The Human Insulin Debate: A case study of contested innovation in medical technology

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ABSTRACT

This thesis describes and analyses a case study of contested innovation in medical technology using actor network theory (ANT). As well as ANT other areas of sociology are drawn upon, such as the public understanding of science, and the sociologies of the body and consumption. The multiple approaches are used in order to develop ANT in novel directions. The particular medical innovation is the introduction and use of human insulin. Human insulin was first prescribed to diabetics in 1981, and was initially welcomed as a technological innovation that would reduce diabetic complications that are associated with animal insulin. However, as human insulin began to be used, the superiority of human insulin began to be questioned by some diabetics, doctors and care groups. One particular concern was the change in warning signs of approaching hypoglycaemia that were reported by some diabetics. Importantly, there was no agreement within the medical and scientific communities as to whether human insulin did cause negative effects.

Data came from different types of documented evidence, including: scientific studies, medical reports, articles published by care groups and letters from diabetics. Aspects of ANT, and certain elaborations of ANT (e.g. the 'network body'), were used to explore this data. Thus, the thesis analyses some of the means by which human insulin was initially constructed as being superior to existing animal insulins, and how, later, actors began to marshal resources in order to redefine the meaning of human insulin. The thesis also describes how diabetics, aided by care groups, were able to have an influence on the insulin species they were to use by stressing the value of their experiential knowledge. Not only this, actors wanting to claim 'facticity' within the human insulin debate had to collectivize texts from both 'lay' and 'scientific' sources.

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1. INTRODUCTION

This research concerns the development, introduction and use of human insulin. Insulin is used by diabetics that are unable to produce enough insulin naturally, known as Type I diabetes or Insulin Dependent Diabetes Mellitus (IDDM). Conventionally, Type I diabetics[1] injected themselves with insulin taken from the pancreases of dead animals - either from pigs or cows. Without insulin, diabetics will die, and as a consequence, the World Health Organisation has identified insulin as a 'life saving drug' (1991).

The amino acid sequence of animal insulin differs from that of natural pancreatic human insulin (see Figure 2-3). Although diabetics have lived a relatively 'normal' life using animal insulin, there were some concerns that the differences between animal and human insulin could cause diabetic complications, such as retinopathy and neuropathy. There were also concerns that the supply of animal insulin would not be able to meet the future demand for insulin. As a result of these considerations, during the late 1970s a number of research groups became interested in producing human insulin in commercial quantities.

The progress of the research groups was presented in the media as a 'race', and later as a 'battle' between two pharmaceutical companies - Eli Lilly and Novo Industri. The race was won by Novo Industri, who converted porcine insulin to human insulin in 1980, with Eli Lilly, who used genetic engineering to produce human insulin, not far behind.

The energetic marketing of human insulin, by both Eli Lilly and Novo Industri, led to the dramatic increase in its use. In 1986 only about 6% of insulin sold in Britain was human insulin, however by 1989, about 80% of insulin dependent diabetics used human insulin. It was not just the marketing of human insulin that led to this increase. Due to media interest in human insulin some diabetics requested to be transferred to the new, technologically advanced human insulin. Some doctors were also under the misconception that animal insulins were all being withdrawn and so transferred their patients to human insulin.

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[1] In future, the word 'diabetics' refers to those with Type I diabetes.

1.1 Themes of the study

Initially the production of human insulin was welcomed, since it was believed that it would reduce diabetic complications that were associated with animal insulin. However, as human insulin began to be used, the superiority of human insulin began to be questioned by some diabetics, doctors and care groups. One particular concern was the change in warning signs of approaching hypoglycaemia that were reported by some diabetics.

As a result of an awareness, by the medical and scientific community, that some diabetics were experiencing problems on human insulin a number of studies were carried out which attempted to assess the possible adverse effects of human insulin. These studies were inconclusive, with some studies showing that human insulin did have a negative effect, and others showing that it did not. This disagreement led to much debate within the scientific and medical community.

As a result of reports from diabetics, and the inconclusive findings of the scientific community, diabetic care groups became involved in the human insulin debate. The British Diabetic Association (BDA) received many letters from diabetics who were experiencing problems on human insulin. Letters from diabetics did not just describe their problems due to using human insulin, but also, the responses of their doctors when they reported their problems. In a significant number of cases doctors would not transfer diabetics back to animal insulin, even though their letters suggested that they were experiencing problems on human insulin. As a result of the concerns of diabetics, the BDA investigated the claim that human insulin caused adverse effects; they formed a number of groups and funded scientific research.

One interesting feature of the human insulin debate is that as a result of dissatisfaction with the way in which the BDA conducted itself, another care group was formed. In 1995 the Insulin Dependent Diabetic Trust (IDDT) was formed. Members of the trust were concerned that the BDA was not adequately representing those diabetics who were experiencing problems on human insulin. In particular, they argued that the BDA were not informing diabetics of the problems experienced by diabetics.

At the present time the human insulin debate is still unresolved. However, there is now a general consensus that those diabetics who are experiencing problems on

human insulin should be returned to animal insulin. Further, pressure has been exerted on pharmaceutical companies, by both care groups and the medical community, to ensure the continued availability of animal insulins.

1.1 THEMES OF THE STUDY

These then are the bare bones of the story I will tell. But, the story I tell is structured by a number of sociological concerns. The backbone of this study is formed using actor network theory (ANT). In particular, I am interested in the ways in which the initial identity of human insulin was constructed as superior to existing animal insulins. This was done by a number of entities who brought together a number of disparate actors, both human and nonhuman. Then, when some actors began to suggest that human insulin caused negative effects for some diabetics, the initially 'superior' identity of human insulin began to be questioned. Key actors, such as scientists and care groups, began to form associations with other actors in order to claim 'facticity' within the human insulin debate. It was not just the identity of human insulin that was being redefined. Actors, in particular care groups, also began to question what was to count as expertise within the human insulin debate.

So, my theoretical perspective comes from the sociology of scientific knowledge (SSK), in particular from science studies, however, this is not to say that this work has not been affected by other areas of sociology. This work has been influenced by such areas of sociology as the sociology of the body and the public understanding of science, and to a lesser extent, the sociology of consumption. By using these other theoretical areas, I hope to develop and enhance actor network theory.

Since this study concerns itself with a medical controversy, something also has to be said about the place of this study within medical sociology. For example, the sociology of health and illness has been interested in the doctor-patient relationship and this is something that I will deal with throughout this thesis. I am also interested in the meaning and definition of 'lay' beliefs, which has been a concern of medical sociology for some time.

However, as Arksey (1998) points out, it has only been in the last decade that some medical sociologists have challenged the notion that medical knowledge has

'superiority' over 'lay' knowledge (Abraham, 1994). The idea that scientific and expert knowledge is superior to lay knowledge is of key interest to this study, therefore, this work will be of interest to those who write within this new area of medical sociology.

This work is also relevant to researchers who have an interest in the experience of chronic illness. The sociology of chronic illness has moved away from describing the burden of chronic illness (Bury, 1991), to looking at the steps people take to manage, mitigate, or adapt to chronic illness (Bury, 1991). Work within this field has looked at the onset of chronic illness as a 'biographical disruption' (Bury, 1982) and this is something that I will draw upon. However, rather than looking at the onset of illness, in this case diabetes, I am interested in the negotiations that diabetics go through when their existing knowledge of their illness no longer seems relevant.

Another area of sociology that I am interested in is the sociology of the body. I take an actor network approach to the body in which the body is seen as a network; that is, the body should be seen as consisting of various heterogeneous relations. ANT has not dealt with the body in much depth and this is something that I wish to correct. Even recent work that has looked at patients and used ANT theory, such as Arksey's study (1998) of RSI, did not develop the notion of the body within ANT.

In my view of the body, the body should be seen as a network consisting of different actors, both human and nonhuman. It is the composition of this network body that affects the actions of an actor. For example, human insulin was inserted into the diabetic network body, and as a result, in some cases, diabetics contacted care groups regarding the change in their warning signs of hypoglycaemia. One important feature of the network body is that there is some flexibility as to which actors/entities become part of the network body. This is illustrated by the observation that not all diabetics use the same species of insulin, or are influenced by the same actors. For example, some diabetics were influenced by the Insulin Dependent Diabetic Trust and others by the British Diabetic Association.

One of the aims of this thesis therefore, is to consider the ways in which actors become part of the network body. For example: How did Eli Lilly and Novo Industri,

two of the major insulin manufacturers, enable human insulin to become part of the network body? Conversely, I am also interested in the influence that other actors, such as care groups, have in removing actors/entities from an individual's network body. A preliminary explanation is that in order for entities/actors to be added or removed from the network body, actors need to marshal a wide variety of other actors and resources.

Another interest of this thesis is the public understanding of science, or more precisely, the division between 'expert' and 'lay' knowledge. I address the types of knowledge possessed by diabetics, care groups, the medical profession and scientists. A particular concern is how actors attempted to establish the relevance of the knowledge that they possessed to the human insulin debate. Further, I am also interested in the value that various actors placed on the knowledge held by others, and how this knowledge became incorporated or collectivized into texts which could assist in the process of establishing facticity.

Scientific knowledge should not be seen as being superior to other knowledge. Lay knowledge is usually of a different order to scientific knowledge since it is likely to be based, at least in part, on the experiences of individuals. A particular interest of this thesis is looking at the ways in which actors, who do not possess scientific knowledge, attempt to claim facticity for their own particular type of knowledge. This is especially the case when scientific evidence is inconclusive. In such cases, care groups, and those actors that they represent, are likely to claim the superiority of anecdotal evidence. Therefore, the public can be 'experts' too. However, their expertise may not only come from experiencing illness, but also through contact with versions of 'scientific' and 'medical' evidence, in the form of newspaper articles and reports in care group literature.

Another concern of this thesis is looking at the way in which bodily experiences become expressed. In particular, I am interested in the ways in which non-experts, at least from the point of view of the medical profession, are able to collectivise their own experiences. Here I am interested in the way in which a diabetic's experience of their body moves from a personal and 'private' experience to one that becomes 'public'. One way in which this occurs is through the publication of letters which

describe a diabetic's experiences. Care groups may collectivize experiences which are used to 'stand against' competing and contradictory scientific evidence. Further, diabetics themselves may use collectivized texts to persuade other actors, doctors for example, of the facticity of their experiences.

The way in which actors identify with particular texts is also important. In this study some scientists were claiming that human insulin did not cause negative effects, while others were claiming that it did. Due to the lack of closure within the scientific community, different groups identified with different 'products' of science. Those that were claiming that human insulin did not cause side effects, such as the pharmaceutical companies, identified with scientific work that showed that human insulin was 'safe and efficient'. On the other hand, care groups, and in particular the Insulin Dependent Diabetes Trust, identified with scientific work that claimed that human insulin did cause side effects. Therefore, one theoretical area that I am concerned with is looking at what sources actors go to when they desire more 'information' on a particular issue.

Finally, although not central, I look at some themes within the sociology of consumption. I explore the ways in which the use of human insulin enabled diabetics to express a particular identity: one that was based on the use of insulin that had the same amino acid sequence as that used by 'healthy' individuals. In a similar vein, the ability of diabetics to change their insulin species expressed elements of control over diabetic treatment.

The framework that I adopt therefore draws upon a number of theoretical areas of sociology. The choice of ANT as the central facet of the work is due to my belief that ANT is able to bring out the heterogeneous nature of actors. It is also able to show the processes involved in network (re)building, in particular, how actors attempt to break apart existing networks and then rebuild them according to their own pattern. However, in ANT, the body has mostly been neglected, so I wished to correct this omission by developing an ANT approach to the body.

Within my framework it was also important to include some discussion of expertise. In particular, I wanted to bring out the conflicts and trials that exist when actors,

possessing different types of knowledge, attempt to claim facticity over particular issues. The issue of expertise is particularly pertinent when there is a lack of closure within the scientific community.

It is my hope that by using a number of areas of sociology, within an ANT framework, I have been able to not only enhance ANT, but also suggest how other areas of sociology can benefit from using an ANT approach.

I have indicated above how this thesis is relevant to a number of theoretical areas. This thesis also has some practical implications. As I will show in later chapters, patient communities can have an influence on the way in which science is conducted, moreover, they can also influence the information and options available to patients. Through contact with care groups patients/sufferers may then become empowered, and as a result of this empowering, may be able to affect medical policy.

Medical communities can also learn from this study. It is important to realise that the experience of patients, in this case diabetics, should be taken as a credible source of knowledge. Rather than 'lay' knowledge being seen, by doctors, as a challenge to their authority, and therefore something that has to be dismissed, 'lay' knowledge should be incorporated into a doctor's knowledge. This is especially the case when there is not a consensus within the scientific and medical community as to whether a particular drugs produces negative side effects.

From a personal point of view, I became interested in the problems associated with human insulin through my father. He has been a diabetic for over 30 years, and in the mid 1980s he was transferred to human insulin. He did experience some problems, and like many diabetics in this study, there was uncertainty as to whether the problems were due to human insulin or to some other 'natural' cause, like the long duration of his diabetes. When it came time for me to put together a proposal for a Ph.D., it occurred to me that the subject of human insulin would be not only be of interest to diabetics, but also to others, not only in academic fields such as sociology, but practitioners and policy makers.

1.2 OVERVIEW OF THE THESIS

The thesis is organised in the following way. Chapter 2 describes the theoretical background of the study. I begin by placing actor network theory (ANT) within other social scientific, in particular within science studies. I then go on to present an overview of ANT. My aim is to define and explain some of the central concepts of ANT. In particular, I describe the key moments of translation: problematization, interessement, enrolment and mobilization. Once I have outlined some of the key concepts, I will illustrate them with a number of studies carried out from an ANT perspective. I then go on to critically assess the importance of ANT. One of the important concepts that I will bring out in this thesis is what has been called a 'program of action', so this will be dealt with in this chapter. This thesis does not only concern itself with ANT. It is necessary therefore to describe other areas of sociology that will be used in this thesis, these are the sociologies of the body and consumption, and the public understanding of science.

Chapter 3 places the development of human insulin within a historical context. In particular, I am interested in outlining the way key actors, in particular pharmaceutical companies, were interested in the progress of the research teams. I will also pay attention to the ways in which key actors first stressed the need for, and then the superiority of, human insulin. I will then go on to theorise the development of human insulin. This chapter is important because it sets the scene for future chapters, in particular, it outlines the meanings of human insulin. In future chapters I will describe how various actors, such as pharmaceutical companies and scientists, drew on these meanings to support their own claims.

Chapter 4 begins to describe some of the negative effects experienced by some diabetics on human insulin. I begin the chapter by outlining the meaning of hypoglycaemia, in particular, how it can be seen as a biographical disruption. I then go on to describe the meaning of hypoglycaemia unawareness, which was one of the most common complaints of those diabetics experiencing problems on human insulin. I also describe some of the initial reactions of a number of key actors, help groups, scientific and medical community, to reports that diabetics were experiencing negative effects on human insulin.

Chapters 5 and 6 deal with similar issues, but from two different perspectives. Chapter 5 looks at the role of the scientific community and pharmaceutical companies in the human insulin debate. I begin by providing an overview of the human insulin debate. I then go on to describe the scientific studies that were carried out that hoped to show whether human insulin did or did not cause adverse effects. I not only describe some of the key studies that were carried out, but I also describe some of the key discussions within the scientific community, particularly over the 'ideal study'. I then go on to describe some of the reactions of the pharmaceutical companies to the possible problems experienced by some diabetics on human insulin.

Chapter 6 goes on to describe the role of diabetics and care groups in the human insulin debate. I begin by describing the role of mediating others, the family and the media, in making diabetics aware of the problems experienced by diabetics on human insulin. I then go on to describe the solutions and resolutions presented by doctors that were accepted or rejected by diabetics. In Chapter 6 I will also describe one important feature of the human insulin debate: the issue of choice of insulin species. I will conclude this chapter by outlining some of the key differences between the two major care groups in this study, the British Diabetic Association and the Insulin Dependent Diabetic Trust.

