tragedy--there are still many of them that are older." Schonberger admits that the data is not definitive, but urges the committee to view the withdrawals in the context of the supply issues they cause. In a contrast to his lack of concern about CJD, he too brings up the scepter of vCJD as the rising threat to the blood supply:

> What is more of concern is what you'll hear about from Rob Will, which is the New Variant CJD, and the reason that that's of more concern is that in part is not only what we do see from it shows that it seems to be behaving differently, and we don't have as much experience (Blood Safety Advisory Committee 1998).

Both Robert Rohwer and Larry Schonbereger frame the issue of nvCJD as a much greater potential problem for the blood supply than CJD. This forms a sensitizing frame for Bob Will's presentation, which comes next.

Bob Will begins by discussing the European policy towards CJD, where the decision was made not to withdraw. Bob Will illustrates that the risk balance issues can be constructed differently. This destabilizes the inevitability of the US policy. And to

show that the UK is not simply avoiding the management of risk, Bob Will contrasts the reaction to CJD with the reaction to vCJD:

> we do not do withdrawals with classical CJD in the United Kingdom, but we have recently adopted a policy or the government has of suggesting that they should be withdrawals of product from all individuals with New Variant CJD who have acted as blood donors, and so far we have found four out of 23 cases who have previously been blood donors with New Variant CJD and active withdrawal of product has taken place (Blood Safety Advisory Committee 1998).

The decision to withdraw 100% of nvCJD implicated product was based, as he states, on the apparent ways in which nvCJD differs from CJD, which include: its newly emergent quality and unknown properties, the young age at which disease strikes, a longer disease course, and the presence of PrP in lymphoreticular tissues, such as the spleen and tonsils.

On the cause of vCJD, Will speculates that:

> If BSE did enter the human food chain in the United Kingdom, as I think it almost certainly did, probably brain and spinal cord tissue, I think most likely spinal cord tissue in mechanically recovered meat, then this product would not necessarily have been uniformly contaminated with time. It may have been used in different products at different times, and individual batches of individual products might have contained different levels of infectivity. So identifying a common exposure 15 years later may be impossible using case control methodology (Blood Safety Advisory Committee 1998).

His mention of spinal cord tissue and brain from cattle as the likely route of transmission to humans will become a major theme in the discussion that follows. The image he presents of young women and men eating these neurological tissues without even knowing leaves a residue that will shape the committee's consideration of the topic, despite their stated purview over blood and not meat.

He leaves the potential size of the epidemic as an unknown that is open to speculation on many levels.

> You...have...a number of variables...including critically the incubation period and incubation period spread, which affects these numbers enormously, and of course we cannot know what the incubation period mean would be if BSE is spread to the human population. And you can get figures of only 100 or so cases, which is what we hope will happen, but you can get very much larger numbers depending upon the incubation period, up to 80,000 patients in a very long incubation period, and higher figures if you extend that (Blood Safety Advisory Committee 1998).

Bringing the conversation back to the context of blood, Will notes that:

> The current situation in the United Kingdom therefore is that there are unknown numbers of individuals who may be incubating New Variant CJD...Some of these individuals may be donating blood and may have infectivity in the blood, which can be present well before the onset of clinical disease. So we are in a new situation in which we have a new infectious agent affecting the human population. I personally don't think that the relatively reassuring evidence from classical CJD in relation to blood can be used as an argument in this instance because it's a new type of infectious disease in a way. Any observational data about what happens with recipients of the donations from the New Variant cases will take years to accumulate...(Blood Safety Advisory Committee 1998).

Following Will's presentation, several of the committee members embark upon the discussion of whether the US should have its own ban on the inclusion of potentially infectious cattle parts, such as brain and spinal cord, in human food. Continued discussion on this topic is evidence that while BSAC is charged with advising on the protection and management of the blood supply, the committee has begun to interpret its role as extending beyond blood specifically, and outwards towards other factors that may influence the safety of the blood supply in the future.

This extension is not inevitable. Very little discussion centered on this topic at the recent TSEAC meeting, despite the fact that the issue was raised by Michael Hansen, a consumer advocate. This indicates that the introduction of a topic is not enough for the topic to assume a significant role in the discourse and activity of the committee. Rather, significance emerges when the topic is taken up by a substantial number of participants.

This transforms the factor into a "significant" element in the perception of risk. Once this has occurred, the element seems to take on a life of its own, driving discussion in certain directions. The element develops an agency not unlike that of a fellow participant, continuously calling attention to itself. Only it cannot speak for itself. It takes form only through the voices of others, its spokespersons. The transformation of a factor into a significant element is a bit like a positive feedback loop in that the more times it is mentioned, by the greater variety of participants, the greater its power becomes.

Dr. Gibbs, the now elderly scientist from Gajdusek's lab who conducted, with Paul Brown, the studies which failed to detect transmission from the blood of CJD patients to chimpanzees, calls into question the detection of CJD in human blood through rodent bioassay. He suggests that the researchers may have accidentally contaminated their blood sample with nervous tissue. Not only does Gibbs classify the detection of CJD agent from human blood as doubtful, but he raises the issue of whether the focus on blood is entirely misguided. He wonders aloud whether the real threat might come from a completely different area:

> I had a call from Geneva just yesterday wanting to know does the United States have regulations on transplantation surgery on donors? And I checked with Dr. Asher at the Food and Drug Administration, and there is limited regulation on I think corneas and skin and heart valves and things of that sort, but on heart organs, there is really no written regulation on that. I'm more worried about that than I am about the blood. I have cases where the patient has had an automobile accident, goes into a coma, never recovers from the coma, had already agreed to donate his organs after death, organs were taken for transplantation and finally somebody looked at the brain and found out that, in fact, he had Creutzfeldt-Jakob Disease. And that's going to happen again and again and again unless we get a good diagnostic test that can--you know, transplantation surgeons are sitting like those birds in the tree waiting for them to die so they can grab the organ fast enough, and it even gets down to the nitty-gritty of the ethics of when is life waning and who's going to make that decision. Is it brain dead? Is it cessation of heart beat (Blood Safety Advisory Committee 1998)?

Gibbs points to the possibility that the metaphor with HIV may have shaped the risk perception of CJD in ways that have diverted attention from other, perhaps more significant, risks. He comes out in clear opposition to the CJD withdrawal policy, citing the UK policy as an alternative. In doing so, he demonstrates the utility of the UK policy as a counter-image for conceptualizing a reconstructed American response to the issue

Mr. Cavenaugh of COTT expresses his concern that the common representation of the supply of blood products as inherently limited is mistaken. He believes that the perceived dichotomy of CJD risk management vs. supply is constructed and malleable.

> The ongoing juxtaposition of safety and supply at opposite ends of the graph only serves to constrict the range of options. When new deferral standards or policies are recommended or implemented such as the 1996 CJD decision, the manufacturers inevitably claim that these policies will lessen the donor pool, thereby negatively impacting the supply of plasma derivative products.
>
> We cannot count the times we have heard from industry that quote "the adoption of broader screening standards and more restrictive deferral policies will result in a significantly reduced supply of products you depend on." This is true only if we accept the proposition that the potential donor pool in this country has already been tapped to the maximum. The potential donor pool has yet to be tapped (Blood Safety Advisory Committee 1998).

All it would take, he argues, is one well-orchestrated nation campaign to improve the blood supply and make blood products more accessible. He feels that hemophiliacs, after all they have endured, deserve such a campaign:

> Simply stated, we have had enough of being the nation's blood supply guinea pigs and test rats. We have already done our part and have shouldered two devastating and deadly epidemics, HIV and hepatitis C. We are tired of addressing these critical safety issues in a vacuous and compartmentalized fashion that never places the questions in the much larger context that they actually occur within (Blood Safety Advisory Committee 1998).

Ms. Hamilton, of the Hemophilia Federation, also frames the issue in terms of the hemophilia community's experiences with AIDS:

> Does anyone hear an echo? An echo which eerily reminds us of the early 1980s? Are we once again being led down a path which will attack and eradicate several thousand more persons with hemophilia? We are constantly being put in the position of having to take the risks and our community is woefully tired of being the canaries in the coal mine even if the risks are perceived (Blood Safety Advisory Committee 1998).

While both of the representatives from hemophilia organizations argued for more restrictive measures relating to CJD, and for a continued vigilance and precautionary stance in reference to transfusion risk, the next speaker, Dr. Winkelstein, representing the Immune Deficiency Foundation (IDF), took the opposite stance.

According to Winkelstein, recent shortages have devastated the community:

> The consequences of this real shortage are very significant to the patients with primary immune deficiency diseases. Attempts at lowering the dose or stretching the dose out to an unacceptable interval, skipping doses altogether, all of these things, put patients at significant risk for life limiting or life threatening infections. I should say that I personally have seen many patients who for one reason or another have not received their gamma globulin and that then developed a serious infection and died, the most recent of which had his first anniversary of his death on January 16 (Blood Safety Advisory Committee 1998).

While admitting that it is difficult, if not impossible, to determine the exact cause of a shortage, he argues that CJD withdrawals have played a significant contributory role.

Dana Kuhn, however, pushes Winkelstein on the issue. Winkelstein admits that there may be other factors contributing to the shortage of IVIG. Dr. Fiegal of the FDA points out that an increase in demand for the product may account for much of the shortage:

> ...we have had other time periods where we've had this same amount of supply, it seems to me more likely that there is an increasing demand for this product. And there is almost an unlimited European demand for this product (Blood Safety Advisory Committee 1998).

His mention of a potential European contribution to the shortage triggers protectionist concern on the part of other participants.

Like the other representatives from hemophilia advocacy organizations, Mr. Coburn of the NHF cites the history of HIV/AIDS as the reason a precautionary stance should be taken towards CJD:

> The hemophilia community, as you've heard, has been devastated by the spread of HIV through the use of regulated blood products in the 1980s. I have witnessed first hand and I have personal experience in dealing with the consequences of that period. As a result, we should be extremely cautious before easing any restrictions as they relate to the safety of the blood supply (Blood Safety Advisory Committee 1998).

Unlike the previous hemophilia representatives, however, he clearly differentiates CJD from vCJD, suggesting that vCJD may be more of a concern. He argues that approaching the issue from a sensitizing frame that includes AIDS does not contribute to overreaction, but rather to a healthy vigilance towards the safety of the blood supply.

Dr. Davey of the American Red Cross reminds the committee that his organization has seen 11 withdrawals for CJD risk since July of 1997 alone, and that this has contributed to a loss of $120 million worth of product over the past few years, leading to substantial shortages of IVIG and albumin. Representatives from hospital association and plasma products associations present data supporting the premise that shortages are being caused, at least in part, by CJD withdrawals. In their view, the CJD withdrawal policy should be reconsidered.

Before adjourning the meeting for the day, Dr. Caplan again raises the topic of food as an upstream source of contamination to the blood supply, arguing that the committee, despite its narrow purview, should be allowed to consider such issues:

> I mean one way to keep the blood supply safe is to make sure that things don't get into it. If we're not convinced that there's enough vigilance with respect to the monitoring of animal populations or with respect to food supply or whatever it is, then my personal view now is that we should say something about it (Blood Safety Advisory Committee 1998).

While Caplan is clearly concerned about vCJD and its potential to comprise a transfusion, threat, he calls into question the current CJD withdrawal policy:

> What does the committee think about the tradeoffs currently made under existing policy including withdrawals to handle the supply? Are we winding up by being risk averse with respect to CJD or other transmissible agents leaving the availability of supply too low for people who need it (Blood Safety Advisory Committee 1998)?

He clearly perceives the shortages as "real", numerically verifiable, and at least to some extent, caused by CJD withdrawals.

By the next morning when the committee reconvenes, it is clear that vCJD has become the focus of attention. Dr. Gilcher expresses his growing concern over vCJD in terms of its emergent and poorly understood properties. He suggests that while current CJD withdrawals may have a negative overall impact on health by constricting supply, the vCJD risk should perhaps be more regulated:

> For example, the new variant Creutzfeldt-Jakob agent may be truly be a different agent, and that would be a greater concern to me because that's an agent we want to keep out...I believe that there is a greater risk in an emerging agent as opposed to an existing agent, so that if we're taking out with a withdrawal or even a recall a group of plasma derivatives, I would want to have us focus on the emerging agents versus the existing agents in terms of that, because right now we're having

> withdrawals that are related to the existing agents that, in fact, may be hindering health care (Blood Safety Advisory Committee 1998).

Other members of the committee express their agreement with Gilcher. vCJD comes to be framed by the committee, in opposition to CJD, as a new, poorly understood, potentially more devastating threat to the blood supply. As vCJD comes to be perceived as metaphorically more like HIV in its early days, the metaphor between CJD and HIV breaks down The subversion of the CJD/AIDS metaphor by the vCJD/AIDS metaphor opens up a space for a new course of action – a diminution of vigilance in one direction with an increase in vigilance in the other direction. Such a replacement of concern allows the committee to maintain internal consistency. It preserves a sense of responsibility and care on the part of the committee while allowing them a "break" to recommend removal of one regulation, something which is rarely done, by replacement of another.

Dr. Gomperts argues that his sensitizing frame, which includes the metaphor with HIV, actually generates more concern over the food chain than transfusion transmission of vCJD. He reasons through metaphors with other TSEs which have been transmitted by food in the past. His transference of blood to food exhibits his concern to prevent "upstream" transmission:

> When I look at the issue of TSE and blood transmission, I'm sort of torn in a number of directions. First of all, I tend to be a little perhaps emotional about it because I personally and professionally have gone through the HIV epidemic, and I don't want to go through another one. And I sort of smell, sense that something could happen...
>
> Looking at what's happening and what has happened, we do know that this infectious agent...can be transmitted and has reliably been transmitted through the food chain. And this we have seen among the New Guinean natives, the people. We've seen it with BSE. There was in our own country some years ago an outbreak in the mink encephalopathy episode which definitely was food-transmitted. So we know that major outbreaks have occurred that way, and that is

> going on right now, of course, in Britain...And if we were to prevent this episode within our country, I think we have to focus on what's going on in Europe and what have the British people and government, how have they dealt with it....what I don't see [in the US] is the second major step that the British introduced, and that is the prevention of utilization of animal brain material in the human food situation (Blood Safety Advisory Committee 1998).

Like Caplan, Gomperts expresses a sense of distrust that the agricultural sector is doing all that it can to prevent BSE from taking hold. For both Caplan and Gomperts, concern for better management of BSE stems from concern over the potential future for transmission to humans, both from cattle and among people through blood.

While considering the potential for BSE contaminated tissue to reach the human food chain has clearly become a significant concern for the committee, government officials argue that such concerns fall outside of the committee's purview. They try to set boundaries on the discussion by making comments such as these by Dr. Chamberland:

> ...we may be of better service to the department that has charged the group if we try and really focus most of what we want to recommend specifically on the transfusion-related issues. I've heard a lot of issues about food safety and animal disease and surveillance. And while those are clearly issues that impact on this, I think for our group to delve into them in a very detailed way would probably get us sidetracked to what we've been principally charged (Blood Safety Advisory Committee 1998).

Despite efforts to reign the committee in, the committee persists in its discussion of the food safety issue. They refuse to let their purview be limited by the constructed boundaries introduced by the federal agencies. They have interpreted their charge in their own way, creating a role for themselves where none was officially granted.

The committee members reach a negotiation phase during which they attempt to formulate a recommendation in terms which will satisfy the majority of the committee members, despite the varied social worlds that they represent. First, Caplan seeks to

frame the concern for food-chain transmission prevention within and subsumed by the blood transfusion prevention efforts.

Seeking to draw the committee back to a focus on blood, Dr. Moore expresses her concern that Caplan is getting too caught up in the specifics of the CNS tissue. She suggests that they recommend that another panel, made up of people from all the federal agencies, look at this issue in more detail. Caplan agrees to her suggestion, and says that he is, "willing to make that as a recommendation to a group such as this to answer it on scientific expertise grounds" Dr. Chamberland worries that BSAC is recommending a redundant activity, one which can already be performed by existing committees. What Dr. Chamberland does not tell the committee is that the existing committee in the USDA with purview over BSE is stacked with members of the beef industry. The committee agrees to refer such questions to existing committees.

Dr. Pilliavin suggests that they consider rescinding the CJD withdrawal policy:

> I would like to at least talk about the possibility of changing the current set of regulations regarding recalls based on what we think we really know about the data. I don't think that at the present time traditional CJD is a danger to the blood supply. And what is a danger to the blood supply is all of these recalls that, number one, prevent there being product for people who need it, and, two, drive up the cost of this product so much that even if it is available, many people are not able to afford it (Blood Safety Advisory Committee 1998).

Dr. Moore expresses agreement with Dr. Pilliavin's proposal. In doing so, she draws on another important element, Dr. Rohwer's calculation of the likely number of pools to which a CJD donor has contributed. On the basis of this calculation, she compares the current CJD withdrawal policy to looking for your lost keys under the light because that's where the light is.

Somewhat startled by this suggestion, Caplan asks the committee whether they

are ready to consider a pullback from the CJD withdrawal policy. Some of the committee members express hesitation. Dana Kuhn reminds the committee of what happened when their guard was relaxed against AIDS, and suggests that the epidemiological evidence is not clear-cut enough to eliminate the possibility of CJD transfusion transmission. Dr. Busch begs to differ, considering that "the epidemiology does not support a transfusion-associated risk of this phenomenon." He admits that the laboratory data is concerning, but argues that Dr. Rohwer's calculation of the donor pools which are affected should put the issue to rest:

> The other I think very important scientific analysis that Dr. Rohwer alluded to...the analysis of the relative risk of a derivative that was made from a pool that had a recall versus one that did not. And the truth is, at least the evidence supports that there's a very long preclinical infectious phase. Given the incidence of CJD and the likely infectious prodromal phase, it's very likely that all derivatives are manufactured from product that could be contaminated...(Blood Safety Advisory Committee 1998).

He brings up the concern, so prominent at the previous TSEAC meeting, about providing a "false sense of security" through the CJD withdrawal policy. Dr. Hoots, however, argues that we also don't know enough about the risk of CJD to remove the regulations. "We have to balance all the issues, and I don't personally think I have anywhere near enough information to balance those issues at this time." Dr. Pilliavin argues that the CJD risk is miniscule compared to other risks, like the risk of blood-type mismatch.

Still including HIV in his sensitizing frame for evaluating the CJD risk, Mr. Allen worries that the committee is rushing too quickly:

> We need to learn from the mistakes that were made in the past and make sure, irregardless of the consequences financially, commercially, we don't repeat them. There's got to be some options where we can increase the production of these

> products, be it through smaller pooling sizes, which has been discussed by the FDA (Blood Safety Advisory Committee 1998).

He suggests that there are other options for decreasing risk while maintaining supply, options like limiting the pool size. The majority of the committee, however, ignores his concerns and continues on the path towards rescinding the CJD withdrawal policy.

As for the impact of model systems on the construction of risk, Dr. Gomperts argues that Brown and Rohwer's spiking experiment provides comforting data that even if a CJD risk did exist, it would be removed by current plasma fractionation techniques. He informs the committee that other companies are now conducting experiments on many different aspects of the plasma fractionation process, including chromatography and filtration, to see how much these processes can remove of the CJD agent.

Concerned about the committee's inability to reach a consensus, Caplan proposes splitting the issue into a request by the committee for more information on the blood supply and what is really causing shortages, and a recommendation to the FDA to suspend the CJD withdrawal policy. He even proposes to make this suspension "temporary" by stipulating that it will be revisited in one year. Several of the committee members express comfort in the idea of a "temporary" rather than a permanent suspension of the ban. Framing the decision as "time limited" takes some of the weight off of removing a safety regulation.

Even Dana Kuhn, a member of the committee who previously expressed his opposition to ending the withdrawal policy on the grounds that safety was not yet assured, agrees to a temporary suspension of the policy. He does, however, advocate for full disclosure through labeling. Kuhn's change in stance is influential. As a survivor of

AIDS and a hemophiliac, his acceptance indicates that even those who were the most affected by the HIV/AIDS transfusion epidemic perceive CJD as a lesser risk.

In the end, the committee voted 8 to 5 to "recommend that during the next year the FDA work with industry to relax current CJD guidelines on quarantine and withdrawal of blood products to the extent necessary to relieve product shortages." David Satcher brought the issue to the DHHS Blood Safety Committee (BSC), which is made up of higher lever officials from DHHS divisions (CDC, FDA, etc.). On July 23, 1998, the BSC considered BSAC's recommendation to review and potentially relax the CJD withdrawal policy. A decision was made to rescind the CJD withdrawal guidance. At the same meeting, it was recommended that withdrawals be instituted for vCJD. This was accomplished on September 8, 1998, when the FDA issued a change to their 1996 guidance on CJD withdrawals to meet the DHHS's request. The document made clear that while blood, labile components, and source plasma would continue to be withdrawn for CJD risk factors discovered post donation, plasma derivatives would no longer be subject to withdrawal or quarantine. Deferrals for CJD and CJD risk factors would continue as before. Meanwhile, vCJD was listed as a new cause for withdrawal of plasma derivatives, as well as labile components.

These two poles, CJD as the old and vCJD as the new, form a space in which distinctions can be drawn and actions can be concretized. CJD attained its perceived relevance to the blood supply through a metaphor with HIV/AIDS. Only through its analogy to CJD does vCJD first come to attention at advisory committee meetings. Meanwhile, the opposition between CJD and vCJD, as represented through temporal and spatial qualities, allows for a replacement of the CJD/AIDS metaphor with a vCJD/AIDs

metaphor. Variant CJD comes to occupy the metaphorical space previously occupied by CJD because it is perceived as a better analogical fit with HIV. The qualities which enhance this metaphorical fit are: the emergent quality of vCJD, the distribution of infectious agent in lymphoreticular tissue, and the unpredictable size of the epidemic. My argument is that only through its displacement by a seemingly more appropriate metaphor (vCJD and HIV/AIDS) could the older metaphor (CJD and HIV/AIDS) be expediently discarded. In other words, the previous analogy has not been undermined so much as supplanted. This displacement functions figuratively to reconstruct the perception of CJD and vCJD simultaneously. Within this context of simultaneity, the removal of certain safety regulations regarding CJD is not perceived as a decrease in vigilance towards risk. Rather, the "net" balance in risk management is seen to be maintained by enhancing safety with regard to vCJD, now viewed as the more threatening of the two risks.

In this movement, we can see the reactionary nature of disease management policy. While presented in a rational manner, through the articulation of animal studies, epidemiological reports, and numerical analyses, the advisory committees, in essence, seem to be reacting to the fear of the moment, transferring their gaze as each new threat comes into focus. The problem, as I see it, is that when they transfer their gaze, they remain focused on the avenues through which previous threats have manifested themselves. Indeed, the structure of advisory committees and their mandated focus on blood, after the HIV epidemic and the IOM report, almost ensures this outcome. It seems that if the government really wanted to respond to newly emerging disease in a productive manner, it would endow its committees with greater flexibility in their purview. This lack of flexibility is most readily discerned in the Blood Safety and

Availability Committee's efforts to make recommendations on keeping BSE-contaminated cattle parts out of the human and animal food supply. Every time the committee members venture into this territory, which they deem to be the most important in terms of preventing the threat of BSE from manifesting in the United States and therefore endangering the blood supply and all other imaginable and unimaginable arenas of risk, they are pushed back by the agency representatives who remind them that their purview is blood, and blood alone.

Ch. 5 – TSEAC considers the management of vCJD risk to the blood supply

When TSEAC convened again in December of 1998, the focus had changed from preventing CJD from entering the blood supply to preventing vCJD from entering the blood supply. And yet, almost every aspect of vCJD remained shrouded in uncertainty. Paul Brown, the chair of the committee, opened the meeting in this way:

> We are being asked to consider answers to questions concerning blood safety and new variant Creutzfeldt-Jakob disease without a shred of direct evidence about infectivity in the blood of patients with new variant Creutzfeldt-Jakob disease, which you would think would be enough to dissuade us from considering the question. It is compounded by the fact that we haven't got a clue how many people are walking around incubating new variant disease to begin with. With these two complete holes in our scientific knowledge, we will make a valiant attempt, early this afternoon, to come to policy decision recommendations (TSE Advisory Committee 1998).

By framing the committee's task as caught between two unknowns, Brown makes it clear from the outset that the day's meeting will have many imaginative components to it. Despite the lack of any firm ground to stand on, Dr. Wykoff of the FDA maintains that the committee must persist in generating a response to this potential threat:

> We do not have all the information we might like to have about new variant CJD, particularly its etiology and transmissibility. This lack of information in no way absolves us of our responsibility to take the most appropriate actions to promote and protect the public health (TSE Advisory Committee 1998).

Dr. Wykoff's conviction that the committee must act despite the glaring uncertainties harkens back to the Institute of Medicine's formal admonishment that the FDA should not have waited for solid evidence of a threat to protect the blood supply from HIV. Clearly, the weight of the AIDS crisis is still driving decision-making.

At the two TSEAC meetings described in this chapter, the influence on the committee members of Future Oriented Statistical Projections (FOSPs) predicting

shortages in the supply of blood and plasma products looms large, just as they did at previous TSEAC meetings. Numerous representatives from the blood industry, as well as representatives from the FDA, frighten the committee with numerical predictions of the dire shortages that could occur if, like the CJD withdrawals, vCJD policies lead to massive removal of product. These FOSPs, because they are stated in terms of concrete numbers, convince several committee members to vote against instituting a vCJD deferral policy.

In addition to FOSPs regarding the potential for inducing shortages, another scepter is raised at these TSEAC meetings, in the form of an oppositional structure between vCJD risk mitigation and the risk mitigation of other diseases, such as HIV and Hepatitis C. While vCJD is only a hypothetical blood transfusion risk, these other infectious diseases have been shown to be transmissible through blood. The combined weight of these two concerns convinces six committee members to vote against a deferral policy for vCJD.

Nine of the committee members, however, are still concerned enough about the potential risk that vCJD represents to the blood supply that they vote for deferrals. Though they all express concern about the tensions surrounding this decision in terms of generating shortages or inflicting risk from other diseases, they maintain that through careful compartmentalization of vCJD risk, measures can be instituted that will have relatively few untoward effects. To do so, however, they must define appropriate boundaries for spatially and temporally configuring vCJD risk. They must also bracket the substantial uncertainties that are invoked by establishing such boundaries.

Thus, in this chapter, we will delve into the way risk and its attendant uncertainties are managed by compartmentalization. This compartmentalization relies on the arrangement of risk via spatial and temporal metaphors. By pretending that the risk has clear boundaries around it, and bracketing the uncertainties surrounding this pretension, a temporary image of the risk as rationally manageable may be produced. The bounding and bracketing permits a quantitative approach, a numerical strategy to the manipulation of risk, to proceed. Dressing the decision-making process in numbers, however tentative and uncertain these numbers may be, comforts the committee, allowing them to go forward in their actions. This illustrates the way in which quantitation provides a guise of rationality and controllability, however artificial. Even the guise of rationality is enough to satisfy the committee members, allowing them to settle on a course of action despite the many unknowns and uncertainties surrounding their endeavor.

Assigning Temporal and Spatial Dimensions to Risk

While the FDA had already issued guidance on the necessity for withdrawal of blood components and plasma products from vCJD donors, based on BSAC's advice, the FDA requested advice from TSEAC on whether further risk reduction measures were merited. First and foremost, the FDA asked whether the committee would recommend deferral criteria in an effort to "reduce the theoretical risk for transmitting new variant Creutzfeldt-Jakob disease, by excluding donors potentially exposed to the agent of bovine spongiform encephalopathy." The FDA postulates a list of secondary questions:

A, Should FDA recommend excluding donors who have resided in the United Kingdom or other BSE country.

B, should FDA recommend distinguishing between donors who were resident in BSE countries during periods of higher versus lower risk of exposure to the BSE agent?

C, should FDA recommend exclusion of donors who had less intense exposure to beef product, based on limited travel to a BSE country. When did they travel, how long were they there, and what did they eat?

In its questions to the committee, the FDA is already pointing to ways of configuring the risk of vCJD in time and space. In the first question, they explicate the notion that BSE exposure risk can be spatially defined and contained by national borders. In their second question, they reveal a predilection towards differentiating vCJD risk depending on the relationship in time to a referential point in the BSE epidemic. This indicates a belief in the differentiability of the amount of risk contained within the spatial borders of the UK at different time points. Third, they point to the possibility of temporally configuring risk based on time as a duration or an "amount", rather than a point of reference, the idea being that the larger the "amount" of time one is exposed to the risk factor, the greater one's risk of becoming infected. Fourth is the notion that consumption behavior, in the form of food choice, determines one's exposure to BSE. This is despite the fact that no one can say with certainty which food products may have transmitted the disease.

The FDA asks TSEAC to consider whether they would recommend the same criteria for withdrawal of blood components and/or plasma derivatives. This suggests that either through spatial differentiation in the blood stream or temporal differentiation via centrifugation and the Cohn fractionation process, blood components and plasma products may harbor different levels of risk. As discussed at the previous TSEAC meeting described in Chapter 4, Brown and Rohwer's rodent model systems revealed a

reduction in the infectivity of plasma products relative to blood components, and a reduction of infectivity in plasma products at later points in the Cohn fractionation process. There are other aspects which may serve to distinguish the risk of blood components from that of plasma products. While blood components are derived from one or only a few donors, plasma products are derived from pooled plasma donated by thousands of donors. While pooling multiplies the chances that one will be exposed to product derived from a vCJD donor, it also dilutes the infectious material. In addition, the two can be separated by the effect of withdrawals on supply. Because of pooling, one implicated donor could potentially lead to the withdrawal of thousands of doses of plasma products. Meanwhile, one implicated donor would only lead to a loss of one to ten units of blood components.

Finally, the FDA asks TSEAC to consider whether "a tonsil biopsy negative for protease resistant prion protein is sufficient to make product withdrawals unnecessary." The differentiation of risk implied here is based on the spatial distribution of the prion protein in known cases of vCJD. This spatial distribution is conceptualized as bodily rather than geographic, and it is understood as bounded by various tissue and organ compartments, rather than nation-state borders. Despite this difference in scale, these two ways of spatially defining and demarcating risk operate in a similar manner. They allow the risk of vCJD to be conceptualized as existing within specific "containers", whether these containers are nations or organ systems. As Lakoff has remarked, creating container metaphors to describe a concept, permits the appearance of rationality in the maneuvering of the concept (Lakoff & Johnson 1980).