Chapter 7, the concluding chapter, aims to theorise the human insulin controversy more comprehensively. I begin by describing the conditions under which diabetics produced texts to care groups, and how these texts were then collectivized and circulated to other actors by care groups. However, I also stress that it is not just care groups who collectivize texts, we also have to be aware of the collectivization carried out by other actors, such as the medical profession. One of the important features in the collectivization of texts is that actors draw texts from a wide variety of sources. In theorising these processes, I draw and expand the notion of the core set. I then go on to conceptualise three key issues in the human insulin debate: the way in which the solutions were presented to diabetics; how agreement between a number of actors was maintained; and, the actions of care groups towards key members in the human insulin debate. Finally, I assess the implications of the thesis; look at any changes that could be made to the thesis; and, point to possible future research.

2. THEORETICAL PERSPECTIVES

2.1 INTRODUCTION

The aim of this chapter is to explore the theoretical perspective that I adopt in this study. My interest is in looking at the process by which actors, whether human or nonhuman, are able to unite actors to form durable networks. In forming durable networks, actors not only need to define themselves as central actors, but also to challenge, undermine and shatter competing networks. I use ANT to do this, as it is very good at describing the work of network builders since it looks at the strategies used by actors to form credible networks.

However, before I look at actor network theory (ANT) it is important to have some awareness of where ANT is situated within sociology. Pickering argues that the early 1970s saw the emergence of a new "approach about thinking about science" (1992: 1) known as the sociology of scientific knowledge (SSK). This new approach began by arguing that scientific activity was social to its core and should be studied like any other social activity. It was argued that "SSK was determinedly empirical and naturalistic" (Pickering, 1992: 1). In this early period of SSK, Pickering argues that the conceptual and geographical map of SSK remained simple and readily surveyed. He argues that there were two main schools. Those in Edinburgh laid out the macro-social approach (Bloor, 1976; Barnes and Shapin, 1979), while those in Bath pioneered a more micro-social approach (summarised in Collins, 1985). However, by the late 1970s the map had begun to change.

In the late 1970s new approaches that had a lot in common with SSK began to surface. Pickering (1992) outlines a number of these developments: ethnographic study (Latour and Woolgar, 1979); work carried out from an ethnomethodology perspective (Lynch et al., 1983; Lynch, 1985; Livingston, 1986); some philosophers of science developed a "new empirically informed approach within their discipline" (Hacking, 1983; Cartwright, 1983); and a discourse analysis program (Gilbert and Mulkay, 1984). Later Latour went in a different direction to Woolgar, and developed his actor network approach with Michel Callon and John Law (Latour, 1987; Latour, 1988). These new studies should be placed under the umbrella of 'science studies'.

Work within science studies has been carried out in a number of locations and

contexts. Some work has studied the laboratory bench, some has looked at controversies (within both scientific communities and the public sphere), and other studies have looked at fringe science. However, although the context of the research may change, what is of interest to the researcher is the process by which certain knowledge claims are successful and others unsuccessful. An overriding theme in these studies is that there is nothing special about the generation of scientific knowledge. Scientific knowledge is, instead, simply one form of cultural activity, which can, like any other form of knowledge production be studied.

ANT fits very well with this perspective, since it argues that all actors are potential network builders. It is not just scientists who enrol 'lay' actors, lay actors also enrol scientists. The important point is that actors need to enrol human and nonhuman actors if they are to form durable networks. By using the new vocabulary of ANT, which uses the same terms to describe the actions of all actors, we do not lapse into treating human and nonhuman actors differently. An awareness of this concept is very important in this thesis because one of the important entities is human insulin - a nonhuman.

However, those using ANT to describe medical controversies have not, by and large, developed the way in which the body should be formulated. My theoretical perspective attempts to correct this by including some analysis of the body from an ANT perspective. As such, the body, as with any network, is heterogeneous, in that it incorporates both human and nonhuman actors. Usually the actors that make up healthy bodies are hidden, but in times of illness, new actors may be included into the body. Not only this, but the relationship that the body has with existing actors, such as relatives, may also be re-negotiated.

In times of illness new knowledge may be incorporated into the network body, and as a result, it will be necessary for me to refer to the types of knowledge that actors possess. Patients' primary source of knowledge about their illness is likely to be taken from their experiences, and this is likely to be different from the knowledge possessed by doctors. Patients who are dissatisfied with the way they are treated by 'experts' may seek out other sources of expertise; one such source is care groups. Care groups are likely to collectivize evidence from multiple sources, both 'lay' and 'expert', which is then used to challenge the authority of the medical profession. In

order to do this, care groups need to bring together disparate actors in order to form a durable network.

Of course, there are alternatives to ANT. One of the reasons for using ANT in this study is its ability to describe the heterogeneity of the networks that permeate our lives. Crucial to this heterogeneity is that networks are made up of both human and nonhuman actors. Not only does ANT argue that the analyst should describe the actions of humans and nonhumans, it also provides a vocabulary by which this can be done. The vocabulary is able to describe the way in which actors problematize existing networks, and at the same time, define themselves as being able to provide solutions.

In this chapter I will firstly describe some of the central themes behind ANT. Secondly, I will describe some of the studies that have been carried out under an ANT framework and point to some modifications. Thirdly, I will deal with some methodological and theoretical criticisms that have been levelled at ANT. Fourthly, I will explore a concept particularly pertinent to the present research that has been used within ANT, that of 'program of action'. The fifth section looks at how ideas behind the sociologies of the body and consumption, and the public understanding of science (particularly the division between 'expert' and 'lay knowledge') can enrich ANT. Then, in the final section, I will point to a number of theoretical areas that I will develop in later chapters.

2.2 AN OVERVIEW OF ACTOR NETWORK THEORY

The journal Lingua Franca claims, on the back cover of Latour's 'Aramis or the Love of Technology', that "Latour [a proponent of ANT] is one of the most rigorous thinkers in the loose combination of disciplines known as 'science studies'" (1996 [1993]). Perhaps what sets ANT apart from other 'science studies' is that it states that there should be no divide between human and nonhuman entities. Therefore, when we talk about society we need to adopt a different approach than has previously been adopted, since other approaches have 'ignored' nonhuman entities, or spoke of them in secondary terms. But, before I continue, we must engage with the principles behind actor network theory.

2.2 An overview of actor network theory

2.2.1 Methodological Principles

At the centre of ANT are three methodological principles or tenets that we must "obey faithfully" (Callon, 1986a: 200). The agnosticism principle states that the observer should be impartial to the scientific and technological arguments of those involved in controversies, and further, the observer should refrain from censoring any entity when they speak about themselves or their social environment. This idea is summed up by Callon:

> "No point of view is privileged and no interpretation is censored. The observer does not fix the identity of the implicated actors if this identity is still being negotiated."
>
> (Callon, 1986a: 200)

The second principle is of generalized or radical symmetry. This states that the researcher should use the same vocabulary for entities, whether they are human or nonhuman. We should also not change the repertoire when we move from the technical to the social. This goes further than Bloor (1976) and the 'Strong Programme', where the principle of symmetry only referred to claims of truth or falsity of viewpoints and arguments in a specific controversy.

Finally, the principle of free association, reinstates what the two other principles have only hinted at. It argues that we should abandon all *a priori* distinctions between natural (or technical) and social events, we should "reject the hypothesis of a definite boundary which separates the two." (Callon, 1986a: 200-1). Added to this, we should not pre-define or impose a pre-established grid of analysis on the categories used, the entities that are mobilised or the relationship between various 'actors'. Indeed, describing the changing interrelations between actors, whether human or nonhuman, is one of the issues at hand.

By using these tenets the actions of scientists (or any other actor, such as a public official or a pressure group campaigner) are treated not simply as carrying out something called 'science' (public policy or collective action). Instead, we should view such actors as attempting to extend their influence and power beyond the networks in which they are situated. For example, scientists attempt to extend their influences beyond the laboratory, into other social worlds, as well as conducting work that can be labelled 'scientific'. Indeed 'scientific' work is expanded to encompass a whole range of different activities. As such, in order to extend their influence,

scientists (or any actor) need to carry out 'heterogeneous engineering' (Law, 1987). This refers not only to the linking of differing social worlds, but also to the association of human and nonhuman entities to form patterned networks. This brings me to what in ANT is termed the moments of translation. Indeed Callon has called his work the sociology of translation (1986a).

However, before I turn to translation, something needs to be said about the vocabulary that is used in ANT. The second principle above argues for a new vocabulary that breaks away from the distinction between nature and society. ANT theorists wish to blur the distinction between "the really social and human-centred terms and the really natural and object-centred repertoires." (Callon and Latour, 1992: 347). In an attempt to do this a new vocabulary is proposed.

Actant is the term that Latour, and others, use for both human and nonhuman entities, and forms part of the vocabulary of the actor network or the non-modern constitution (1993). An actant is defined as any "entity able to associate texts, humans, nonhumans and money." (Callon, 1991: 140). By using the term actant instead of actor it is hoped that the boundary between the human and nonhuman will be blurred. An 'aim' of an actant is to carry out heterogeneous engineering in order to form heterogeneous networks.

Traditional Term	Actor Network Term
actor	actant
social relations	actor network
interaction	translation
discovery	negotiation
proof	immutable mobiles
data	inscriptions
social roles	delegation

Figure 2-1: A vocabulary for a new ontological status for society and things

The use of new terms maps out a new ontological status for society and things. Some of the terms, in this new vocabulary, are listed in Figure 2-1. I will define, and return to these terms, throughout this, and subsequent chapters.

2.2.2 Moments of Translation

Heterogeneous engineering involves carrying out practices that aim to entice other actors into a particular network, and is carried out through what has been termed

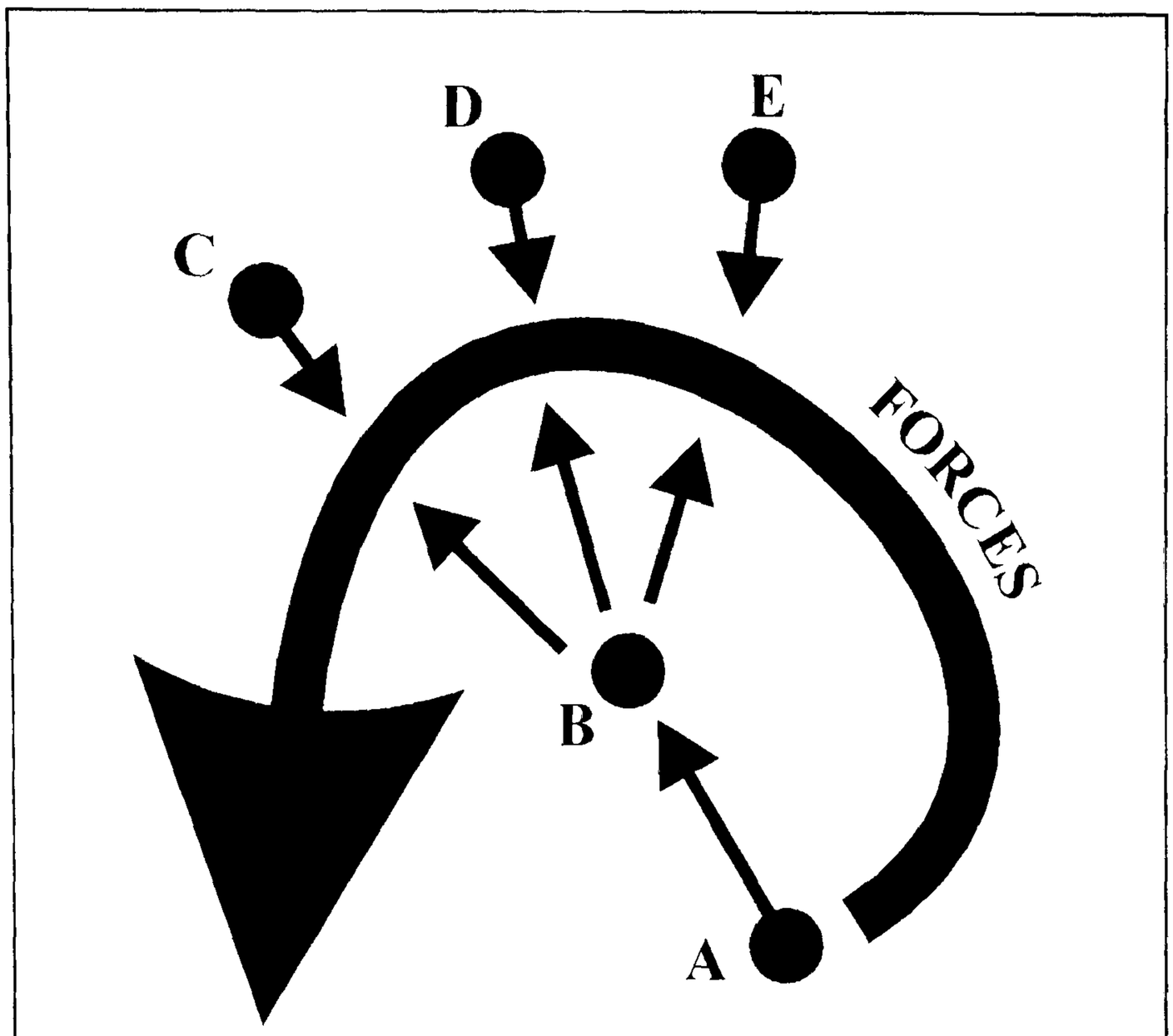
moments of translation. Before I describe these moments, we first need to be aware of what we mean by translation. Translation can broadly be defined as the process whereby "the identity of actors, the possibility of interaction and the margins of manoeuvre are negotiated and delimited." (Callon, 1986a: 203). The process of translation can be divided into a number of factors, it involves the translator, something that is translated, and a medium in which the translation is inscribed or mediated. To get a better understanding of translation I will now look at the moments of translation.

2.2.2.1 Problematization, Interessement, Enrolment and Mobilization

The aim of the moments of translation is to create a network of heterogeneous actors, and involves four moments or phases of translation. Although these moments are presented sequentially, it is important to be aware that they are not necessarily discrete moments and in a particularly study there may be some overlap between the moments (Arksey, 1998).

The first moment is that of problematization. It involves actors' preliminary attempts to determine a set of actors and define "their identities in such a way as to establish themselves as an obligatory passage point" (Callon, 1986a: 204). The process of problematization therefore involves two movements. Firstly, a particular problem is identified by an actor and how it relates to other actors. Secondly, the defining actor attempts to become indispensable to the targeted entities by defining themselves as the means by which the defined problem can be solved, and thus become the obligatory passage point. Singleton and Michael argue that obligatory passage points (OPPs) act as "unavoidable conduits - narrative bottlenecks - through which they [entities] must pass in order to articulate both their identity and their raison d'être." (1993: 229-230).

The second moment of translation is interessement. Problematization hypothetically sets up the identities and wants of other entities, interessement however, involves the "group of actions by which an entity attempts to impose and stabilize the identity of the other actors it defined through problematization." (Callon, 1986a: 208-209). Interessement entails "one entity attracting another by coming between that entity and a third" (Callon et al., 1986: xvii) as shown in Figure 2-2.



A uses various forces, anything from brute force to persuasion by the use of texts and other inscriptions, to interest B, by breaking existing ties that B has with C, D, E etc. (if they exist).

Figure 2-2: To show the elementary form of interessement

The means by which existing ties are broken and others re-established are unlimited. As Law writes, interessement may:

> "...operate through the medium of interests, but also via naked force, apparent inevitability, love, duty, bribery, physical fact, superior command of information, spirituality or lack of imagination."
>
> (Law, 1986: 71-72)

Particular examples of interessement devices include conferences, scientific papers and promotional material, although the precise devices will depend on the networks involved.

The third moment of translation is enrolment. Although enrolment is not an actual technique, it describes the success of interessement and the various multilateral negotiations that it involved. With successful enrolment comes the acceptance of identities and problems by those involved, the discontinuation of ties with other competing entities, and the defining actor becomes accepted as an obligatory passage point. It is however important to be aware that just because an entity has been enrolled, does not mean that it always will be.

The possible transient nature of enrolment leads us to a particular definition of power. Power should not be seen as something that can be possessed or stored, rather power is the "consequence of the energy given to the token by everyone in the chain who does something with it, as in the case of rugby players and a rugby ball." (Latour, 1981: 267). Therefore, when an entity becomes part of a network it is giving its power to that network. The multilateral nature of power involves both the "'capturing' of the other and the other's 'yielding'." (Singleton and Michael, 1993: 229). Further, it is only when an entity begins to lose its power that it realises that it was 'made of' the wills of others.

The fourth and final moment of translation is mobilization. This final moment can be seen as a consolidation of the previous moments, and the success of mobilization will affect the robustness of the network. Mobilization can be seen as the methods by which a small number of entities are able to silence and speak for others, or as Callon argues, "To speak for others is to first silence those in whose name we speak." (1986a: 216). For example, when scientists present their work at conferences they are acting as a representative of all the enrolled entities behind their work. However, for the entities to remain mobilized the enrolling entity will have to continually carry out translations to enable them to represent (silence) the enrolled entities. The aim of an enrolling entity is to construct a durable network, that is, a network that will not easily disintegrate. Indeed, the ability to form durable networks is dependent on the capacity of certain actors to interrelate both society and nature into a coherent network (Callon, 1986a).

One way in which actors become silenced is through the production of inscriptions. When scientists present their work at meetings, their work will be represented in the form of inscriptions. When presenting their work at a conference it is unlikely that the original scientists will repeat their experiment at the conference or seminar. Instead, scientists are more likely to present a number of graphs, figures, data sets and other textual representations, which simplify/obscure the translations. In order to produce

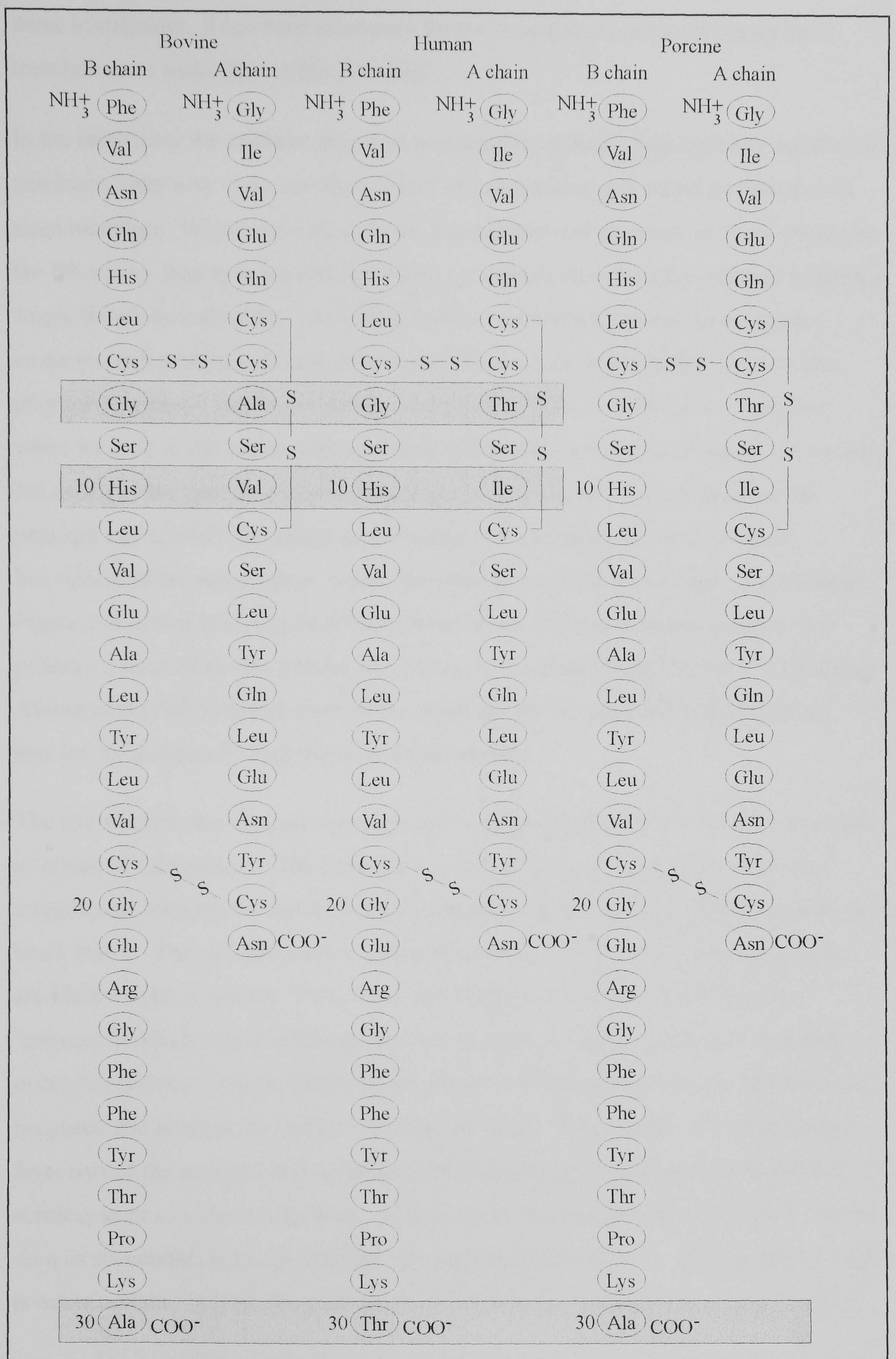


Figure 2-3: Amino acid sequences of three insulins

these inscriptions, it has been necessary for the scientists to carry out a number of translations to make the visible invisible.

In the laboratory the scientist may pass any number of entities through any number of machines, they may carry out any number of calculations and attend any number of team meetings. Where once all sorts of uncertainties and negotiations were visible in the laboratory they now become invisible; the complexities become silenced to form a single (black-boxed) entity. As Callon writes, "Out of laboratories come quarks, enzymes, and proteins, all new actants that did not exist before being brought into play by statements, tables, machines, or embodied skills." (1995: 54). Therefore, when we look at the amino acid sequence of a number of insulins (Figure 2-3) we are not aware of the specific chemical reactions and techniques used to separate the peptides and identify the amino acids, instead we are presented with a textual inscription of the end product. Other inscriptions are more explanatory, for example, Figure 2-4 (taken from Chien (1996)) shows some of the translations necessary to produce a form of human insulin, and Figure 2-5 (adapted from Office of Technology Assessment (1982)) shows some of the translations necessary in the development process for genetically engineered pharmaceuticals.

The site where heterogeneous elements are brought together or translated Latour calls a 'centre of calculation'. The laboratory is one such site. Through the laboratory complicated translations are performed to produce seemingly uncomplicated units or black boxes. The various entities within the network, that comprises these entities, are black boxed or hidden. Part of the sociology of translation is looking at the "process in which sets of relations between projects, interests, goals, and naturally occurring entities - objects which might otherwise be separate from one another - are proposed and brought into being." (Callon and Law, 1989: 58-59). These relations form part of the network that constitutes what comes to be 'known', or the product of science, such as scientific theories. In such cases 'heterogeneous engineering' can be seen as successful, although whether this heterogeneous network will always be stable is never certain. Indeed, the production of 'knowledge' is always under negotiation.

Inscriptions not only act as a form of simplification, but also as a means of acting at a distance. Enrolment can be more problematic when the enroler and the enrolee are

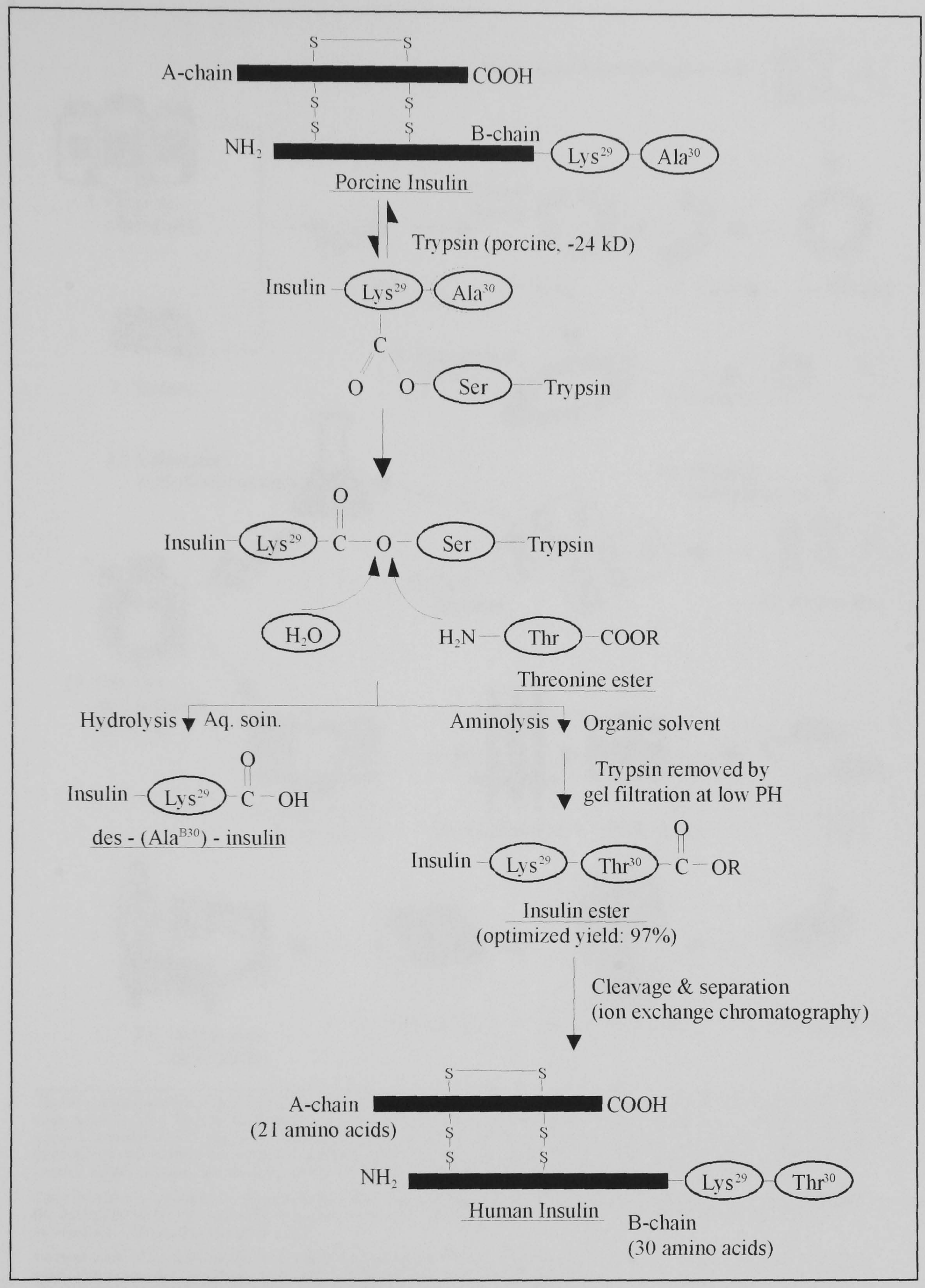
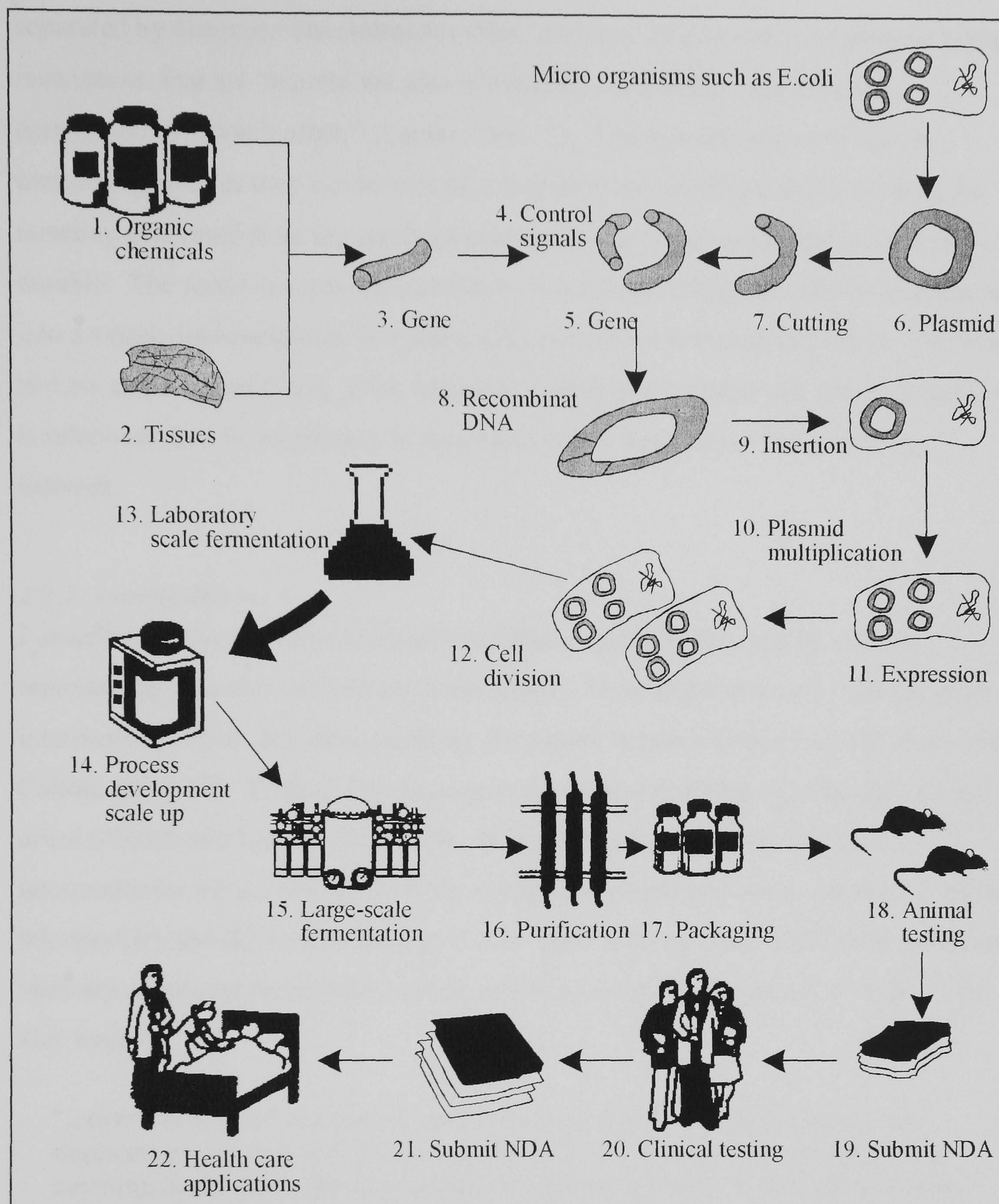


Figure 2-4: Procedure involved in the conversion of porcine insulin to human insulin by Novo Industri Nordisk (taken from Chien (1996))



The development process begins by obtaining DNA either through organic synthesis (1) or derived from biological sources such as tissues (2). The DNA obtained from one or both sources is tailored to form the basic 'gene' (3) which contains the genetic information to 'code' for a desired product, such as human interferon or human insulin. Control signals (4) containing plasmids (6) are isolated from micro-organisms such as E. coli; cut open (7) and spliced back (8) together with genes and control signals to form 'recombinant DNA' molecules These molecules are then introduced into a host cell (9).

Each plasmid is copied many times in a cell (10). Each cell then translates the information contained in these plasmids into the desired product, a process called 'expression' (11) Cells divide (12) and pass on to their offspring the same genetic information contained in the parent cell.

Fermentation of large populations of genetically engineered micro-organisms is first done in shaker flasks (13), and then in small fermenters (14) to determine growth conditions and eventually in larger fermentation tanks (15). Cellular extract obtained from the fermentation process is then separated, purified (16), and packaged (17) for health care applications.

Health care products are first tested in animal studies (18) to demonstrate a product's pharmacological activity and safety, in the United States, an investigational new drug application (19) is submitted to begin human clinical trials to establish safety and efficacy. Following clinical testing (20), a new drug application (NDA) (21) is filed with the Food and Drug Administration (FDA). When the NDA has been reviewed and approved by the FDA the product may be marketed in the United States (22)

Figure 2-5: The development process for genetically engineered pharmaceuticals (adapted from Office of Technology Assessment (1982))

separated by distance. One solution to this 'problem' of distance is to produce textual inscriptions that are "mobile but also immutable, presentable, readable and combinable with each other." (Latour, 1986: 7). Since inscriptions can also be immutable mobiles they can be moved, compared and combined without losing the meaning generated from the centre of calculation. In other words, the inscription is durable. The result is a text which because it combines a large amount of information into a simple representation, is a powerfully persuasive text (Latour, 1987). However, as Law and Michael (Law, 1994; Michael, 1996a) have pointed out, this immutability is relational, that is, its potency is dependent on the authority of the generating network.