Thus, within the first twenty minutes of the meeting, the major axes upon which further deliberations will hinge have been introduced. To recount, for vCJD risk these are: spatial (national, bodily), temporal (referential, durational), and consumptive. The spatial differentiation of risk accounts for two components, one which takes the globe and the boundaries of nation-states as its canvass, the other which takes the body and the boundaries of tissue and organ systems as its canvass. The consumptive properties of risk are perceived as varying along an axis with central nervous system (CNS) tissue at one end, muscle meat somewhere in the middle, and a vegetarian diet on the other end. The referential temporality of risk can also be separated into two distinct components: time with reference to the BSE epidemic and time with reference to the course of the disease in the body. Durational temporality is associated with the spatial distribution of risk, in that the amount of time spent in a "high risk" space is conceptualized as indicative of exposure. All of these axes of differentiation are based on underlying assumptions: that vCJD is caused by the transmission of BSE to people through cattle CNS tissue, that the borders of nation-states form a container around BSE risk, which follows from the assumption that the borders of nation-states have meaning in terms of encapsulating and preventing certain types of trade and risk exposure; that vCJD prions affect some organs and systems and not others, which relies on the assumption that the borders of tissue systems in the body are distinct enough to be differentiated from one another; and that the course of the BSE epidemic and the course which vCJD takes upon the body can be demarcated into phases or periods. If one accepts these assumptions, vCJD risk can be presented as forming a gradient upon each spatial and temporal axis outlined above.

Upon each of these axes, vCJD risk is interpreted as having a distinct orientation, with more risk at one end and less risk at the other.

In addition to these spatial and temporal axes, there are certain structures which have been constructed as oppositions, i.e. availability of blood products vs. removal of vCJD risk. These oppositional structures create the central tension that motivates committee discussion and disagreement. Via these oppositional structures, each action that is taken to reduce vCJD risk is seen to have a counter-reaction in other domains, such as the availability of life-saving products and risk from other diseases.

Bob Will's opening presentation resinscribes and further explicates many of the spatial and temporal distinctions latent in the FDA's formulations, providing a helpful illustration of the concepts described above and how they come to be seen as capable of containing risk and bracketing uncertainty. First, Bob Will explicates the reasoning behind the postulated causal relationship between BSE and vCJD by describing their temporal and spatial juxtaposition:

> If we hypothesize that it is in some way causally linked to exposure to the BSE agent, then most of the cases should occur in the country with the greatest exposure, which is the United Kingdom, and so far there have been, as I say, 34 cases of new variant CJD in the United Kingdom, and only one case in another country, and that was in France. The timing of the occurrence of new variant CJD is consistent with a link with BSE. If we look at the minimum incubation period in kuru and human growth hormone recipients, it is about four-and-a-half years. We can hypothesize that exposure to the BSE agent in the human food chain occurred in the 1980s, and seeing the first cases of a linked disease in the human population with onsets in 1994 would be consistent with this type of incubation period (TSE Advisory Committee 1998).

The coincidence in space and time (given the long incubation period) of BSE and vCJD is presented as evidence for a connection between the two. It also forms the basis for postulating spatial and temporal boundaries around vCJD risk.

Will notes, however, that there are a few caveats to this causal hypothesis. The first caveat he raises is the occurrence of a single vCJD case in Fance. Because France, however, imports large quantities of meat products from the UK and travel between the two countries is common, Will suggests that this individual may have been exposed to BSE through the consumption of UK cattle products. Here, the permeability of national borders, through trade and travel, is invoked to explain anomalous data. In Will's usage, the idea of "leakiness" operates to preserve the broader image of geographical containment of BSE risk. Thus, the interplay between nation-states as contained and simultaneously leaky provides a conceptual basis for differentiating risk based on spatial boundaries while allowing for certain exceptions.

Finally, he describes recent data on the spatial distribution of PrP in the bodies of vCJD patients. Infectious prion protein is found in the lymphoreticular tissue, including spleen, appendix, and tonsils, of vCJD patients, but not of sporadic CJD patients. This finding is interpreted as indicating both that vCJD is different from CJD, because it has a different spatial distribution in the body, and also that vCJD is more likely to travel through the blood stream, since lymphoreticular tissues are functionally related to the blood stream. It is primary due to these spatial differences that vCJD has so readily eclipsed CJD in terms of concern over blood transfusion.

The interpretation of these spatial differences, however, is contested by Raymond Roos. Through his comments, the uncontainable uncertainty partially masked in Will's monologue reemerges. As Roos points out, the difference in detectable distribution in PrP between vCJD and CJD may be a matter of amount rather than an absolute difference. After all, according to Aguzzi, the western blot can only detect an excess of 10>5 prions

per gram of tissue. If the level of PrP is lower than this, the western blot might not be able to detect it, making it appear that vCJD and CJD have a different bodily distribution when in fact they do not. In this case, bioassay in susceptible animal species would be necessary to resolve the dilemma. In support of this point, Paul Brown points out that in primates infected with CJD, he was able to detect infectivity in the spleen and appendix of the animals through bioassay.

Despite this uncertainty, Will indicates that the UK has moved towards a policy of withdrawing plasma products and blood components when a patient is diagnosed with probable vCJD. Will informs the committee that the UK is currently tracking six individuals who are still alive and who are known to have received blood components from someone later diagnosed with vCJD. While the government has not notified any of the recipients, they plan to follow them through a "look back" study, checking death registries periodically to see if any of them has been diagnosed dementia. While such a study is envisioned as providing the definitive data on whether blood from a vCJD patient can transmit disease, there is no way of knowing how long the study must continue for results to be considered valid. This is due to the uncertainty surrounding the incubation period in a human-to-human transmission of vCJD.

Most of all, the indeterminacy of the incubation period becomes a complicating issue for projecting the likely number of future vCJD cases, and therefore the necessity of taking precautions with respect to the blood supply. Here, the temporality of the disease itself is seen as the source of the most confounding uncertainty. This is illustrated quite well by an interchange between Dr. Leitman and Dr. Will. Dr. Letiman points out that the incidence of vCJD so far, with only 34 cases yet detected, works out to only one in 10

million. Dr. Will, however, states that with such a long incubation period it is impossible to predict what proportions the epidemic will rise to:

> The difficulty with diseases with a long incubation period is that it is too late to say that that indicates that they will only have a small amount of cases. There is, to my mind, still a possibility that there could be large numbers of cases in the future. We certainly hope not (TSE Advisory Committee 1998).

The concern is, if a very large epidemic does arise, by the time that it is recognized it will be too late to do anything to prevent transmission through the blood supply, as was the case with HIV. Thus, the temporality of the disease drives both the uncertainty involved, and, through a metaphor with HIV, the necessity for action.

After Lunch, Alan Williams of the American Red Cross (ARC) presents the results of a survey designed to elicit information on the effects of deferring donors on the supply of blood. In the survey, donors were asked whether they spent time in UK during the BSE epidemic. The results of this survey comprise the first solid quantitative data that the committee has been presented with. While numbers were given for the incidence of vCJD by Dr. Will, these were shrouded in uncertainty by the temporality of the disease with its long incubation period.

The simplicity of the numbers provided by Alan Williams thrills the committee. 11.7% of donors who responded to the survey said that they had spent time in the UK between 1984 and 1990. This proportion was even higher in coastal areas like San Francisco, where 16.3% had traveled to the UK during the given time period. This pointed to a clear spatial differentiation of the propensity for shortages should UK donors be deferred from donating blood.

In a twist on the configuration of risk, Williams points to the propensity for another oppositional relationship in addition to shortages. He notes that many of the donors who report travel to the UK are also the most highly educated, and therefore the (statistically) least likely to have other infectious diseases like HIV and Hepatitis C. He presents the results of a Future Oriented Statistical Projection (FOSP) based on this insight. He calculates, through a crude form of numerology, that by deferring everyone who spent time in Great Britain, the blood collection system would lose a significant number of repeat donors, who are considered to be safer donors because they have been tested multiple times for HIV and Hepatitis C. The loss of these donors would need to be made up for by recruitment of first time donors, he tells the committee, who are at a higher risk of harboring HIV or Hepatitis C (one again, statistically). Therefore, he warns the committee, deferring donors for vCJD risk may increase the risk of transmitting other infections. This projection generates a new tension for the committee members to struggle with. In addition to the aforementioned oppositional structure between vCJD risk reduction and shortages, a new oppositional structure has been introduced. This new tension is configured as opposing the risk of transmitting vCJD with the risk of transmitting HIV and Hepatitis C. Because vCJD is constructed as a hypothetical risk and HIV and Hepatitis C as "known" risks, this projection convinces several committee members to vote against deferrals.

Dr. Weinstein of the FDA builds on Williams's presentation by projecting the effects that calculated donor losses would have on the plasma derivative industry. Weinstein urges the committee to be wary of a future in which, "The cost for plasma may rise precipitously," or, worse yet, "Plasma distributes may decide, however, to honor

contracts that they have with foreign manufacturers rather than to supply the U.S. need first" result in an availability crisis. Things would be even worse, he predicts if withdrawals of plasma products for vCJD risk were entertained:

> This is because plasma derivatives are made from pooled donations from 5,000 to 60,000 donors. Every plasma derived product on the market would contain plasma from at least one of the roughly 900,000 deferred donors. It takes about 90 to 200 days to manufacture a plasma derivative and make it available for sale. After the initial large withdrawal of product, there would be a long period where withdrawals would occur because of adverse information received after donation. If we assume that only one in 10,000 donors report post-donation -- which is a very conservative number -- that they met the donor deferral criteria, this would lead to approximately 100 withdrawals from recovered plasma donors. This is more than all the CJD withdrawals that took place between 1995 and 1997, which amounted to 63 (TSE Advisory Committee 1998).

The image of potential shortages that Weinstein paints is bleak. It is also rather concrete in contrast to the potential threat from vCJD. He is also careful to frame the projected effects of a vCJD withdrawal policy through a metaphor to the recent CJD withdrawal policy, rather than the HIV/AIDS crisis. In this way, Weinstein strengthens the metaphorical relationship between vCJD and CJD and seeks to differentiate it from HIV. In other words, he draws vCJD into a sensitizing frame that relies more on the recent experience with CJD withdrawals, deemed to be a mistaken action, then the experience with HIV, in which thousands of hemophiliacs became infected due to inaction. He ends by clearly setting up the opposition so that it is concretized in the committee members' minds: "Any deferral or withdrawal recommendations have to be made in light of this, that products will not be available to treat patients."

Adding fuel to the fire, Dr. Kleinman from the American Association of Blood Banks (AABB) projects an estimated loss of 1.4 to 2 million units each year. This, he

warns, could result in a major impact on availability. He also builds on the warnings of previous speakers, projecting that

> By deferring these predominantly repeat donors with theoretical CJD food-borne risk and by recruiting first-time donors to replace them, it is possible that implementation of the geographic exclusion criteria under discussion will negatively impact blood safety as it pertains to HIV and other known transfusion-transmissible infectious diseases (TSE Advisory Committee 1998).

Dr. Dailey from the American Red Cross (ARC), in a similar vein, presents five "scare" projections that build on each other. First, he estimates that, based on the REDS survey, "819,000 donors would be deferred, incurring the unnecessary fears of these donors, and increasing the concern of the public regarding the safety of the blood supply." This is a scenario that had not yet been raised at this meeting. Third, he estimates that, "Over one million new donors would need to be recruited. Moreover, these would be first time donors," which, by increasing the risk of other infectious diseases, would decrease the safety of the blood supply. Fourth, he raises the concern that tracking the authenticity of donor-provided data will "consume considerable time and resources of blood collecting organizations" thus inhibiting their ability to conduct life-saving activities. Fifth, and worst of all, as far as availability is concerned, he projects that, "It is highly unlikely that increased recruitment efforts, however strenuous, will be able to overcome the deficit caused by this deferral." In summary, he encompasses these individual projections into a bleak future scenario: "These proposals, therefore, will have a devastating effect on the American blood supply" when in fact they were only put in place, "to prevent a problem that has never occurred."

Thus, representatives from the plasma products industry and blood collection centers, building on the data and projections provided by Alan Williams, collectively

create the image of a future in which vCJD deferrals and/or withdrawals will generate shortages, decrease the safety of the blood supply, and spread fear amongst the public. It is from these oppositions that the committee's tension in generating a "balance" between vCJD risk and these other risks is derived.

Illustrating the power of these projections to shape opinion, members of the committee take up these projections and restructure them through reference to their own experiences. Base on her experience as a hematologist, Dr. Leitman expresses her hesitancy to reduce a speculative risk that might never occur, when the effects on the blood supply would be massive. As a physician, Dr. Roos mentions that he has patients who require IVIG, and, knowing the supply is already tight, he is hesitant to contribute to further shortages. As an epidemiologist, Dr. Burke openly worries about increasing the risk of HIV, HepC. In these expressions, we can see the effect of the grim future projected by the blood industry. These future projections have come to operate as agentic forms in the discussion, pushing certain concerns to the surface and obscuring others.

Chairman Brown, however, takes issue with the blood industry's construction of an unavoidably grim future scenario should deferrals be enacted. He argues that the assumptions upon which they are based are not necessarily the correct assumptions. Each of these projections utilizes the raw data from the REDS survey on the high proportion of donors who have traveled to Britain. Brown argues, however, that most people who travel to Britain do so for only a short period of time, and therefore are at low risk of having contracted vCJD. He argues that by deferring only those who spent a substantial amount of time in the UK, incurring the most risk, a much smaller loss to the blood supply would

result. The REDS survey, unfortunately, did not ask respondents how long they spent in the UK.

Seeking to negotiate common ground between the two poles of vCJD risk and availability, Schonberger sees hope in Brown's line of reasoning. He presents a scenario in which the concerns over availability and risk reduction can be "balanced" through a careful choice of the temporal duration required for deferral:

> We need to find some criteria that covers as big a group of the cases that are occurring -- which for example might be right now like five years' residence in the United Kingdom between the period, say, 1980 and 1995, the period of risk that we are talking about...that would be considerably smaller than the type of data that we heard in the questionnaires. Again, we are not talking about a complete and total avoidance of the problem; we are just sort of adjusting to ameliorate it (TSE Advisory Committee 1998).

Schonberger introduces an alternative future scenario based on a "compromise" between alleviating hypothetical vCJD transmission risk and maintaining the availability of blood. In doing so, he moves the discussion forward by allowing people from different social worlds, who normally associate themselves with different sides of the issue, to negotiate.

Schonberger's efforts at negotiation bear fruit, at least as far as Dr. Roos is concerned: "I agree with what Larry said. There should be other ways to minimize the impact on blood." In the end, nine committee members and temporary voting representatives from BPAC voted for some sort of deferral policy based on vCJD risk, and six vote against.

Of the six who voted against a deferral policy for vCJD risk, almost all of them cited the potential for creating supply shortages as their primary concern. Several of them, like Susan Leitman, also cited the potential for increasing the risk from other infectious diseases by recruiting more first time donors to make up for the loss:

> If we increase the donor population by 10 percent first-time donors, the rates of transfusion transmitted viruses will not be zero. It might only be five, 10 or 20, but it won't be zero. I find even a single case unacceptable as a trade off (TSE Advisory Committee 1998).

Three of the six members who voted against deferrals stipulated that they would immediately change their vote if there was a single case of vCJD in a transfusion recipient. In stipulating the criteria for changing their position, these members indicate that, despite the specter of the HIV/AIDS transfusion transmission crisis, they are not ready or willing to act upon a purely "hypothetical" risk to the blood supply. In other words, postulated threats such as "shortages" are perceived as more "real" and concerning to these committee members than the threat of vCJD.

Of the nine who voted for deferrals based on vCJD risk, almost all indicate that the long incubation period of TSEs played a role in their vote. Their concern stems from the idea that mass transfusion transmissions could occur before the risk becomes apparent. According to Dr. Brown, who voted for deferrals, it is too early to tell how large the epidemic of vCJD will become and whether the disease will prove to be transmissible by blood:

> I am coloring it by the fact that there is a long lead time between cases and what you can do something about.I think there is an outside chance that there may be a wild epidemic of new variant CJD in Great Britain. If there is, I think we will look back and very much regret that we didn't take that into consideration when we had a chance to (TSE Advisory Committee 1998).

As a veterinarian, it is not surprising that Linda Detwiler invokes a metaphor with BSE to reason about the length of the incubation period and the potential for unrecognized transmissions to occur:

> I vote yes...There are two reasons. One would be, more times than not I have heard with these diseases, especially BSE, we have to wait until we get all the evidence. Unfortunately, with the long incubations, by the time we get all the

> evidence we are usually five to 10 years behind the curve, so you should have done it yesterday. The second is, something that was done with BSE and scrapie, scrapie was not known to be a human pathogen, and we heard that all the way through. It is not going to be, it is not going to be, it is not going to be, or there is no evidence that BSE is a risk to human health. That went on in the mid-1980s all the way up to 1996 when it was made public...(TSE Advisory Committee 1998).

By invoking the recent experience in the UK with BSE, Detwiler frames her concern about nvCJD not within the HIV crisis, but within a crisis that she is intimately familiar with. Detwiler, a veterinarian at the USDA, organized the working group on BSE and played a leading role in developing the US response to BSE. She also maintains close connections with veterinarian colleagues in the UK, giving her an insider view of the UK experience.

Prusiner bases his vote for deferrals on information derived from animal models about the spatial distribution of the disease. In doing so, he indicates that he perceives a strong metaphorical fit between these animal model systems and the human form of the disease.

> ...what concerns me the most is that when we look at animals...in the preclinical phase, when you look at every single lymphoid work, the spleen, the thymus and lymph nodes are positive. The titers in those organs are the second highest in the animal. It is the brain, and only the brain, that is higher (TSE Advisory Committee 1998).

On this basis, he notes that he is still concerned about sporadic CJD and its potential transmissibility by blood. Other than the representatives of hemophilia organizations who spoke during the public hearing, Prusiner is the only participant, and certainly the only member of the committee, to openly express concern about the recent reversal of the CJD withdrawal policy.

While HIV played a role in the discussion and framing of the meeting, Ms. Harrell, a consumer representative, is the only member of the committee to cite HIV in

the reasoning for her vote. She argues that "the reluctance to reduce the repeat donor pool to reduce the theoretical risk of HIV allowed that disease to become epidemic in the United States."

The next issue that arises is whether to limit the consideration of deferral policies to those who have traveled or resided in Great Britain. Based on the aforementioned discussion surrounding the spatial juxtaposition with BSE, the committee votes yes, that deferrals should be limited to travel or residence in Great Britain alone. This is despite the fact that many countries within Europe had already seen their first cases of BSE, or were in the midst of their own mini-epidemics, and, as previously mentioned, a single case of vCJD had been diagnosed outside of UK borders, in France. It is also despite the fact that Will had already invoked the leakiness of nation-state borders as a means of explaining the anomaly of the French case. While the recognition of such leakiness might have served to decrease the belief that vCJD risk could be containable by nation-state boundaries, instead it had the opposite effect. To understand why this was so, it is important to recall the pressure that the committee was under to come up with some sort of risk mitigation measure, as well as the weight of the oppositional structures which ensured that any action would produce a negative reaction. By limiting the scope of any recommendations to the UK, a single country, rather than including all of Europe, it would be possible for the committee to act without substantially, it was hoped, disrupting the balance of supply and the balance of risk from other infectious diseases. The treatment of vCJD risk as spatially contained by the UK's borders, despite the leakiness of these borders, provided the committee with a convenient mechanism for limiting the fallout from their recommendations in other, related, domains.

Certain committee members, however, such as Stanley Prusiner, cast doubt on the ability of the UK border to contain BSE risk. He openly questions the construction of the border as a contained boundary, and suggests that all of Europe is at risk, and perhaps beyond. But, as Robert Will reassures the committee

> Of course, one of the reasons for doing European surveillance is to determine the relative proportions of new variant CJD cases in other countries, should they, indeed, occur. My final point is that the timing of exposure to BSE agent may be different in different countries than in the United Kingdom (TSE Advisory Committee 1998).

His comments suggest that while, for the time being, he feels that it is okay, for the purposes of risk mitigation measures, to treat vCJD risk as contained primarily within the UK's borders, this is subject to change over time. This illustrates a temporal component to the spatial conception of vCJD risk, or better yet, illustrates the way that the temporal and spatial components are perceived as inextricably interconnected.

Next, the committee considers a question of intertwined temporalities: For how long and during what period must a person have traveled to Britain in order to be considered at risk of vCJD? A complex and interweaving discussion follows, which I have separated into the two forms of temporality I described previously, referential and durational, for analytic purposes. Durational temporality describes the attempt to conceptualize time as an "amount" that is seen to correspond to a proportion of exposure risk. Paul Brown explains this concept with a Russian roulette analogy:

> A cumulative risk, it seems to me, with respect to TSE and most other infections, is a game of Russian roulette. That is, one hit and you are dead. The question is, what are the odds of getting a hit. It is like a six shooter. The question is whether it is a six shooter or whether it is a stet gun with 100,000 bullets in it, 100,000 chambers, only one of which has a bullet. I think that all we need is one bullet. The question is when are you are going to get it. The longer you are exposed to the possibility of getting it, the greater your chances of getting it (TSE Advisory Committee 1998).

In this statement we see the construction of a metaphor between time and exposure, the idea being that the longer someone spent in the UK the more they would have been exposed to BSE contamination. Evidence for the applicability of this metaphor is drawn from the CJD transmissions through Hgh injection. Dr. Schonberger reminds the group that: "in the study of human growth hormone, the one risk factor that we worried about identifying was the duration of treatment." If the metaphor was found to be useful in managing other TSE transmissions, Schonberger indicates, it may be useful for considering this one.

Dean Cliver warns that the metaphor may not have a tight fit: "We can't put that dimension on this and expect to gain anything by it at this point, because there is no data base on which to quantify risk with time." Nonetheless, the committee embarks on a discussion of the relationship between time spent in UK and exposure risk. As the potential for consensus seems to disintegrate, Prusiner intervenes:

> I would like to suggest a different approach here; that we ask the AABB to go back and look at the survey, the people who responded yes, they have been outside. Come back and question these people. Now, maybe they will get 80 percent or 90 percent or 70 percent of the people to respond. We would have some data for the next meeting. This could be done or a new study started. I mean, this is a two-month interval in which all these questionnaires were put out. We are talking about six months from now, in June having the next meeting. I think we would have some data and that is what everybody would like to see. We have no data whatsoever, and all the questions that we are bringing up would be framed in the questionnaire and the appropriate data acquired (TSE Advisory Committee 1998).

The committee votes unanimously to ask Alan Williams to conduct another survey to gather information on duration of stay in the UK. Lurie suggests to Williams that he collect data on the effect that deferring donors with a given duration of stay in the UK

would have on the proportion of other risk factors, like HIV and Hep C, as well. As Brown describes it:

> What we want is, when you do the analysis, assuming you ever get it done, that you take cuts, and for each cut you tell us what the consequences are in terms of lost donors and the numbers of new first-time donors that have to be recruited to replace them (TSE Advisory Committee 1998).

Intertwined with the discussion on durational temporality and its relationship to vCJD risk is the concept of referential temporality and its relationship to vCJD risk. The committee members, with the participation of their UK colleagues, construct the choice of a referential time period for which BSE exposure risk can be deemed "significant" as dependent on two factors: the number of cows infected with BSE at a given time, and the amount of highly infectious tissue, brain or spinal cord mostly, that would likely have entered the food supply at that time.

The first case of BSE was detected in 1985, but subsequently cases were identified in the tissue pathology collection as early as 1984. Given that the exact date at which the first cow came down with BSE will never be known, it is left to the committee to surmise, given their experiences with other TSEs, when BSE exposure began. This forms a boundary on one side, a temporal reference for the beginning of risk, while the end of exposure to BSE forms a boundary on the other side, a temporal reference for the end of risk. In this way, temporality, like spatiality, comes to be perceived, albeit temporarily, as "bounded" on all sides. It comes to be envisioned as a "container" for risk. Risk exists inside of this period of time, but not outside of it. The risky person is constructed as someone who spent a certain amount of time (the temporal container constructed through the Russian roulette analogy) in the UK (the spatial container constructed through the notion of borders that bound disease) within a certain period in

time (from the beginning of human exposure to BSE to the end of human exposure to BSE). The simultaneity of being "inside" these three containers at once is perceived as producing "significant risk." In this way, the committee is able to bracket uncertainties for long enough to consider concrete recommendations.

Like the borders of nation-states, however, the boundaries of time are leaky. It is around the potential leakiness of these boundaries that much of the discussion and disagreement over setting a referential time period occurs. Referencing the graph of BSE incidence over time as well as Roy Anderson's extensive modeling of the likely number of undetected BSE cases that must have occurred, Rohwer argues that the time at which exposure began could have been much earlier than the time at which BSE was "discovered" by MAFF scientists:

> But when you look at that plot you realize that in 1985 when the first BSE case was identified, there were already thousands of animals infected. If you apply Anderson's extension, his estimate that for every diagnosed case of BSE there were five to 10 other cattle which were slaughtered before they got BSE, then you are in the neighborhood of 10,000 or more animals that were infected at the time that the first case was observed. Those birthdays go back to 1982 or 1981, I believe; perhaps even earlier; I am not sure. So, in picking a date, I think it would be smart to err on the side of conservatism (TSE Advisory Committee 1998).

Cliver, however, expresses concern about reaching too far back in setting the boundary of risk: "I think if we are going to include people who lived there in the 1970s, you are getting off into territories where there is no reason for concern.

The committee decides to set the other end of the referential time boundary as the date at which people in the UK can consider to no longer have been exposed to significant amounts of BSE-infected tissue. One committee members suggests that the boundary be set at the beginning of the ban on the inclusion of specified bovine offals, including brain, spinal cord, and lymphoreticular tissue, in food. While this ban was

enacted in 1989, however, there is considerable disagreement over when the ban was actually enforced, as discussed in Chapter 2. As Dr. Metters of the UK Department of Health admits:

> There was some leakage in the SBO ban through the early 1990s. That came to an end in 1995. Since 1996, it has been very tight. I am giving you this as sort of fractured information, because clearly, it varied (TSE Advisory Committee 1998).

Even though it was not "uniformly" implemented until 1996, Metters still suggests that 1989 should be the cut-off for risk because it was "the biggest single reduction in risk for the human population, from that day forward until 1996 when it was really policed." Others, however, are uncomfortable with this suggestion. As Linda Detwiler phrases it:

> If you look at the epidemic in cattle, it really did peak in 1992-1993. You have seen the figures on kind of the route of the ban and compliance, where it wasn't really very, very strict compliance until 1995 or 1996. Not only with the SBO ban, but would you cut it off at 1990? My gut would be to go a little bit further than that. Are there figures for looking at how much it was enforced right away from 1989 (TSE Advisory Committee 1998)?

From her interpretation of the data, the SBO ban would have been ineffective during the time period of greatest incidence of BSE in the cattle herd. Despite Bob Will's assurances that the current enforcement of the SBO ban has decreased the risk of exposure essentially to zero, committee members express concern that a certain amount of BSE infectivity is still leaking into the human food supply. In order to capture this possibility, Alan Williams is asked to ensure his survey considers time spent in the UK between 1980 and the present.

Even though the entire preceding discussion, including all of its temporal and spatial elements, is merely an indirect means of getting to the central question of whether or not someone was exposed to infected meat, the idea of asking about consumption directly is dismissed out of hand. It is deemed unlikely that a donor can be trusted to

recall what he ate during a trip, perhaps many years in the past, to Great Britain. In addition, the very notion of what it means to be "vegetarian" and whether or not this is protective for vCJD is called into question by citing the case of the vegetarian woman who developed vCJD in the UK. In the end, there is deemed to be no means for accurately assessing whether someone would have eaten a BSE-containing product while in the UK.

Leaving the exact boundaries of the deferral policy to be worked out at the next meeting, when new survey data should be available, Brown then moves to the question of whether withdrawals of plasma products should be requested if a person meeting vCJD deferral criteria (travel to UK during an unspecified time and for an unspecified duration) is found to have donated to a plasma pool. Rohwer sees the deferral strategy as a partial measure which can be enacted without producing too much strain on the blood supply. On the other hand, a withdrawal policy could produce much more strain, given the size of plasma pools. This is framed within the recent experience with the CJD withdrawal policy. Brown reminds the committee that the CJD withdrawal policy was recently rescinded due to the strain it produced on supply.

By framing the question of whether vCJD withdrawals should take place within the context of CJD as the appropriate precedent, rather than HIV, the answer to this question is biased towards a negative. Leitmain maintains that: "I don't think we can go for withdrawal of plasma derivatives. There won't be enough to meet patient needs." In the end, all of the committee members voted against withdrawing plasma products due to identification of an at-risk donor except for Barbara Harrell, a consumer representative.

What is remarkable about this meeting is the way in which the frame within which vCJD risk to the blood supply is considered has shifted to metaphorically include the recent CJD withdrawal experience. Because of the shortages and complaints that resulted from withdrawals for CJD risk, withdrawals for vCJD risk are viewed in a negative light. When the TSEAC met to consider CJD risk to the blood supply, however, it was largely HIV which was invoked as a metaphor. From this perspective, withdrawals were deemed necessary.

While HIV is still invoked during the consideration of vCJD risk to the blood supply, it has been constructed in such a way that it plays a dual role. Rather than simply serving as a moral metaphor, in which case references to HIV would seem to support strong precautions regarding vCJD, HIV is structured as in "tension" with vCJD. By creating the perception of a tension between vCJD risk reduction and HIV risk reduction, members of the blood industry weaken the metaphor between vCJD risk and HIV risk. The projection that deferrals for vCJD risk would increase the risk of HIV was first introduced by Alan Williams. Based on the REDS survey data, he argued that people at higher risk of vCJD, due to time spent in the UK, tend to be at lower risk of HIV, due to level of income and education, as well as estimates of the likely number of first time donors who would need to be recruited to make for deferrals. While Williams is the first to introduce and describe this projection, he is not the last. A myriad of presentations by individuals from within the blood industry and the FDA repeat and build upon this projection, drawing further implications. Members of the committee, as well, repeat these projections and reformulate them through their own experience. The neutralizing effect of this set of projections diminishes the power of HIV as a moral metaphor for vCJD. Still,

some committee members, like Ms. Harrell, the consumer representative, continue to invoke a metaphorical fit between past experiences with HIV and present experiences with vCJD. In its dual role, therefore, the HIV experience can be deployed either as a reason to act in a "precautionary" manner with respect to vCJD, or, increasingly, as a reason not to.