2.2.3 Intermediaries

I described above the role of textual inscriptions and how they can be seen as representing a number of (hidden) translations. An inscription is one example of an intermediary which describes anything that passes between various actants (Law and Callon, 1992: 25). Further, this passing or circulation describes a particular setting[2] or event (Akrich and Latour, 1992: 259). By studying the circulation of these intermediaries we are able to study the relationship between various networks. Each intermediary should be seen as a *particular* 'point of view', and when these points of view are circulated researchers become aware of a particular version of 'truth'. As Star writes:

> "...every viewpoint is a part of some picture, but not the whole picture. The implications are that only in the articulation of viewpoints can we understand anything about truth, that is a fundamentally interactional, social phenomenon."
>
> (Star, 1991b: 278)

Callon (1991) argues that there are four main types of intermediary, as shown in Figure 2-6 with examples. It is crucial to realise that intermediaries are likely to be networks (or their representatives), even though they may be represented as a single (or singularized) artefact. For example, a scientific paper is comprised of a collection and representation of many entities, actants and intermediaries. As with inscriptions, the effect of intermediaries is dependent on the (continued) authority of the generating network.

---

[2] Assemblies of humans and nonhumans where the competences and performances are distributed. It is these assemblies that is the object of analysis (Akrich and Latour, 1992: 259).

Intermediary Type	Examples
Texts (literary inscriptions)	Reports, books, articles, floppy discs etc. Scientific articles, Balance and IDDT magazines.
Technical artefacts	Scientific instruments, machines, robots and consumer goods. Human insulin, syringes, and blood glucose monitoring equipment.
Human beings	The skills, knowledge and the know-how that they incorporate. The skills a diabetic possesses in order to maintain a healthy body.
Money	In all its forms.

Figure 2-6: Types of intermediaries

In the definition of an actant above, I pointed to the circulation and generation of intermediaries, in the form of texts, humans, nonhumans and money. There is an important distinction between intermediaries and actants. Intermediaries can become actants when they are able to generate other intermediaries. For example, when human insulin is passed between the doctor and patient it is an intermediary. However, if the patient then experiences problems on human insulin, and speaks to their doctor, clinic or other diabetics about their problems, then human insulin becomes an actant. Another example is the insulin pen. An insulin pen is an insulin injection device, about the size of a pen, which includes a needle and holds a vial of insulin. Using the pen set insulin doses can be administered, by the diabetic, in a convenient way. When passed between the patient and doctor it is an intermediary. However, if, because of its convenient method of insulin administration, it enables the diabetic to do things they were unable to do using a traditional syringe, it becomes an actant.

However, as Callon points out, "the division between actors and intermediaries is a purely technical matter" (1991: 141) and is dependent on the focus that the researcher chooses to take. We may look at a scientific paper and study how it affects other actors, in which case it is an actant. On the other hand, we could look at scientists in general and how papers are constructed, published and circulated, in which case the paper passes between various groups. Michael makes the interesting point, taken from Law (1994), that deciding whether an entity is an intermediary or an actant is "essentially a question of who/what can 'persuade' us that they comprise such a locus

of agency" (Michael, 1996a: 55).[3]

I have now given an outline of the main base of actor network theory. In the next section I would like to describe some of the studies that have been carried out under the auspices of ANT. I have two aims: to illustrate the concepts of ANT in detail, and to outline some additions and modifications to ANT.

2.2.4 New and Old Studies

One of the most often cited papers on actor network theory is Michel Callon's (1986a) study of the fishermen of St Brieuc Bay in France. He describes how three scientists wished to develop a conservation strategy for the scallop (the Pecten Maximus species) population of the bay. At the time of the study the stocks were becoming depleted due to over-fishing. In order to develop the conservation strategy it was necessary for the scientists to interest a number of key groups: local fishermen (not to over-fish); the scallops (to reproduce more frequently); and the scientific community (to agree with, and support, the methods proposed by the three scientists).

What followed was a process of problematization where the identities of the three principle actors were defined. The fishermen where defined as needing to 'assure a long-term profit'; the scallops as wanting to 'perpetuate themselves'; and scientific colleagues as wanting to 'increase knowledge about Pecten Maximus'. Importantly, it was the scientists who set themselves up as the pathway, the obligatory passage point, by which these aims could be achieved. In the second moment of translation, interessement, the scientists had to separate the various actors from their existing ties using a number of different interessement devices. With the use of towlines scallops were (physically) disassociated from those actors that threatened them. For the fishermen, the interessement devices included texts and conversations, which attempted to persuade the fishermen not to over fish. The researchers also produced graphs, charts and data to persuade the scientific community that the techniques that they were employing would work.

---

[3] Taken a step further, we can argue that entities are literally persuading us of their power and importance. Indeed, why do any of us investigate certain areas and not others? Why do we identify with particular theories and methodologies and not others? In each case we are persuaded of their importance. We are persuaded to investigate certain areas of society because of our belief that this area has had an influence on other areas of society. We use particular theories and methodologies because they persuade us that they are able to produce something credible.

For the first year or two the scallops did reproduce more frequently, the fishermen did not over-fish, and the scientific community did not openly question the research team. In other words, the various actors had been enrolled. Further, the research team can be said to represent the 'wants' of the various actors involved. However, on one Christmas Eve the fisherman over fished. Added to this, other scientists began expressing doubts over the researchers' theorising about 'sustainable development' (Arksey, 1998: 202) and the scallops stopped reproducing.

This example illustrates the nature of power. For the research group, their power was made up of the wills of the fishermen, scallops, and the scientific community. Yet when the enrolled groups no longer followed their defined 'wants' they removed their will from the scientists, at which point the scientists could no longer claim to be 'acting on their behalf.' Although Callon portrays this as a betrayal, we have to recognise that it may well have been that the fishermen always had some unexpressed doubts over the scientists techniques. Perhaps this is illustrated by their lack of involvement in the work of the scientists, Callon writes:

> "They [the fishermen] watch like amused spectators and wait for the final verdict. They are prepared simply to accept the conclusions drawn by the specialists. Their consent is obtained (in advance) without any discussion."
>
> (Callon, 1986a: 213)

We need to be aware that there may be other influences that affect the collapse of a network. Wynne (1992) has pointed to the power struggles that go on within wider culture, by which I mean the discourses that permeate across networks, such as the 'need to provide for your family'. Importantly, "it is possible to focus upon these big cultural factors as they are realised in the identities of actors" (Michael, 1996a: 157). The key point here is that we should be aware of the cultural backdrop or grounds to such micro-processes (although this is something that ANT researchers might dispute) (Michael, 1996a: 157).

Pressures originating from the cultural backdrop may not show themselves within a particular network until some specific point, when they may be perceived, by the analyst, as a betrayal of that network. It may be no coincidence that the fishermen decided to over fish on Christmas Eve, when it can be argued that there were extra economic pressures, from wider culture, to provide for their families. Therefore, the

movement from acquiescence to betrayal may not reflect a binary opposition. Work by Singleton and Michael (1993) has shed light on this feature, and this is where my attention now turns.

From reading earlier actor network accounts the reader can be forgiven for seeing networks as being "nested one within the other." (Lee and Brown, 1994: 784). However, other work has shown that networks are not necessarily clean and clear, but rather, the appearance of this (temporary) crispness is the result of the "singular flow of the narrative of a particular study." (Singleton and Michael, 1993: 232). As a result some authors have suggested that networks should be seen in terms of ambivalence and marginality.

Singleton and Michael (1993) carried out an analysis of general practitioners' (GPs') discourses around the UK Cervical Screening Programme (CSP). The study describes how GPs were enrolled into the screening program with particular identities, such as ambassadors of medical science and skilful providers of the cervical smear test. However, other elements that did not enter into the CSP actor network entered into the GPs' network. For example, the CSP network represents an unproblematic circuit of associations: women-GPs-laboratory-GPs-women. In this network women present themselves unproblematically to doctors. Thus, within this network there was not a place for unco-operative women, that is, those who consistently do not attend their screening test.

Another point is that GPs 'complexify' and problematize themselves in order to ensure that they are seen as important actors within the CSP. For example, at times GPs stressed their autonomous role in interpreting smear test results that came back from the laboratory. Yet, at other times, when they wished to stress the efficiency of the CSP program, they represented the laboratory as the 'source of true knowledge about cervical smears.'

Singleton and Michael view GPs as 'internal network builders' who construct their own GP Cervical Screening Programme within the governmental programme. This new network does not totally disregard the definitions of the governmental screening program, nor does it totally accept all its definitions, as Singleton and Michael write:

> "To overstress uncertainty and multiplicity would be to endanger the governmental CSP and undermine the GP role; yet, to follow unflinchingly the government's model of the GP role would be to render that role unworkable..."
>
> (Singleton and Michael, 1993: 259)

Importantly, this ambivalence may help us to understand that betrayal and defeat are no longer dramatic events. Instead, betrayal should be seen as the result of a "congealment of a disparate array of ambivalences into a focused pattern of resistances" (Singleton and Michael, 1993: 259). In previous actor network studies these ambivalences would usually be 'out of focus', only to appear later as a betrayal that seems to come 'out of the blue'.

It is also important to realise that some actors may be marginal but not silent. For GPs marginality was internal to the relevant network, however another form of marginality stresses exclusion of a network from the target network analysed by the theorist (Star, 1991a). Michael and Birke (1994) use the example of pro-animal experimentation scientists who refer to various 'others', such as the cosmetic industry and pet owners, to represent themselves in a more positive light. The exclusion is something that is actually constructed, as Star writes, "Every enrolment entails both a failure to enrol and a destruction of the world of the non-enrolled" (1991a).

From the point of view of objects themselves, it is interesting to look at a novel paper by Bruno Latour, which looked at the sociology of a door closer (1988; 1992). In the paper Latour describes how a, "'purely' technical artifact [the door closer] is a highly moral, highly social actor that deserves careful consideration" (1988: 298). He describes how a door, a nonhuman, carries out a number of tasks that could be carried out by a human, for example, doors allow people through them and also prevent people (noise, rats and dust) to go through them. If the door was not there, every time a human wanted to go through a wall, s/he would have to dismantle the wall and then rebuild it to prevent others from passing through it. As a general descriptive rule Latour tells us that:

> "...every time you want to know what a nonhuman does, simply imagine what other humans or other nonhumans would have to do if the character was not present."
>
> (Latour, 1992: 229)

There is however another problem with doors, they can be left open. One solution

would be to employ a doorman or groom to open and close the door. Such a solution may lead to other problems, for example, the groom would need to be trained and disciplined, s/he may fall ill, and it would be costly. However, it is possible to fix a door closer (a nonhuman groom) to the door to do the opening and closing. Through looking at the door closer Latour has shown that simple, mundane artefacts should have a place within social theory.

Latour's study of the door closer is relevant to my work because it illustrates how it is possible to study a 'mundane' artefact. Further, it also illustrates how various translations occur to alter the characteristics of an artefact, to redefine its meaning. For example, a door closer may allow people to pass through the door, but may also prevent those unable to open the door to pass through the 'gap in the wall'. In such cases then, the door is a barrier to the disabled or those carrying packages: as Langdon Winner may say, 'artifacts have politics' (1985). However, with the use of weight detectors and electronic motors, anyone may be able to pass through the 'gap in the wall'.

However Bijker asks, 'Whose politics do artifacts have?' (1995). It is choices made in the design of artefacts that instil politics into artefacts. These choices affect the way that 'others' can engage with this artefact. One of the aims of the researcher is to study who gives what politics to an artefact and to unravel the negotiations that were necessary for an artefact to have particular features. It is also important to study how these features may sometimes change. I will show later in this thesis how the meaning of human insulin changed due to various translations.

As a final example of work carried out under the auspices of ANT, I would like to look at the case of the metered dose inhaler (Prout, 1996). The metered dose inhaler (MDI) is used in the treatment and management of asthma by supplying the patient with therapeutic substances when needed. The MDI has advantages in that: it can deliver a dose direct to the lungs and so is absorbed quickly; patients report relief of symptoms with few side effects; the device is easy to use; and patients appreciate the controlled dose (Prout, 1996: 205). Importantly however, studies have shown that the substances in the MDI can be dangerous. The drugs contained within MDIs have an effect on the heart and a large dose can cause arrythmia and a risk of death.

In order for the MDI to be seen as successful it needs to balance two contradictions: on the one hand it needs to deliver measured therapeutic doses at the appropriate time; on the other hand, access to these substances has to be restricted since they are potentially dangerous. Prout argues that the MDI 'stands in for' (what Latour calls delegation (1992)) biomedical control by encoding the ability to meter a dose within the MDI. Importantly, it is necessary for the MDI to give autonomy to the patient, but also restrict access to the therapeutic chemicals in the MDI to a biomedically pre-determined quantity. Prout also points out that the device works to reduce criticism of biomedicine, by providing a device that helps asthma sufferers who were previously unhappy with existing therapeutic devices (1996: 207).

Prout also describes how the user needs to be configured to use the inhaler. It was found that many users were not getting the full benefit from the MDI because they were using it incorrectly. A number of attempts were made to enable patients to use the MDI better, for example, instructions were given to patients, some physicians began to teach patients to use the MDI, and variations on the original MDI were produced. These activities can be seen as attempts by the enrolling network to maintain enrolment. Without such activities the MDI would not help asthmatics, and so the medical profession would lose some of its authority.

What the study also illustrates is how a "whole series of natural, technical and human elements are brought together and packaged into a particular device" (Prout, 1996: 213). The package includes: the inhaler with its therapeutic substances; the clinicians and other medical professionals; and the user and his/her competencies.

In this section I have described some of the main principles behind ANT. As should be clear, one of the important features is that we should not divide the human and the non-human. Instead, society is made up of heterogeneous networks which are the result of various acts of translation by actants. The aim of the analyst is to describe under what circumstances these heterogeneous networks are formed, and how the needs and wants of the actants involved are translated and defined. I would now like to look at some of the methodological and theoretical considerations within ANT.

2.3 METHODOLOGICAL AND THEORETICAL CONCERNS

Within ANT one particular methodological concern is the identification of actants.

ANT has mostly concentrated on 'powerful' actants, and as a result, there has been a tendency to neglect the oppressed and underrepresented in society. Although, as Law points out, when studying 'powerful' actors we are not so much celebrating but deconstructing them. When studying actors we are interested in the alliances of heterogeneous materials that enabled an actor to become a powerful actor (1991). One reason for the concentration on powerful actants, by researchers, could be that some actors are able to silence the less powerful, or as Callon claims, "successful translation quickly makes us forget its [an actant's] history." (1986b: 28). This, of course, does not completely answer the question, since we do not have an account of how the oppressed in society manage - how they might mobilize, as it were, counter-networks.

Indeed Law (1991) suggests that it is dangerous to concentrate on the heroes, and asks the question: How is ANT to give a voice to marginal actors? Star (1991a) points out that these marginal actors are never completely lost, and may lurk in the background informing enrolled actors, indeed, "We are all marginal in some regard, as members of more than one community of practice" (Star, 1991a: 52).

As Arksey (1998) has pointed out, the vast majority of actor network stories have concentrated on the 'heroines' of the story. This may be because many studies have been concerned to explain the power of scientists (Arksey, 1998: 202). Arksey's book looking at the network-building accomplishments of the relatively powerless, sufferers of RSI, attempts to counter this imbalance.

Another concern is that in dealing with human and nonhuman actors we could be swamped by the number of available actors; as Rachel wrote, "I was paralysed by the choice of actants to follow - humiliated by their agility - confounded by their constantly changing forms." (1994: 810). Therefore, for practical reasons, it is necessary for a researcher to justify why particular actants have been included, as no particular study can include all those actants that may be involved in a particular story. Within ANT there is also no final analysis, as Lee and Stenner, referring to Strathern (1996), have pointed out:

2.3 Methodological and theoretical concerns

> "...there is no final word, no line to draw under an analysis to bring it to a close, no necessary completion of accounts. Thus there is no necessary end to the elements that may contribute to a network, no general criteria by which ANT may bring an end to the list of what belongs and what is responsible."
>
> (Lee and Stenner, 1999: 93)

Indeed we are only telling a 'story', that is, just as scientific accounts of science are 'stories', so is the work of academic theorists. The work has to be a story because another researcher, studying the same episode, may produce a different account. Latour and Woolgar call this the 'problem of fallibility', in which "all forms of description, report, observation and so on can always be undermined" (1979: 282). This includes my own.