Despite the tension invoked through negative projections of shortages and increasing transmission of other infectious diseases, which proved convincing enough to dissuade six committee members from taking action, nine of the committee members are still concerned enough about the uncertainties surrounding vCJD and its potential to infect the blood stream that they vote for instituting deferral measures. Their concerns rest on the spatial distribution of the infectious agent in the bodies of its victims, which brings it in close proximity to the blood stream, as well as the unknown number of individuals who may be harboring it. In order to limit the potential negative effects of vCJD deferrals, i.e. by producing shortages or increasing the transmission of other infectious diseases, they seek to delimit the boundaries for deferrals and thus strike a balance through the oppositional structures which frame their discussion. To do so, they make efforts to treat vCJD risk as, at least partially, contained by nation-state borders, certain referential periods of time, and certain durations of time. All of this, of course, is shorthand for bracketing the uncertainties. The committee is aware that by invoking such limits they are avoiding the deeper issues, as brought up during the meeting, of when and how BSE actually began. And yet, in the end, the decision is made to wait for the results of Alan Williams's next survey to provide solid, concrete numbers to distribute amongst

these putative containers of risk. It is only by treating the risk as containable and manipulable that the committee can act at all.

June 2, 1999

Alan Williams returned with the requested survey data at the June 2, 1999 TSEAC meeting. Williams split the travel question into two different referential time periods: 1980-1989 and 1990-1996. 15.5% of donors reported travel to the UK between 1980 and 1989 and 13.4% between 1990-1996. For the total time period, 22.6% reported travel, indicating that some donors had made trips to the UK during both periods.

Respondents who had traveled to the UK were then asked to mark a box indicating an interval that best approximated how much time they had spent in the UK as a sum of all trips. The choices were: between one and four days, between five and 11 days, between 12 days and one month, between one month and five months, between five months and nine months, between nine month and one year, between one year and three years, between three years and five years, and five to 17 years. Cumulatively, 22.6% reported staying for one day or more, 19.7% of respondents had stayed for more than 4 days, 11.8% for more than 11 days, 4.9% for more than one month, 2% for greater than five months, 1.3% for greater than 9 months, 1.2% for greater than one year, 0.7% for more than three years, and 0.4% for five years or more.

Based on these numbers and these numbers alone, Williams presents the committee with what he terms the "theoretical risk associated with U.S. blood donor travel to the U.K." To do so, he makes one key substitution. He draws on the discussion of the previous meeting, in which a relationship was configured between the time spent in the UK

(durational temporality) and exposure risk, and defines "person days spent in the UK" as the risk of contracting vCJD. Of course, this substitution ignores many of the other key factors discussed at the previous meeting, such as the amount of meat one may have consumed while in the UK or the referential time during the BSE epidemic that one was in the UK. Despite these caveats, and the uncertainties they represent, he proceeds in equating the person-days spent in the UK, as demonstrated through his survey, with the actual risk of contracting vCJD.

Further, because the survey results were only indicated in intervals (i.e., the respondent was asked to check a box indicating an interval), Williams used the midpoint of the interval to calculate the person-days spent in the UK. While one can readily see that for someone checking the box between one and three days, this will make little difference in the overall calculation, for someone checking between three and five years, it could clearly make quite a big difference. For someone checking the box "five years or more," it could make the biggest difference of all. Despite the possibility for misrepresenting the number of person days spent by individuals in the UK due to the statistical way he handles the calculation, he concludes that:

> For the greater than five year time period, 49.2 percent of the risk would be related; adding to that the three to five year interval, 67.1 percent; one to two years, 77.8 percent; and so forth (TSE Advisory Committee 1999).

Through his statistical calculation, Williams creates a numerical and graphical representation of vCJD risk among blood donors. Given the solidity of all these numbers, it might be easy to ignore the numerous uncertainties he overlooks in getting there, as well as the critical assumptions he makes in his calculations.

He then statistically projects, based on the survey, the number of donors that would likely be lost for a given time-period as the deferral criteria. Given a certain cut-off, he simply adds together the total number of people checking the box for that given interval and all intervals of greater length. This leads him to project losses such as:

> For a one-year deferral, it would be an impact of loss of 1.5 percent of the blood supply; for six months, 2.2 percent; three months, 3.4 percent; one month, 6.4 percent; and one week, 14.9 percent. And then that can be compared with the values for theoretical remaining variant CJD risk (TSE Advisory Committee 1999).

Upon questioning, Williams is forced to admit that his colorful projection of an increased risk of transmitting HIV or HCV, which figured so prominently at the previous meeting, was found to be lacking any statistical basis in this new survey. With this admission, one of the oppositional structures which so dominated the previous meeting was devalued, but it did not disappear completely, as will be shown through the subsequent discussion.

Of all the assumptions involved in Williams's calculations, and there are many, the one considered most suspect by committee members is his choice of using the midpoint of the time interval in the survey to calculate the person-days of exposure. Cliver suggests that the use of the midpoint will skew the results, making it appear that there is a greater number of person-days spent in the UK, and thus a greater risk reduction, per interval than there really is. He, and later McCullough, suggest that for people checking this box, it is likely that the greater percentage of them spent closer to five years than 17 years in the UK, or that they were likely to be towards the lower end of this range. Thus, using the midpoint to calculate person days for all of them buries this potential variable and obscures the uncertainty involved in this estimate. Because the midpoint for this interval is greater than twice the low-end of the interval, McCullough maintains that such a simplification may in

fact result in a calculation that is actually double the number of person-days accumulated by this group. This, in turn, as McCullough points out, would double the appearance of the risk reduction achieved by deferring this group.

Brown points out another uncertainty underlying Williams's calculation, this involves the assumption that each exposure to BSE would function independently, in terms of risk of contracting vCJD, from every other exposure to BSE.

> I would like to introduce a qualification to being completely smitten by the notion of person-days, as opposed to time spent, just to point out that person-days depend on the notion that 100 hamburgers, for example, distributed in any way will have the same risk. That is to say, if one person stays 6 months and eats 100 hamburgers, it is the same overall risk as if the 100 hamburgers were eaten by 100 different people who visited United Kingdom for one day. That assumes that the risk of a single exposure is the same as the risk to multiple exposures in a single person. And that's an assumption. We do not have any evidence bearing on that question. So that, for example, if a person is twice exposed within a week, he may be more susceptible to an infection than two different people exposed once during the same time period. So cumulative person-days may not be as attractive a way to analyze risk as it may be appearing (TSE Advisory Committee 1999).

Despite the concerns of committee members that Williams has falsely simplified things, perhaps misrepresenting the underlying risk and ignoring substantial uncertainties, the committee still accepts his calculations and, not only accepts them, but, later in the meeting, uses them to establish and rationalize its deferral recommendations. The fact that, on the one hand they can point to and condemn these assumptions and the uncertainties they hide, and on the other, use these calculations as a basis for decision-making, indicates the comfort with which numbers provide them. They end up using these numbers because it is the only way for them to treat the risk as "containable" and "calculable" and to proceed in a pseudo-rational manner.

After Williams's presentation, Steve Nightingale vividly describes a dire future projection of the nation's blood supply. Even without deferrals for vCJD risk, he warns,

the nation is facing a severe shortage. He bases his projections on data collected by Marian Sullivan at the National Blood Data Resources Center, an industry funded research group. He states that:

> ...extrapolating from the current trends...the available blood supply in the year 2000 would be 11.7 million units of red cells, and total demand would be 11.9 million units... the summary is that demand for blood is increasing at about 1 percent per year and supply is decreasing at about the same rate. The extrapolation from the current trend says demand is expected to exceed supply in the year 2000 (TSE Advisory Committee 1999).

While Sullivan's calculations are based on experience in the recent past, they project supply and demand into a period which has not yet occurred, and therefore cannot be known with certainty. They treat the future, however, as though it will be a replica and continuation of the past. Like the French planners who designed the Maginot line, Sullivan has excluded the possibility for innovation or change. She has assumed that both the blood industry, and patient demand, will continue in their current direction unabated.

While Nightingale admits that there are a number of assumptions and uncertainties involved, he maintains that these Future Oriented Statistical Projections are an adequate representation of the future of the blood supply. Because TSEAC has specifically been asked by the FDA to balance the need for vCJD deferrals against the need for a sufficient blood supply, these FOSPs are interpreted as having a direct bearing on the committee's decision-making. Thus, they become a point of contention, especially for consumer-oriented members of the committee like Dr. Lurie, who argues that:

> ...you've made an extrapolation based just on two points, as you say; and which, in effect, makes it seem as if the two lines are independent of one another. I like to think that the blood transfusion industry, aware of the change between '94 and '97, is, in fact, reacting in some way, presumably by increased recruitment. So there is a kind of inevitability applied to all of this that doesn't really quite seem right to me (TSE Advisory Committee 1999).

Although Lurie seeks to destabilize these FOSPs by pointing out both the unknown quality of the future and the potential for those involved to follow a different course than the one predicted, representatives from other blood industry organizations reinforce the FOSPs by citing them again and again, producing an image of the future in which the blood supply becomes frighteningly inadequate. According to Ms.Gregory of the AABB:

> ... Extrapolating recent trends, the National Blood Data Resource Center predicts that demand will exceed supply by the year 2000 if no changes in deferral criteria are applied. Therefore, even with no changes in deferral criteria, it is becoming increasingly difficult to maintain an appropriate level of supply. Spot shortages during holiday periods and during the summer will be even more difficult to alleviate. Any new deferral criteria for donors will decrease the number of donations available. Thus, a policy that defers even a very small percent, such as one to two percent, of available donors will have a detrimental effect on blood availability (TSE Advisory Committee 1999).

As a counterpoint to all of these negative projections of a dwindling supply, an unquantifiable vCJD blood transfusion risk, and the potential for possibly increasing the risk of other transfusion-related diseases, Schonberger raises the possibility of a more hopeful future scenario occurring through technological innovation. He bases his hope on the experience with Hgh, in which a technological solution, in the form of recombinant human growth hormone, saved the day.

> When we had the problem with the human growth hormone, the solution turned out to be to switch to molecularly engineered hormone. Is there any such solution to our blood problem in the near future? Does anybody have any information on that; that is, using some substitute that would not require the human donator (TSE Advisory Committee 1999)?

In his set of questions, Schonberger attempts to inject subjunctivity into the conversations. He is pointing out that the future is unknown, and it is possible that technological solutions to some of the problems at hand will be found. Ewentein, however, casts doubt on the hope implicit in Schonberger's question by indicating that it is unlikely that all of the clotting

products can be produced recombinantly, implying to the committee that they should not rely on the open-endedness of the future to solve their problems.

Representatives of the blood industry also construct a future-oriented image of the deferrals for vCJD exposure risk as capable of producing stigmatization, fear, and despair amongst those who are deferred, and capable of destabilizing public trust in the safety of the blood supply. As Dr. Davey of the ARC describes it:

> Deferred donors may face possible stigmatization for being somehow unsafe, and may have undue concerns about being at risk for a dread disease. Also, and I think this is important, the message that the committee will send to the public with these deferrals is that Mad Cow Disease is a current blood transfusion safety risk in the United States.... We will develop a group of hurt, angry and scared donors. And whether deferral is permanent or temporary, it's going to be very hard to give these folks the message that they're deferred for a risk that really we know nothing about and is purely theoretical. It's up to the blood centers to have to deal with these donors. It's up to the blood centers to have to get new donors, and that's going to be tough indeed. And again, I think it's important to realize that public perception of the safety of the blood supply is also at question here, and deferrals will indeed raise the public perception of risk of TSE in the American blood supply (TSE Advisory Committee 1999).

Dr. Davey generates an image of the potential vCJD deferral policy as a monster that must not be unleashed, for fear of inducing what would be tantamount to widespread panic about vCJD and the safety of blood. Dr. Sayer extends this imagery even further:

> Donors find themselves being deposed. They find themselves involved in lawsuits. They find themselves being sent off to their physician and then incurring costs in terms of understanding what the health implications for some of the information is... no amount of education is really going to be successful (TSE Advisory Committee 1999).

Not all of the committee members are happy with the direction the meeting is going in. Dr. Prusiner expresses discomfort with the blood industry's projections of the effects of deferrals:

> I'm really uncomfortable with these arguments that you just made. In fact, I'm exceedingly uncomfortable because to end the conversation with the patient by saying what you just said is just not accurate. There are large numbers of answers. I mean, we went through this at the University of California and a whole set of discussions with a committee to try to set a policy. And the fact is that there's a lot of scientific information, and then there are a lot of clear unknowns. And the unknowns have to be clearly stated to the patient. And for you to stand there and say what you just said I think is unfair to the committee, it's unfair to the population of the country, and it's really not accurate (TSE Advisory Committee 1999).

Dr. Lurie builds on Prusiner's contention by citing experience with malaria:

> To the assertion that the development of travel restrictions would signal to the public that Mad Cow Disease is a problem, I guess I have two comments. The first is the Institution of Travel Restrictions for Malaria does not seem to have communicated to the American public that malaria is a problem in the blood supply (TSE Advisory Committee 1999).

Further, he projects that the institution of deferrals for vCJD risk would actually enhance the public perception of the safety of the blood supply, rather than undermine it:

> What I think the message the American people will take from this is that a group of people have wrestled with the problem and have done the most they can to protect the blood supply from Mad Cow (TSE Advisory Committee 1999).

In a move to lighten the task of the committee, Paul Brown proposes that the committee focus on regulating blood components, such as red cells and platelets, and dismiss concern over plasma products. He bases his suggestion on the results obtained from he and Rohwer's rodent model systems, which indicated a difference in the amount of infectious agent contained in blood components and plasma products. Recall that, as recounted in the previous chapter, he and Rohwer conducted a series of experiments in which the infectivity in blood decreased after processing, with more processed plasma products appearing to have less infectivity. His phrasing that the "processing of plasma for derivatives has been unequivocally shown to result in very large losses of any infectivity"

demonstrates the tightness of the metaphorical fit he perceives between these model systems and the production of plasma products for human use.

Protestations are raised immediately. Many of the committee members are unconvinced of the metaphorical fit between the rodent model systems and the human situation. Dr. Prusiner especially takes issue with the use of the model system in which Brown and Rohwer spiked human blood with scrapie-infected hamster brain in an attempt to mimic infected blood:

> I want to emphasize that it's the physical state of the prions that's very important because these are proteins. They aggregate to many different size particles. And what you choose as the spike...can influence enormously how it's cleared. And usually these particles are -- these are non-ideal particles. They're not even like HIV where we have a particle which we -- we have one HIV virus, then we have another one, and another one, and another one and they all behave the same pretty much. That's not true with the prions. So I think that we're -- that people are getting a little false sense of security here with very preliminary data, unless you have much more data than I know about (TSE Advisory Committee 1999).

Even Rohwer himself warns against over-interpreting the meaning of the experiments he and Brown conducted within respect to the human blood supply:

> I do agree with Stan that we've only looked at a couple of different processes by a couple of different models. It's not a closed situation. And I certainly myself would not be in favor of invoking that as a reason for making this choice (TSE Advisory Committee 1999).

Brown continues to argue that on the basis of his results, plasma products should not be considered a risk. Using the mouse model system as a metaphor, he suggests that pooling would dilute infectivity even further, below a level at which it can transmit disease. In GSS infected mice, he says:

> ...we know that it takes at least five times more infectivity to produce an infection when given IV than when given IC; that is, intracerebral. This means that a dilution effect in pooling can operate...when you do the arithmetic you find that the likelihood of having five intracerebral infectious units in a single vial of product is very low...So pooling and its dilution effect, with respect to getting five IC

> infectious units together in a single dose, is a real thing and it's a safeguard (TSE Advisory Committee 1999).

Even Paul admits, however, that the metaphorical fit between the mouse model system and human transmission is not likely to be exact: "On the other hand, it is in rodents. It has only been demonstrated twice, two independent experiments. And it's in a model which is not new variant CJD."

Rohwer argues that the results from the rodent model systems gathered so far do not indicate whether there is a threshold dose, and therefore whether infectivity can indeed be diluted to the point that it does not transmit infection. For Rohwer, this cannot be known because they did not inject all of the diluted samples into animals.

> Paul, I would encourage us not to invoke the pooling argument because I strongly disagree with it and do not feel that that's likely to be playing a role. And we could go on and on about it, and try to resolve it here, but it is a technical issue that it is possible to take two different positions on it. And I don't think it's possible to resolve it here, so I don't think it should be invoked. I think we should consider the -- it is a worst case situation that if you take 10^4 infectious units and disperse them into a pool, you have the potential of distributing that to 10^4 individuals ultimately in separate product units (TSE Advisory Committee 1999).

The disagreement that develops between Brown and Rohwer illustrates how two scientists, even working together, can disagree over the interpretation of results, and especially their meaning for risk management policy. No model system is a perfect fit for the question under consideration, and there are always a myriad of assumptions and perspectives that enter into the interpretation of data. The results of model systems, while capable of focusing concern, are not capable of resolving risk management dilemmas. They merely provide further raw material for constructing, negotiating, and reconstructing a sensitizing frame of metaphors through which to envision risk.

In the end, 12 members of the committee vote in favor of deferrals for both blood components and plasma products and 9 members vote against them. Of those voting against, the primary reason given, as in the previous meeting, is the concern over maintaining adequate supply. Thus, the future projections produced by the blood industry have had a significant effect on the committee members. Some, like Leitman, even continued to cite the countervailing concern that deferrals for travel to the UK would increase the risk of transmitting other infections, like HIV and Hepatitis C, through blood. Several of the members who voted against vCJD deferrals stipulated that they would change their vote immediately should a case of transfusion-transmitted vCJD occur.

In contrast, those who voted for a deferral policy clearly did so on a "precautionary" basis, choosing to take action despite the lack of solid data that vCJD is a transfusion risk. Belay, in his reasoning, highlights the contrast between vCJD and CJD which has figured so prominently in committee presentations and discussions:

> I'm concerned about two issues. The first one is the studies that showed the presence of the new variant CJD agent in lymphoreticular tissues. And the second concern I have is the absence of evidence against blood-borne transmission of new variant CJD. The kind of data that's available for classic CJD is not available for new variant CJD, so I vote yes (TSE Advisory Committee 1999).

In addition, many of those who vote for deferrals "bracket off" the supply concern, and future projections of shortages, as something to be dealt with separately, rather than something that is inherently in tension with, or in opposition to, risk reduction measures. Harrell brackets supply concerns by noting that safety should be the primary concern.

> ...As far as it affecting the blood supply, I think that that is something that may be totally separate that we will have to consider. But first, we don't want anything to come into the country that is not already here. And if there's something that we can do, then we should do that (TSE Advisory Committee 1999).

Prusiner brackets it by arguing that the economy has a way of taking care of supply issues independently from the risk reduction concerns.

> I think that the economy has a way of solving these problems, and I think that will happen. I think the real problem here lies that we have a very imperfect data set, and we're dealing with a disease which is universally fatal. This is really the problem that we face (TSE Advisory Committee 1999).

While many of those who voted against the deferral policy configured a reduction in vCJD transmission risk and the blood supply as in opposition to each other, Harrell and Prusiner subvert this representation, arguing that the two can be managed independently. Lurie, on the other hand, views them as intertwined but maintains that there is a way of balancing them without sacrificing one for the other. "There are scenarios available to us," he maintains, "that allow us to minimize that" (TSE Advisory Committee 1999).

While Barbara Harrell, a consumer representative, was the only committee member to invoke the metaphor of HIV in her vote for deferrals at the previous meeting, at least outwardly, Dr. McCullough, a hematologist who was personally involved in the management of the HIV epidemic does so on this occasion. He sees the risk management decision before the committee today as analogous to that involving HIV in the 1980s:

> I'm also impressed by having sat through in 1983 and 1984 discussions of [AIDS transfusion risk]...And possibly also, I'm influenced by having been the fodder for congressional hearings and a 60-minutes expose on things that might have been done differently at some of those times. So I'm going to vote yes. I have tremendous confidence in the blood systems of this country that they will be able to...respond if changes are made (TSE Advisory Committee 1999).

Dr. Detwiler and Dr. Rohwer both metaphorically invoke the BSE epidemic as reasons for acting with a precautionary manner towards vCJD. Detwiler reminds the committee that BSE was considered a "theoretical risk" for human health, and even a doubtful one at that, until 1996. The BSE metaphor lends support to the idea that TSEs

are "surprising" and "unpredicatable" diseases, but nonetheless can be managed with appropriate prevention techniques that reduce or eliminate the circulation of infectious tissues.

Given that the recommendation for deferrals passed, just as it had at the previous meeting, though by a small margin, the next issue becomes the setting of deferral criteria for vCJD. At the previous meeting, the 'duration' of travel within the UK was constructed as a metaphor for BSE exposure, and therefore vCJD risk. At the previous meeting, however, the committee, did not believe they had enough information on the distribution of time spent by donors in the UK to make a decision. They wanted more numbers to work with. At this meeting, Alan Williams has returned with survey results and calculations purported to represent a standardized unit called "person days spent in the UK." Alan Williams reinforces the idea that "duration" can be used as a reliable metaphor for vCJD risk by treating it as such in his oral presentation and graphs. Though the basis for the "person-day" calculations, and its relationship to the risk of contracting vCJD, is questioned by committee members, it remains the only quantitative data available for the committee to work with. Quantitative data, because it can be manipulated in ways which qualitative data cannot, is preferred by the committee members. The importance of the manipulability of numbers is evidenced by Prusiner's reliance on these representations in his reasoning about deferral:

> If one looks at Alan Williams' handout, the second -- third-to-the-last page of slides, and put up this graph which I thought was very informative on residual variant CJD risk --... So I think if people look at that slide -- I mean, we can start thinking about everything from one week to one and a half years with this slide. And I think everybody -- most people, I would argue, at this table would argue that one week is too severe, and this creates something which is intolerable for the blood supply...But clearly, by six months, if one looks at that, and then one looks at this handout that Alan Williams provided us that was not stapled, if one picks

> the number six months, then of all of the -- if you look at the cumulative person days, then almost 95 percent of the cumulative person days are eliminated by picking a figure of six months...I'm zeroing in on between six months and three months. This seems to me to be a very reasonable way to achieve a 90 percent reduction in risk without making a huge dent on the blood supply (TSE Advisory Committee 1999).

In Prusiner's description of his reasoning, "cumulative person days" and "exposure risk" have become interchangeable. This indicates the tightness of the metaphorical fit that has been constructed between them, such that, by this point in the meeting, and despite all the aforementioned uncertainties, they have now come to stand in for each other with relative ease. In the remainder of the discussion, these two terms "person days in the UK" and "vCJD risk" are indeed treated as interchangeable. It is important to keep in mind that this interchangeability has only been achieved through a careful, and questionable, bounding of the spatial and temporal construction of vCJD risk and the subsequent transformation of these bounded variables into a single, standardized variable "person-days spent in the UK." This process of risk construction, its containment within discernable borders, and its transformation into a singular, quantitative value has occurred over the course of only two meetings. It was aided by the collection of surveys, the FOSPs produced by Alan Williams, the opinions of vCJD experts, such as Robert Will, and the discussion of the committee members. All of the spatial and temporal uncertainties that were once recognized and debated have been successfully bracketed in order to come to a decision. In a sense, this bracketing of the uncertainties and unknowns and the treatment of these constructions, at least on a temporary basis, as semi-stable certainties, is what allows for a decision to be reached regarding risk management. Without the bracketing of uncertainties, action might remain imponderable forever.

The committee members agree to set the criteria by voting on which of the time periods indicated in Alan Williams's survey should be used as the durational component of the deferral policy. That way, they have specific numbers they can point to for the projected resulting risk reduction and effect on the supply. Three of the committee members vote to set the cut-off at greater than 5 years, one votes for 3 years, five vote for one year, seven vote for 6 months, and four vote for four months. The median vote of 6 months is taken as the committee's recommendation, applying another statistical concept to the already statistically-loaded construction.

In this vote we see the power of future oriented statistical projections (FOSPs) to shape risk management decision-making, despite the numerous uncertainties and assumptions involved. This power stems from the ability of these FOSPs, through a variety of spatial and temporal metaphors, to bracket these uncertainties. Once bracketed, the uncertainties can easily be buried under a layer of numerical analysis, for just long enough to come to a decision. This allows for action to be taken under the guise of rationality, and for the appearance of control in what is, fundamentally, an uncontrollable, and unpredictable, situation.

In the years that followed, this appearance of control, and the temporary image of a "containable" vCJD risk, were thwarted. Increasing numbers of BSE cases appeared across Europe. Five more vCJD cases were identified in France. Small numbers of vCJD cases began to appear in other European countries. The ugly uncertainties, once bracketed through a reliance on spatial and temporal metaphors in an effort to compartmentalize risk, refused to behave as they were supposed to. Eventually, the discrepancies between the messy reality of vCJD and the representation of simplicity and containability that had

been constructed became too much for the FDA and the committee to bear. Gradually, TSEAC came to realize that their effort to represent and manage the vCJD risk as though it were contained by national borders was no longer tenable. Still, they persisted in viewing it, treating it, and manipulating it as though it were containable by continental borders. In October of 2002, the FDA, based on TSEAC's advice, instituted a deferral for people who had spent more than 5 years in Europe. The cut-off remained lower for the UK, decreased from six to three months, indicating the continued perception and representation of a hierarchy in risk.

In addition, it came to light that the Department of Defense had imported substantial quantities of beef from the UK during the peak of the BSE epidemic. This potentially contaminated meat had been fed to US military recruits based all over Europe. Because of the substantial exposure, TSEAC recommended, and FDA imposed, deferrals for military recruits who were based in Europe for more than six months.

The gradual extension of vCJD deferral policies to cover increasing numbers of people who might have been exposed to BSE while in Europe illustrates the way in which uncertainties, once bracketed through reliance on spatial and temporal metaphors, continue to reemerge. The committee responds, however, not by eliminating the image of a containable risk, but by extending the boundaries of what can be considered containable. Extending the spatial boundaries to contain all of Europe indicates a belief that the US, at least, will remain free enough of the disease that our own internal risk is negligible. This is an assumption which is hardly ever questioned, despite the fact that the US imported meat and bone meal from the UK during the peak of the BSE epidemic and did not institute its own ruminant feed ban until 1997, and then with many loopholes. By

treating the risk as containable outside of our borders, TSEAC avoids the difficult questions that would arise if an internal risk were perceived.

Ch. 6 - The United Kingdom Confronts CJD and vCJD Transfusion Concerns

As a means for comparing and contrasting the production of sensitizing frames across nations, I will review the British construction and rationalization of measures for managing the perceived risk of vCJD and CJD to the blood supply. Because their positioning with respect to the BSE epidemic, as well as the metaphors that officials and scientific advisors turned to, differed with respect to the US, it is not surprising that the UK came up with a strikingly different risk management strategy. Though the appearance of rationality was carefully constructed through risk assessments, advisory committee meetings, and similar techniques, the UK's risk management strategies were, it will be shown, no more logical than those which the US chose. In effect, the UK government did what was demanded of it in a time of heightened concern, applying any risk management measure that might appease the public appetite for regulation.

In the UK, and in the aftermath of BSE, the government was under great pressure to manage the risk of vCJD to the blood supply. While the metaphor between vCJD and HIV played a role in highlighting blood as a concern, it was the previous experience of betrayal with relation to BSE that remained in the public consciousness, leading to demands for tighter regulation. In this heightened atmosphere of concern, but with no actual transmissions of vCJD by blood, the UK Department of Health asked SEAC for advice on how to manage the blood supply. With nothing else to go on, it is not surprising that SEAC latched onto the first promising scientific result that came its way. Adriano Aguzzi, a famed TSE scientist in Switzerland, claimed to have identified B-cells, a specialized form of White Blood Cell (WBC), as the carrier of prions in blood. On the basis of Aguzzi's result, and despite its failure to conform to several other results in the

field, SEAC became convinced that if they could remove the WBCs from blood, they could remove the risk of transmitting vCJD. So, drawing on an analogy with this single model system, they recommended universal leukodepletions of blood, pending the stamp of rationality provided by a risk assessment.

Meanwhile, the hemophilia advocacy groups in the UK, worried about a repeat of HIV, demanded that the UK begin importing plasma products from non-BSE countries to prevent vCJD contamination. While not recommended by SEAC, the UK Department of Health caved into this request, and enacted this measure despite a lack of any pre-formulated rational guise. When the risk assessment requested by SEAC was finally conducted, however, it was modified, numerically, to provide justification for both the leukodepletion of blood as well as the importation of plasma products. In this way, all of the UK's risk reduction measures, post-hoc, were given the stamp of rationality in the form of an easily manipulated (due to the uncertainties and massive assumptions involved) risk assessment.

A Different Response to HIV

In the UK, as compared to the US and many other industrialized countries, there was very little political fallout over HIV transmission by blood transfusion. As Lorna Williamson, a transfusionist with the NBS, described in an interview: "a number of countries, like Canada, Japan, Ireland, really reacted to the whole thing in ways that were very difficult for the professionals to deal with. Whereas in the UK actually it was more of a feeling that everything that could've been done was being done." This difference in the UK reaction to HIV would come to play an important role in the sensitizing frame

through which the UK approached the regulation of blood and blood products with respect to CJD. As a result, the UK implemented less strict regulations than other industrialized countries where the fallout from HIV had been intense.