If there is no 'final' interpretation, then why should we accept that of the analyst? As Collins and Yearley argue, if a researcher wants to speak on behalf of an entity:

> "He [*sic*] must show a firm grip on the nature of the scallops [entity]...In fact, we readers would prefer him to be more of a scallop [entity] expert than the others [other experts] if he is to speak authoritatively on the subject."
>
> (Collins and Yearley, 1991: 316)

However, I would argue that it is a knowledge of the heterogeneous networks that is important, of which the scallops, or any object or human, is only one part. As an actor network theorist I must show knowledge of all the 'implicated actors'.

Some have argued that, "The language changes, but the story remains the same." (Collins and Yearley, 1991: 315). Thus, Collins and Yearley argue that actor network theory simply re-describes what could be said in another way. They claim that an actor network account can look like the account of a conventional historian of science (Collins and Yearley, 1991: 315n.14). From this view it does not add anything new to science studies.

Yet, it is necessary for actor network theory to change the language for the very reason that the original language, of the social sciences, does not do justice to the heterogeneity and relationality of the world. As noted above, it is argued that by using the same language for both the human and nonhuman we are able to criss-cross the human/nonhuman divide, and "so hope to overcome the difficulty of siding with one, and only one of the camps" (Callon and Latour, 1992: 354).

Further, it is argued that everyone in society deals with heterogeneous networks, that is, we are all heterogeneous engineers who "seek to associate entities that range from people, through skills, to artefacts and natural phenomena." (Law, 1987: 129). In a sense ANT sets itself above other theorists. Although we all deal with heterogeneous networks, it is those who believe in generalised symmetry who have the theoretical means to give non-humans their 'rightful' voice in society. It is those who use ANT who are able to fully accept the nonhuman - they are able to follow the 'rules' of liberal democracy. For Latour and others, liberal democracy does not just include the human, but also the nonhuman. As a result, to follow the rules of liberal democracy means giving an equal voice to the missing masses - the nonhumans. This brings me to the politics of ANT.

As already mentioned, ANT does not claim a separation between the human and the nonhuman. Latour has argued that if we believe in liberal democracy, if we believe in equality, then there is no reason why we should discriminate between the human and nonhuman. As Latour writes:

> "You discriminate between the human and the inhuman. I do not hold this bias (at least not this one) and see only actants-some human, some nonhuman, some skilled, some unskilled-that exchange their properties."
>
> (Latour, 1992: 236)

Although Lee and Brown (1994) argue that there are many vocabularies to choose from, it is one of liberal democracy that has been the most popular amongst actor network theorists. We are however caught in a kind of logical trap:

> Do you believe in liberal democracy?
> Should it be applied to *all* parts of society?
> Then you must believe in actor network theory.

We are, in theory, caught within the trap on all levels. Who could, in principle, deny the concept of equality and liberal democracy (the first statement), once we accept this then we cannot deny the second, since it means we deny the idea of liberal democracy (the first). We are then led to agree with the final statement. If we do not accept that liberal democracy should be applied to all parts of society, then we are denying a version of liberal democracy itself. Of course, this is dependent on the definition of 'society'. For Latour and others, society consists of not just humans, but nonhumans as well. In their version of liberal democracy all actants, human and

nonhuman, have a place, a voice, in society.

As a result of these steps there is a "foreclosure on all alternative descriptions of the world through the assertion of total democracy and complete ontological monadism." (Lee and Brown, 1994: 781). Indeed Latour has claimed "We will never do any better." (1988: 231). I would prefer to be more cautious, and follow Joan Fujimura (although not talking particularly about ANT), when she argues that, "There is no finally stable ground on which any of us...base our stories" (1991: 237). However, Callon and Latour do not claim to be totally contented with their theory, as they write:

> "We believe...that although it is experimental, uncertain, and incomplete, it should be carried all the way, with the help of the many clever and excellent scholars inspired by the various science studies schools..."
>
> (Callon and Latour, 1992: 367)

Indeed, a number of theorists, from a number of disciplines, have carried out work within an ANT framework, for example: human geography (Murdoch, 1997); management (Busch and Juska, 1997; Soderbaum, 1993); and health (Arksey, 1998; Prout, 1996; Singleton and Michael, 1993). Murdoch points out that one reason for this is that, "human geographers and sociologists have begun to focus on the prospects for theories without dualisms." (1997; p. 731).

An obvious question that arises within ANT is: Where is the account from the nonhumans? Or as Collins and Yearley have asked: 'Just how radical is the symmetry?' Collins and Yearley argue that from a truly radical point of view we would need to hear an account from the scallops or from the electric vehicle. Does the fact that we have no account of human insulin written by e-coli affect radical symmetry? Collins and Yearley argue, "Fortunately we do not need an answer to these questions before we continue our analysis." (1991: 313n.13). However, one answer is that when scientists talk about their work they talk about nonhumans, since it is central to their work. As Callon and Latour write, "Scientists never exist simply as people talking among people about people" (1992: 353).

It has also been pointed out that:

> "...the notion of symmetry elides a critical examination of how and why some entities are assigned to one end of the continuum, whereas others are assigned to the opposite end."
>
> (Casper, 1994: 845)

That is, we have already decided that DNA fingerprinting, scallops, human insulin and countless other entities, are nonhuman at the outset without examining their constitution. Latour argues that this separation occurs in society through the process of purification (1993). The process of purification creates two "entirely distinct ontological zones" (Latour, 1993: 10), which compose part of the modern constitution. However, as Latour points out, "The constitution explained everything, but only by leaving out what was in the middle." (1993: 47). This 'middle' comprises hybrids, quasi-objects and quasi-subjects (Latour, 1993) or what Haraway (1991) calls 'cyborgs' and 'tricksters', which form part of our everyday life. One of the aims of actor network theory is to open up the purification process by 'following the actors'. By following the actors we are able to elaborate just how human and nonhuman entities attained their respective status. It may then be possible, contra Casper, to describe how and why entities have been purified into two extremes.

We should also be aware that the purification of society into a nature and society pole means that we are not generally aware of the hybrid nature of entities. Humans exist within networks made up of both the human and nonhuman, just as nonhuman objects are. As Latour writes:

> "We are never faced with objects or social relations, we are faced with chains which are associations of humans (H) and nonhumans (NH). No-one has ever seen a social relation by itself...nor a technical relation...Instead we are always faced with chains which look like this H-NH-H-HN-H-HN..."
>
> (Latour, 1991a: 110)

Indeed, one of the aims of the actor network theorist is to 'bring out' the nature of these hybrids or networks; to describe how they are constructed; how identities are defined; what is needed to maintain these networks; and under what conditions such networks break down. In sum the aim is to make the invisible visible. By doing so we are able to demonstrate the way hybridity is composed of both the social and the natural, and the human and the nonhuman. The argument is not that we are creating something that doesn't exist, rather, we are showing how parts of society become invisible or visible. As Susan Leigh Star writes, of what Anselm Strauss has taught

us, "Visibles are not automatically organized into pregiven abstractions. Someone does the ordering, someone living in the visible world" (1991b: 265).

2.4 PROGRAM OF ACTION

Now that I have presented an overview of ANT, I would like to describe one particular facet of this approach that I will be using throughout my research. I will adopt and expand the work of Akrich and Latour and their symmetrical vocabulary for describing human and nonhuman assemblies (1992). I am particularly interested in this work because although it has been broadly used in a number of studies (Latour, 1992; Akrich, 1992; Latour et al., 1992), it has not been fully developed. From my reading, the symmetrical vocabulary for describing human and nonhuman assemblies has not been used extensively. Although work has drawn on this vocabulary, it has not been used to describe the changing nature of human and nonhuman assemblies. In particular, I am interested in using this vocabulary to describe the resistances and negotiations that occurred around a particular artefact, namely human insulin.

I described above how an enrolling actor defines a particular set of identities, problems and solutions through the moments of translation. In particular, the enrolling entity defines itself as the point of passage through which defined objectives can be achieved. With successful enrolment the defining entity can be seen as the spokesperson for the network; for example, when a union representative is campaigning for increased wages, he/she is acting on behalf of those workers who are members of the union. However, enrolling entities are likely to speak 'in different ways' to different potential 'enrolees'. When a pharmaceutical company wishes to interest the medical profession it may talk in terms of the health of individuals and patient care. However, when the same company's board meets one of the aims discussed is likely to be increasing profit.

Networks therefore, usually have more than one aim. In the St. Brieuc Bay case study, the aims ranged from increased reproduction for the scallops to long-term profits for the fishermen. Although these aims existed simultaneously within the network, they were not all defined as applicable to all entities within that network, i.e. the scallops were not defined as being worried about long term profits. These simultaneous aims can exist side by side, unless there is some great disparity between

the aims.

These aims we call a program of action.[4] The program of action can range from something as simple as a hotelier wanting guests to return their keys (Latour, 1992), to the aims of multi-national corporations. Importantly, the defining of a program of action is dependent on the point of view taken by the analyst, for example, a hotelier may wish guests to lock the door after them, while guests may wish easy access for their friends.

The fact that the programs of action of different entities are not the same, suggests the notion of an antiprogram. An antiprogram is any program of action that is in conflict with another program of action, taken from the point of view of the analyst (Akrich and Latour, 1992), or the holder of a given program. It is important to stress that an antiprogram is not judged against some 'objective' scale of the 'way it should be'. Instead, the antiprogram is judged against a particular definition of the social world that has been proposed by the potentially enrolling network. It is this network that defines 'the way it should be'. Akrich and Latour point out that "what is a program and what is an antiprogram is relative to the chosen observer." (1992: 261).

Latour often uses the example of the Berliner key[5], where the hotelier wishes that guests close and lock the main door behind them. This is the program of action from the perspective of the hotelier. From this perspective guests may wish to have easy access through the door (for friends, for example) and in some cases may leave the door open, this is the antiprogram. However, from the point of view of guests, the program could be that they wish to have easy access through the door, and the need to open and lock the door is an annoying antiprogram.

Of crucial importance when looking at programs and antiprograms is the function of intermediaries. I described above how one of the features of translation is the necessity of a medium in which translations are inscribed. These mediums are what we call intermediaries and can come in many forms - texts, technical artefacts, human beings and money. When we look at a program of action we can describe the intermediaries that are put in place in order to ensure compliance with a particular

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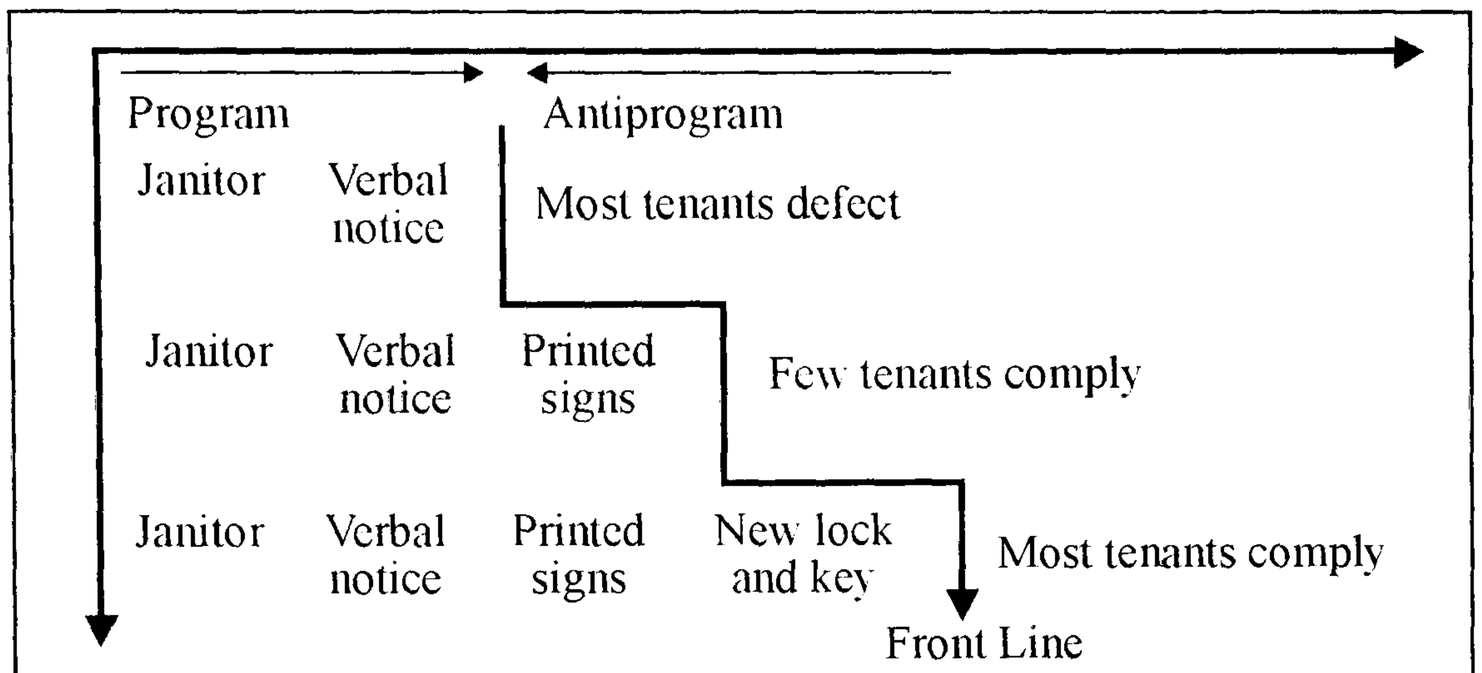
[4] Latour has also used the word 'programme' (Latour et al., 1992) to describe the same approach. In my thesis I have adopted his most frequently used word, that of program.

[5] For the complete story see Latour (1991b) and also Latour (1992) and Latour et al. (1992).

program of action. By studying the flow of intermediaries we are able to map the division between programs and antiprograms, what Latour and others call the 'front line' (Latour et al., 1992). As a researcher we are not only interested in the movement of the front line, but also in what intermediaries are circulated, by whom, their content, and the intended audience. When there is no front line, there is no perceived controversy in a given situation.

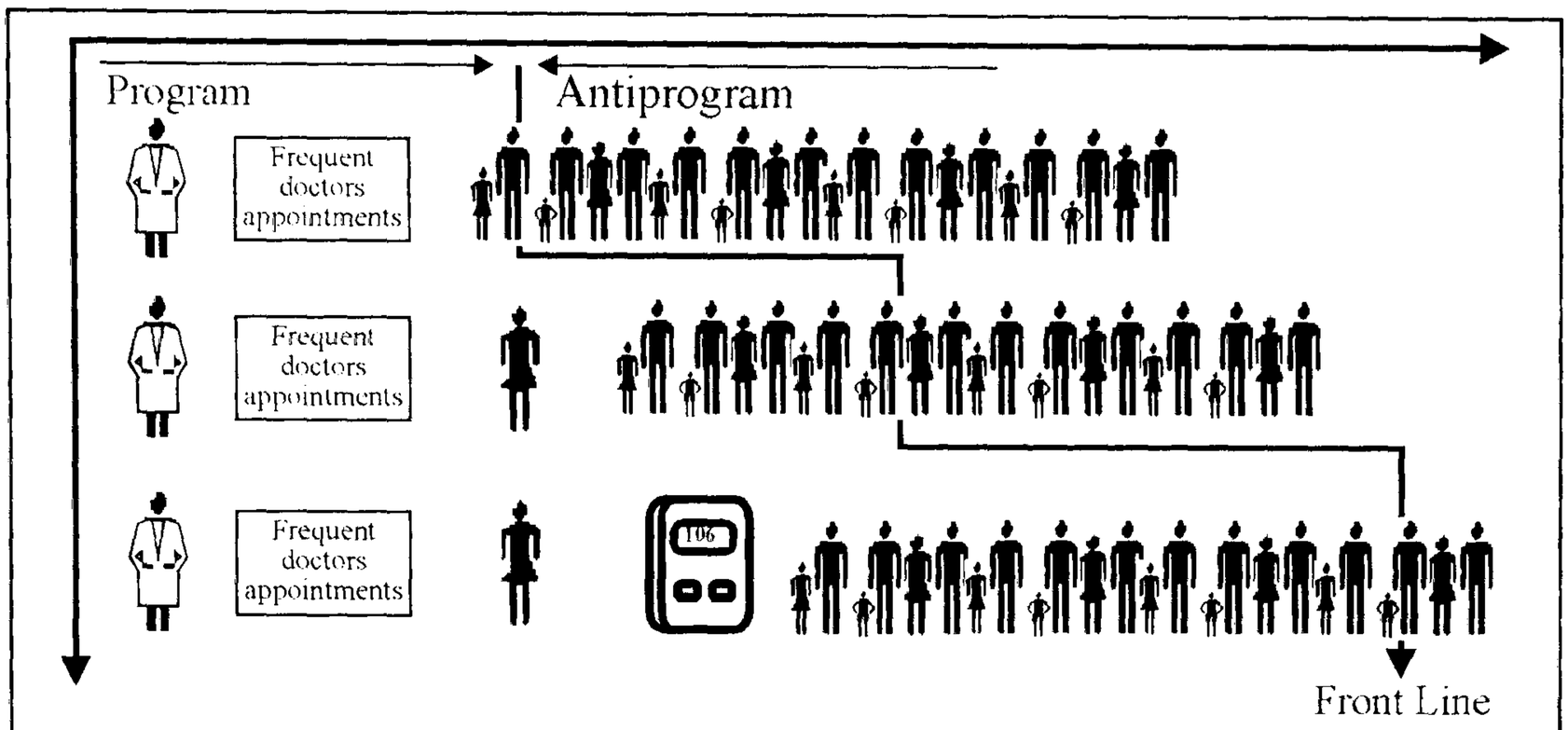


The janitor successively adds oral notices, written notices and finally a new lock and key to modify the attitude of his/her guests. Finally, most tenants comply and lock the door after them.

Figure 2-7: Programs, antiprograms and the front line

If we look at Figure 2-7 we can see that the janitor wishes guests to lock the door after them, yet most guests do not follow this program of action. At successive stages the janitor uses different intermediaries to compel guests to follow his or her own program of action. In the first stages, the network can be seen as having little durability. Although the janitor has defined that guests should close the door, they have not done so; in other words they have not been enrolled. However, through a string of intermediaries the front line is reduced, that is, more tenants comply to the janitors wishes. The intermediaries that are used "to cope with the contradictory demands of many antiprograms" (Akrich and Latour, 1992: 262) are called re-inscriptions. Re-inscription is, in principle, the same thing as inscription. However, whereas inscription occurred at the outset, by the engineer, inventor, manufacturer, or designer, re-inscription occurs when two differing programs of action meet (by very definition, a program and a related antiprogram). Since re-inscription occurs when there are conflicting programs, it should be seen as a feedback mechanism, which is the response to a particular antiprogram. Re-inscription should also be seen as a

complication, since it involves the introduction of more intermediaries and so the total number of assembled human and nonhumans will increase. The complication not only occurs because of the increased size of the setting, but also because these new entities have to be maintained (kept within) the setting.



The doctor wishes that his/her diabetic patient follows a particular program of monitoring in order to maintain the patient's health. She/he does this by using frequent appointments to assess the patients control. informs family members of the risks. and suggests the use of home monitoring equipment.

Figure 2-8: Ensuring a diabetic follows a particular diabetic routine

A similar complication may occur with newly diagnosed diabetics. Various intermediaries may be used to ensure that patients follow a particular diet, or maintain a steady blood glucose level (Figure 2-8). In cases where care groups are campaigning against a particular drug they may attempt to re-inscribe the description of the drug from 'without side effects' to 'with side effects'. In the case of prescription drugs we can say that there is a medical/institutional program of action for that drug. However, in some cases care groups attempt to re-define this medical/institutional program of action to one that is more in line with their own program of action. Success may occur when the pharmaceutical company is forced to withdraw the drug, forced to print warnings of possible side-effects on the product's packaging, or doctors become more strict about prescribing the drug.

One question that we need to ask is: When is an inscription a re-inscription? A re-inscription can be seen as something that is added to an artefact that has been 'black boxed', that is, when it has left one network to go to another. As I described above, inscription is carried out by engineers, scientists, inventors, manufacturers, or

designers. When scientists, or whoever, inscribe a vision of the world into an artefact they produce what has been called a 'script' or 'scenario' (Akrich, 1992). Just like a film script, artefacts define a structure or framework of action for the actors involved, and a space in which they are supposed to act (Akrich, 1992). This 'script' is the result of inscription. Inscribers hope to persuade human and nonhuman actors to act out this 'script'. However when, from the point of view of the original inscriber, the script is not followed, then some kind of re-inscription is necessary.

Akrich and Latour have argued that "the choices made for the re-inscription defines the drama, the suspense, the emplotment of a setting" (1992: 262). In other words, re-inscription is the dynamic transformation of a silent artefact into a polemical process (Latour, 1992: 258n.25). Researcher study the process by which black boxed inscriptions or silent artefacts come to be re-inscribed. However, we also have to be aware that where once a particular movement was seen as a re-inscription, it can, in time, be seen as an inscription. Take for example the mixing of different strength insulins. Originally this was carried out by the diabetic at the time of injection, and so was a re-inscription. However, it is now more common for diabetics to use premixed insulin, which is an inscription for the diabetic.

Therefore (re-)inscription is a continual and dynamic process. As each re-inscription is carried out on an artefact, it may change the meaning of that artefact. For example, when medical drugs are being produced for consumption they need to go through a number of networks (e.g. regulatory bodies, clinical testing, marketing and the media) at each of these stages the meaning of the artefact may change. One of the aims of a network is to be able to control or predict the re-inscriptions that may occur around an artefact. For example, a pharmaceutical company does not want to employ resources on developing a new drug only to have its application for a licence refused.

It is also important to understand what is actually inscribed in artefacts by those who designed them. Obviously inscribers need to be very aware of those who will eventually use an artefact so that the chance of re-inscription is kept to a minimum. Akrich and Latour (1992: 261) define two dimensions to these inscriptions - prescription and proscription. Prescription refers to what an artefact allows from the human and nonhuman actants that it anticipates, while proscriptions refers to what an artefact disallows. In order to illustrate this, I will use self administered insulin as an

example.

Insulin decreases the amount of glucose in the blood, by promoting its uptake by cells. Therefore, through the administration of insulin, a diabetic is able to control the levels of glucose circulating in the blood stream (prescription). As a result, insulin allows diabetics to live a relatively 'normal' life. However, the administration of insulin does not allow a diabetic to take large amounts of insulin that can be stored in the body for days. Neither does it allow a diabetic to ignore their diet or take spontaneous exercise without careful consideration.

When we wish to describe the prescription and proscriptions of an object there are a number of places in which they can be found. In those artefacts that are black boxed they can be found in user's manuals and contracts, or we can study disputes or look at what happens when artefacts go wrong (Akrich, 1992: 210). For example, insulin packaging contains a leaflet about the insulin, describing such considerations as side effects, storage of the insulin, interactions with other medicines, and how to correctly take the insulin. From reading such a leaflet we could construct a list of prescriptions and proscriptions of a that artefact.

Another important feature of an artefact is its pre-inscriptions. Pre-inscriptions can be described as:

> "...all the work that has to be done upstream of the scene and all the things assimilated by an actor (human or nonhuman) before coming to the scene as a user..."
>
> (Latour, 1992: 257n.16)

In our insulin example, a doctor or nurse may have explained to the diabetic something about diabetes, insulin and how to inject themselves. This will especially be the case for newly diagnosed diabetics. Therefore, when a diabetic uses their insulin, they will already know how to use their syringe, where best to inject themselves, and how they may need to change their daily routine. With such pre-inscriptions, a diabetic already has a degree of knowledge and various competences in place to be able to use the insulin.

Now in cases where pre-inscriptions, prescriptions and proscriptions do not match the user of an artefact, it is likely that an antiprogram may develop. A diabetic who does

not understand what they have been told by their doctor may experience problems with the management of their diabetes, no matter how good the insulin is. To illustrate this point I rework a case study in the field of the 'public understanding of science'.

Brian Wynne has looked at the affect of the Chernobyl disaster on farmers in Cumbria (1992). This study can be reworked to explore the meeting of expectations of users (pre-inscriptions), allowances (prescriptions) and disallowances (proscriptions). Wynne found that not only did farmers develop an antiprogram around the disaster but also on a wider level. Wynne describes how the Ministry of Agriculture, Fisheries and Food (MAFF) went about carrying out scientific tests on the contaminated farmland. However, the farmers' knowledge and expertise was not drawn upon in carrying out the scientific tests. In this case, the pre-inscriptions of the farmers, in the form of their knowledge and expertise, was downgraded by the scientists and not thought to be of any importance.

The farmers however, believed that their existing knowledge was credible, and so reacted against the negative perception of their pre-inscriptions by the MAFF scientists. The farmers developed a program of action which was reacting against some of the scientists' values. These values included: the methods and assumptions made by the scientists in the search for truth; the downgrading of their own knowledge; the claim by the scientists that there were no negative effects from Chernobyl, and especially Sellafield; and, the claim of the 'natural' authority of science.

It also appears that Chernobyl was a trigger to other unexpressed antiprograms. As Wynne writes:

> "The way in which farmers' scepticism was expressed suggests that Chernobyl acted to release a large historical backlog of more disbelief, mistrust, and alienation from the authorities, which related to Sellafield, and which had been quietly simmering over the years...This would also explain the apparently abrupt change in their position from acceptance to hostility..."
>
> (Wynne, 1992: 295)

One reason why this antiprogram may have been unexpressed was because the farmers were members of many networks, as Wynne writes, "farmers identified with

family, friends and neighbours who were part of the Sellafield industrial workforce" (1992: 299). The work by Wynne also illustrates the nature of a feeling of powerlessness, and that farmers had unexpressed antiprograms outside of their community. He quotes two farmers:

> "You can't argue with them because you just don't know..."
> "We can't argue with them, but you can think your own ideas. I still think it [the radioactive caesium] was here before"
>
> (Wynne, 1992: 299)

What is important here is that actors have to play, at least initially, the roles that have been proposed to them. A diabetic is expected to play the role defined by the medical profession. Diabetics need to take care of their health, watch their insulin dose, and diet. Upon using a new artefact (e.g. human insulin) a diabetic may become aware of problems with the management of their diabetes. Some problems may only require a small amount of re-inscription, such as a slight change in insulin dose, which can usually be carried out by the diabetic. However, other re-inscriptions may be more complex, such as a belief that an insulin has serious side effects. The ability to carry out these re-inscriptions will be dependent upon: the degree or amount of re-inscription required; the network within which the artefact is located; and, the existing knowledge, motivation and potential allies of the user.

In some cases, I may wish to carry out some simple re-inscription such as sticking a note on my office door asking people to close it after them. In this case re-inscription can be accomplished simply - that is, drawing on few resources. In other cases, actors may group together to campaign for the re-inscription of a medical drug from 'safe' to 'dangerous'. To enrol the networks necessary for such a change, it would be necessary not only to involve campaign groups, but also have contact with the medical profession, regulatory bodies and pharmaceutical companies. Re-inscription therefore is an important and complicated act, since it may involve drawing upon a number of actors and resources. Further, these actors or networks may already have a particular relation to the artefact of concern. For example, the medical profession may initially view the drug as safe and efficient. Such links may need to be broken before re-inscription can occur.

Another concern is that just because there is no perceived front line does not mean

that there is no antiprogram. Just as trust has been shown to be contingent (Wynne, 1996) so, I would argue, are antiprograms. There are many reasons why researchers and enrolers may not be aware of a particular antiprogram. One reason could be our differing identities and power relations within networks. For example, there is much advice to diabetics on how to avoid long-term complications. Studies have shown however, that diabetics feel that this advice is impractical, and many have their own 'secret' antiprogram, that is, they do not follow the program given to them by their doctor. The Diabetes Control and Complications Trial (DCCT) found that intensive insulin treatment (known as tight control) more than doubles the risk of severe hypoglycaemia (Gale, 1989: 1264), but reduces the chance of long-term complications. However, studies have shown that many diabetics prefer to have high blood sugar level, so as to reduce the risk of a hypoglycaemic reaction (Cox et al., 1992; Green et al., 1990). Therefore, as work from the public understanding of science has shown, the acceptance and application of knowledge is dependent on the practicality of this knowledge within particular contexts.

Importantly, this antiprogram, towards tight control, may not show itself in the doctor-patient relationship, though when diabetics are talking amongst themselves they may articulate such an antiprogram. In many cases this antiprogram, against the program of what is medically defined as 'being in control' (Rajaram, 1997: 286), may only become evident to doctors when many years later complications begin to show themselves. As Wynne points out, "lack of overt public dissent or opposition towards expert systems is taken too easily for public trust" (1996: 50).

However, in other cases we need to be aware of the perception of powerlessness. Although an individual may be able to envisage some antiprogram, they may not search out further relevant knowledge, because they feel that it will not accomplish anything. As pointed out by Irwin et al, "'information' does not exist in a social vacuum, but is weighed in terms of previous experience and cultural evaluations" (Irwin et al., 1996: 55). Indeed Michael (1996a; 1996b) has illustrated how, through discourse, various constructions of ignorance can be found, in which a lack of knowledge should not be seen simply in terms of a 'deficit model' of knowledge. What seems to be important are the identities that individuals have of themselves and other bodies, and the positioning of themselves and other bodies within a particular

network.

It should also not be taken for granted that just because an individual is presented with a possible trigger to gain information that they will actually do so. Michael has shown how a Radon measuring device, "was not an irresistible stimulus to find out more about radiation", indeed "it spurred the volunteer actually not to find out" more about Radon (1996b: 119). One reason for this could be that the device came to signify the more or less passive role of the volunteer (Michael, 1996b: 119). This is one of Michael's discourses of ignorance, which is based around a division of labour. In such cases individuals have roles (concerned citizen or Radon scientist, patient or doctor) which define what knowledge they should possess; 'specialist knowledge' is deferred to others, whose role it is to know, or monopolise, this 'specialist knowledge'. There was no need for volunteers to search out knowledge about Radon because there were specialists whose job it was to protect them from Radon, if it was a problem.

Therefore, in any discussion of programs of action we have to be aware that there are wider influences on the actors involved than simply the immediate humans and nonhumans. Indeed, I explained above how one criticism of actor network theory is that they have neglected the 'wider culture', or what we may call, more diffuse networks.

2.5 ENRICHING ANT WITH OTHER AREAS OF SOCIOLOGY

In this section I would like to look at three theoretical areas that I will be drawing upon in order to enrich my work within actor network theory. These areas are: the sociology of the body, the sociology of consumption, and the public understanding of science, in particular, discussions concerning 'expert' and 'lay' knowledge.

2.5.1 The Body as a Network

In this section I would like to develop a concept of the body that draws upon ANT. As stated in the introduction, a concept of the body has mostly been neglected by actor network theorists. One of the aims of this thesis is to develop a notion of the body within actor network theory. However, before I describe how I will treat the body, it is worthwhile considering some of the most recent work carried out by

researchers who have attempted to describe the body within an actor network framework (for example, see papers in Berg and Mol, 1998; for one of the earliest papers that referred to the body see Mol and Law, 1994).

Cussins (1998) claims that when patients enter fertility clinics bodies become un-black-boxed. She argues that clinics allow access to bodily processes and body parts. Importantly, it is through the use of artefacts, such as a speculum, that body parts, such as a patient's uterus, are "enabled to display properties in their own right" (Cussins, 1998: 181). It is through heterogeneous engineering (linking) that parts of the body become visible.

Willems (1998) has looked at the way in which drugs define the body. He has argued that types of treatment within medical practice (in his case, drugs and inhalers), make similarities (salbutamol forges a connection between the occasional hayfever patient and the adolescent sportsman with slight asthma) and differences (asthmas and lungs), rather than simply mirroring existing similarities and differences. His important point is that as artefacts are accommodated within the body, they do not simply allow the body to resume functions that are restricted by disease. Drugs also define disease and reorganise the body by creating new identities for it (Willems, 1998: 118).