In contrast, the appearance of vCJD in the UK resulted in substantial and immediate political fallout, fallout which could not be contained. It spilled over into public life and resulted in a profound destabilization of the UK political system, a public investigation, and a demand for greater future accountability for decision-makers. Thus, when it came to the issue of vCJD and the potential risk to the blood supply, this threat was handled largely within the frame of reference of the BSE crisis. While HIV/AIDS provided a point of reference for transfusion-transmitted infection, it did not play the role of a moral metaphor as it had in the US.

When AIDS struck in the 1980s, the UK blood transfusion system was comprised of two separate services - the National Blood Transfusion Service (NBS), which covered England and Wales, and the Scottish National Blood Transfusion Service (SNBTS), covering Scotland and Northern Ireland (Krever 1997). Both were founded during World War II. Through the National Health Services Act in 1948 the two services became part of the National Health Service (NHS). Plasma was fractionated at one of two fractionation centers, the Bio-Products Laboratory in England and the Protein Fractionation Center in Scotland.

Prior to the HIV crisis, all of the blood transfusion services in the UK were struggling to achieve "self sufficiency," the ability to sustain the blood supply without the importation of blood and plasma products from abroad (Krever 1997). While the SNBTS came closer to attaining this goal than the NBS, both suffered set backs due to the sudden

increase in demand for Factor VIII in the 1970s and 80s, leading to an increase in importation of plasma products from the US. The US products were derived from paid donors, donors who were viewed in the UK as tainted and risky.

This perception was the product of Titmuss's 1970s book. Through statistical studies, Titmuss illustrated that the rates of hepatitis in recipients of blood from paid donors were far higher than in recipients of blood from volunteers (Titmuss 1971). The British prided themselves on their all-volunteer donor system, which had been much lauded in Titmuss's book. The cleanliness and sanctity of this system had attained an almost religious status, believed to prevent, to the greatest extent possible, the transmission of undesirable pathogens (Titmuss 1971). This perception was called into question as the AIDS epidemic grew.

Initially, AIDS was viewed as a phenomena contained within the United States, and particularly within the homosexual population. Peter said that the first time he remembered AIDS being mentioned in relation to hemophilia was at:

> ..a meeting with the International Society of Blood Transfusion in 1982 where Dan Danielson, who headed up the FDA's section on blood products was giving a report on cause of death amongst hemophiliacs... At the end of his report he said these two hemophiliacs have actually died from this gay disease. And nobody in the audience - and you know the auditorium was full of people – nobody in the audience reacted to that at all...It was just a casual incidental remark. It didn't register. And that was the middle of 1982. But by the end of '82, I think people were beginning to think maybe this could be a blood-borne virus and maybe that was the cause of it. But in January '83, John Watt, our director, went to the states, went to the FDA and came back and he was convinced that it wasn't a virus. It was some immune disorder to do with some strange activities that people get involved in, and I think by then I didn't actually really know what to think (Ponte 2003g).

It was an analogy with intravenous drug users, who would be exposed by the same route as blood transfusion recipients, that initially triggered Peter's concern.

At another international meeting of the blood community in 1983, Foster learned more about AIDS from a representative of the CDC:

> he described the epidemiology very well, and also the particular hemophiliacs who were being infected and had no other risk factors. That became clear by mid '83 so by then we knew that it was a virus and we felt it was just a matter of time before it got into our blood supply. It was in the U.S. The question was when will it get into our blood supply. Because there was no test, the virus hadn't been isolated (Ponte 2003g).

In the same year, the notion that hemophiliacs could be susceptible to contracting AIDS through blood products made its way into the British scientific press (Jones et al 1983). A series of Lancet editiorials highlighted the threat to British hemophiliacs through the importation and use of plasma products derived from paid U.S. donors (Lancet eds.).[11] Shortly thereafter, the first British hemophiliac came down with the disease (Daly & Scott 1984). Despite this incident, Mr. Kenneth Clarke, the Junior Minister of Health, maintained that: "There [is] no conclusive evidence that...AIDS is transmitted by blood products" (Farrell 2004). Such language parallels similar statements issued by members of the plasma industry in the U.S. during this period.

The directors of the regional blood transfusion centers, however, were concerned. They began to question whether severe hemophiliacs should be treated with UK-derived cryoprecipitate instead of imported Factor VIII. It was decided, however, that given the benefits of Factor VIII therapy and the absence of direct scientific proof that plasma products could transmit AIDS, this action should be postponed. As Lorna Williamson describes this period, the hematologists, while aware that AIDS presented a risk, never believed that it would explode in the way that it did. "I remember sitting in hemophilia

[11] While the British Blood Transfusion System had been attempting to move towards self-sufficiency for years, and had largely attained this goal with respect to blood components, the growing demand for plasma products proved to be an insurmountable challenge. In addition, the Thatcher government marginalized the efforts towards self-sufficiency in plasma products and emphasized the importance of a free market (BB).

clinics in '85-'86 and people were saying that, you know, probably only a minority of people who caught this virus would suffer any disease from it." This notion, based on the minimal number of cases that had been reported in the hemophilia community, dampened the perceived likelihood of mass disease. What no one realized at the time was just how long the incubation period could be, and how many people were already infected.

When AIDS began to spike in the hemophilia population of England, the Scottish National Blood Transfusion Service (SNBTS) believed that the Scottish population would remain unaffected. The identification of AIDS in hemophiliacs in England was attributed to England's higher rate of importation of American blood products (Farrell 2004). Due to their almost complete self-sufficiency, the SNBTS thought themselves to be immune to the type of infection rates that were seen in England. They viewed their self-sufficiency as a boundary between them and what was still considered to be a foreign disease. According to this image, the Scottish blood supply was an impervious container of wholesome volunteer blood. Soon after, however, it became apparent that HIV had contaminated the Scottish blood supply as well, through their home grown donors.

The response of the UK hemophilia society was to push for compensation for the victims of HIV/AIDS from behind the scenes. As Brickman and Jasanoff have pointed out, during this time period UK governmental decision-making relied largely on back-room negotiations amongst officials and established stakeholder groups (Brickman et al 1985). The Hemophilia Society of the UK, as an established stakeholder group representing the hemophiliacs of the UK, had substantial ties to parliament, ministers, and other power brokers. It levied this clout to broker deals behind closed doors, in the traditional UK manner. The UK Hemophilia Society settled litigation out of court without

demanding the kind of large-scale public inquiry that took place in many other countries (Kreager). Unlike the US, where the IOM dissected the decision-making process of the authorities involved, the UK never held AIDS decision-making open to public scrutiny.

The lack of a political scandal over the AIDS/HIV contamination of blood and blood products, and the avoidance of public scrutiny over government decision-making, led to the development of a sensitizing frame, or set of guiding metaphors, within the UK that was markedly attenuated with respect to that which formed in the U.S. and in much of Europe in relation to the safety of the blood supply. While the FDA began deferring recipients of Hgh from blood donation as early as 1987, the UK did not follow suit until 1989 (95/10.26/9.1). This is despite the fact that the UK's first case of CJD in an Hgh recipient was discovered in early 1985, not even a year after the first American case, and several months before the second two American cases that solidified the association. While the UK extended the deferral to include human gonadotropins derived from pituitary glands in 1993 (Year Book 1994), a year later the UK opted not to apply deferral criteria to recipients of dura mater transplants on the basis that it "could create unsuperable difficulties and uncertainties for the transfusion service" and that "the practicalities of identifying and deferring dura mater recipients from donation would greatly outweigh the potential advantages" (Year Book 1994).

Although Germany and France issued multiple recalls of plasma products for CJD risk, much as the US had, the UK never issued a single recall on this basis (Year Book 1995g). Like the US, both Germany and France had been affected by enormous political scandals that erupted over the transmission of HIV to blood transfusion recipients. The situation in France was arguably the most extreme, as investigations had not only resulted

in public scrutiny, but in the imprisonment of scientists and government officials who had failed to warn of the dangers HIV presented to the blood supply or who had failed to act swiftly enough to protect the blood supply. This may explain why France had the highest recall rates for CJD of any of the above-mentioned countries. In 1994 alone, 77% of the Factor IX and 71% of the French supply of IVIg were withdrawn for concern over CJD (Year Book 1995g). Over half of the withdrawals were triggered by recognition of risk factors, such as family members with the disease, rather than an actual diagnosis of CJD. In fact, it was the French constituency that asked the CPMP, the body which regulates pharmaceuticals in Europe, to consider establishing European-wide withdrawal guidelines for CJD in 1995 (Year Book 1995b). And it was the British constituency that convinced the committee not to issue such guidance on the basis that, "there was no reason for recall, whatever the origin of the risks." In another example of the apparent lack of alarm over a possible CJD transfusion risk in the UK, the UK considered, but decided against, instituting a look-back policy for recipients of CJD blood in 1995.

Later in the same year, the CJD ad-hoc committee established by the CPMP reconvened to consider the CJD withdrawal issue in light of the FDA's recent decision to withdraw such products. The committee advised the CPMP to continue its policy of not issuing withdrawal for such products. The CPMP framed their choice to diverge from American policy as based on "a different view of a theoretical risk" (Year Book 1995e). In fact, though, the views of the theoretical risk expressed at the CPMP ad-hoc committee meeting were not all that different from those expressed at the TSEAC meetings in the U.S. In their reasoning, they cited the lack of epidemiological evidence for CJD transmission, especially "in groups of patients receiving plasma derived products

regularly" (Year Book 1995a). As in the US, the European advisory committee placed great value on hemophiliacs as sentinels for blood-borne diseases. The members of the ad-hoc CPMP committee on CJD also made a similar argument with respect to the "false security" provided by withdrawals based on the likelihood that undetected CJD donations were entering the supply anyway. As the CPMP committee phrased it, "Withdrawing the last few batches of product when a donor may have been donating for many years, some when 'incubating' CJD" would have a negligible impact on the safety of the supply (Year Book 1995a).

Dr. Purves asked Dr. Sloggem to write a "what if" position paper, which can be viewed as a kind of qualitative, and partially quantitative, risk assessment of the likely effects of following an American-style policy of withdrawal of plasma products for CJD contamination concerns (Year Book 1995i). First, Sloggem described the potential difficulties in tracking the dissemination of product, particularly albumin that has been added as an excipient to recombinant clotting factors, or, worse yet, vaccines. He predicts that the recall or quarantining of vaccines "may not only affect unused bulks which could represent many thousands or millions of doses, but filled and issued product...That clearly would be a major news item." The adverse publicity, he projects, could harm the already sensitive campaign to vaccinate children. An entire page of the report is devoted to the potential for massive shortages, citing the US and France as two examples of countries where such shortages have resulted from CJD withdrawals. The concern was also raised that certain specialized products that are manufactured by only a few companies may disappear completely. Based on a quick quantitative analysis, Sloggem

projected that as much as 30% of donations could be withdrawn. Sloggem draws on a parallel between the current issue and the experience with HIV and HCV.

> If a parallel is drawn with HIV and HCV transmission via blood products, it could be held that MCA should have learnt from the previous experience and withdrawn everything...With HIV presumabley it would be considered that hemophiliacs should have been made aware of the risk as it emerged, or at risk product should have been withdrawn...Nothing was known of the properties of the HIV virus to take steps to safeguard the blood product supply...If the public perception with CJD was that no action was inappropriate, then MCA/DoH might be accused of not learning from previous blood product transmission incidents (Year Book 1995i).

Thus, while the metaphor between HIV and CJD was invoked, it did not result in the decision to withdraw as it had in the US. This differential impact of the metaphor on risk perception and management corresponds to the relative impact of HIV transfusion transmissions, in terms of political fallout, in each country.

In the same year, Dot and David Churchill, the parents of Stephen Churchill, who at the age of 18 was diagnosed with CJD, later to be reclassified as one of the first cases of vCJD, began writing letters to the chairman of the UK National Blood Authority (NBA). The Churchills expressed concern that while the Canadians had recently recalled a large batch of plasma products because of a single donation from someone later diagnosed with CJD, the UK had no policy in place to do so. They wrote that:

> We are also aware that the disease is known to involve an incubation period of many years, being known as a slow virus. As no-one can say that the infective agent cannot be transmitted via blood tissue...it terrifies us that had Stephen's blood been used for transfusion you would have been unaware that you would have been infecting any recipients, albeit inadvertently (Year Book 1995d).

The Churchills went on to identify several areas of concern, including the tracking system for units of blood and the actions to be taken when a post mortem examination identifies CJD. In later letters, after having met with other families affect by CJD, the Churchills

questioned the lack of clarity in the UK recommendations for blood deferral. They described a meeting of the CJD Support Network, through which they had met many of these families:

> It became apparent from the discussion that there are no set standards being applied by the local collection centers and the variation ranges from 'no implication' to 'no donation.' This is causing much concern amongst those who have traditionally donated and are now simply confused. In most cases the relationship is either as child of the victim or as sibling. We ourselves are part of what appears to be a growing number of parents of victims which represents another class (Year Book 1996b).

Meanwhile, the SEAC meeting on November 23, 1995, was the first meeting at which a significant discussion was devoted to the topic of blood transfusion and the risk of CJD transmission. To begin with, Dr. Rejman of the Department of Health presented on the animal model systems in which infectivity had been detected in blood. As Rejman noted, however, the results from human blood were equivocal. While several rodent bioassays were positive, the primate assays were so far negative. This is despite the fact that the species barrier between humans and primates would supposedly be lower.

Rejman emphasized that despite the somewhat concerning, and difficult to interpret, results from laboratory experiments, the epidemiological data to date indicated no evidence of transmission by blood. He recounted the recent decision in the US to go forward with withdrawals despite the lack of evidence. SEAC was asked to consider whether the UK should embark on a similar policy. Dr. Rejman warned that in the UK, unlike the US, where plasma donors are paid and therefore donate on a schedule, it would be difficult to track donors who later go on to develop CJD. He added that the withdrawal of albumin, which is used as an excipient in many products, could trigger shortages of Factor VIII and vaccines.

The task put to the committee was phrased, by Rejman, as determining whether there was "any new evidence that goes beyond theoretical risk of transmission of animal or human TSE agent through blood." While Dr. Rejman emphasized that there was no increased incidence of CJD in hemophiliacs who received plasma-derived Factor VIII, John Pattison called into question the generally accepted metonymy between the hemophilia community and blood transfusion recipients. He argued that simply monitoring the hemophilia community cannot stand in for surveillance of all transfusion recipients.

The committee, prior to the discussion on blood, had just heard evidence that pieces of spinal cord and other central nervous system (CNS) material were entering the food supply at an unanticipated rate, despite the Specified Bovine Offals (SBO) ban of 1989 which specifically forbade such tissue from entering the food supply.[12] It was uncovered that the CNS material was mainly entering the food supply through the production of mechanically recovered meat (MRM). Given this context, Dr. Watson was understandably confused by what he described as an inconsistent consideration of risk. On the one hand, there was material known to carry high levels of infectivity entering the food supply, and on the other, there was blood, which was only hypothetically considered to be infectious. Professor Pattison pointed out what he believed to be a major difference between the two: blood is an essential treatment, while MRM is a non-essential food product. Agreeing with Pattison, Rejman suggested that unlike MRM, strong evidence would be required to withdraw an essential product. Dr. Matthews, however, noted that they were discussing human blood, a material for which there would be no species barrier.

[12] This event is described in more detail in Chapter Two.

In the end, SEAC advised that "there is no new evidence of risk from blood suggesting the necessity for new measures." In good scientific form, however, SEAC did not close-off future consideration of the question, recommending the continued "collection of data on recipients/donors of blood where patients die of CJD"(Year Book 1995j).

At SEAC's February 1st meeting, concern over the development of a new variant of CJD was coming to a head. Dr. Will reported on 5 pathologically confirmed cases of this peculiar form of CJD. He noted "an extensive and unusual pattern of PrP deposition," including lymphoreticular tissue, that differed from classical CJD. At the same meeting, the committee discussed the issue of CJD transmission by blood again. Pattison expressed his opinion that Paul Brown's paper 'Can Creutzfeldt-Jakob disease be transmitted by transfusion?" in which, as discussed in Chapter 3, he called into question the results of scientists who claimed to have detected infectivity in the blood of CJD patients through rodent assay, was excellent. John Collinge, who had recently attended an FDA workshop on the topic, warned the committee not to be overly reassured by the present data. He suggested that transgenic mice may provide a more appropriate model to mimic the human system of blood transfusion.

In October of 1995, the Sunday Times raised public concern over the transmission of CJD by blood. This was one week after it ran a story suggesting that a farmer who had come down with CJD may have contracted it from a BSE infected cow. The story on blood was titled, simply, "Brain Disease may be in Blood Bank" (Year Book 1995h). The reporter cited the detection of infectivity in the blood of rodent TSE model systems and quoted John Collinge as saying that the possibility of CJD transmission through blood

transfusion "is something we must think about." Hematologist Arul Mehta, however, warns against alarming "huge numbers of people who are sick." Drawing on a comparison to the early days of AIDS, he argues that without a test for the infectious agent, there is no way to tell whether it is carried in blood or not: "There is an awareness of the possible problem of CJD in blood but the problem is that there is no test. We didn't know about AIDS until a test was developed" (Year Book 1995h).

In Britain, concern over the transmission of CJD through the blood supply began to coalesce at the same time that concern over BSE transmitting to humans was reaching a crescendo. In the policy arena and in the press, the two issues were raised in a temporally and spatially related manner. Given these circumstances, it is not difficult to understand why, almost immediately after vCJD and its potential link with BSE were officially announced in March of 1996, the blood of vCJD patients became a central concern. As Peter Foster told me:

> Within a few days of the announcement in the UK of variant CJD, the head of SNBTS, Cash, actually convened a meeting of all of the UK blood transfusion services and the CJD Surveillance Unit from Western General, with professor James Ironside, and the department of health in the UK and we all attended a meeting to discuss the situation. So that was immediately recognized as being potentially a problem for the transfusion services in the UK. And at that point that they began to lay down the mechanisms whereby the transfusion services could be notified of any individuals who were believed to have this disease so they could check if they had been blood donors. So that began immediately (Ponte 2003g).

This is despite, and in contrast to, the disregard for any potential threat from CJD contamination of blood. The steps that the UK had taken, deferring donors who had received Hgh or had family members with CJD, were the very minimum recommended by the World Health Organization and endorsed by the Council of Europe in its "Guide to the preparation, use, and quality assurance of blood components" in February of 1995,

which sets the legal standards for product licensing in the EC (European Commission). The UK had never withdrawn any products for potential CJD contamination, though withdrawal of vCJD implicated products would become a political necessity.

While the newness of vCJD can account for part of this difference in response, the cultural and historical context in which the perception of a vCJD transfusion risk coalesced certainly contributed to the attention it received. In March, Britons were startled by the news that their government had lied to them for almost a decade about the risk that BSE presents to humans. The political fallout was intense. This was in no small part aided by the press in the U.K. which, for years prior to the advent of vCJD, had been issuing warnings about the possibility of cattle to human transmission. When it finally happened, affected families were poised to demand a public investigation. Unlike the hemophilia society, the association which sprang up to represent the victims of vCJD, the "Human BSE Foundation", was not satisfied with mere compensation. They wanted to know what went wrong and who was responsible. They demanded accountability from the government, its civil servants, and its scientific advisors. They demanded a public inquiry.

CJD on trial: Human growth hormone transmissions

The advent of vCJD and the accompanying public indignation added fuel to the complaints of families who had been affected by CJD-contaminated human growth hormone. Before vCJD, the demands of families and advocates of affected Hgh recipients had largely framed their demands within the HIV/AIDS experience, suggesting that a fund for recipients of the hormone, like that for hemophiliacs with HIV, be initiated.

However, they placed a priority on public investigation of the incident which differed markedly from the U.K. hemophilia society's stance in regard to HIV/AIDS transmission. In fact, families of eight victims of CJD who had received Hgh filed suit against the Department of Health after it turned down requests for a public inquiry. After the advent of vCJD in 1996, calls for an inquiry into the Hgh transmission of CJD increased. In a remarkable coincidence, the trial for the Hgh victims of CJD opened at the High Court in London only a month after the fist vCJD cases were made public, a date which had been scheduled well in advance .

The trial offered the public their first glimpse into what was known about TSE transmission risks and when. Documents revealed that the Department of Health had been warned about the possibility that Hgh preparations might transmit CJD in 1976, when Alan Dickinson phoned the UK Medical Research Council (MRC), which was then in charge of Hgh distribution, to tell them it had just occurred to him that scrapie-like agents could be transmitted through such means (Dyer 1996). The MRC sought advice from two virologists about the possibility that Dickinson had raised. Both agreed that the transmission risk was a real, but remote, potential. According to Dr. Wildy, one of the virologists consulted, this possibility required experimental evaluation. But in the meantime, he advised that:

> ...work on growth hormone has to go forward and any clinical use of this hormone must be regarded as a risk, albeit incalculable. We are in the uncomfortable position of suspecting the worst but not knowing how bad the worst is. Any clinician who uses growth hormone must be made aware of the gruesome possibilities and the imponderable probabilities (Owen 1997).

In the end, however, the MRC never brought Wildy's advice, or Dickinson's phone call, to the attention of the advisory committees responsible for overseeing the production and distribution of Hgh.

The plaintiffs in the case charged that the Department of Health and the MRC were negligent in their failure to periodically review the risks of the Hgh program, to impose strict criteria excluding demented patients from pituitary gland extraction for purposes of manufacturing Hgh, and to select the safest method for manufacturing Hgh (Owen 1997). In the period prior to Dickinson's phone call in 1976, the plaintiff's case hinged on the idea that knowledgeable scientists and clinicians should have been cognizant of the risks, given recent reports of iatrogenic transmission of CJD in the literature. Paul Brown, however, serving as an expert witness for the defense, argued that "Awareness of the risk would have required a highly unlikely sharing of knowledge of veterinarians, neurologists, virologists, and endocrinologists" (Owen 1997). The judge agreed with Paul Brown that before Dickinson's phone call, there was no way the MRC could have anticipated the transmission of CJD. He ruled, however, that they were negligent not to have done anything after they received the phone call in 1976. He suggested that the program could have been partially suspended as early as 1977, preventing hundreds of potential infections from contaminated human growth hormone.

The case was widely hailed in the UK as the first successful multi-party suit claiming negligence on the part of the government and pharmaceutical manufacturers. Undoubtedly, the Hgh trial, and the judge's decision to grant the plaintiff's claims of negligence, formed an important precedent when it came to BSE. The judge of the Hgh

trial even suggested that the case might have been more properly handled as a public inquiry, a choice that was made when it came to investigating BSE.

The Hgh trial, coming as it did on the heals of the BSE epidemic, played a significant role in the sensitizing frame through which the UK considered the vCJD blood transfusion risk. The trial of Hgh revealed the lack of a government response to prevent the transmission of CJD despite warnings from scientists. The information uncovered in the Hgh trial, and the light in which it cast the government, contrasted with the low-key way in which the HIV transfusion transmissions were handled. It set the stage for an even more public scrutiny of what went wrong during the BSE crisis, and added to calls for more transparency and more precautionary management of the public health by the government.

vCJD and blood transfusion concerns

While the perception of a risk of blood transfusion transmission of vCJD coalesced along with the announcement of the new disease, it was not until March of 1997 that the issue was brought to SEAC for consideration (Year Book 1996n). Ironside and Hill had already published their report on the finding of prion protein deposits in the tonsil of patients with vCJD. Even though Hill and Ironside did not make any connection between tonsil and blood infectivity in their published report, this potential connection was discussed at the SEAC meeting. While they stopped short of advising the recall or withdrawal of any implicated product, they emphasized that a tracking system would "allow any resulting problems to be recognized at the earliest opportunity" (Year Book 1997a).

By October 8, the French had already discontinued a plasma contract with the UK Bio-products Laboratory for fear of importing vCJD infected blood, and were considering a complete ban on blood and blood products from the UK. Only two days earlier, the chief medical officer had assured the British public that with regards to vCJD, "The government will take any measures necessary to safeguard the integrity of the supply of blood and blood products" (TSE Advisory Committee 1998). Within UK government circles "opinion was hardening to the view that once trace, any unused products should be withdrawn provided there is an alternative supply" (Year Book 1997b).

At a SEAC meeting later that month, similar sentiments were expressed. While the members recognized that "It is not possible at present to estimate accurately the risk of transmitting nvCJD by blood transfusion" they recommended that a risk assessment be conducted "to inform decisions on any measures which may be necessary to protect recipients" (SEAC 1997).

The level of public concern, however, did not allow them to wait for the results of this risk assessment before advising action. Under pressure to do something, anything that might rationally be conceived of as decreasing the potential transfusion transmission risk, they turned to a study that had recently been conducted by Adriano Aguzzi in which he purported to show that B-cells were the carriers of TSE infectivity. Because B-cells are a type of white blood cell, SEAC advised that by removing white blood cells, or leucodepleting the blood, it might be possible to reduce the risk of transmitting vCJD. They suggested "that the Government should consider a precautionary policy of extending the use of leucodepleted blood and blood products as far as is practicable" (SEAC 1997).

While leucodepletion had been shown to reduce febrile reactions and other adverse events in transfused patients, SEAC was making the leap, based on experiments done in a single lab, that it might also reduce the risk of transmitting vCJD through blood components, should vCJD prove to be transmissible through blood. Adriano Aguzzi had presented the results of two of his recent experiments to SEAC, which he interpreted as indicating that B-cells were the likely carrier of infectivity in blood.

The first experiment involved PrP knock-out mice, which are not normally susceptible to infection with prion disease. In these mice, the spleen could be made to regain its susceptibility to scrapie infection by first irradiating the mice and then injecting the mice with hematopoetic stem cells carrying PrP. Irradiation kills all of the rapidly dividing cells in the body, such as the lymphocytes in blood. Hematopoetic stem cells are precursor cells that can mature into a variety of cell types, including white blood cells. By first irradiating and then reconstituting with fresh hematopoetic cells of a different genotype, Aguzzi effectively produced chimeric animals, animals with a different genotype in their reproductively active cells from their longer-lived cells. The observation that such chimeric animals were susceptible to scrapie seemed to indicate that a mobile component in the blood could account for the initiation of the first stage of infection, the colonization of the lymphoreticular system. In fact, as measured by incubation time assay in transgenic mice overexpressing the prion protein (tg20), Aguzzi's lab found that the level of infectivity in chimeric mice expressing PrP only in the mobile components of blood was very close to that detected in wildtype mice that express PrP throughout their bodies.

Aguzzi's lab carried out a second experiment using a variety of transgenic mouse models in an attempt to identify which component of the immune system was required for infectivity. Some of these mice were missing genes necessary for the production of B and T cells, some for the production of B cells only, and others for the production of T cells only. Aguzzi found that while the mice deficient in functional T cells went on to develop the disease normally, those deficient in B cells never developed disease. Some of the mice lacking functional B-cells, however, upon examination of their brains, were found to have spongiform change and malformed prion protein. Aguzzi postulated that in these mice, the infectious agent had somehow reached the brain, but by a much slower process, one which did not give the mice time to develop symptoms of the disease before they died of other causes. Aguzzi explained away this anomalous result by postulating that while B cells were necessary for the normal route of pathogenesis, a deficiency in B cells uncovered an alternative, less efficient mechanism of propagation, one "which may cause scrapie in situations of immune deficiency" (Klein et al 1997). Aguzzi concluded with the "suspicion that B cells may be the physical carriers of prions" and that this necessitated the "re-evaluation of the safety of blood products" (Klein et al 1997).

If not for the historical context into which Aguzzi's results manifested themselves, with all of the aforementioned sensitizing metaphors pointing to concern over vCJD transmission by blood, it is unlikely that anything would have been done with Aguzzi's results until they had been verified by another lab. Due to the context of alarm and concern in which they appeared, however, they were immediately granted an air of importance and incontrovertibility beyond their substance. Despite any uncertainties or concerns over the metaphorical fit between his model system and human disease,

Aguzzi's results triggered a profound reaction from the transfusion policy community, and from the scientific advisors on SEAC. Aguzzi took advantage of this climate to promote his results, as well. As he warned in the British media:

> If we wait until we see transmission of new variant CJD through blood then we may have waited 20 years too long because of the incubation. So I think it would be irresponsible just to wait and see. That has been done for BSE and we don't want to repeat it (1997).

Within the larger sensitizing frame containing analogies to recent experiences with probable transmission of BSE to humans and Hgh transmission of CJD, in which the government and its advisory committees had been blamed for acting too slowly or not at all, it was impossible for the government, and for SEAC not to act on the basis of these result. SEAC further bracketed the uncertainties involved in interpreting Aguzzi's results by pointing to the similarities between the tissue distribution of vCJD and scrapie in rodents, such as the ones Aguzzi had used in his study. In both cases, the lymphoreticular system was much more heavily infected than in sporadic CJD cases. SEAC carried this metaphorical transposition, in combination with Aguzzi's results, a step further and suggested that infectivity might travel through the body by hitching a ride on "circulating lymphocytes." Thus, they suggested that "it is logical to seek to minimize any risk from blood or blood products by reducing the number of lymphocytes present."

Aguzzi's experiments were accepted and vaulted by SEAC despite the fact that, even at the time, they were known to conflict with earlier results from the Neuropathogenesis Unit (NPU) in Edinburgh. Hugh Fraser and Christine Farquhar had observed that relatively high doses of ionizing radiation had no detectable impact on the scrapie disease process (Fraser & Farquhar 1987, Fraser et al 1989). This indicated that reproductively active cells, like the mobile components of blood, such as B-cells, did not

play a direct role in scrapie infection. Rather, it seemed that some cell with a long life-span played a key role. Taken together with other experiments from the Edinburgh lab, in which splenectomy was observed to increase the incubation time of scrapie (Fraser & Dickinson 1978), it appeared, at least to the scientists at the NPU, that some long-lived cell within the spleen, not a mobile component, played the crucial role in scrapie pathogenesis.

While most of the scientific community was awed and inspired by Aguzzi's results, Moira Bruce, also of the NPU, was suspicious. After all, B-cells are rapidly dividing, short-lived components of the immune system. Still convinced by the radiation experiments that the crucial cell involved in transporting scrapie infectivity from the periphery to the brain must have a long life span, the B-cell seemed an unlikely candidate. But she had an idea for a better candidate - follicular dendritic cells (FDCs). FDCs are so named because they exist in the follicles of lymph nodes and spleen and have multiple dendritic processes, long branches extending outwards from the cell, that form a three dimensional matrix, often referred to as a reticulum (Kapasi et al 1993). FDCs trap immune complexes containing foreign antigen and present these complexes to B-cells to stimulate an immune response. Because FDCs have a long life span, they are thought to act as a long-term repository of antigens, continually stimulating B-cell memory and secondary antibody response, important processes in fighting infection.