Mol (1998) has studied atherosclerosis, a disease of blood vessels. Mol has studied what is involved in linking the object 'atherosclerosis' of the laboratory with that of radiological imaging or the outpatient clinic. She argues that the process of linking needs a lot of work. For example, in order to reveal an association between a patient's complaint and clinical diagnosis of atherosclerosis, practical work has to be carried out. It is through practical work, whether in the form of pressure measurement or angiography, that links are made. Each time practical work is carried out to reveal links it is necessary for actors to engage with many different materials, such as forms, knives, hands, gloves etc. Importantly, the links are not present inside the body, but rather, lie within the practices that are carried out by various actors.

There is other recent literature. Looking at muscular dystrophy, Callon and Rabeharisoa (1998) have described the way in which, through tests and trials, a 'collective patient' is created. The important point is that the body is extended beyond the flesh through technologies to other persons and organisations. It is

through studying trials and tests within medicine that the body can only be understood. Moser and Law (1999) describe the case of Liv, who is physically disabled. Their concern is in the ways in which people move between specificities - specific networks of heterogeneous materials. For Moser and Law dis/ability is about specific passages between equally specific arrays of heterogeneous materials. Or to put it another way, incomplete or missing specificities lead to dis/ability. As a result, the body is to some extent defined by the specificities that an individual encounters. Moser and Law illustrate this when they point out that Liv, who wants to be active, is dis/abled in a way that is different from someone who is happy to sit in a chair at home all day (1999: 216n4).

Moving back to a more general discussion of the body, Law (1992) has argued that human beings should be viewed in the same way as other actor networks; just like other networks they are patterned networks of heterogeneous materials. It may therefore be more correct to think about the 'body as a network', to bring out the complex nature of the body. In normal conditions networks are hidden, the network is durable. A sociology of the body theorist would say that the body is absent (Leder, 1990) since we are not aware of its processes. As Kelly and Field (1997) have argued, the body "goes relatively unnoticed until such times as illness or other things impinge on it" (1997: 363).

In illness, the 'body networks' become visible:

> "Through pain, disability and death, our normal modes of bodily dis-appearance tend to become profoundly disrupted. The body, in other words, becomes a central aspect of experience, albeit in an alien form: it dys-appears (i.e. 'appears' in a dys-functional state)."
>
> (Williams, 1998: 61)

As a consequence of this 'biographical disruption' (Bury, 1982) it is necessary for the 'body' to interact more openly with other networks, for example doctors, pharmacists, care groups, other patients, drugs and new technologies. Of course, the 'healthy' body is always engaged in many networks but, as mentioned above, these are usually invisible. Chronic illness will therefore affect the boundaries of the self, and a large part of chronic illness education is concerned with helping the patient to regain a sense of self. Those with chronic illness also need to re-interact with other networks and contexts, such as family, friends and technologies. Bury uses the term 'strategy'

to refer to the "actions taken [by those with chronic illness] to mobilise resources and maximise outcomes" (1991: 461-462). Through these interactions an individual may come to a 'negotiated settlement' with their body and illness.

When an individual once again becomes 'settled', the body returns to a kind of equilibrium. When an individual initially experiences, and is diagnosed with, chronic illness it may be necessary for them to adapt to new circumstances. As mentioned above, it is necessary for them to re-interact with other networks and contexts. In a sense, the once invisible becomes visible. A newly diagnosed diabetic needs to pay attention to what they eat and cannot take long walks without preparing themselves. However, over time, an individual accepts various features of their chronic illness, and the visible becomes, to a lesser extent at least, invisible.

In illness therefore, there is a movement from 'being a body', where the body poses no trouble to us, to 'having a body', where there is a disjunction between the body and our sense of it. In such cases the body is felt to belong to someone else, such as the medical profession. However, in time the body again becomes something we have mastery over, as Turner writes, the body is seen as a:

> "...collection of practices over which we might have a certain mastery or sovereignty...techniques for presenting and maintaining and reproducing bodies in time and space."
>
> (Turner, 1992: 40-1)

Turner calls this a state of 'doing a body'. What is interesting here is that when the body is seen in terms of 'having a body', the representation of the body is carried out, to a large extent, by the medical profession. That is, in the form of diagnosis and control. Importantly, the representation of the lived body is taken on by those who have not (usually) lived that ill body, i.e. a doctor. However, when some mastery of the body is regained the representation of the ill body is taken on by the ill body itself. The patient is then seen in terms of 'doing a body', where mastery moves from the medical profession to the patient. Where care groups are involved, the representation of the body, by the ill body itself, is even more evident. It will be even more evident because we are more likely to become aware of the narratives that the 'ill' bodies themselves produce. What is important here is that representation of the body becomes collectivised. A network is formed of those bodies that wish to form a group

of 'ill' people, and this network becomes represented (or performed as Law (1994) would put it) through letters, meetings and newsletters. This will be elaborated in Chapter 6.

Another dimension of a body is the simplified network body, or representative body. This body is the body that is used in clinical trials. Such a body is seen to be a representative of all those bodies within a particular population. When experiments are carried out on such bodies, and results published, it is expected that the results can be generalised to all similar bodies. Results from the simplified body produce an exemplar body. It is on this exemplar body that a program of action of what other bodies will do on a particular drug is based.

However, when a number of individuals experience and express symptoms that are different to that of the exemplar body, we can say that they are forming an antiprogram. In such cases, negotiations will take place in order to accommodate for this unrepresented body. As we will see, these negotiations can include the marginalisation of the non-exemplary body by the medical profession. One example of this marginalisation is in the non-diagnosis of RSI, where some doctors dismissed the possibility of a biological basis for RSI, telling their patients to 'pull themselves together' or 'it's all in the mind' (Arksey, 1998: 127). In other cases, the boundaries of the exemplar body may be expanded, to accommodate for the symptoms experienced by some patients.

In this study, I would also like to develop something that can be called a network body. It seems obvious that as individuals we are not separated from the world outside of our body. As Haraway argues, "Why should our bodies end at our skin, or include at best other things encapsulated by the skin?" (1991: 178). Indeed, the image and experience that we have of our own bodies is influenced by other entities. Rose describes the body as an assemblage consisting of an interconnection of "...parts, forces, movements, affects of other humans, animals, objects, spaces, and places" and that "It is within these assemblages that subject effects are produced, effects of our being-assembled-together" (1996: 171). The concept of the network body attempts to draw out the dimensions through which we are constituted by these other entities, by the network, of which our bodies are a part. As Falk has argued, the body is never found in its 'natural' state (1995: 95) since the 'techniques of the body' are present

from the start of social life (Mauss, 1973 [1935]). Technologies are always acting on our bodies.

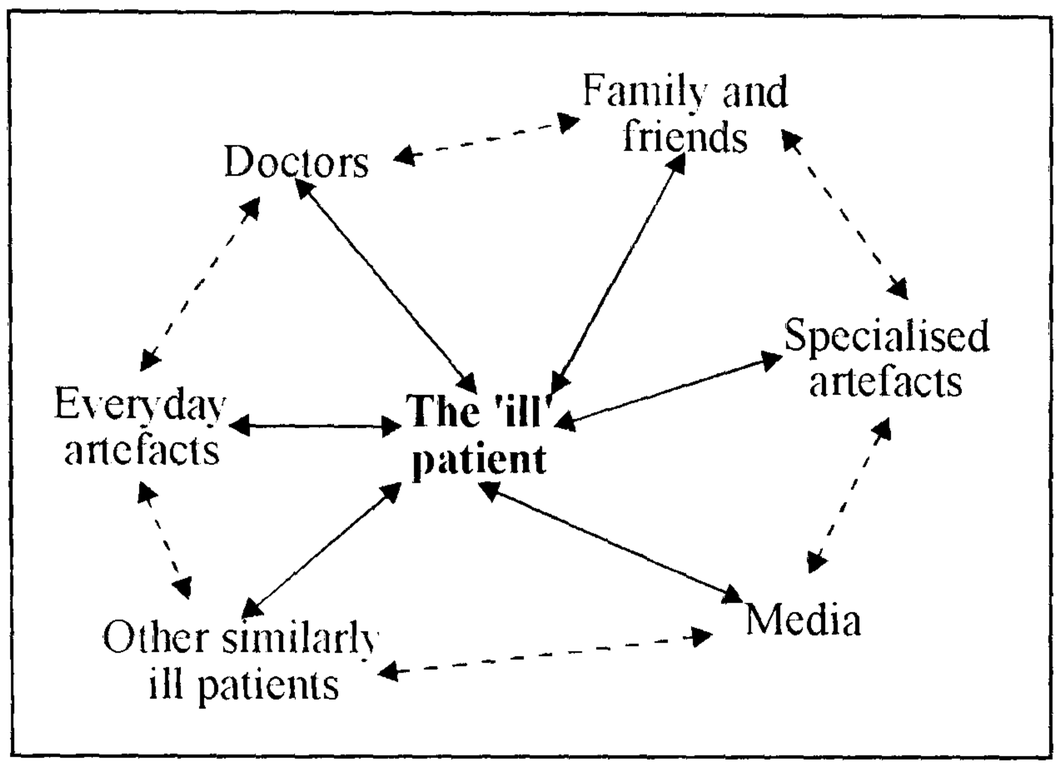


Figure 2-9: A simplified version of a network body

There are a number of dimensions of the network body that need to be addressed. Firstly, the influences on the body are both human and nonhuman, and as a result, the network body consists of both human and nonhuman entities (Figure 2-9). Although in 'normal' circumstances we are unaware of these entities - they are invisible - in times of illness elements of the network body become visible. Not only this, but in times of illness new entities, new relationships, will be brought into the network body. For example, when an individual is diagnosed with a particular illness they may need to take greater care over their diet, they may have more frequent contact with their doctor or may have to use specialised artefacts, such as crutches or monitoring equipment. When these entities are initially incorporated into the network body they are visible, however, over time, as an individual becomes accustomed to the new entities and they become part of 'everyday life', they become invisible.

Secondly, entities within the network body do not exist without reference to the other entities in the network body. For example, a doctor may suggest that monitoring equipment would be useful for the patient. Further, changes made to particular parts of the network body may have an influence on the nature of other entities. For example, initially a newly diagnosed diabetic may need to make frequent visits to their diabetic clinic. However, as the diabetic becomes accustomed with blood monitoring equipment, and is able to take care of their own diet, the dependence on the clinic will be reduced.

A third, and related point, is that the network body is dynamic in its nature, it is constantly changing - the body is an 'unfinished body (network)'. Over time it is likely that the 'ill' network body will come to a 'negotiated settlement'. However, there will always be new entities (new medication, new doctors or new relationships) that come to be incorporated into this network, which may, once again, disrupt the network.

It must also be stressed that technologies and the human cannot be separated from each other, as Prout has argued for the metered dose inhaler, "technologies and people mutually constitute each other" (1996: 200).

As stated earlier, this thesis aims to correct one of the failures of actor network theory, namley to adequately deal with the body (although see Callon and Rabeharisoa (1998), Cussins (1998), Mol (1998), Willems (1998); and Moser and Law (1999) for some attempt to correct this failing). When talking about the network body it is also important to be aware of another body of work, that which deals with hybrids (Haraway, 1991; Latour, 1993; Martin, 1994).[6] When I talk about the network body I am resisting the tempatation to purify, that is, I treat humans and nonhumans the same. Added to this, the network body is the result of translation, in that it mixes nature and culture (Latour, 1993). Further, all individuals are irreducible to a unity (Moser and Law, 1999). Moser and Law (1999), speaking of Haraway's cyborgs (1991), argue that a cyborg is made of composite parts that cannot be reduce to one another. Importantly, because the parts are "internally related to one another" (Moser and Law, 1999: p. 215) they are different from the way they would be individually. Take for example human insulin, inserted into one network body it may 'cause' no problems, yet within another 'problems' may exist. Changes in the effect of human insulin have more to do with other entities within the network body, and the relation these entities have with human insulin and each other, than with human insulin in itslef.

In the present context I want to talk in terms of programs and antiprograms with regard to the body. When a body becomes ill, one can say there is an antiprogram to

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[6] Of course, there are differences in the way in which authors treat the subject of hybrids (Latour, 1993) and cyborgs (Haraway, 1991). One major difference is that Latour argues that hybrids have always been around, but in modernity we have paid scant attention to them. On the other hand, Haraway argues that cyborgs are relatively recent. My preference is to agree with Latour.

what the individual feels that their body should be doing, what it 'normally' does - that is, their usual program. However, through time the individual may 'come to terms with' their own antiprogram, so that it becomes transformed into something that can be coped with within the illness. The means by which this could be accomplished are varied. For example, patients may use other artefacts to help them or enrol support from family and friends. When the antiprogram is reduced the individual may feel that they are no longer alienated from their own body.

Further, referring back to what I have already said, it is important to realise that the body as an object has particular allowances (what can be called prescriptions), and through illness these allowances (prescriptions) may change: allowances are likely to be re-negotiated, and new boundaries of what the body will allow may be set. Take for example, the use of blood glucose monitoring equipment by diabetics: such equipment is used by diabetics to check their blood glucose levels and so know when it is necessary to digest glucose. Such equipment may allow the diabetic to live a 'normal' life.

One particular area of interest is what happens when an individual comes to terms with their illness, but then experiences some disruption to their understanding. Newly diagnosed diabetics are often counselled to be able to deal with their new condition, in effect, they are given a new set of prescriptions by which they are able to (re)understand their own body. These techniques then become part of the network body, and form a set of pre-inscriptions. When a new medication is prescribed the drug may fit neatly into the network body with its use being based on pre-inscriptions (such as moving from injecting one type of insulin to another). In other cases, new inscriptions have to be laid down in order for the medication to be used effectively (such as moving from tablets which stimulate the production of insulin to having to inject insulin). An area of interest is what happens when it is expected that a new medication will fit within the existing network body, but from the sufferer's point of view, does not. In this study, human insulin was expected to act in a similar way to animal insulin, yet a number of diabetics experienced noticeable changes in their symptoms on human insulin compared with animal insulin. This will be explored in detail, in future chapters.

2.5.2 Consumption

Another interest is how work on the sociology of consumption can be applied in this study. 'Consumption' is now regarded as signifying much more than simply consuming things; we also consume the signs of goods. The rapid take up of human insulin by the medical profession (and to some extent patients) may have had something to do with human insulin being portrayed as the 'modern' insulin. Further, consumption is not simply a matter of selecting a particular object or sign. Instead, the selection of artefacts reflects not only on the identity of the individual, but also back onto culture and the object itself. As Michael writes:

> "...on the one hand, consumption is a means by which the sociality of the lay local [non-expert knowledge within local cultural conditions] is practised; on the other, the lay local shapes the meanings of the activity and 'objects' (technologies, knowledges, images, etc.) of consumption."
>
> (Michael, 1998: 317)

It is important to understand that we consume many 'things', and together, these may effect the meaning of an activity or 'object'. For example, diabetics may consume human insulin and also consume information from the Insulin Dependent Diabetes Trust (IDDT) and British Diabetic Association (BDA). Together this consumption may redefine the original meaning of human insulin, from one 'without side effects', to one 'with side effects'.

Much has been written in the sociology of consumption on the way meanings are attached to objects. Baudrillard has argued that we now live in a state of hyper-reality in which any object, in principle, could take on any meaning, in other words, or all that we have are signs. The consumption of food is an interesting case, since it can be argued that we biologically 'need' food, just as we need insulin. Bourdieu (1984 [1979]) has argued that eating is less about survival and more about expressing social meanings. On the other hand, Warde (1997: 199) points out that the use value of objects is often underestimated. Yet there are meanings attached to food, indeed:

> "Looking at the edible/inedible classifications of a certain food culture reveals the fact that not nearly everything that is (objectively) edible and available is really eaten (for example, insects rich in protein)."
>
> (Falk, 1994: 69)

The division between edible/inedible may be adapted to be used within this study.

2.5 Enriching ANT with other areas of sociology

Edmund Leach (Leach, 1964) defines three categories for a edible/inedible distinction:

1) Edible substances that are recognised as food within the normal diet.
2) Edible substances that are recognised as possible food, but are prohibited or else allowed to be eaten only under special conditions.
3) Edible substances that are not recognised as food at all.

In many cultures the process by which an objectively edible food can be transformed from 2 to 1 involves an element of ritual. Falk (1994: 13) talks about a cultural order in which there is an alimentary code (food taboos, ritual rules) that defines what can be eaten, by whom, how and when. When the boundaries grow weaker then it is likely that 'taste' moves from a community taste to an individual one, although still being "related and conditioned by cultural representations" (Falk, 1994: 13).