To test her theory, Bruce bred Severe Combined Immunodeficiency (SCID) mice, which lack both B and T lymphocytes, with PrP knockout mice to produce a line of mice that neither expressed PrP nor produced functional B and T lymphocytes (Brown et al 1999). She then injected hematopoetic cells derived from bone marrow, which

reconstituted the B and C lymphocyte population. By using the bone marrow from PrP expressing mice, she could produce chimeric animals that express PrP in lymphocytes but not in FDCs. She found that these mice were resistant to splenic infection with scrapie. On the other hand, if she used bone marrow from PrP knockout mice to reconstitute the lymphocytes of PrP expressing SCID mice, splenic infection proceeded without complication. As Bruce describes her experience:

> Throughout this large series of experiments, the spleens of PrP chimeric mice were consistently capable of supporting scrapie replication only if FDCs had a functional PrP gene; we detected no replication in mice with PrP-deficient FDCs, even in the presence of PrP-expressing lymphocytes...(Brown et al 1999).

Bruce felt that she had shown the B-cells were not the carrier, that they were merely required for the maturation of FDCs, which were the real culprit in peripheral infection with TSE. In addition, Brown and Rohwer's studies in rodent models of scrapie, as discussed in Ch. 4, indicated that a significant amount of infectivity is not associated with white blood cells at all, but exists freely in plasma. As Peter Foster of the SNBTS remembers:

> ...at that point they were saying you should be thinking about leukodepleting plasma to get rid of white cells, based on a publication that came out at that time by Aguzzi. It was published in Nature, where he claimed very, very strongly that the agent was found in white cells. This came out with a press release. It was on television. And of course, he was wrong. And there was already literature that suggested he might not be right, by Moira Bruce, but that didn't get reported. You know she is a very quiet lady. So it was Aguzzi's views that were taken into consideration (Ponte 2003g).

Lorna Williamson of the NBS has a similar recollection, and a similar concern over the way decisions were made at that time:

> evidence from Adriano Aguzzi's group in Zurich...got picked up as maybe saying that the B cell was, if you like, a carrier for PRPscrapie, and that therefore the B cell could be a source of transmissibility, which has turned out to be a false trail in a way (Ponte 2003d).

It is clear that, post-facto, the regulators and scientists involved feel that they were misled by the certainty with which Aguzzi's conclusion that B-cells were the carrier of infectivity was stated. It was upon this temporary instantiation of certainty that years of risk regulation were based. What the ensuing debate between Aguzzi and Bruce did, in effect, was allow for the opening up of black boxes surrounding assumptions about prion disease and model systems that had long been closed, or ignored, in order to pursue scientific ideals. As Latour notes:

> The word black box is used by cyberneticians whenever a piece of machinery or a set of commands is too complex. In its place they draw a little box about which they need to know nothing but its input and output... That is, no matter how controversial their history, how complex their inner workings, how large the commercial or academic networks that hold them in place, only their input and output count (Latour 1987).

Latour uses the analogy of Pandora's box to describe the process of investigating controversies to reveal the opening of black boxes that had previously been closed. This is, in essence, what arose from the controversy between Bruce and Aguzzi over the role of B-cells and FDCs. In the following section, I will seek to peel back the layers of uncertainty that had been hidden by years of scientific research and show how they reemerged through the disagreement between Bruce and Aguzzi. This analysis reveals the temporary character of the closure of such black boxes which, while allowing for the avoidance of dealing with uncertainty for a time, are bound to pop open again and reveal their inscrutable insides when contradictions accumulate. Despite the destabilization in knowledge that occurred following this controversy, the risk mitigation measures which had been put in place based on Aguzzi's results remained. This, in turn, reveals the difficulty in rescinding risk reduction measures once they are enacted. To do so would

reveal the lack of rationality at the heart of such measures, and destabilize the modernist pretension to control fate and plan for the future. Once the Maginot line has been constructed, it remains in place, despite its acknowledged uselessness.

The first black box we will open is the role and function of FDCs. To begin with, the origin of FDCs, particularly in the mid-1990s, was in doubt. Within the field of immunology, debates raged over whether they could develop from hematopoetic stem cells, or if they derived from cells already present in the spleen or lymph node. In a 1994 review entitled "Follicular dendritic cells: whose children," Heinen and Bosseloir note that "identifying the precursor cells that give rise to FDCs has been made difficult by the fact that FDCs are long-lived, seldom divide, and change their morphology and phenotype during humoral immune response" (Heinen & Bosseloir 1994). A bit like Woody Allen's character Leonard Zelig, who takes on the characteristics of the people around him, the FDC can adopt the surface-characteristics of multiple cell types, including monocytes (Heinen et al 1984), fibroblasts (Imai et al 1986), lymphocytes (Johnson et al 1986), and endothelial cells (Ruco et al 1991), among others. In fact, the surface antigen which was thought to be most characteristic of FDCs, the DRC1 antigen, has been reported on lymphocytes as well (Naiem et al 1983). While several studies lent indirect support to the notion that FDCs originate locally from within the lymphoid organs (Dijkstra et al 1984, Villena et al 1983), other studies pointed to a potential for FDCs to develop from hematogenous stem cells (Parwaresch et al 1983, Szakal et al 1995). Indeed, even in her 1998 paper on the role of TNF signaling in the production of FDCs and germinal centers, Maria Tkachuk notes that there are controversial opinions as to the origin of the FDC, and that her observations can be interpreted within either

framework. She draws her conclusion in such a way as to leave either possibility open: "FDC precursors either cannot be transferred by BM/FL transplantation or they require the expression of TNFR1 by stromal cells for homing" (Tkachuk et al 1998). This uncertainty would, necessarily, complicate the interpretation all of results listed above, because Bruce and Aguzzi both depend on the notion that FDCs and lymphocytes have distinctive origins (FDCs from stroma and lymphocytes from hematopoetic stem cells) in the design of their experiments as well as the interpretation of their results.

The second black box we will open, which complicates any comparison between the results of Aguzzi and Bruce, derives from their use of strains of mouse-adapted scrapie with different histories. Their choice of strains brings us all the way back to the beginning of the era in which mice became the model system of choice for scapie. When Chandler succeeded in obtaining the first mouse-adapted strain of scrapie in 1961 (Chandler 1961), he did so using brain collected from Pattison's goats experimentally infected with the drowsy form of scrapie (Pattison & Millson 1961). The drowsy phenotype of scrapie had been isolated from goats that were infected with the brains of sheep that had been infected from the original scrapie sheep brain pool (SSBP1) derived at Moredun by D.R. Wilson in 1953 (Pattison 1988). Subsequently, the strain of scrapie isolated from drowsy-goat passage in mice by Chandler was transported into the United States, both by Hadlow and Gajsusek. Once in the United States, the Chandler isolate was passaged many times in mice through its use in many different laboratory experiments. Because of the association with the Rocky Mountain Laboratory where Hadlow worked for many years, the strain became known as the Rocky Mountain Laboratory strain, or RML. This is the strain that Aguzzi used in his experiments.

On the other hand, Bruce used a mouse-adapted strain of scrapie referred to as ME7. This strain was isolated at around the same time as the Chandler strain, but from a completely different source. Ever since Gordon and Pattison had been lured away from Moredun to work at Compton, there had been a fierce rivalry between the two. Following Chandler's success in transmitting scrapie from goats to mice, Ian Zlotnik of the Moredun Institute initiated a series of transfers of infectious material from naturally infected sheep (i.e. sheep that developed scrapie on the farm without injection of infectious material) to mice (Zlotnik & Rennie 1962). He gave each transmission experiment a number, which corresponds to the strain derived from that experiment. Thus, ME7 refers to the strain isolated from Mouse Experiment # 7, in which the spleen of Suffolk sheep suffering from scrapie was pooled and injected into mice (Zlotnik & Rennie 1963). Upon examination, lesions characteristic of scrapie could be seen in the brains of these mice as early as four months and clinical symptoms appeared in 5. This was the shortest incubation period Zlotnick observed in any of his mouse transmission experiments, and it was shorter than the incubation period initially observed by Chandler in his transmission experiment. It thus became a strain of choice for experimental work at Moredun.

In some of her early work at Moredun, Moira Bruce assisted Alan Dickinson in defining the biological stability of different strains of mouse-adapted scrapie. ME7 was observed to maintain reproducible properties even upon transmission into mice of a different genotype and back again (Bruce & Dickinson 1979). Dickinson and Bruce classified ME7 as having "Class I stability," a designation reserved only for strains that "retain their identity irrespective of the genotype or even the species of hosts through

which they are passaged" (Bruce & Dickinson 1979). Bruce and Dickinson also note that ME7 is "the most commonly isolated agent from natural cases of scrapie in sheep, having been identified as a component in over half of the primary isolates" from natural scrapie sheep that they had studied (ibid).

When I asked Moira why she had used the ME7 strain to conduct her pathogenesis experiments, her reply encapsulated the history and preference for ME7 at Edinburgh in a nutshell:

> Well it had always been our standard strain. It was one of the first to be isolated. And it's actually a very well behaved strain. Some of the strains are not stable when you switch between PrP genotypes. But ME7 is stable. And it's stable when you – there's just no complications. It's very easy to work with. Plus the fact that ME7 is the one that is most often connected with sheep scrapie directly. So in terms of closeness to the natural disease, at least natural scrapie, it's about as close as we can get. And it's very predictable. I mean they're all very predictable. But ME7 just seems more so. We like it. It's nice and solid. It has this sort of solid personality. It's very reliable (Ponte 2003e).

In contrast, according to Moira, "RML has a very complicated history. It's a million miles from the natural disease because it came from SSBP1...then it was put into goats" (Ponte 2003e). Importantly, she points out, RML has always been passaged in s7 mice, from its beginnings as the Chandler isolate and throughout its history in the United States. At the IAH, she says, "Well there are two strains that we've been able to isolate from Chandler isolate." The scientists at the IAH refer to one of these strains as 139A, and the other as 79A. In Dickinson's transmissions of these two strains, 139A appeared to be very stable, maintaining its characteristics upon passage through mice with different genotypes, while 79A appeared to be less stable (Dickinson & Outram 1979). The problem, according to Bruce, is that when she reads published reports from labs that work with the RML strain, she never knows exactly how to interpret them. Is the RML strain

they are using more like 139A or 79A? Or does it have completely different characteristics? It is possible, Moira thinks, that different labs may, without knowing it, be using different strains even though they are all referred to as RML. As Moira says, 139A and 79A "have similar incubation periods and pathology in PrP A mice, which is what everyone uses. So you wouldn't necessarily know that there was anything different." Upon passage in PrP-B mice, however, the difference in incubation period and lesion profile would become apparent. Since PrP-B mice are rarely used, however, this has rarely been tested. Of the descriptions of RML reported from Prusiner's lab in the 1990s, Moira says, "the characteristics...for RML were actually more like 79a than 139a" (Ponte 2003e). It would still be difficult to know, however, if what other labs are using is the same or different, since each lab will be using a strain of RML with a different passage history.

The point of this discussion is that, by matters of contingency, Moira Bruce and Adriano Aguzzi found themselves working with completely different strains with completely different histories, and possibly very different properties. Their choice of strains was contingent upon their location within the historical trajectory of strain passage and exchange between laboratories. Chandler conducted his mouse inoculations in Compton, where Pattison conducted his goat experiments, and thus had access to Pattison's goat-adapted scrapie strains. By virtue of the fact that Hadlow worked across the hall from Chandler at Compton during that time, and that Gajdusek visited Compton during his travels, the Chandler isolate was the strain which made its way to the United States and became ingrained in the American continent as the quintessential laboratory strain, or research tool, for examining scrapie transmission characteristics and

pathogenesis. In the guise of RML, the Chandler isolate was spread around the world upon networks that stemmed from various laboratories in the United States all the way to Switzerland. The global networks through which Adriano Aguzzi obtained his strain of mouse-adapted scrapie contrasts with the local origin of Moira's. Moira Bruce, due to matters of preference and comfort, found herself working with a strain that was isolated by predecessors within her own laboratory from a scrapie infected sheep at their local animal breeding facility.

Their choices, however, made their results potentially incomparable, and destabilized the possibility for making generalizations about TSEs based on either of their reports. Moira reasons that the contradictions between her observations and Adriano's could be due to a differential cellular tropism between the two strains: "Well, I think that the difference in our results could be due to ME7 having a much more restricted pathogenesis that involves these follicular dendritic cells. Its ability to get into other cells in the immune system is a bit limited." In other words, she quips,

> Our results are actually a lot cleaner than Adriano's because perhaps there isn't the involvement of leukocytes so much. So when we knock out FDCs with x-rays, it has an absolute character. Some of Adriano's results would suggest that perhaps bone marrow derived cells might be involved as well, more important than they might be in our model system (Ponte 2003e).

If this is the case, however, and different strains can possess such different cellular tropism, then it becomes almost impossible to infer anything about vCJD from experiments done on scrapie. The metaphorical relationship which allowed one to stand in for the other is destabilized, for if one strain of scrapie cannot even stand in for another strain of scrapie, how can any strain of scrapie stand in for vCJD?

In 1997, however, these black boxes had not yet been opened sufficiently, and all of these uncertainties had not yet been uncovered. Meanwhile, pressure from the public to do something, anything, to mitigate the risk of transfusion transmission of vCJD was continuing to build. On October 29, when the plasma from a donor later found to have vCJD had been tracked, a UK fractionation center issued the first recall of blood products for new variant CJD. Less than one week later, on November 4, a second batch of blood products was recalled (Ellis 1997). It was noted that in this case, as well as the last, it was likely that most of the blood products produced from the implicated donation had been consumed before the recall. This angered the public, and raised the stakes for risk reduction efforts even higher.

Two days after the second recall announcement, Health Secretary Frank Dobson issued a press release stating that the government had accepted SEAC's advice related to nvCJD and blood products. He agreed that the DH would commission "an assessment of the risks of human to human transmission of nvCJD through blood and blood products" (Dobson 1997). Meanwhile, he instructed the NBS "to start work towards the possible extension of leucodepletion of blood in order that they are prepared in the event that the risk assessment indicates that this would be a sensible precautionary measure" (Dobson 1997).

The NBS set up a project to explore the feasibility of instituting universal leucodepletion of blood. According to Lorna Williamson, this required a large-scale study. While bedside filtration had been adequate to leukodeplete the small amount of the blood supply which had been leukodepleted up to this point, large-scale leukodepletion would require new technology. It was also known that if blood sits around for too long

before leukofilration occurs, the leukocytes break into pieces. The fragments are small enough that some of them can pass through the filters, potentially, it was thought, allowing fragments of cells with their attached prions to get through. The transfusion service decided that in order to prevent this possibility, leuckocyte filtration must be done within 24 hours of collecting the blood (Wallington 1998a). This, in turn, would require a refashioning of the entire blood collection system. According to Lorna, "we said right at the beginning of this project, if we're going to leukocyte deplete systematically it'll be done in the blood centers, it'll be done within a day or two of collection, and it'll be done with quality control." The NBS prepared a report for the Department of Health detailing how this could be accomplished. As Tim Wallington remarked, "The Service finds itself profoundly influenced by a complex and fast moving set of circumstances to which it must respond" (Wallington 1998b). He believed it was important, however, to "respond in a manner that not only focuses on the safety of the blood components and products transfused, but also leaves the NBS a fully functional Transfusion Service" (Wallington 1998b). The changes required were on such a scale that Wallington doubted the ability of the agency to survive. In fact, based on projections by the NBS, it was estimated that "universal leucocyte-depletion could not be justified on the basis of identifiable clinical benefits and cost savings" (Murphy 1998). Nonetheless, "concern about the safety of blood transfusion in relation to nvCJD has led to an urgent consideration of universal leucocyte-depletion of blood components in the UK" (Murphy 1998).

Relying on the results of two studies from a single lab on which to base a decade's worth of blood regulations to mitigate the risk of vCJD was certainly not the optimal solution. It was, however, the only solution with even an appearance of scientific

rationality on hand. Given the choice between doing nothing and acting upon uncertain results, SEAC, the UK government, and the NBS elected to bracket the uncertainties temporarily and strive for action. They were, in essence, reacting to the experiential threat of the moment, highlighted by recent government failings, and dictated by political necessity.

Plasma Product Importation

While the HIV/AIDS crisis did not play a configuring role in the sensitizing frame with which SEAC approached a potential CJD transfusion risk, or even the potential vCJD transfusion risk at first, it did for the hemophiliac community. Having endured the deaths of thousands of their ranks, Hemophilia advocacy groups were quick to draw an analogy between HIV and vCJD, pointing to the possibility for vCJD to spread via plasma products, such as Factor VIII. This was something that had not been considered by SEAC at their previous meeting. Instead, they had reserved the majority of their concern for blood components, which are not used in the routine treatment of hemopheliacs.

In November of 1997, the United Kingdom Haemophilia Centre Directors' Organization (UKHCDO) brought the HIV metaphor to bear on concerns over the vCJD transfusion risk. They met and decided that if SEAC chose to ignore the potential risk to plasma products, they would have to publicize it themselves. In a letter to the Lancet, in which they openly drew connections to past experiences with HIV, the UKHCDO called for two measures (Ludlam 1998). First, in all cases where recombinant products are available, patients should be treated with these products. Second, in the cases where

recombinant products do not exist, the UKHCDO recommended the importation of plasma products from non-BSE countries.

The UKHCDO's second recommendation reveals the way in which they, like TSEAC, conveniently configured the risk of vCJD as though it could be contained by national borders. This allowed them to call for a measure that would manage risk simply by importing products from regions where BSE had not yet been detected.

> The choice lies between concentrates manufactured from plasma collected in countries with cases of nvCJD and BSE, or in those geographical regions in which there are no recorded cases of either of these conditions. From our understanding of the epidemiology that nvCJD occurs almost exclusively in the UK, it is likely that any risk of transmission would be reduced by the use of concentrates prepared from donor plasma collected in other countries, such as the USA, where there are no recorded cases of nvCJD and BSE (Ludlam 1998).

In treating vCJD risk as containable by national borders, they, like TSEAC, choose to overlook the uncertainty induced by the leakage of meat and bone meal, cattle products, and cattle across borders, as well as the lengthy incubation period, during which it is impossible to tell whether other countries may be harboring BSE. BSE is a tricky disease to manage partly because, as already discussed, the lengthy incubation period and difficulty in diagnosis can disguise its presence for years, even decades. Temporally, this extends uncertainty significantly into the future.

Despite these uncertainties, the UKHCDO's letter, and the recommendations made within it, reverberated through the medical literature. Their recommendations were interpreted from within the sensitizing frame including the recent Hgh trial as well as the BSE cover-up, for which the government had been blamed. In this context, Nature reported that "Foot-dragging by the British government is exposing hemophiliacs to an avoidable risk of infection with the new variant of Creutzfeldt-Jakob disease" (Butler

1997). In the end, the pressure was too much for the government to bear. Frank Dobson announced that UK plasma fractionation centers would no longer be allowed to prepare plasma products from UK plasma. He authorized the NHS to import blood plasma from countries without BSE, noting that "This will reduce the possibility of repeated recalls of blood products in the future and thereby help to maintain public confidence in these products" (Reaney 1998). In his reasoning, Dobson explicitly noted that, "though the risk of nvCJD transmission is hypothetical, nevertheless the fear of it is very real to this group which has previously been affected by both HIV and Hepatitis C transmitted from Factor VIII" (Reaney 1998). His statement reflects the effectiveness of the UK Hemophilia organizations in bringing HIV into the sensitizing frame surrounding the interpretation of and reaction to vCJD risk. The result is that even before the government could adopt any mechanisms to rationalize this decision, it was forced to take it on purely experiential grounds. The rationalization would come later, as described in the next chapter.

To recount, due to the relative lack of political fallout from the transfusion transmission of AIDS in the UK, the HIV metaphor did not create the immediate perception of concern surround CJD that it had in the US. As a result, the UK never seriously entertained a US-style CJD withdrawal policy. Concern over vCJD as a transfusion transmission risk, however, arose almost immediately after the disease was announced. This difference can be partly accounted for by the context of great political fallout, in which the UK citizenry felt betrayed by the UK government's insistence, over the course of a decade, that BSE would not infect humans. In addition, the recent Hgh trial, in which it was uncovered that the government had neglected warnings of CJD transmission risk, formed an important metaphor within the sensitizing frame through

which the vCJD transfusion risk came to be perceived and greatly feared.

While the metaphor with AIDS did not play a role in the government's early reaction to CJD and vCJD, the hemophilia community brought it to bear through their own activities and succeeded in incorporating it, belatedly, into the sensitizing frame from which disease management decisions were taken. Through their urging, and partly through this alteration in the sensitizing frame, they were able to push for greater regulations with respect to plasma products. It was primarily the metaphors to the BSE and Hgh cover-ups, however, that created an uproar among the public and engendered the political necessity for action regarding this newly perceived, hypothetical risk of vCJD transmission by blood.

Meanwhile, the measures recommended by hemophilia organizations, and later adopted by the government, remained metaphorically tethered to the same notion of vCJD risk as coincident with nation-state boundaries that had prevailed in the US. This exposes the metaphorical stability such cartographic lines form in our modernist imagination. Despite the repeated admonition by the public health community that infectious disease knows no boundaries, we persist in acting as though it does. Nation-state borders are readily invoked when they provide a convenient mechanism for compartmentalizing disease management decisions. In this way, borders are attributed almost magical abilities to "trap" and "contain" an infectious entity. This is despite the fact that trade of meat and bone meal, cattle parts, and cattle had occurred freely between the UK and many other countries during much of the BSE epidemic, a fact which was conveniently overlooked when political necessity intervened. Leaky boundaries, it appears, are easier to manage than no boundaries at all.

In a similar fashion, Aguzzi's results provided a convenient, though temporary, spatial metaphor, with respect to infectivity distribution in blood, that allowed leucodepletion to be invoked as a risk management policy. By treating vCJD infectivity as thought it could be contained within the B-cells of blood, and no where else, SEAC was able to claim that leucodepletion would reduce the risk of transmitting the disease through blood. Together, the two risk reduction measures implemented by the UK, and their historical contingency, illustrate the unstable and negotiated character of the choice of appropriate metaphors for a given disease as well as the constructed nature of risk management decisions. Despite the grasping quality with which the UK government came to their risk management choices, it was found necessary, after the fact, to cloak them in a guise of rationality. The way in which this was accomplished, a posteriori, will be described in the following chapter.

Ch. 7 - Risk Assessment in the UK

Since the announcement of vCJD, quantitative risk assessments have come to play an increasingly common role in decision-making when it comes to issues involving TSEs in the UK. Before the announcement of vCJD, all through the first decade of the BSE crisis, only one formal risk assessment of BSE had been conducted. Since the announcement of vCJD, the number of risk assessments conducted on BSE and vCJD have grown exponentially. One of the primary roles of SEAC has become the evaluation and certification of such risk assessments. In this section, I will consider the factors that led to this increasing reliance on risk assessment. I will explore how members of SEAC perceive and evaluate risk assessments. Finally, I will build upon the previous section in examining the ways in which risk assessment can serve to rationalize and legitimize policy choices, but leave the public more in the dark, by masking uncertainty.

The first factor which played into the changing role of SEAC and its increasing reliance on formalized risk assessment was the implementation of an Inquiry to investigate how BSE was handled by the government and its scientific advisors. An Inquiry into BSE had been called for publicly even before the announcement of vCJD, but the recognition of a possible link between vCJD and BSE intensified the public demand. The government held out as long as possible – until, in fact, it had no other choice. The Torries, led by John Major, lost a great many seats in the subsequent election and the Labor Party, led by Tony Blair, came into power. The "Human BSE Foundation," which had been founded by a group of parents whose children had died of vCJD, finally achieved the goal it had been lobbying for since its inception – a full-scale investigation

of decision-making around BSE. They wanted to know why their children had been infected and killed by meat that their government had repeatedly stated was "safe" to eat.

The Inquiry was conducted by Lord Philips, a reputable Justice, with the help of several committee members, including one scientist, Dr. Malcolm Ferguson-Smith. Each of the civil servants and every member of each of the advisory committees that had provided advise on the management of BSE were asked to submit testimony. Of those who submitted written testimony, a number were asked to provide oral testimony. At the end, the Philips committee came out with a report identifying the areas in which mistakes had been made and providing recommendations.

The Inquiry concluded that the government, first and foremost, needed to be more open and transparent about considerations of potential risk to the public health. Secondly, it concluded that the government should not hide behind its advisory committees when it comes to making policy decisions. Advisory committees are there to advise, not to take the final policy decisions.

I spoke with Peter Smith, a member of SEAC who had submitted evidence to the Inquiry, in his office at the London School of Hygiene and Tropical Medicine. It was a broiling hot day and his office was without air conditioning. I asked Peter to reflect on the BSE Inquiry and the changes it had brought about.

He began by describing what he felt had gone wrong with SEAC and its relationship to the government:

> When I joined the committee, the committee was heavily involved in all of those areas in ways that it shouldn't have been. I mean, it wasn't privy to information that really put it in the best situation to advise on risk management...But the committee had got itself into a situation where if it said something should be done, particularly at that time, the Government had little option but to do it...In the early '90s, the Government would say "Our scientific advisors tell us that BSE

> is not a human health problem. Beef is safe." And so they would use that as sort of a shield. They'd use it to say, "Well, we're only doing what our scientific advisors told us to do. If it goes wrong, the application is therefore not our fault, we're only doing what we were told to do" (Ponte 2003i).

Despite SEAC's designation as a scientific advisory committee, Peter reflects that SEAC did not always make decisions on scientific grounds. Politics came in as well:

> Some of these decisions are made on political grounds as much as on scientific grounds, and as a rule that's public policy, and that's rightly in the hands of Government, and Government should not be in the position, as it was in 1996, of saying, "Well, we'll do whatever our scientific advisors tell us to do." That puts both us and them in a very exposed position (Ponte 2003i).

While the government was happy to have SEAC take the responsibility for policy decisions relating to BSE, SEAC seemed somewhat oblivious to the position it had been forced into until the advent of the Inquiry. As Peter puts it: "When it really did come back and bite was when the BSE inquiry was set up." At first, he and the other members of SEAC thought the Inquiry would be a rather low-key event, where they would privately discuss what went wrong and arrive at conclusions together. But the Inquiry took a more aggressive approach:

> We and a hundred other people got a letter which was tailored to individuals, which were called 'letters of potential criticism'... Now, these letters were not made public, but one knew at the end of the day that unless those criticisms were satisfactorily answered, then that was going to be made public, and you had to live with that forever (Ponte 2003i).

Some individuals bore the brunt of the blame that the Inquiry doled out. Peter Smith feels that, in particular, John Wilesmith and Bob Will were treated unfairly. Peter also worried that the Inquiry would frighten scientists from serving on government advisory committees in the future.

Given these concerns, as a continuing member of SEAC, and later its chairman, Peter pushed for changes in the way the committee operates. He interpreted the Philips

Inquiry as indicating that risk management, as far as possible, should be removed from the committee' purview:

> So that what we tried to decouple, I think reasonably successfully in the last five years or so is essentially risk assessment, which is very much our job, from risk management, which is not our job and we shouldn't be involved in. And risk communication sort of falls in the middle (Ponte 2003i).

Peter Smith believes this approach is justified:

> I actually think we don't have the skills, and we're not there to make, the policy decisions. We may have views, but at the end of the day, we let politicians make these decisions, and they have to weigh up things which include the science, but are not solely based on the science. And they're there to make decisions; if they make the wrong decisions, they're sacked. I mean, that's the way our society works, and I think that's probably a good way of doing it (Ponte 2003i).

When I asked Adriano Aguzzi, another member of the committee, what he thought about this approach, he said that it "is one way I try to save my ass." Clearly, the feeling that SEAC needs to avoid being put in the position, in the future, of making policy decisions is a strong one.

As Peter Jinman, a veterinarian serving on SEAC, describes the current situation on SEAC and its efforts to construct a shield around itself:

> Peter Smith will constantly remind us and say, let's be careful here and leave this is up to the minister, and absolutely right...we can give him all the best weapons and tools and explain to him the limits of those weapons and tools, and then say, "I'm sorry mate, but you're on your own...(Ponte 2003h).

Harriet Kimbell, the consumer representative on the committee (another addition brought about by the BSE Inquiry), notes that it is sometimes difficult to avoid giving risk management advice:

> Of course, it's terribly tempting to say, "We think this is dangerous and therefore we think that you should ban it," or whatever, but now it's much more – there's much more of a division since the reporting of Phillips which says, "No, these advisory committees are just there to look at risk assessment and then give the information to Government or whoever is going to do the management side of it."

> Constantly the Chairman is saying, "You know, that isn't our role; our role is risk assessment and to evaluate risk assessment and see whether there is a risk or there isn't a risk, and if there is, how big it is in our view" (Ponte 2004b).

What has happened, however, is that SEAC has become a body largely devoted to the review of risk assessments which it does not conduct itself, because the committee members have day jobs, but which are farmed out to companies, like Det Norsk Veritas, or conducted by government agencies. Almost every meeting involves the review of some risk assessment or other, whether it pertains to the potential for tonsillar tissue attached to bovine tongue to infect humans, the potential for dental instruments used on vCJD infected individuals to infect other individuals, or the potential for transmission of vCJD through the blood supply. Harriet views these risk assessments and SEAC's role in evaluating them, as somewhat problematic:

> I'm highly skeptical of them, highly skeptical of them, because they don't, to me, have any hard data. I mean, some of them have a bit of hard science in them, but we have seen some which are just mathematical jiggling in my view. I mean, somebody plucks a figure of risk out of thin air and then the whole map of the risk assessment is based on that figure. And of course they come to SEAC and say, "Do you think we're overestimating, underestimating or are we about right on this level of risk?" Well, to me that means nothing, and I've taken this up a number of times particularly. We've had one or two that have been completely mathematical. I mean, it's like a bloody book of logarithm tables – I mean, it's just completely unintelligible. And what I'm told is these risk assessments are not designed to present you with absolute figures in terms of percentages of risk; what they're designed to do is to identify places, points within a food chain or whatever chain it may be, where potentially something ought to be done to minimize risk. And I suppose if you look at them on that basis, and if you take for example surgical instruments, you can say, "All right, this is where the risk occurs. Now, how can we – what can we do to minimize the risk?" And if you do a proper risk assessment, you can say, "Well, if we wash the things and if we sterilize them and then we autoclave them and then we do this and we do that, at each stage we're reducing the risk by a magnitude of X." Now, what "X" is, they tell me, is not that important, but the fact that you've identified points of risk or points where something could intervene and help the risk, is a good idea. But they're often put forward as much more absolute documents. They'll put forward "50 is the risk," and if the risk is low, then we don't need to do something. Or Government will say, "We don't need to do something." If the risk is high, Governments will say,

> "We do need to do something." But in essence, the figures that you're working with are just math. And I'm highly skeptical, I like to see some hard science. It's not any good to say, "Okay, here's a surgical instrument. There is X percentage of matter or prions left on there. I would like somebody to take a metal instrument, do some experiments on it, and determine how much prion is actually left there, at least at some point (Ponte 2004b).

Ian McConnell, an immunologist and member of SEAC, also sees problems with SEAC's increasing reliance on risk assessment. He points out that the assumptions that must be made to construct such risk assessments, and the huge uncertainties which attend to them, result in a confusing range of projections that often provide little help to policy makers. Ian cites the example of an assessment conducted to estimate the risk of transmitting vCJD by surgical instruments used to perform tonsillectomies.

> They commission a risk assessment through a variety of fairly careful, and able, companies who are into this question of risk assessment. So they then take all the available data and with that they'll then say, "Well, you know, we'll assume that there are so many operations done. We'll assume that there're certain operations. We'll assume that there are certain instruments." You then work out how much tissue is going to be left behind. You know, how well are things cleaned. You go through the whole business of trying to come up with a figure for what risk you're running. Right? And then it's up to SEAC – but SEAC is only advisory! SEAC then advises the department of health that "here is a new piece of data. We think it is important. The risk assessments indicate that the risk of transmitting prions on the end of an object for certain from a patient with CJD, should they be operated on, is one in a million to one in 1,000, accounting for 80 to half a million transmissions. You've got to have a number. You've got to carry out some risk assessment that gives you some feeling of the risk. And then the officials say, "Well, why are there such huge confidence intervals?" And you then come back to the question of well, you don't know the transmission kinetics, you don't know the dose, you don't know what the route was, etcetera, etcetera. So there are too many unknowns. It's not like dealing, let's say, with HIV where you have a known virus, you have a known kinetics, you have a known immune response, you have a known population, you have a known method of transmission, and so on and so forth, right? So, that's why they end up giving-- trying to give -- some kind of a figure. And some of those figures will be useful, and some will be useless. So, I mean, to be able to say that there's 80 to half a million is not terribly helpful, you know, to the Department of Health (Ponte 2003b).

Despite, or perhaps because, of the large confidence intervals, the Department of Health mandated that tonsillectomies should only be performed with disposable instruments. After receiving complaints from a number of surgeons, the Department of Health quickly rescinded this position. As Ian ruminates on this course of events:

> So you seen then it comes down to a balance of the consequences of using disposable instruments. You know, is the risk higher that people will bleed to death because you're trying to use plastic object forceps? You know, surgeons have had great difficulties with some of these instruments (Ponte 2003b).

In the end, the personal experience of surgeons came to weigh more heavily on the department of health than the numbers provided by the risk assessment. And yet it was the risk assessment which had triggered such action in the first place.

Peter Jinman questions the whole purpose of conducting risk assessments when there are so many unknowns about which assumptions must be made and the results are vague and difficult to interpret. He remembers in one instance, asking a question of the person who had conducted a risk assessment about how he came up with a certain input value. "And it came down to the fact," he said, "that somebody thought somebody had told somebody that this is what the figure ought to be" (Ponte 2003h).

Robin Carrell, a protein chemist, reports that that the risk assessments he has reviewed during his time on SEAC often drive him to exasperation:

> These people were doing their best, but they are guessing and guessing and guessing. And it makes it pseudo-scientific. In science we're always taught, always doubt the statement that has two "ifs" in one sentence. And you look at those calculations, they have rows and rows of "ifs" (Ponte 2003j)!

Still, Robin believes these risk assessments have utility, as long as they are viewed as what they truly are – a series of possible guesses and "not necessarily the best possible guesses" (Ponte 2003j).

Many of the SEAC members I spoke with expressed a similar characterization of the risk assessments they had reviewed. They also felt that it was important to communicate the uncertainty involved in risk assessment to the public. They saw a failure to do this as one of the major failures that the Inquiry had found in the actions of SEAC and governmental agencies prior to the advent of vCJD. As Ian McConnell put it:

> I think you need to say to people you're uncertain. You say you don't know. I mean, what's wrong in saying you don't know? We say we don't know a lot of times in scientific meetings. I think it's wrong to sell the pass to people that these buffoons sitting around the table know everything. In some cases, we're as ignorant as the man on the street. And we're about as wise as yesterday. And I think if that's the case, you should communicate it. And you can simply say, "I don't know. We don't know." There are plenty of situations where you simply don't know. And I think you have to communicate that. You have to communicate. People mustn't think science is some kind of certainty that's handed down on tablets of peer reviewed publications. You have to communicate the whole mess of science, and say it's messy. You know, it's hugely messy (Ponte 2003b)!

Peter Jinman expresses a rather similar view:

> So rather than saying, "this is the position," saying, "this is our best estimate, our best guess of what the position is, but, you know, it could be this or it could be that. You can't be certain, and there is divergent scientific opinion in some areas." And we try to incorporate that into the advice, and that's part of Phillips too, that that should be built in, rather than what Government would like, which makes decision-making easier, is if we'd just say, "Well, this is how it is, and this is what the risk is – it's .0076, and you must choose to act on that basis." There are unknowns, and the problem that you want to try to avoid, and that's what the UK screwed up on, is to be absolutely definitive about it. I mean, people-- you just have to trust people to understand what's unknown. And the UK, when the BSE outbreak came out, they said, "There's absolutely no chance at all for you guys to get sick, and don't worry about it. It's a cow disease, it's not a human disease. Look, I'll feed my own daughter. And da-da-da-da. And no problem!" And then, when cases started to occur, they lost all credibility (Ponte 2003h).

Despite the overwhelming belief expressed by members of SEAC that the uncertainties involved in risk assessment should be communicated to the public, the public remains, in some very important ways, shielded from these uncertainties. Even though the committee

meetings have now been partially opened the public, another response to the BSE Inquiry, preliminary discussions of risk assessments still occurs behind closed doors. When Peter Bennett, who conducts risk assessments for the Department of Health, told me this, I was a bit surprised, especially since he had just explained to me that risk communication "has to be more of a two-way process, rather than just the powers-that-be explaining things, you have to engage with the public" (Ponte 2003f). But, as Peter maintains, "there are occasions when we actually want to bounce ideas off the scientists in a relatively safe closed session," as they had on a recent risk assessment of bone graft material. I asked him how they decided when a risk assessment should be presented in the closed-session and when it was ready to be presented in the open-session:

> Well, I mean, obviously there is a very prolonged grey, grey area...The nightmare scenario is, we could go to open session, and you know the committee could actually find that they disagreed with the assumptions of the risk assessment, that it was actually utter, complete nonsense. And we could've done it wrong. Now you can say, well, as a scientist, one ought to be able to bear that embarrassment. The problem, though, with open sessions, though, is you get a journalist there, and the headline the next day is "SEAC slams government scientists." That would be the worry. Anything to do with CJD has the sort of potential to blow up like that. And the other one is, if you like what we come up with something which does look very worrying, and then have to reverse it. Or vice versa. If we come up with something that looks reassuring, and then it comes out, actually quite early in the process of consultation, that the assumptions were too optimistic. So we'd rather have one go at it behind the scenes, as it were (Ponte 2003f).

In order to prevent the media, and by extension the public, from witnessing disagreements pertaining to the uncertainties involved, early discussions of a risk assessment are conducted behind closed doors. By the time a risk assessment is presented in an open session of SEAC, most of the disagreements over the way assumptions have been and uncertainties smoothed over have already taken place. By shielding the public from this decision-making process, though, the risk assessors and SEAC are in effect

"performing" the risk assessment as though it were more certain than it really is. Given these tendencies, it is no surprise that the public, as Peter Bennett says, over-interprets the certainty of numbers provided by such risk assessments.

What is doubly distressing is the disconnect Peter Bennett displays in not linking the practice of hiding disagreements over the assumptions involved in constructing a risk assessment from the public and the lack of the public's understanding of uncertainty. This type of action, it seems to me, flies in the face of the conclusions of the Philips' Inquiry. According to the Inquiry, the public should be made more aware, not less aware, of the uncertainties involved in scientific evaluation and the decision-making process through which they are dealt with.

Another aspect I find disturbing is that many members of SEAC feel that they have dealt with the Inquiry's recommendations simply by focusing on risk assessment to the exclusion of risk management concerns. While this division certainly shields SEAC from blame for risk management decisions, I believe that is the only positive effect it may have. As Peter Jinman points out, simply abandoning practical policy and implementation issues may in fact undermine the risk assessment process by obscuring and multiplying the uncertainties involved:

> You're making judgments on the parameters that have been put into the risk analysis anyway. And those are practical ones. So you always start from a risk analysis that involves a certain amount of risk management because it's already saying well, as long as we can keep this risk at that level on the input side, we could put it into our equation and it will come out giving you an answer of why. But you're already managing the input (Ponte 2003h)!

This view complicates the logic, as expressed by Peter Smith and put forward, that risk assessment can, or should, ever be fully separated from risk management. The estimates of input values for a risk assessment, and therefore the results of the risk assessment,

depend largely on the effectiveness of the implementation of a given risk management strategy. Likewise, the effectiveness of risk management decision-making depends on the results of risk assessment. In this way, the two are inextricably linked in a circular relationship with each other. From this perspective, attempts to further delineate a separation between risk assessment and risk management may be misguided. Continued separation may only serve to magnify the uncertainties and further remove risk assessment from anything having to do with reality.

What the committee should do, and what I believe the Philips' Inquiry intended it to do, is to become more open about the very uncertainties that complicate and confuse the construction of risk assessments and the decision-making process. Removing the committee from risk management issues only serves the interests of the committee members by preventing them by shielding them from responsibility for anything that goes wrong in the future. However, when risk management decisions are so clearly tied to risk assessment, it could be a mistake to separate the two from each other. I am not arguing that SEAC should have to make actual policy decisions – these should indeed be left to the politicians – but they should not have to avoid talking about the implications for risk management on the way they view the risk, or vice versa. After all, their assessment of the risk of any given situation depends integrally on a swath of policies that have been implemented or could be implemented in the future.

The increase in the number of risk assessments requested by the government on TSEs since the advent of vCJD is an indirect outcome of SEAC's refusal to be implicated in further policy decisions. Before vCJD was announced, the government hid behind SEAC when it came to the responsibility for policy decisions. After vCJD, and the

Philips Inquiry, SEAC decided it would no longer allow itself to be used as a shield. The government, however, still desired a means to avoid responsibility for policy outcomes. Risk assessment provides that means. If for every policy decision taken regarding TSEs, a risk assessment is conducted, and the government claims to have taken the decision on the basis of that risk assessment, then only the risk assessment can be held to blame if the outcome is bad. Risk assessments have come to occupy a metaphorical role to that which SEAC's advice used to provide. They have become, in effect, the new shield with which governments, not only in the UK but around the world, attempt to protect themselves from potentially damaging political fall-out. But these risk assessments, as the members of SEAC point out, are often based on a series of questionable assumptions about unknown values. As Peter Jinman phrases it, "rubbage in, rubbage out" (Ponte 2003h).

Incidentally, governments do not usually commission multiple risk assessments on the same issue, because if they do, they are likely to come up with contradictory results. Such was the case when the UK government was first considering the possibility of the transmission of vCJD through the blood supply. After Philip Comer conducted his risk assessment for Det Norske Veritas (DNV), Peter Bennett conducted one for the Department of Health. As Peter says:

> DNV's conclusion led them to worry more about blood components, on the basis that they have bigger doses with which to contract it, which is quite true. Our risk assessment led one to worry more about plasma derivatives, on the basis that if you look at it like any other communicable disease, then the shear number of contacts that you might have if you're pooling things in batches of tens of thousands is much greater...It doesn't mean that either of them was wrong, it's just that we chose to focus on different aspects (Ponte 2003f).

As Peter indicates, the biases involved in deciding which questions are asked and how to ask them determines, to a large degree, the outcome one obtains from a risk assessment.

Given that this is so, it would seem wise to let the public in on the process of risk assessment from the very beginning, revealing to them the messy debates and difficult decisions that must be made to achieve a result, however uncertain.

Ch. 8 – Changing perceptions of vCJD transfusion risk

A number of years would pass between the implementation of the previously described risk reduction measures and the first detection of a case of vCJD transmitted by blood. During that time, a number of studies were conducted on various model systems which contributed to the sensitizing frame for evaluating the risk. Each of the model systems had to be weighed for its metaphorical fit with the human situation under consideration. Scientists found different reasons to lend credence to different studies, based on what they perceived as significant similarities to the human scenario of vCJD. This illustrates the concept, as often remarked upon in science studies, that it is impossible to resolve a controversy through recourse to science alone (Ezrahi 1980, Latour 1987, Nelkin 1984). Scientific results are always underdetermined, meaning that there are a number of interpretations which can be lent to them (Collins & Pinch 1998). As such, a scientist can always be found who will interpret the applicable results in a contradictory manner to other scientists, providing for unending debate (Jasanoff 1987b, Toumey 1996).

One of the most influential studies that appeared during this time was conducted by Fiona Houston and Nora Hunter in sheep. As often happens in science, their influential study was not the result of rational planning for its importance, but came about, in the beginning, as an adjunct to a much larger study. The larger study made available certain tissues, such as blood, from infected sheep on a contingent basis. Karen Knorr-Cetina, in her early laboratory studies, has remarked upon this phenomena. Scientific research, rather than being designed in a strictly rational manner, is often implemented due to the contingencies of the laboratory situation and the availability of

certain materials, and model systems, for study (Knorr-Cetina 1981). In the following narrative of Houston's experiment, I will describe the ways in which contingency and fortuitousness played into the design and results of the study.

Fiona Houston is of Irish descent with dark brown hair and hazel eyes. Trained first as a veterinarian, she grew bored of clinical practice and longed to do research. She undertook a PhD at Compton in 1993 to study the life-cycle of a cattle parasite that resembles malaria. Toward the end of her PhD, as she was looking for a job, she learned that Compton was looking to hire a researcher with her skills in large animal veterinary medicine. Nora Hunter's group had just received a large grant from the BBSRC to examine the pathogenesis and epidemiology of scrapie, as there had been renewed interest in the disease since the advent of BSE. As Fiona recalls:

> There was a sort of drive to understand things better in the sheep population because then scrapie was becoming more of a concern. I think there was just a lot of attention on TSEs in general and the fact that they'd been saying, "Oh, there's no problem with BSE," all along, and then suddenly it turned out we were getting new variant CJD. And they were worried about the development of BSE in sheep.

The idea behind the pathogenesis experiments was to learn more about the development of the disease in both scrapie and BSE infected sheep, in order to compare the two. For one thing, it was deemed important to be able to distinguish one from the other in order to detect BSE should it infect the sheep population. As a sort-of side project to this much larger project, Nora Hunter decided Fiona Houston could examine the potential for infectivity in the blood of sheep infected with BSE to transmit the infection. In retrospect, Fiona describes sheep as an ideal model system for mimicking human transfusion because:

> ...we can transfuse large volumes of blood in the absense of a species barrier. Also in naturally infected sheep, and in sheep experimentally infected with bse,

> there is widespread accumulation of PrPsc in lymphoid tissues, very similar to that seen in vCJD patients. Because sheep are similar in size to humans and have similar volumes of blood, simpler techniques can be used in collection of the blood (Ponte 2003a).

Fiona noted that such a model system was desirable due to the controversy surrounding the interpretation of the existing data regarding the infectivity of blood in TSEs rodent model systems.

The idea Nora and Fiona had was to conduct a two-part experiment. In one part, blood from sheep infected with BSE would be transfused into sheep. In another part, blood from sheep infected with scrapie would be transfused into sheep. Neither experiment, however, had ever been attempted. In both cases:

> ...these animals were part of a pathogenesis experiment and were being killed at different time points during infection. Before they were killed, blood was collected and either transfused as whole blood or processed to buffy coat. That was then transfused into recipients which were kept as part of a separate flock at Compton. These were New Zealand sheep that had been imported and therefore should be free of TSEs. And they were of the same breed and genotype as the donors (Ponte 2003a).

The choice of importing sheep from New Zealand, a country believed to be free of scrapie, for this experiment was made in part to avoid the interpretive difficulties that could be introduced by using sheep that might have been exposed to scrapie in the field.

The first of the transfused New Zealand sheep began to develop symptoms in the summer of 2000, two years after Fiona had begun the experiment, and long before all of the animals had even been inoculated. I asked Fiona what her first reaction was:

> Well, I think by the time I saw it, and it was pretty unmistakable. It was scratching quite a lot. And then I thought, "Oh, no." You know, well your first thought is, "Oh, did we mess up somewhere?" You know, but yeah, it was just like, "Oh, my goodness." And so I thought, well, as I say, the clinical signs were pretty unmistakable, so I went ahead and postmortemed it and then I just talked to Chris Bostock and various people like Moira Bruce too, and what did they think about it. And they were a bit shocked as well (Ponte 2003a).

The first sheep that developed symptoms had received blood from a donor sheep that had been fed 5 g of BSE-affected cattle brain 300 days before (Houston et al 2000). This donor sheep would not go on to develop symptoms until about 300 days after the blood donation, indicating that the collection of blood had been made half-way through the incubation period. Fiona and the other researchers interpreted this as indicating that the blood of BSE-infected sheep, and possibly vCJD infected humans, could be infectious during the incubation period of the disease. This indicated, they surmised, a risk that vCJD could indeed be transmitted by transfusion from donors who seemed perfectly healthy. As they phrased it in their publication: "This report suggests that blood donated by symptom-free vCJD-infected human beings may represent a risk of spread of vCJD infection among the human population of the UK" (Houston et al 2000).

They made the decision to go public with the results and publish them before the end of the experiment because they felt like, in the climate that had developed around vCJD, they had to. Still, a number of scientists criticized them for publishing on the basis of a single result. According to Fiona, however, they made the right decision:

> I think the initial reaction was, "Oh, this is just one sheep." And a lot of people questioned it and said well, you know, maybe we messed up or, you know, maybe it was just something, you know, it was cross-contamination or whatever...So we were criticized quite a lot for publishing just on the basis of one case, but it's again one of those situations where if you didn't say anything and then confirmed it a couple of years later, you know, people would turn around and say, "Well you knew about this two years ago and you didn't say anything."...there's so much of this surrounding TSEs because the public perception is that the government just covered things up and said everything's okay and didn't really tell the truth about BSE. And so now you're almost pushed to the other extreme where if you know anything, no matter how difficult to interpret it is - I mean if you've just got one animal, it is difficult to interpret what's going on (Ponte 2003a).

While controversy raged surrounding the interpretation of a single positive animal, it was not long before three more animals that had been transfused with blood from BSE-infected sheep developed symptoms of the disease. And, even more surprisingly for those directly involved in the study, four sheep that had been transfused with blood from sheep that had acquired scrapie naturally in the field developed symptoms as well. This was a shock because no infectivity had ever been detected in the blood of animals or humans "naturally" (i.e. not experimentally) infected with TSE. Previously, it had been thought that perhaps some aspect of inducing experimental infection might predispose the animal's blood stream to becoming infected.

The rates of infection by transfusion, as measured thus far, were ranging around 10% for both BSE and scrapie. And the experiment had barely begun. In their publication, Fiona and the other researchers stated bluntly that: "these results confirm the risks of TSE infection via blood products and suggest that measures taken to restrict the use of blood in the UK have been fully justified" (Hunter et al 2002). Indeed, if such measures had not been in place already, the publication of this study surely would likely have ignited a public uproar and a quick response on the part of the government.

By the time she spoke at a meeting of the European Plasma Fractionators Association in 2004, the transmission rates in her experiment were on the order of 20% for BSE and 40-50% for scrapie. The negative controls were still alive and none of them have shown signs of TSEs or had any demonstration of infection.

Overall, Fiona continues to believe that sheep provide a relatively good model for the human disease. Her interpretation is that the metaphorical fit is supported by the "similar distribution of PrPSc in lymphoid organs" between BSE-infected sheep and

humans. And as for the higher rate of transfusion transmission in the sheep model systems than in the rodent model systems, she believes they are not all that inconsistent given the difference in the volume of the transfusion:

> I didn't really think about it at the time, but I mean talking to people like Bob Rohwer, I mean he's always been very supportive of our results and he said well, it is consistent with what they see in the rodent models, it's just that, you know, they've got a low volume. I mean, if they've got ten infectious units per ml, the infectious dose is very volume-dependent. There may not be any higher levels of infectivity in sheep blood, but it's just that if you give five hundred ml you're giving at least a hundred times what you can give to rodents (Ponte 2003a).

Indeed, Bob Rohwer, sees Fiona's results as an important addition to his own:

> In the case of the sheep, they're only transfusing 4-6% of the blood volume, but it's a large volume, its 250-500 mls, and they're getting very predictable transmissions. In the case of the hamster, it was 33% of the blood volume, but it's only 2 ml. So it seems to be the total infectivity that's important, not the percentage blood volume of the animal that's determining of transmission (Rohwer 2003).

Thus, the metaphorical fit between the sheep model and human transfusion was interpreted by both Rohwer and Houston to be strengthened by the similarity in volumes of blood transfused. Despite what Fiona views as a relatively good correspondence between the sheep model system and the human situation, she notes that there are still several uncertainties that cloud the interpretation of the sheep results with respect to drawing conclusions about vCJD. "You can't just extrapolate directly from one species to another species," she says. For instance, she notes that while the distribution of PrPsc in bodily tissues is similar for vCJD in humans and BSE in sheep, that the distribution of PrPc, the starting material for PrPsc, amongst blood components is strikingly different:

> One of the interesting things is that when you look at just distribution of PrPC in different species, it seems very different on different blood components. So for example, in hamsters it's very difficult to pick up PrPC on any blood components. In humans, it's very high on the surface of the platelets. It's also high on lymphocytes and monocytes. But you also get low levels on red blood cells, in

> humans, and I think even on some of the granulocyte populations. And in sheep, we only consistently find it on the mononuclear cells (Ponte 2003a).

However, she qualifies this observation with the statement that:

> You can't really extrapolate directly from PrPC because it doesn't always correlate with where PrPsc gets made. But it does give you an indication that there are differences in the normal protein, so there may well be differences in the abnormal protein (Ponte 2003a).

When I asked other scientist, in 2002 and 2003, what they thought of Fiona's results, and how it affected their perception of vCJD risk, the majority said that it heightened their perception of a vCJD transfusion risk. As Moira Bruce put it, the worrying bit is "that animals or people may be harboring very high levels of infectivity in their peripheral tissues well before there's any clinical manifestations of the disease." Indeed, this is the worry that had driven concerns over iatrogenic transmission of vCJD since the beginning. While the worry had existed before, it was reinforced by Fiona's results, if one accepted the sheep model system as a metaphor for human disease.

I asked members of SEAC, also in 2002 and 2003, how Fiona's results impacted their perception of the risk of vCJD transfusion transmission. Peter Jinman said that it had increased the concern which was already felt amongst committee members:

> Well, we've always had a concern that if we could end up finding that blood could be contaminated and be a carrier and precipitate disease, then we've really got a problem because clearly it would put a real question on who could be a blood donor...So yeah, I mean, we were obviously concerned because it now looked as though we've got a positive way of which it could be transmitted. It's got to be added to the list of tissues which could be considered dangerous. But then you have to have the proportional argument which says what's the chance of it actually transmitting, and that then is another risk analysis based on the number of animals, based on the amount of exposure, based on the farming, based on the feeding machines (Ponte 2003h).

Peter Smith's response was similar:

> ...it confirmed a strong suspicion that we'd had anyway that there was a risk of infectivity in sheep blood, with the possibility that makes it actually more likely because of the similarity of the pathogenesis in sheep and in humans – that there may well be infectivity in human blood...the fact that you can demonstrate it in sheep blood is of obvious concern (Ponte 2003i).

However, Peter suggests that the metaphorical fit between sheep and humans with BSE may not be as tight as other scientists believe:

> ...draw immediate parallels between sheep and humans in that sheep blood is different from human blood and the way it responds to leukodepletion, for example, I understand is different, in that it's more likely the white cells are going to be damaged in leukodepleting sheep blood than human blood (Ponte 2003i).

Even before such experiments have been done, he is already suggesting he will doubt the significance of results in the sheep model system for the human situation if leukodepletion is shown not to be effective. Such studies are currently being conducted. I asked him if this meant there was a problem with the sheep model system. He insisted that:

> As a model system, it's a good one for humans, but the carryover may not be total. Nonetheless, it's obviously of great concern with respect to human health, and those are the things we try and convey to the Department of Health (Ponte 2003i).

In other words, Peter Smith while reticent to accept a complete correspondence between the model system and the human situation, views the results as concerning.

On the other side of the Atlantic, most members of TSEAC, too, perceived a better metaphorical fit with Fiona's sheep than with rodent model systems. As Suzette Priola, the chair of TSEAC, commented:

> I think of the BSE sheep studies because one thing that appears pretty consistent is that when BSE goes into another animal species it does similar things, regardless of the animal species...so the BSE sheep experiment is closer to the vCJD human thing than the others. Some of the studies that Bob Rowher or those guys have done use animal model systems like the 263K system where the

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> infectious agent is more restricted...So it's not quite like variant CJD in people (Ponte 2004e).

Fiona Houstons's results with the sheep model system, however, were not interpreted by every scientist as heightening the plausibility of vCJD transfusion transmission risk. Paul Brown, at several international meetings in 2003, argued that Fiona Houston's results made it seem less likely, not more likely, that vCJD would prove transmissible by blood. In a complicated maneuver, he drew out metaphorical similarities between vCJD and sCJD through recourse to Fiona Houston's model system, a move which was in turn based on a metaphor between non-variant TSEs, such as scrapie and sCJD and a complimentary metaphor between variant-TSEs, such as BSE and vCJD. He argued that if the similarities between vCJD and sCJD could be accepted as sufficiently tight, then lack of evidence of transmission of sCJD by blood could be taken to indicate the lack of a risk from vCJD blood. As he phrased it: "If you accept that sCJD is not a risk" for blood "it follows that vCJD will not be a risk either." As he phrases it:

> to me this to me is the crux of the issue, because if we believe that blood, at least plasma products, from sporadic CJD blood is not a risk, and if we can show that using the same head-to-head comparison between vCJD and sCJD, and if we find that the comparisons indicate a large degree of similarity then the logical conclusion is that the blood from vCJD won't be more of a danger than blood from sCJD, which we all agree is 0, or so close to 0 that it should be considered negligible (Brown 2003).

While he admits that lymphoreticular tissue is undoubtedly more infectious in humans with vCJD than in humans with sCJD, complicating the metaphorical fit, he discounts this anomaly because, "the infectivity in blood interactive tissues is not necessarily correlated with infectivity in the blood. And there have been two or three studies that show infectivity in the spleen is not obligatorily associated with infectivity in the blood" (Brown 2003).

Then, drawing on the extended metaphor between non-variant forms of TSE, on the one hand, and variant forms of TSE, on the other, he argues that Fiona Houston's sheep experiment supports the analogy between vCJD and sCJD as a tight metaphorical fit. On the basis of this metaphor, he interprets Fiona Houston's experiment as indicating that there is no difference between the transfusion transmission properties of variant and non-variant TSEs in the sheep model system.

> A recent study by Houston in sheep showing that BSE infected sheep could transmit the disease by transfusion up to 30% of the time. That is bad odds. But, you also get 30% infectivity in scrapie. And this is a direct comparison. So where if you look at BSE in sheep all by itself you would be panic stricken, but if you look at natural scrapie now transmitting up to 30% you are a little more relaxed (Brown 2003).

At the EPFA meeting, he makes the same point by citing Cevernakova's experiments with BSE-infected (variant) and GSS-infected (non-variant) mice. Both exhibited infectivity in the blood stream, although GSS, like sCJD, is not considered to be a blood risk for humans:

> You can trust me, there's really no significant difference between either one of these models with respect to incubation period or infectivity titer. Similarly, if we take a blood component from mice in both models and inoculate it intercerebraly, we get similar results. If we take buffy coat, the infectivity titer of the GSS-mice is 106, with a fairly wide spread. The infectivity titer of vcjd is 18 with a fairly wide spread. Here, in this particular instance, vcjd looks less dangerous, if we can call it that...plasma, using the same comparison, is indistinguishable. So in this model, comparing a non-variant CJD mouse-adapted strain with a variant-CJD mouse-adapted strain, there is nothing to choose between the two (Brown 2003).

In other words, he interprets both Cevernakova's and Houston's results as supporting his claim that sCJD and vCJD are similar enough to be considered identical with respect to their transfusion properties.

On the basis of these animal model systems, which he interprets as indicating that in all species concerned, variant TSEs and non-variant TSEs behave the same with

respect to blood transfusion, he argues that in humans, vCJD and sCJD should be expected to have the same behavior with respect to blood transfusion. Then, he insists, it is likely that vCJD is no more of a transfusion risk than sCJD.

> ...if we accept that non-variant strains of TSE are not a risk, and we show that variant, or BSE strains, behave experimentally like non-variant strains, then the logic is we have nothing to worry about with variant strains either. Everything hinges on our acceptance of the fact that non-variant strains, or non-BSE strains, are not a risk factor. If you don't accept that then we're in deep trouble, because if they are a risk, and BSE and variant are behaving like them, then they would be an equal risk. My approach is a direct comparative approach that totally depends on acceptance of the fact that non-variant CJD strains are not a risk with respect to blood transfusion (Brown 2003).

When Paul gave this talk at the IABS meeting, Bob Will called Brown's interpretation into question, arguing that the pathogenesis of TSE strains, or the tissue distribution of the infectious agent in the body, is a better basis on which to derive metaphorical meaning. In this view, the classification of a TSE strain as variant or non-variant, the basis of Paul Brown's metaphorical structure, is of little relevance. What is of relevance, according to Will, is that in humans with vCJD, sheep with BSe, and sheep with scrapie, the pathogenesis, or spatial distribution of the infectious agent within the body, is very similar. In all these systems, the lymphoreticular tissues exhibits high levels of infectious prion-protein, something which is not found in sCJD. On this basis, he argues that Houston's results can be interpreted as having great relevance for the consideration of human vCJD transfusion risk:

> BSE in sheep is of peripheral pathogenesis, like vCJD. Scrapie in sheep has a peripheral pathogenesis, like vCJD. It may be that those factors are quite relevant to the relations of this experiment, rather than the fact that sporadic may make sense entirely that sporadic evidence is not related to transmission through blood products, and that may relate to the pathogenesis itself and that is why I think the Houston experiment is a matter of concern (Will 2003).

This is an important example that illustrates the way in which the significance of results from animal model systems can always be interpreted in a myriad of ways by different scientists, depending on which metaphorical relationships are deemed to be more fundamental. Both Brown's interpretation and the interpretation given by Will are plausible interpretations of the results from the sheep model system. Because experimental results from model systems are underdetermined with respect to their meaning for the human situation, they are incapable, in and of themselves, of resolving controversy. This indicates that, as shown previously by Collins and Pinch (1998), Nelkin (1984), and Latour (1987), laboratory science alone is insufficient for resolving scientific controversies with political implications. Because model systems are entirely metaphorical in terms of their meaning for the human situation of concern, the choices one makes in establishing the system one will use to evaluate the fit between different metaphors in large part determines the inferences one will draw from the experimental results.

Questioning the cause for concern in the absence of a case

It had been several years since the implementation of the risk reduction measures in the US and the UK, and there was still no sign of any transmission of vCJD by transfusion in humans, despite ongoing surveillance. The concerns of many regulators and scientists began to wane during this period, and calls were made for rescinding the regulations. In effect, the lack of any sign of transmission of vCJD by blood became part of the sensitizing frame from which the risk management decision was evaluated. The political fallout over BSE and HIV which had, in part, provided the impetus for these

measures, had also faded into the past. Amid growing concerns over shortages and other untoward effects of the risk reduction measures, reevaluation of the necessity of the measures was increasingly called for. It was as if the French had built the Maginot line and then, after Germany had failed to attack for several years, called for abandoning it.

The debates and concerns that were raised during this period are largely the result of the incredibly long, by human standards, incubation period of TSEs as well as the increasing realization that the vCJD epidemic was not going to be as large as previously feared. The temporality of infectious diseases like TSEs is not something that people are used to conceptualizing mentally. The only previous epidemic that was anything like vCJD, in terms of the extended temporality involved, was HIV. With HIV, however, it became readily apparent that large numbers of cases would result, as the incidence continued to grow exponentially over an extended period of time. By contrast, after the first few years of the vCJD epidemic, the number of cases diagnosed each year stabilized and, more recently, has even begun to fall. While it is too early to conclude that this is the end of vCJD, the changing curve certainly raised this possibility in many people's minds, creating more doubt over the current measures.

This change in incidence was utilized to update FOSPs predicting the future course of the vCJD epidemic. Previously, these projections ranged from the hundreds to the millions. With the new data on incidence, however, the upper limit on most projections had come down significantly, to numbers in the thousands rather than the millions, and the range of possible projections had narrowed. Bob Will encapsulated the situation at an European Plasma Fractionators Association (EPFA) meeting on prion

disease in Edinburgh in 2003, at which regulators and scientists from around the world had gathered:

> We now have 143 cases of vCJD, mean age of death 29...What is happening with the number of cases with time is critically important in terms of projections for what may happen in the future, but of course there's understandably major concerns, this is just looking at the number of onsets per annum of variant CJD, and you can see this very worrying pattern from 1994 up to 1998, when it looked like we could be on an exponential trend, but in recent years there has been a decline in the mortality rate, and also in the number of onsets per annum, which is clearly demonstrated here. The data for 2002 is not quite complete, but it looks like this trend has been sustained downwards for 3 years. This is, of course, good news...This is the quadratic analysis which is the best fit currently statistically and suggests that the epidemic for variant CJD has peaked and may be in decline (Will 2003).

At this meeting, Will also announced that, as of yet, an ongoing follow-up study of the recipients of blood from donors with vCJD continued to find no evidence of transmission of the disease by transfusion. He mentioned, however, that there were many factors which colored the statistical interpretation of the data, including the relatively small number of recipients who had not yet died of other causes, usually related to the reason they were transfused in the first place. Only a few of the recipients had lived longer than 4 years past their transfusion. When dealing with infections that have a long incubation period, such as HIV, this sort of interpretive difficulty is common. It is compounded when, as pertains to vCJD, there is no test which can be done to determine whether someone is infected until after they die. Bob Will expressed his belief that, despite the long wait in obtaining results and the difficulty in interpreting them, this study:

> ...is a critically important study, because it's the only way we will ever know actually whether vcjd is transmissible through blood, because it doesn't matter in my mind how many animal studies are done, that doesn't necessarily tell you what's going to happen in reality (Will 2003).

In other words, none of the animal studies provided an exact replica of the human transfusion of vCJD. As he expresses it, there will always be a fundamental lack of congruence, a question concerning the metaphorical fit between animal models and human beings. This lack of congruence could revolve around physiological, experimental, and genetic differences that could be pointed to as potential reasons for a difference in outcome. According to Will, epidemiology, especially targeted epidemiology in the manner described, is the only way of determining whether humans are susceptible to transmission of vCJD by blood.

As time continued to pass with the absence of any transmissions from vCJD through transfusion in the UK look-back study, as well as the appearance that the vCJD epidemic in the UK was waning, regulators, scientists, and advisors on both sides of the Atlantic grew wary of the concern and regulations surrounding vCJD transmission through blood. On both sides of the Atlantic, concern was growing that the vCJD deferrals, designed to protect against a highly theoretical risk, were causing damage to the blood supply and creating difficulties with collection. In the US, Arthur Caplan, former chair of the BSAC, argued that the USDA's deferral policy was "a big response to a very low risk. You can kill people," he warned, "by not having enough blood available" (Jacobson & Serafini 2003). Many of the members of TSEAC who had been on the losing side of votes to recommend deferrals also expressed displeasure with the continuing deferrals.

In the UK, similar matters were being discussed. At the EPFA meeting in Edinburgh, Peter Bennett of the Department of Health asked Bob Will how long the

international community would have to wait before they could be assured of the safety of blood from donors with vCJD:

> If you have a significant number of known recipients of blood components, and none of them go down with vCJD for a reasonable number of years, it starts to tell against blood being infected. if, in addition, some of the earlier recipients actually got their blood prior to the introduction of lymphocyte depletion, which some of them did, that suggests that if blood is infected they should have received really rather large doses. At what point does it become seriously odd, if none of them come down with disease (Bennett 2003)?

First of all, Bob Will casts doubt on Peter's assumption that the exposure to infectivity in blood was greater before leukodepletion was implemented than after. He had become somewhat convinced, by the results of Brown and Rohwer as well as others, that leukodepletion might have little effect on the likelihood of transmission:

> I think the assumption that people necessarily received large doses of infectivity through blood transfusion prior to leukodepletion may be incorrect, we simply do not know. That's the first thing to say (Will 2003).

Secondly, he pointed out that determining when enough data had been collected to prove vCJD blood was safe would always be a matter of judgment. Given this caveat, he felt it was still too early to say:

> I think that, as time goes by, and as these cases are followed up, clearly the implications from the study become stronger, and i think it's a question of judgement as to how long you think you have to go on before you can say anything definitive. My concern about it was if it is transmission of infection through peripheral route, through blood, it is highly unlikely to be a very high dose from the animal studies that have been done. Much lower than in brain than orally in food. We simply don't know what the incubation could be, but it could be 10, 20, 30 years, and therefore I think it will be many years before we can be interpreting this study in a very positive way. That's my personal opinion, you may take a different view, it depends on the assumptions you make about the levels of infectivity in the incubation period. I think it's too early to regard this study as very reassuring, its very small numbers and the follow up is still relatively short (Will 2003).

Bob Will's reasoning illustrates the way in which the potentially lengthy, and entirely unknown, incubation period of vCJD extends the uncertainty around the transmissibility of the disease through blood.

While much doubt was expressed, both in the US and the UK over the necessity of the risk reduction measures given a lack of cases, certain individuals, like Bob Will, who had first-hand experience with the BSE epidemic and Hgh transmission of CJD, warned against rescinding risk mitigation measures. They argued that TSEs had shown to be surprising and recalcitrant actors before, and the same could occur now. In effect, their sensitizing frame included past mistakes based on previous sensitizing frames and the uncertainty generated by the prolonged incubation period. Through these past experiences, they postulated not an exact prediction of what would happen with vCJD, but an admonition to be cautious. Their focus, however, was still constrained metaphorically by the past.

When is a case a case?

On the 8th of December 2003, less than a month after the EPFA meeting had ended, the CJD Surveillance Unit received notification that one of the recipients of blood from a vCJD donor had been identified as a potential case of vCJD. James Ironside examined the tissue very carefully and determined that the distribution of PrPsc in the brain was similar to what had been observed in other vCJD cases. Moreover, multiple florid plaques, which had become the defining characteristic of vCJD, were noted.

At a TSEAC meeting in February, Bob Will provided further information on the donor:

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> Now, as far as the donor was concerned, this was a 24-year-old individual who donated two units in 1996. One unit was transfused to the index case, red cells; and one unit was transfused to a patient who died of cancer after five months. Platelets were included in a platelet pool from this donor but have not been traced, and plasma from both donations were included in different plasma pools. The donor, who was, of course, healthy at the time of the donation, died three and a half years later of pathologically confirmed variant CJD...(TSE Advisory Committee 2004)

In other words, the donation was made when the donor was symptom-free. While the donor was young, the recipient was much older:

> Now, in 1996, the recipient, age 62 at that time, was transfused five units of red cells, one from the variant CJD donor...The recipient developed depression six and a half years after the blood transfusion, and within months developed ataxia, painful sensory symptoms, apraxia, cognitive impairment and myoclonus...The individual died 13 months after the onset of symptoms, and the post mortem which I stress was restricted to the brain, confirmed the diagnosis of variant CJD (TSE Advisory Committee 2004).

Like other cases of vCJD, genetic analysis revealed that the patient was homozygous for methionine at codon 129. Bob Will found this reassuring because it was consistent with the hypothesis that only individuals with the MM 129 genoytpe were susceptible to vCJD

The age of the recipient, an age far above most patients who are diagnosed with vCJD, increased the perception, in the eyes of many, that the case was likely due to transfusion. Still, the possibility that the recipient had eaten meat from an infected cow could not be ruled out. That is why, when presenting the came to parliament on December 17, John Reid, the UK health minister, phrased it as: "It is therefore possible that the disease was transmitted from donor to recipient by blood transfusion. This is a possibility, not a proven causal connection." However, Bob Will felt fairly confident that this was a transfusion transmitted case, especially after the statistical analysis conducted by Simon Cousens of the London School of Hygiene and Tropic Medicine. As Will puts it:

> ...he analyzed this by looking at the expected number of cases of variant CJD in the recipient population who had received a blood transfusion from a variant CJD donor in the absence of transfusion- transmitted infection. And on a crude analysis he felt that the chances that this was unrelated to the transfusion was one in 15,000; and accounting for the age of the recipient population and the age of the recipient who developed variant CJD, one in 30,000 (TSE Advisory Committee 2004).

Furthermore, Will indicated that: "in my view, because of this particular occurrence and the importance for public health, I think for the purposes of protecting the public it should be regarded as a case of transfusion- transmitted variant CJD" (TSE Advisory Committee 2004).

Will specifically cited Fiona Houston's study on transfusion transmission in sheep as reason why, although the possible transfusion transmission case of vCJD was shocking, it was not surprising. Moreover, he felt that the data from the sheep transfusion study, where infection could be transmitted as early as half-way through the incubation period, were consistent with the case they had identified:

> ...if this is transfusion- transmitted variant CJD, it means that the donor contained infectivity in the blood three and a half years before developing clinical symptoms, and it means that the incubation period in the recipient was six and a half years. And I would argue that these incubation periods are consistent with this study in which BSE was transmitted by blood transfusion from donor sheep during the incubation period and with an incubation period in the recipient sheep that is fairly similar to direct intracerebral inoculation. So we think the intravenous route is probably fairly efficient, and I think that the possibility of transfusion-transmitted variant CJD is consistent with previous scientific data (TSE Advisory Committee 2004).

The perception that the intravenous route was more efficient than had previously been thought was furthered by a study published alongside the CJD Surveillance Unit's write-up of the case in the Lancet. This study was conducted by Corinne Lasmezas in Paris, France on cynomologous macaques, a species of primate which, when infected with vCJD, exhibited a similar tissue distribution of infectivity. She found that when she

intravenously injected brain homogenate from vCJD-infected macaques she could transmit the disease just as easily, and with the same efficiency, as if she had inoculated the animal intracerebrally (Herzog et al 2004). This result bore directly on the question of transfusion transmission because it could be interpreted as indicating that even a small dose of infectivity, as might be contained in blood, would be capable of transmitting infection.

As for the other 48 individuals who were known to have received blood components donated by someone with vCJD, Will reminded TSEAC that 31 of them had already died of causes unrelated to dementia:

> The great majority of them have died within two years, and in fact, the absolutely majority within one year of the transfusion, and this reflects the severity of the underlying disease process. But it also means that, if the incubation period by blood transfusion was measured in six, seven, eight, ten years -- we don't know -- it is very unlikely that any of these individuals would have had time to develop variant CJD (TSE Advisory Committee 2004).

Will admitted that because of the way they had designed the surveillance program, it was impossible to know for sure whether any of these individuals had been harboring vCJD, because they had never been informed and no autopsies had been performed:

> So how confident are we that none of these other individuals have developed variant CJD? Well, I have given you the information that is available on these cases. For ethical reasons we have not been able to track them in anymore detail, but I stress that we have a number of levels of surveillance, including direct referral of cases if there's a suspicion of CJD, and a neuropathological network such that brain tissue will be sent to the Surveillance Unit if any such patient dies. So we cannot be certain about these individuals. All I can say is that we have no good evidence that any of these other individuals themselves developed variant CJD (TSE Advisory Committee 2004).

As for the seventeen recipients of blood from vCJD patients who were still alive, it had been decided that they should be informed. "That having happened," Will noted, "four of

the individuals have already contacted either a neurologist or the Surveillance Unit directly because of extreme concerns about the situation that they are in."

As Will pointed out, the possible transfusion transmission of vCJD had raised much public concern in the UK, with headlines announcing, "CJD Time Bomb: Hundreds Face Wait" and "Thousands at risk of vCJD from Blood Transfusion." As Will admitted, it was impossble to tell, at this point, what the extent of the risk really was.

> What is the risk to the U.K. population? We do not know how many individuals are incubating variant CJD and may be acting as blood donors. So there may be a population of individuals who have been exposed to blood transfusion that would not have been identified by the TMER study (TSE Advisory Committee 2004).

In March of 2004, John Reid, the Health Secretary of the UK, announced that, as an added protective measure, in order to prevent the recirculation of the vCJD infectious agent through blood transfusion, people who received a blood transfusion since 1980 would be barred from donating blood. This was not a new idea in the UK. As early as two years prior, when I had interviewed Lorna Williamson of the UK National Blood System, she had indicated to me that this possibility was under consideration. Concerns, however, about the potential loss of donors had prevented implementation. As Lorna estimated then, the loss "for whole blood donors it's probably around 10 percent, but for aphaeresis donors, you know, where they come and go on a aphaeresis cell separator and we collect platelets from them, that's higher, that could be 15 percent, and these are difficult donors to recruit. They have to be committed, they need a good blood platelet count, they need good venous access, etcetera." She added that, while difficult to make up for such a loss, other countries, such as France, had already implemented a ban on donations from people who were previously transfusion. The idea was as much to prevent the circulation of as-yet unidentified infectious diseases as it was to prevent the circulation of vCJD. With

Hepatitis C and HIV, especially in France, the political fallout from not doing more to prevent transfusion transmission had been hard. This was one way, they perceived, of preventing such problems in the future.

Robert Rohwer says he has been advocating for this type of measure in the US for quite some time:

> ...since the very first time I talked to the FDA. The only mitigating measure that would make sense to me is to prevent, or to defer, donation by people who previously received transfusions. That way people may get it from the food route or something like that, but we won't be expanding the epidemic beyond those people, you know. It will stop there. But as soon as you start, and as soon as you open up a chain of transmission then you essentially have created a situation, which occurred with kuru and with BSE, and you can end up, you know, you may not see it, but in the case of a slowly developing disease like this you may not see it, or it might take two generations to see it. But somewhere down the line people become cursed by this stuff (Ponte 2004d).

In this statement, he has metaphorically configured the concern through analogies with past experiences with kuru and BSE. The circulation and recirculation of infectious material in those two diseases have highlighted the potential, in his eyes, for such recirculation in vCJD.

While for many years Rohwer has perceived recirculation through blood transfusion of people who have already been transfused as a potential means of recycling of vCJD, due to the ready availability of metaphors, metaphors which also drove the UK and France to enact such policies, there are still potential avenues that remain adumbrated by the sensitizing frame which has been applied. Because vCJD has been so tightly woven to a metaphor with BSE, both the UK and the US remain tied to a view of vCJD risk as almost completely contained by UK borders. This is evidenced by the cornerstone of disease management policies in both the US and UK. In the US, the primary defense of the blood supply remains the exclusion, or deferral, of individuals who spent time in the

UK, and to a lesser extent, the rest of Europe. Relying on similar metaphorical reasoning and similar images of containability, the UK's primary defense for plasma products remains the importation of plasma for their production from the US.

By the time Robert Will presented to TSEAC again in October of 2004, there had been another case of potential transfusion transmission of vCJD, though this case had not resulted in outright disease. The CJD Surveillance Unit had detected the infectious prion protein in the spleen and cervical lymph node of a vCJD blood recipient who died from other causes. The detection of this "second case" of transfusion-related vCJD, as he described it, was a result of the decision to notify recipients of blood from vCJD donors after the 1st case, which led to an autopsy after the recipient's death.

This was a puzzling case, especially as this recipient was not MM homozygous at codon 129 like all of the other cases of vCJD, but instead was heterozygous MV at this locus. Given that he was the first case of this genotype to be identified since the emergence of vCJD, it was difficult to interpret what this might mean for the future course of the vCJD epidemic. Did the PrPsc which had been detected in his spleen and cervical lymph node indicate that he was incubating the disease, and would have become sick if enough time had lapsed, or did it indicate that he was harboring a subclinical infection which would never manifest itself as outright disease, but which, potentially, could be transmitted to others? Because most projections of the vCJD epidemic assumed that people with codon 129 MV or VV would be immune to vCJD, how did this change the shape of the likely curve? What would this mean to future generations?

Despite all of the unanswered questions, scientists and physicians sitting on SEAC interpreted this case as confirming that transmission could take place through

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transfusion. The Department of Health in the UK congratulated itself in reacting swiftly to the first potential case of vCJD blood transmission, and continued on its course of excluding previous transfusion recipients from donating. TSEAC considered that, by and large, they already had enough deferrals in place to minimize most of the risk to the blood supply. This perception was furthered by a risk assessment conducted by Steve Anderson, in which he estimated relative contribution to vCJD transfusion risk of US donors. In making his projections, Anderson assumed that the BSE cow that had recently been detected in the US was the only one of its kind, rather than representative of a wider epidemic, and thus came to the conclusion that the risk of someone from the US developing vCJD without having traveled to Europe was negligible. The FOSPs produced years ago by Alan Williams were invoked as a further means of justifying the US's current approach. Their tremendous uncertainties and assumptions having been successfully bracketed, they were claimed to indicate, unquestioningly, that the US had already eliminated 90% of the vCJD blood transfusion risk.

The question is - with improved surveillance and testing protocols, will the US find more cases of BSE? Will vCJD occur in US citizens who have never traveled to Europe? And if so, what will this mean for transfusion transmission of vCJD within the US? These are questions which are still partially obscured by darkness. Hopeful that none of this will come to be, scientific advisors, health officials, and consumer advocates continue to avoid them. It is possible that BSE will be of limited consequence in the US, in which case regulators and scientists will continue to congratulate themselves on a job well done, despite all the uncertainties that have been bracketed through their attempt to produce a rational policy.

Due to the way in which the risk of vCJD has been configured through metaphors to BSE, HIV, and Hgh transmission of CJD, and despite the evolving character of the BSE and vCJD epidemics, the US and UK continue to rely on the same primary line of defense – plasma products derived from American blood. The dependence on American plasma as the primary defense against vCJD has become the Maginot Line of US and UK blood policy. It is too hard to say, yet, whether it will remain effective, or whether it will be rendered obsolete with time. What can be said, though, is that in their efforts to appear to manage risk in a rational manner, the US and UK have relied on a series of metaphors that focus light on certain possible avenues of risk while leaving others in darkness. Such metaphors have allowed them, for a time, to treat risk as containable by spatial and temporal boundaries, and uncertainties as bracketed, in order to generate modes of action.

Ch. 9 - Conclusion

According to Bakhtin, the relationship between time and space in a novel is crucial to the formation of plot (Bakhtin & Holquist 1981). Time and space are connected through a series of chronotopes that produce narrative flow. In tracing the historical development of the novel as a literary form, Bahktin chronicles the development and use of different chronotopes to produce different experiences of time. First, there is the kind of temporality that flows between two points but does not change the characters involved. Then there is cyclical temporality, which repeats itself through seasons, days, years. The characters are brought together, things happen, but their lives return to normal at the end. Finally, there is the kind of temporality that markedly transforms the characters through the chronotope of metamorphosis.

The narrative that I have constructed around prion disease is of the metamorphosis type. I have focused on the formation and outcome of events that, like knots in a rope, impede the smooth and regular flow of time and create a transformation in understanding and action. This is a nominalist methodology (Rabinow 1999), and may be likened to Foucault's concept of eventalization, a way of doing history that focuses on societal transformations in perception, those events which provide a sudden break between old ways of thinking and new ways of thinking (Foucault et al 1991). Kuhn treats this form of temporality, of a sudden transformative break, as part of a cycle of science that flows between periods of normality, or continuous and predictable plugging away at problems, and scientific revolution, when concepts are turned upside down and reworked in such a way that a conversion in perception has occurred (Kuhn 1962).

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Temporality is a central focus in the story of TSEs. It takes on different forms – the slowing of time in the form of the long, drawn out incubation period of the disease, the quickening of time when revelations appear, institutions are called to question, or a breaking-point in perception is reached. Most of all, it is a temporality that is difficult to pin down, and hard to comprehend. The temporal confusion arises in part from the incubation period of the disease in question, which can last for months, years, or even decades. It rises in part due to the impossibility of detecting the disease during this period. It leads to all sorts of misunderstandings, disagreements, and contradictory predictions. Within this mileau, central actors are under pressure to make critical decisions that will affect the course of the nation.

Difficulty arises because, in situations like these, neither the past or the future, and perhaps not even the present, can be understood with any clarity. As Mead points out, the past and the future are but boundaries of our experience, boundaries which we can only comprehend through the lens of the present in the form of memories or predictions which are colored by our present experience (Mead & Murphy 1932). However, as Ricoeur has noted, the meaning of the present only takes shape from the vantage point of the future, when things which could not have been known in the present become clear, such as the outcome of certain actions. But because we cannot know what the future will bring, we can only formulate meaningful action in the present by pretending that we do, or that we at least have a good idea of what possibilities the future will bring.

Aristotle designates the term "emplotment" to indicate the human attempt to order experience teleologically, with reference to a specific future. This framing gives meaning to actions taken in the present, a meaning which otherwise would be difficult to grasp.

This is because, as Aristotle believes, most of the events that occur in our daily lives are merely the result of chance and have no hidden meaning or particular order to them. Yet, as human beings we are tied up in a constant struggle to produce meaning. One way of producing meaning is to arrange sequences in the form of a plot. As Mattingly phrases it, Aristotle contrasts "life as lived which is liable to trivial succession, one thing just happening to follow another, to life as emplotted, structured by a compacted movement with a clear beginning, middle, and end" (Mattingly 1998). The point is that even though we can't know what the future will be when we are in the present, we act as if we do. We operate in the present as though we have an ending, or a series of potential endings, in mind. It is the evaluation of all these possible endings, in terms of both likelihood and impact, that in part determine our choice of action in the present.

But how, exactly, are events emplotted? Through what means can a future be envisioned, a future which, we as modernists, would wish to control? As Lakoff points out, our understanding of the world, and our experience of it, is metaphorical in nature. "The essence of metaphor," according to Lakoff, " is understanding and experiencing one kind of thing in terms of another" (Lakoff & Johnson 1980). Metaphors are a powerful tool for conceptualizing the events around us, and for emplotting them within a structured series:

> New metaphors have the power to create a new reality. This can begin to happen when we start to comprehend our experience in terms of a metaphor, and it becomes a deeper reality when we begin to act in terms of it. If a new metaphor enters the conceptual system that we base our actions on, it will alter that conceptual system and the perceptions and actions that the system gives rise to. Much of cultural change arises from the introduction of new metaphorical concepts and the loss of old ones (Lakoff & Johnson 1980).

The matter of experiencing the world through metaphor is not an individualistic pursuit. It is fundamentally interactional in nature:

> Because defining concepts emerge from our interactions with one another and with the world, the concept they metaphorically define will be understood in terms of what we will call interactional properties (Lakoff & Johnson 1980).

Throughout this dissertation, we have seen various examples of how the debate and discussion surrounding the management of TSEs revolves around an interactionally produced system of metaphors, which I have referred to as a sensitizing frame. The analogical elements within the sensitizing frame reference past experiences with other diseases and model systems. The relevance of any element in the sensitizing frame is based on the perceived strength of its metaphorical relationship to the matter under consideration. Because this relationship is always open to negotiation, the sensitizing frame is constantly restructured through continuous discourse and debate. And it is always contested.

In Chapter 2, I recounted the recognition of BSE. While pathologists, epidemiologists, and other scientists viewed scrapie as the most salient metaphor for BSE, the utilization of this metaphor was at first opposed by officials in MAFF. Such a metaphor, as they saw it, would entail economic ramifications, similar to those that had ensued from scrapie. While this struggle over the use of the metaphor prevented dissemination of information for some time, it was eventually allowed to propagate.

Following this propagation, the perceived metaphorical relationship between scrapie and BSE became a potent source of policy. Based on this analogy, John Wilesmith determined that BSE was likely caused by the feeding of sheep remains to cattle. Also on the basis of this analogy, as well as an analogy with TME, he overlooked

cattle-remains as a potential source of infection and driver of the epidemic and generated a FOSP which estimated that the BSE incidence had stabilized and that no cattle born after the ruminant feed ban would become infected. This FOSP was then recycled by Richard Southwood and his committee, was cited by MAFF to justify a grace period in instituting the ruminant ban, and continued to be propagated by government ministers making reassuring claims about the future of the epidemic.

Also relying on the metaphor with scrapie, the Southwood committee determined that, like scrapie, BSE would likely not be a source of human disease. While they were careful to state many of the uncertainties surrounding the application of this metaphor, these uncertainties were bracketed by officials and scientists at MAFF who cited, throughout the decade that followed the discovery of BSE, Southwood's prediction that humans would not be effected as though it were rationally derived and completely certain.

When it was revealed that BSE could transmit to humans in the form of vCJD, a political backlash ensued. UK citizens blamed their government, and their government's scientific advisors, for incorrectly portraying the risk. Since then, the BSE crisis has become a salient metaphor in British society for potential harms which are imagined to spring from other avenues, such as genetically modified (GM) foods. Governmental and industry claims that GM foods were safe and that there was no scientific evidence of danger were treated with skepticism. As Brian Wynn notes, "Such statements were seen to be identical to the ways in which BSE had been handled. The mobilization of science to support such claims failed to impress people" (14). For British citizens, BSE provided a weighty and powerful metaphor for framing their conceptualization of the risks entailed

in genetically modified foods and other areas, such as vCJD blood risk, as described below.

In Chapters 3, the construction of the sensitizing frame surrounding fears of CJD transmission through the blood supply in the US was described. This sensitizing frame came to incorporate metaphors from prior experiences with HIV, Hgh transmission of CJD, and kuru. The HIV metaphor was invoked frequently, especially by hemophilia advocates and members of the advisory committees who were hemophiliacs. It formed the background of the FDA's concern that something must be done to manage CJD even though no cases of transfusion transmission existed. It generated great fear despite the continuing absence of epidemiological evidence indicating a transfusion transmission risk for CJD.

A number of metaphors to animal model systems also formed influential components of the sensitizing frame through which CJD transfusion risk was configured. In fact, it was the detection of infectivity in the blood of TSE rodent models that first triggered the concerns over CJD transfusion transmission, within the background context of HIV which illuminated these concerns immediately. Operating from within this sensitizing frame, TSEAC opted to call for the withdrawal of blood components and plasma products later found to have been donated by someone with CJD.

The blood industry fought back by constructing FOSPs, based on recalls which had already occurred, of the large-scale shortages that could occur due to the CJD withdrawal policy. Representatives of the industry also built on these FOSPs to raise concerns about stigmatization of donors, an increase in the risk of transmitting other infectious diseases, and rising costs of blood products. These concerns were configured

as in opposition to, and inherently in tension with, attempts to reduce the hypothetical CJD transfusion risk. The solidity of the numbers that could be produced through such FOSPs, in contrast to the ephemeral nature of CJD concerns, convinced several TSEAC members that the withdrawal policy was not only a mistake, but produced a false sense of security.

It is, however, notoriously difficult to remove a risk reduction measure once it is in place. Despite the fact that the CJD withdrawal policy was increasingly called into doubt, it might have remained in place indefinitely had not another transfusion transmission concern materialized – vCJD. The materialization of this threat, and the way it intervened in US policy, is described in Chapter 4. The transference of the sensitizing frame which had first generated concern over CJD to vCJD, and with it the transference of metaphors with HIV and other infectious threats that impacted the blood supply, combined with the newness of the disease, allowed vCJD to absorb the brunt of fear. In the same move, the US removed its CJD withdrawal policy and instituted a vCJD withdrawal policy. All subsequent transfusion concerns would be focused on vCJD.

There was, however, relatively little known about the actual properties of vCJD. The unknowns surrounding vCJD included the number of people who might be incubating the disease, the future course of the disease, and whether it would even prove to be transmissible through blood. While suppositions about the properties of vCJD were made through utilizing metaphors to animal models of TSEs, models which had previously been invoked to think through CJD, it was difficult to project the limits of vCJD. Because, however, the US regulators and officials had established vCJD as the

new potential transfusion threat, it was necessary to do something. And that something must at least attain the appearance of rationality.

In Chapter 5, I recount how the appearance of rationality was constructed through several maneuvers. First, the risk of vCJD was treated, through a metaphor with BSE, as containable by spatial and temporal boundaries. These spatial boundaries were limited, at first, to the UK, but gradually, as cases of BSE continued to emerge, were extended across Europe. The temporal boundaries were based on what was considered to be the limits of the BSE epidemic, though of course these limits, especially the beginning of the epidemic, would never be known with any certainty.

After these boundaries had been invoked as capable of containing vCJD risk, it was possible for Alan Williams, through a survey he had conducted, to produce FOSPs of the amount of risk that could be eliminated and the number of donors who would be lost through given numerical intervals for a deferral policy. While TSEAC was quick to point out a number of the uncertainties that were bracketed by using this methodology, the manipulability of the numbers produced was seductive. TSEAC used the outputs of Alan Williams's FOSPs to construct, in a seemingly rational manner, the vCJD deferral policy. Thus, the significant uncertainties surrounding vCJD were marginalized for the purposes of maintaining an image of controllability.

In Chapter 6, I describe the similarities and differences in the sensitizing frame with which the UK approached the hypothetical CJD and vCJD transfusion risk. Unlike the US, the UK had not enacted a CJD withdrawal policy following the HIV crisis. HIV, because of the alternate way in which it was handled in the UK, did not blossom into the potent metaphor that it did in the United States and several other European countries,

notably France. As a result, in contrast to these other countries, the UK never became concerned about CJD as a transfusion risk.

With a political crisis over BSE in the background, however, the UK responded forcefully to transfusion transmission concerns over vCJD. Past experience with HIV belatedly entered the sensitizing frame through the concerns of hemophilia advocacy groups. While citing HIV in their reasoning for the implementation of vCJD risk reduction measures, the most important metaphors pressuring the UK government into action were the BSE crisis and the Hgh transmission of CJD.

In all of the chapters, but especially chapter 8, I detail how animal model systems such as scrapie or BSE in hamsters, mice, primates, and sheep have become heavily used metaphors in attempting to conceptualize the risk of transmitting CJD and/or vCJD through blood. In all cases, there are those who argue that the animal model should be considered similar to prion disease in humans, and those who argue it should not. Because the interpretation of the results from animal model systems is underdetermined , controversy cannot be resolved simply through further experimentation (Collins & Pinch 1998). Contestations over the meaning of results continue until socially resolved (Latour 1983).

Like the French in their construction of the Maginot Line, however, the application of metaphors both makes it possible to conceptualize certain avenues of risk while limiting the ability to perceive others. As Lakoff notes, "In allowing us to focus on one aspect of a concept...a metaphorical concept can keep us from focusing on other aspects of the concept that are inconsistent with that metaphor..." (Lakoff & Johnson 1980). The problem is, while we are in the moment, it is difficult to see how metaphors

are both enabling and blocking our perception. For example, after BSE was discovered, the metaphor to scrapie both enabled it to be conceptualized as a transmissible disease, but also blocked the perception that it could be transmissible to people. Likewise, when it comes to secondary transmission of vCJD, metaphors to HIV have heightened awareness of the blood system as a possible avenue of transmission, while obscuring other avenues. The interactional construction of metaphorical relationships is therefore of vital understanding in assessing how we do, and do not, conceptualize certain aspects of a potential risk.

Because the management of risks is oriented towards the future, it is positioned between two poles – the potential for a positive, hopeful future, and the potential for a negative, fearful future. The imagining of possible futures that might attend to TSEs, therefore, is a subjunctive enterprise held in tension by these two extremes. In the mass narrative of TSE management policy, technological solutions to problems becomes the instantiation of the trope of "hope" – they are the optimistic horizon that the committee members and policy makers continually look forward to, the scientific solution that will solve all of the complex and difficult problems they are dealing with today. This constant hope of a "brighter future" and their need merely to 'stave off the worst' until then offers them a bit of reassurance when it comes to discussions.

When it comes to the blood supply, it is often imagined that many of the problems relating to donor selection and prevention of transmission could be prevented if only there were a blood screening test. However, this "technological hope" for a blood screening test is not without its downsides, including the possible production of stigmatization, fear, and availability problems. The only way of overcoming these

downsides is through another "technological hope," that of a magic pill or treatment that will cure TSE. In combination, these two potential technologies provide the "great hope" and "optimistic future" that all are looking forward to and biding their time until they get there.

In addition to these technological hopes, there is also the more general hope that the disease will just peter out eventually, dying off of its own accord. This potential is cited frequently in the context of discussions over BSE and vCJD as a reason for justifying why little or no management may indeed be required.

As for conceptualizing the fearful side of potential TSE outcomes, scientific experiments, anecodotal accounts, and epidemiological studies may provide the raw material for projecting pessimistic futures. Pessimistic futures are easy to envision when it comes to prion disease, because it is so hard to tell what is happening in the beginning of an epidemic. Larry Schonberger describes one pessimistic scenario which was imagined following the recognition of vCJD in Britain:

> I mean, imagine these guys thinking, "God, look at the millions and millions of people in the UK being exposed, and what happens if this disease really takes off?" You know, what if it could transmit to humans more easily than anybody had thought? And in a way, it still hasn't been totally settled whether there could be a huge problem. Although the more time that goes on where we don't see it, the more comfortable people are getting. But that, quite frankly, is the underlying basis for so much of the concern and support. Could all these people in the UK who've been exposed, are they just destined, ultimately, to develop some bad prion disease (Ponte 2004c)?

As Robert Rohwer indicates, these sorts of fears of a widespread, uncontrollable epidemic stem from the temporal nature of the disease: its long incubation period during which it is virtually undetectable, and during which cycles of transmission can occur:

> ...as soon as you open up a chain of transmission then you essentially have created a situation, which occurred with kuru and with BSE, and you can end up,

> you know, you may not see it, but in the case of a slowly developing disease like this you may not see it, or it might take two generations to see it. But somewhere down the line people become cursed by this stuff (Ponte 2004d).

While these are evocative verbal expressions of the potential for terrible futures which can be imagined with respect to TSEs, there has been, more recently, an attempt to quantify and project these futures in a more systematic way through the discipline of risk assessment. Formalized risk assessments are playing an increasing role in the conceptualization of future scenarios in relation to TSEs, as well as in relation to many other potential dangers in life, as described in Chapter 7. The growing prevalence of these forms of stylized imagining of the future deserve a special consideration given their ascendancy.

The idea of separating the process of risk assessment, the evaluation of risks, from risk management stems from attempts, beginning in the 1970s, to delineate science from policy, and to circumscribe the grey zone that lies somewhere in the middle. In 1972, Alvin Weinberg developed the term "trans-science" to describe this grey zone between the two poles. He saw "trans-science" as characterized by questions "which can be asked of science and yet which cannot be answered by science" (Weinberg 1971). As Sheila Jasanoff has pointed out, the development of this concept was an attempt to do boundary-work (Jasanoff 1987a). It reaffirmed scientists' professional authority and ability to regulate themselves on matters deemed to be "purely" scientific. It also gave policy-makers some leeway in deciding issues that involve science, but are not seen to be answerable with science. The concept of trans-science, in essence, allowed scientists to admit to uncertainties in their discipline without losing credibility.

Throughout the 1970s, EPA attached more weight to studies indicating a risk than those that did not (Jasanoff 1987a). They did this because they saw their purview as protecting public health, and thus thought it better to err on the side of caution. This was challenged by Reagan administration officials and the chemical industry in the 1980s. It was argued that the generic approach of the FDA overlooked factors such as the dose-response relationship and the extent of exposure a person was likely to receive. These parties called for a more formalized approach to assessing risks, one which would involve the incorporation of some measure of the dose-response relationship and exposure into the format of a quantitative risk assessment. These parties won a major victory when a judge ruled that OSHA's proposed regulation of benzene was illegal because it was not based on a quantitive risk assessment (Jasanoff 1987a). After this incident, OSHA, and the EPA, sought to enshrine all of their rule-making decisions in the language of a quantitative risk assessment.

Attempts were made, thereafter, to remove the scientific assessment of risk from the political and social concerns that color decision-making. This was an attempt at purification, a process which, as Latour has described in We Have Never Been Modern, often results in the proliferation of science-society hybrids which develop into confusing masses of issues that resist resolution (Latour 1993). As Jasanoff phrases it, "political demand for separating science and policy seemed to deny the existence of any ambiguous border area where the two kinds of issues are inextricably joined" (Jasanoff 1987a). She recounts how Congress called for the establishment of a National Academies of Science committee to examine the issue. The committee came to the conclusion that policy choices are inevitably involved at the very core of risk assessment, and that it was

therefore unrealistic to entirely separate the process of risk assessment from that of risk management. This did not prevent them, however, from suggesting that regulators should aim for such separation as an ideal. As the report stated:

> Before an agency decides whether a substance should or should not be regulated as a health hazard, a detailed and comprehensive written risk assessment should be prepared and made publicly accessible. This written assessment should clearly distinguish between the scientific basis and the policy basis for the agency's conclusions (Jasanoff 1987a).

As Jasanoff explains, the draw to cloak policy decisions in an ever-more objective guise through the exercise of risk assessment was too powerful for regulators to ignore:

> In spite of the NAS committee's assertions to the contrary, agency officials saw some advantages in treating risk assessment as a wholly scientific enterprise, at least for rhetorical purposes. Emphasizing the objectivity of the procedure offered a means of persuading the public that regulatory decisions are based on a core of rational analysis and of enhancing public confidence in the impartiality of agency decisions (Jasanoff 1987a).

This aura of objectivity was especially furthered by the emphasis on calculation and quantitative output values. These sorts of output values, which are reported with statistical confidence intervals and all the trappings of a proper statistical analysis, can be somewhat deceptive. As David Asher of the FDA (who cautions that his views should not be taken as representative of the agency) put it:

> The problem with risk assessments is that people forget that they're not establishing facts; they're offering expert advice. And people look at these distributions, if they're thorough enough to present the risks and the assumptions as distributions, and they see those bars around them and they interpret them as being standard deviations around a known mean value. And they're not. What they are is estimates of the most probable magnitude of the components of the chain of failures that would have to take place in order for the adverse event to occur with the variability and uncertainty, which are usually kind of subjective, and the problem is that the quality of the data, because they're presented in a form that people are used to seeing for empirically measured values with variability around them, the quality looks better, more reliable than it really is. And people tend to forget that what you're looking at is an expert estimate, not a measured value (Ponte 2004a).

Because the results are reported in a format usually used to present the results of scientific experiments, given x number of trial runs, they appear to be more solid than they really are:

> It's not like measuring the results of pressure testing 10,000 O-rings to see the likelihood under such-and-such of pressure of one of the rings blowing up. But it looks like the O-ring data, you know (Ponte 2004a).

As described in previous chapters, however, the process of constructing a risk assessment is quite malleable and can easily, with the flick of a few digits, be pushed in one direction or another. David illustrates this malleability by providing an example from the space program:

> ...this whole type of analysis comes from the way engineers used to look at the likelihood of an accident occurring, for instance, from a structure. They would do an analysis, a so-called failure analysis, of what the steps that might fail are and the likelihood of each step failing. Now, one of the classical examples of how those things are misused was an analysis that was allegedly done for NASA many years ago for the likelihood of a rocket in the space program failing. And it is said that they got an estimate from a contractor who did an analysis - of a likelihood of 1% failure; that is, one launch out of 100 should have a catastrophic accident and fail. And, allegedly, I have no personal knowledge of this, they rejected that analysis, got somebody else to do their own risk analysis, and that one gave them a likelihood of one in a hundred-thousand, not one in a hundred. So it was a substantial difference. But they liked the second one better. Soon after that, there was a rocket failure (Ponte 2004a).

Or, as he said at a TSEAC meeting: "One problem associated with all risk assessments is that they are susceptible to bias because the probabilities of failure at each step are assigned at least partially subjectively" (TSE Advisory Committee 2004).

Having pointed out some of the ways in which a risk assessment can be manipulated by bias or for political interests, or can be misrepresented as more accurate and solid than it is, David Asher argues that risk assessment can still provide a useful framework for thinking about a given problem, if presented transparently:

> That having been said, properly done, it should be more transparent than the same kind of thing when it's presented as the ordinary expert advice where people are essentially doing the same thing subjectively in their minds, except you can't see any of the steps that are going into making the decision (Ponte 2004a).

In other words, Asher sees a role for risk assessment in guiding discussion over a risk, but not in "objectively" calculating a risk. Risk assessments, he says, should ideally make the underlying biases of the risk assessors transparent, such that they may become matters for discussion and debate:

> Everybody is biased, everybody. I mean, it's part of being human. And, arguably, in a probabilistic risk assessment, the chance of your disclosing your bias is greater, because the experts who don't do that kind of analysis have all the same kind of biases; it's just you may not know what they are. What kind of biases am I talking about? Well, to me, there are several that are pretty common. One is so-called precision bias. People think that their estimates are more precise than they might be. And another one might be called the optimist/pessimist bias. That's how you get these enormous differences between two assessors in what a risk might be, because people who tend to think that the risk of these things is not very great tend to feel that way about every step of an analysis. And people who are worrywarts, very risk averse, tend to be that way with every step of the analysis. NIBSC once had two people use the German system to look at the risk of a product. They had an eight-log difference, because the steps in the German system are logarithmic steps, in the estimated risk for this same product given to them by two assessors. How do you get, you know, <laughs> how do you get a hundred-million fold difference in estimated risk? I think the most likely reason is because pessimists, for every step they take the highest estimate, whereas optimists don't. That's the only reason I can come up with for how two people looking at the same information can come up with estimates that are so different (Ponte 2004a).

In fact, many of the same biases that affect people's actions and choices in everyday life impact the way that risk assessors construct their risk assessments. For example, the desire to treat risk as containable by spatial and temporal boundaries allows for the manipulation of concepts of risk by making them seem similar to concrete objects.

Finally, even though sensitivity analyses are included in most risk assessments, which test the impact of changing different input values on the final results, the choice of

input values for the sensitivity analyses are also subjective. Thus, the ultimate weakness of a risk assessment is that if "the probabilities are not reliable, then the estimates may not be," and, as David Asher notes, "we know that life is full of surprises" (TSE Advisory Committee 2004).

Theodore Porter suggests that the increasing use of quantitative valuations reflects the tension between bureaucracy and democracy (Porter 1995). Quantification exists, he proposes, because of the need to appease the public and critical institutions. It is not a purely technocratic matter. In fact, if technocrats were left to their own devices, they would not bother quantifying everything. But it is because they need to appear impartial and appear as if they are serving the public good that objectivity is performed through numbers. Regulators would never voluntarily subject themselves to the rigidity and discipline of numbers, but they do so because it allows them to protect their authority and credibility in the eyes of the public.

Porter traces the quantification of public life to 19th Century France, where engineers were increasingly called upon to calculate the utility of different policy measures for the population (Porter 1991). He speculates that on the one hand, the growth in the use of numbers, or statistics, in government corresponded to a "vast modern extension of the range of state power" while, on the other hand, it became associated with the belief that "the public should be kept informed and even a need to justify action or inaction to that public" (Porter 1991). He proposes that while "bureaucratic growth and administrative centralization were preconditions to the quantification of public life" (Porter 1991), such quantification would not have been necessary, at least not to the extent that it came to be used in France, had the government not adopted democratic

principles. In dictatorships or aristocracies, he argues, it is not necessary to govern by numbers:

> Where there is little political openness, there is also little opportunity or need to draw on formal, rationalized models as a basis for decision-making rules. Hence the quantification of public life has reached its most highly developed form under the political pressures characteristic of modern democracy (Porter 1991).

Thus, as democracy has proliferated throughout the world, so has the use of quantification to justify, and provide the precondition for, decision-making. Risk assessment, as a particular form of public quantification, grew to be a staple in American government long before they became a staple of British government, though the British were quick to uptake this approach when they deemed it politically useful. Formalized risk assessment has since become enshrined in the statutes of international bodies, such as the OIE and the WHO.

Thus, the history of the quantification of risk assessments is a history of attempts to gradually circumscribe risk and bracket uncertainties to a portion of the policy-making process where they can be dealt with by turning them into numbers, however questionable this transformation might be, and then producing quantitative, apparently objective outputs. The problem in all of this, as I see it, revolves around the very idea that science should not contain uncertainties to begin with, and that somehow these uncertainties can be washed away.

Science is uncertain through and through. Scientific concepts are constantly being hypothesized, negotiated, reconstructed, and transformed through processes involving discussion, debate, and experimental endeavors. In other words, science is not a stable, solid entity that can be pointed to at any one time as absolute truth. Scientists, and professionals who make use of science, are taught to be malleable and to change along

with the changing times, to evolve along with the ever-evolving process of scientific thought and investigation.

The uncertainty and indeterminacy of science, however, is often hidden from the public. Collins laments about this in his article on "Certainty and the Public Understanding of Science." He argues that in most television programs on scientific topics, science is represented as a simple and straightforward process that provides easy to interpret results. This image is produced by reconstructing scientific discoveries to make them appear as if everything works perfectly the first time (Collins 1987). In the process of doing so, time and work are collapsed to present a simple narrative. The disorderly processes involved in interpreting a result appear orderly. The tests and measurements used are black-boxed so that all background noise and uncertainty is washed away.

While Collins recounts several television programs on science where uncertainty in the current state of knowledge was revealed, the narrative was constructed in such a way as to lead the viewer to believe that, eventually, certainty would prevail. Current uncertainty is devalued by the image of future certainty, just as, in Leigh-Star's argument, global certainty may efface local uncertainty (Star 1985).

Collins surmises that "there is a relationship between the extent to which science is seen as a producer of certainty and the distance from the research front" (Collins 1987). In fact, he proposes that distance from the research front is the very source of the perception of the solidity of facts. Because "the general public are by definition maximally distant from the research front" they tend to view science as a process that produces certainty (Collins 1987). This is the result of efforts made, both by scientists

and policy-makers, to present the scientific process as more certain than it is. In return, when debates become heated and scientific uncertainty is "revealed" to the public, frustration results.

D.A. Henderson, a prominent public health expert, sees this lack of transparency, and failure to disclose uncertainty, as part of the reason the announcement of vCJD triggered such a backlash in the UK. Henderson describes a meeting with the chief medical officer of the UK in which he first learned about BSE. He says that when he walked into the CMO's office:

> He was pacing the floor, and that day was the day the information broke in the press about this. So I said to him, gee I'd love to see the curve with the onset of cases and the dates of onset and some of the other information. He looked at me and said "I don't have it." It's the ministry of agriculture, they have it. And then he said "how, when you were working in your various capacities," I directed surveillance at CDC for a number of years, "how would you handle this?" And I said "well, we've been through this sort of thing a couple of times." We went through it with the killed polio vaccine, and we ran into trouble with the oral polio vaccine, we had a couple of big problems, and I think we came through that with one principle - the most important thing: You make it known where you are and what you're doing, all the cases, you make sure you're out in front with the information. And you don't go and reassure the public and say that everything's alright you tell them what you know and be honest. If you don't do that, you're in big trouble. And that was echoed again with Tylenol, the same thing. We went through that. And then the Brits didn't do that. They didn't make the information available (Eichberg 2003).

Henderson believes the agricultural industry of the UK, as well as the public health of the UK, would have benefited, early on, from a frank discussion of the possibilities that BSE entailed. Moreover, he believes that the admission of uncertainty in public statements could have prevented the loss in trust that occurred when vCJD was revealed.

The efforts of the UK government, however, when it came to handling the BSE crisis, revolved around producing unambiguous and intractable statements about the state

of knowledge, statements that were framed as far more certain than science would ever suggest. The few scientists who challenged these statements were presented as fringe scientists and were largely excluded from governmental negotiations and membership on committees like SEAC. As Collins warns in his prescient piece, "science, as the apparent purveyor of certitudes, may sometimes be accorded inappropriate support and prestige for issues to which there is no simple answer" (Collins 1987). Such was the case when BSE arose in the UK, and such is the case today with BSE in the US. While the USDA and the FDA cloak their statements in language that is "science-based" and "scientifically justified," they neglect to state all of the uncertainties involved in the scientific experiments, the anomalies that have arisen through use of different technologies, and the interpretations that invariably color each conclusion.

In order to act out their roles as citizens in a democracy, the public should be given the tools and information to develop a reflective understanding of science. Collins proposes that this would entail an "understanding of the way science seems to generate certainty and what this means for its relationship to other kinds of knowledge" (Collins 1987). This would require that the public be given not only more knowledge of the background to disputes, or more familiarity with the findings of science, but that the public be given the means to see science as it truly is – a conglomeration of studies and results that are metaphorically interpreted through multiple discourses and debates to produce temporary understandings of how the world might work, and, in the realm of policy, allow for the formulation of modes of action. While I realize that such a possibility may seem far-fetched, given Porter's insight that the mixing of democracy and bureaucracy will always produce forms for obfuscating decision-making, I believe it is

worth the efforts to attempt to thwart our modernist tendencies to always present decisions as rationally produced when they are clouded by uncertainties and unknowns.

Summing Up

In summary, I have applied a nominalist methodology to the management of Transmissible Spongiform Encephalopathies (TSEs), or prion diseases, in both the US and UK over the past two decades. I approached my objects of study with an open mind and an attention to details. I sought to evaluate the production of forms through significant events, events which I have recounted in the preceding chapters. The forms which I have witnessed in their emergence involve mechanisms for generating an image of rationality and managability when uncertainties and unknowns prevail.

My work builds on and contributes to ongoing work in science studies. Uncertainty, and the way it is dealt with in both the laboratory and policy arena, has been analyzed in a variety of ways. Renee Fox has viewed the major uncertainties that arise in the laboratory as deriving from differences in scale (Fox 2000). When moving from microscopic images of a cell to whole animal, or from the results of genetic microarrays to an actual disease, there are a variety of leaps that must be made to apply results from one system to another. Star extends this type of analysis beyond the laboratory, where she sees uncertainties as arising from a change in scale between the local and the global (Star 1985). Changes in scale also figure prominently in Latour's analysis of the production of scientific facts, where results are obtained by the serial translation, or mapping, from one domain to another (Latour 1983)

The contribution I have made to this area of science studies is the development of a way of analyzing such changes in scale, which must be accomplished in the production of disease management policy, as being managed through a system of interconnecting metaphors. This system of metaphors determines the way in which model systems, whatever their scale, are interpreted for the purposes of influencing disease management policy. This is, however, a contested and interactional domain. The system of metaphors which allows for the management of risk and the bracketing of uncertainty is constantly reconstructed through contestation, negotiation, and the impingement of new metaphors.

Certain theorists of the 1960s and 70s held the view that the tendency to transfer policy decisions to technocrats signaled an "end to ideology" (Bell 1999, Lane 1966). This was based on the belief that science was devoid of values and produced absolute certainty. What they missed, however, was what future scholars of science studies would uncover, that science is inherently uncertain and subject to constant change. Uncertainty presents a whole host of complications when it comes to the policy domain. As Ezrahi has described, uncertainty, when it emerges, may have the effect of discounting the scientists on both sides of a policy debate, making the establishment of policy impossible (Ezrahi 1980).

And yet there is pressure to act in some manner or another to mitigate risk. This pressure arises from our modernist desire to manage and plan the population, such that the contours of the future may be produced to match the productive potential of the population (Foucault 1995). This pressure puts technocrats in a bind, however. On the one hand, there is an ever-evolving, highly uncertain representation of the world. On the

other, there is the political necessity to create the appearance of control and manageability (Porter 1991).

As Jasanoff has recounted, the EPA has made attempts to wall-off decision-making in a procedural manner, to avoid the underlying uncertainties inherent in the science involved (Jasanoff 1998). This technique, however, failed. Chemical companies objected to the management of risk through procedures that eliminate the changeable role of science, and the court sided in their favor. Uncertainty and changeability have become ingrained in our approach to risk management. And yet these uncertainties must still be managed so that they do not overflow. As my study has shown, they are managed by bracketing them temporarily, through a variety of metaphors, to produce a semblance of rationality and manipulability.

The results of my study are applicable not only to the field of disease management policy, on which my study is based, but also, I believe, to the management of other risks which we seek to preemptively manage. These risks include terrorism, environmental pollution, and economic disaster, to name a few. In each of these, there are substantial uncertainties and gaps in our knowledge. For each of these, assumptions about the likely contours of the danger and the ways in which it will manifest are configured through metaphors which include past experiences and model systems. Each of these dangers are, in some way, treated as though they are containable by spatial and temporal boundaries. Certain regions are seen at risk and not others, certain people are seen to be at risk and not others, certain times are seen to be risky and not others. These spatial and temporal boundaries are the result of a bracketing of uncertainties. This bracketing, while temporary in nature, obfuscates the irrationality and experiential quality of risk

management decisions. Like the French in their construction of the Maginot Line, we seek to avoid danger by applying strategies based on metaphors. But the avenues through which danger may manifest in the future may be different from what anyone expects, or is capable of perceiving, from within the available sensitizing frame. In the end, one is left to wonder, all modernist tendencies aside, whether our attempts to manage risk and control the future are any better than taking a random stab in the dark.

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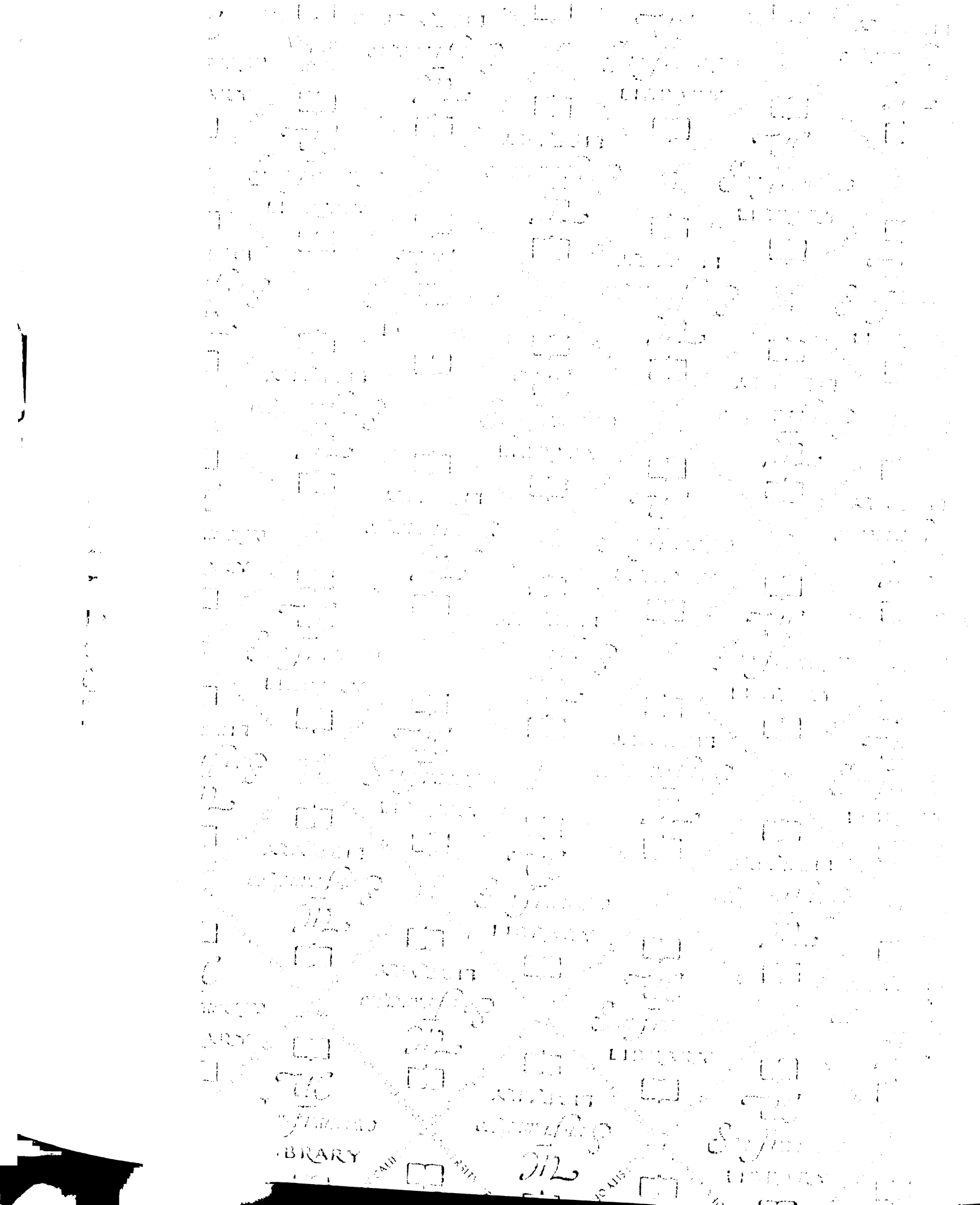

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