It may be possible to argue that in modern society the 'ritual' of the consumption of medical drugs involves the process by which a drug is deemed to be edible. This process involves clinical trials of the drug to test its efficiency and advantages to the patient. By 'advantages', I mean the process by which one drug becomes deemed as 'better' than previous drugs or treatment. This may be seen in a similar context to the changes that occur from time to time over discussions of nutrition (for example, the recent discussions over Vitamin B-6 (see Collier, 1998)).

When a drug is defined as 'edible' it then becomes available at consumption sites (the pharmacy) through what we might call a particular 'consumption path'. A consumption path is the means by which a particular artefact is obtained, for example, in order to get a medical drug, I need to go to a doctor, get a prescription and then take it to the pharmacy. These sites and paths can be rather inflexible, being maintained through the circulation of standardised intermediaries. For example, you now need a prescription to get insulin. In order to get a prescription I need to present myself to my doctor, go through a number of tests, and be medically defined as diabetic. However, before August 1998, it was possible to obtain insulin over the counter, although the pharmacist had to be convinced that it would be used correctly. After August 1998, insulin became a prescription only medicine (POM). This change was partly due to the use of insulin in suicide attempts, and by body builders instead of steroids. However, the consumption path can be subverted, such as when actors attempt to obtain POMs on the black market. In such cases, it is interesting to study

how and why the path changes.

When those who use a drug attempt to redefine the drug as 'inedible', because they are experiencing negative effects, then they have to work against its ritualisation as an edible (without side effects) drug. In effect, they have to undo an object's meaning, and redefine it in their own terms (re-inscription). This will be examined in detail with reference to human insulin.

Another point of interest is how various artefacts become translated into one; that is, rather than consuming two linked but separate artefacts, only one artefact is consumed. For example, insulin pens use cartridges of insulin which fit into a pen, the insulin no longer needs to be measured at each injection and the insulin can stay in the pen until it runs out. In the case of the insulin pen, the insulin, the injection system (pen or syringe), and the process of measuring the correct dosage become closely linked. Once joined together it becomes 'hermetically sealed' or what Lee (Lee, 1993) might call a compound commodity. In such cases, the network body becomes reorganised with new (translated) artefacts being introduced. Such an introduction may also change the identity of the patient, they may feel more able to travel or eat out since the injection system is self contained and easily portable.

Artefacts therefore shape the capacities of the body (Michael, 1996a). In the case of the door closer described above, some actors - the very little or the very old - were discriminated against. In the insulin pen example, the consumption of the artefact enables the body. Limits are removed from the enrolled diabetic through the use of the pen. Such positive changes in the network body will afford new allowances to the patient. It is therefore through the consumption artefacts that an actor's identity is reconstructed.

One way in which an actors identity may change is through an awareness of 'normality'. It can be argued that consumption of the insulin pen network makes a diabetic more 'normal', since they are able to present themselves to others as 'normal'. However, we have to be careful what we mean by 'normal' - normality is always under negotiation. When an actor becomes ill they are no longer 'normal'. Yet over time, when they come to a negotiated settlement with their body, normality is redefined; normality is having regular insulin injections, having an awareness of

hypoglycaemia, etc.

This definition of 'normality' is the result of being part of a broad diabetes network. However, diabetics are also aware of wider culture, where there are other definitions of 'normality'. It is one of these 'other' definitions of normality that can be expressed through the consumption of the insulin pen. The meaning of normality is therefore not static, since it is dependent on an actor being within a particular heterogeneous network. Normality is therefore both context and temporally dependent.

2.5.3 Lay and Expert Knowledges

Another theoretical area that I intend to address is that concerned with the relation between 'expert' and 'lay' knowledge, in particular, the (inter)discipline of PUS. In order to provide the reader with some reference points, I will briefly suggest some problems with the expert-lay division.

From the outset we are presented with a problem of definition. What do we mean by 'lay' or 'expert' knowledge? The term 'lay' is often used to refer to the 'public'. However, the term 'public' is itself problematic. Davison et al. (1997) have argued that the term 'public' has been used as a residual category to refer to a non-expert or lay audience. Davison et al. call for a richer notion of 'publicness' which recognises the diversity of publics and the importance of 'interested publics'. By 'interested publics' we mean members of groups who are not 'experts' in a particular field, but have an interest because of their membership to a specific group (Schibeci et al., 1997: 171).

Michael et al. (1997) point out that many studies neglect the mediating professionals, that is those groups that straddle the social worlds of science and laity, for example science journalists and science teachers (in their case biotechnology teachers). I would argue that diabetics can be seen as mediating professionals and as an interested public. They are mediating professionals because diabetic education is embedded within the management of diabetes. That is, diabetics are actively encouraged to understand their diabetes. As Williams and Patrick point out, diabetes is a complicated disease which demands close co-operation between the patient and the diabetes care team (1992b: 375). As a result, there is a reduction in the competence gap, specifically relating to diabetes, between the diabetic and the doctor.

The concept of a competence gap illustrates the nature of differing power relations between 'experts' and 'publics'. One reason for this is the different knowledge that is drawn upon by different networks. Doctors and their knowledge have been defined as legitimate. Legitimacy has been defined as a "political-legal process whereby a set of practices is accepted as authoritative and becomes dominant through the political process of justification" (Willis, 1994: 55). Doctors' political-legal legitimacy has a basis within both scientific and clinical legitimacy (Willis, 1994: 65). Importantly, doctors are privy to a special body of knowledge that has been defined as authoritative, and itself, legitimate. This special body of knowledge has been in part produced by the combination of inscriptions at centres of calculation. These centres, the laboratory or institution, produce texts which are authoritative since they themselves refer to other texts and use methods, such as statistical analysis and the experimental method, that are deemed as able to produce 'truth'.

There is however another origin of the authority of doctors. On a macro level doctors are legitimised through the state, that is, doctors are given the 'right' to practice medicine. However, on a micro level, doctors become clinically legitimised through contact with patients (Cooper, 1997). Patients legitimise doctors through accepting any diagnosis that they are given - the 'double-bind' situation. Bloor and Horobin (1975) refer to the 'double bind' situation when patients are expected to use their own judgement and experience to both seek medical advice and describe their experiences, yet they defer final judgement to the doctor for treatment. In this case, the authority of doctors comes from the wills of patients, or more specifically, through their lack of questioning.

However, in some situations patients do not blithely accept the authority of a doctor. In such cases there may be a questioning of the legitimacy of individual doctors, but not a challenge to the medical profession as a whole. Aronowitiz would argue that such encounters do not lead to radical epistemological critiques of biomedicine (1992).

Where publics question the knowledge of particular doctors and a particular diagnosis they may form an 'epistemological challenge' (Williams and Popay, 1994: 123) based on their experiential knowledge. It is likely that this challenge will be influenced by information from other sources, such as the media and care groups. In such cases the

value of the knowledge possessed by the doctor may be questioned, as Macintyre and Oldman argue:

> "Those who suffer from chronic illness, particularly ones that doctors can do little about, develop a special knowledge of their condition. This knowledge is of a rather different order from that held by doctors, and from the point of view of the patient, it is subtly superior."
>
> (Macintyre and Oldman, 1977: 55)

In terms of ANT, where an actor (a patient) no longer identifies with another actor (a doctor) who is defined as being central, then there is a problem in the network: the network is no longer durable. The patient may no longer be enrolled within the network. It is likely that the patient will no longer identify the doctor as an expert, at least in this particular case.

Actors may then attempt to form their own network that may in some way compete with that of the medical profession. This may not be easy to accomplish. For those who wish to challenge the medical view, it is necessary for them to enrol various actors, such as some members of the medical profession, into their newly forming network. What these actors attempt to do is form their own network with their own expertise, since they are no longer able to identify with the doctors version of expertise. This expertise is likely to be different from that of the medical profession, but may have involved a reworking of medical science to render it functional for the actors' day-to-day reality (Arksey, 1998).

It is important to look at what types of knowledge constitutes expertise, and further, to look at the value of knowledge as distributed within, and by, a network. Doctors are likely to place more value on expert knowledge, while diabetics may place more value on their own experiences (although how, or even whether this is expressed, is something for investigation). It is also important to realise that similar networks may give value to different types of knowledge. For example, the Insulin Dependent Diabetes Trust (IDDT) appear place more value on experiential knowledge than the British Diabetic Association (BDA), and as a result, different actors, depending on their own program of action, became allied to different care groups.

Although some have argued that it is interesting to "study the patient's illness experience and illness world as a social reality apart from the conception and

definition of illness as formulated by biomedicine." (Hydén, 1997: 52). It is nevertheless important to study the meeting point of 'lay' and 'expert' knowledge. Any change in the use of human insulin by a diabetic is likely to come about as a result of negotiations between the possessors of 'lay' and 'expert' knowledge the patient and the doctor respectively. Due to the uncertainty of scientific studies and of the lack of any proved side effects of human insulin, the patient's experiences, within the doctor-patient relationship, forms a crucial part of this thesis.

The doctor-patient relationship should also not be seen as being isolated from other networks. As I will show throughout this thesis, diabetics drew on information from a number of different sources, such as newspaper reports and care groups. In some cases these other networks affected the actions of diabetics, and in turn, affected how some diabetics interacted with doctors. I follow Williams and Popay when they argue that "lay knowledge may incorporate expert knowledge but it is interpreted in terms of the experience of everyday life" (1994: 120, with reference to Davison et al., 1991). Therefore, when a diabetic experiences problems on human insulin, they are more likely to identify with selected 'expert' knowledge.

2.6 SOME FINAL THOUGHTS

In the previous sections I have introduced a number of concepts and issues that I will be addressing in later chapters. However, there are several issues that I have only hinted at. In this final section I would like to point to a number of areas that I will develop later in the thesis.

One particular area is the nature of information. I have already argued that care groups attempt to translate the feelings of individuals into a more coherent and collective argument. There are a number of questions that stem from this. For example, how do larger sympathetic networks (such as care groups) treat the claims of individuals, and how are these larger networks mobilised? How does a personal antiprogram become a collectivised and possibly more effective one?

It is also important to be aware of the way in which information, in particular texts, become collectivized by actors. As actors, such as care groups and scientists, produce texts they are likely to include texts from other actors. For example, throughout the human insulin debate, many articles were published in the scientific press which

discussed and summarised the important issues in the debate. These articles included issues that were discussed in other texts, importantly however, these texts were not just those produced by scientific actors, but also 'lay' actors. I call this process of inclusion, collectivization. The important point is that actors have a degree of flexibility as to which texts they collectivize. For example, the IDDT tended to select and collectivize scientific texts which 'reified' the negative experiences of diabetics on human insulin. On the other hand, the BDA tended to collectivize texts which showed that evidence against human insulin was inconclusive. I will return to the issue of collectivization in Chapter 7.

There is also the important question of how individuals become motivated to search out knowledge around a particular artefact. In the study by Lambert and Rose on a genetic metabolic disorder, Familial Hypercholesterolaemia, they point out that:

> "...the members of the [Familial Hypercholesterolaemia] Association were seen as likely, through personal necessity, to be particularly motivated to 'understand' the relevant science..."
>
> (Lambert and Rose, 1996: 69-70)

In this study a similar motivation is in evidence. When diabetics experienced 'unusual' effects of human insulin, some searched out further knowledge about human insulin. This leads us to such questions as: What sources do individuals look to for information? In what ways do individuals express their feelings? How do various groups respond to individuals concerns? What effect does the network body have on the search for information? I have already hinted at some of the areas of the public understanding of science that are relevant to this study, for example, discourses of ignorance and trust. In future chapters I will draw further on this important body of work.

In cases where the 'official' meaning of an artefact is questioned, various mechanisms are used to regain control of what is inscribed within that artefact, and to resist counter-inscriptions. One method by which this occurs is 'inoculation' (see Michael, 1997 for an inoculation against ridicule). Inoculation comes into play when the function or usefulness of an artefact is 'questioned'; for example, when controversy occurs around a particular drug, the manufacturers will stress that it is safe because it has passed through a battery of scientific tests. Inoculation therefore should be seen

as a defensive characteristic.

As actors form an emerging counter-network to the official meaning of a drug, questions may be raised about the quality and representativeness of the clinical studies carried out. Further, actors may attempt to enrol other networks, including the scientific community, to form a 'credible' challenge to the official meaning of the drug. Although care groups are likely to place more emphasis on anecdotal evidence than the scientific community, they are likely to also draw upon work from that community.

This leads us to consider the division between what can be broadly called 'lay' and 'expert' knowledges', and whether there are particular processes by which these boundaries are maintained. There is also the associated question of how certain lay groups attempt to gain access to the knowledge within these different domains, while also providing their own anecdotal evidence through letters, articles and informal surveys. Indeed, pivotal here, is an examination of how certain groups are able to claim superiority for their knowledge. The scientific community may claim that clinical studies produce superior knowledge, while care groups may claim that such knowledge does not take account of the use of medical drugs in everyday life. Moreover, complicating this simple division, the scientific community (Gieryn, 1995) and care groups are not homogeneous. In the present study, the IDDT was set up to represent diabetics on human insulin because they felt that the British Diabetic Association was not adequately representing diabetics.

A final thread in this work is how, through the process of gaining support for a particular program, the inscriptions around a particular artefact changes. The basis for any re-inscription is the decision by some actors to go against a particular antiprogram. For example, a diabetic may no longer view human insulin as a 'modern' insulin, and choose to return to animal insulin. Perhaps this is psychological re-inscription, since the diabetic no longer believes that human insulin is a superior insulin.

My particular interest is in the process by which individual antiprograms become 'collectivised'. A collectivised antiprogram is likely to have a greater influence on an institutional program than an individual antiprogram because it will involve a greater

number of allies. In this case study, care groups attempted to re-inscribe the medical program for human insulin. This re-inscription can be seen as a challenge to the authority of the defining (inscribing) network, and as such, may be met with strong resistance.

Those groups who oppose the program of action will therefore have to build associations or networks. The power of a particular network will be dependent on the strengths of the links that it has with other networks. Networks 'aim' to produce 'knowledge' that is viewed as credible. The 'aim' is for statements produced by a network to become immutable mobiles. When this occurs, the producing network becomes powerful and can be seen as an 'obligatory passage point' to the understanding of a particular phenomenon. For example, if the statement - 'human insulin produces an increased chance of hypoglycaemia unawareness' - becomes indispensable to those talking about human insulin, then this becomes 'knowledge'. Producing such knowledge may only be achieved by associating with other networks, in this case study this was done through the uniting of care groups, patients, members of the medical profession, and some members of the scientific community.

However, it is not only a matter of producing such knowledge. For a network to be powerful it has to be 'plugged into' other appropriate networks. As Haraway writes of Latour:

> "The laboratory for Latour is the railroad industry of epistemology, where facts can only be made to run on the tracks laid down from the laboratory out. Those who control the railroads control the surrounding territory."
>
> (Haraway, 1991: 248n.2)

Therefore, in order to produce 'facts' work has to be produced in the laboratory, and this case study is no different. However, because of the uncertain nature of these results, patients and care groups attempted to stress the credibility and value of their experiential knowledge.

2.7 CONCLUDING REMARKS

I have argued that we should not 'purify' ANT: that is, one of my aims is to enrich ANT by bringing in other theoretical areas of sociology and cultural studies, namely the sociology of consumption and the body, and also the public understanding of

science. With reference to the many vocabularies for talking about society, Callon has argued that it is up to the "sociologist to choose the one that seems the best adapted to his [*sic*] task and then to convince his [*sic*] colleagues that he [*sic*] made the right choice." (1986a: 200). I will adopt a number of vocabularies in an attempt to produce an interesting and coherent story. By drawing upon other perspectives I hope to produce a credible story, which, remains 'true' to the key tenets of ANT.

Inevitably it is up to me, the researcher, to be able to stand by my work, with my particular set of theories. As Joan Fujimura remarks:

> "When I write...I must take responsibility and hold myself accountable for the final perspective. The point is to be made explicit to myself and my audiences just where I stand, my operating perspective, and the ground on which my concepts are constructed."
>
> (Fujimura, 1991: 237)

3. THE DEVELOPMENT OF HUMAN INSULIN

3.1 INTRODUCTION

This chapter has an important place within the thesis as it will outline some of the prescriptions (in ANT terms) of human insulin, that is, what human insulin would allow from its users. Those in the medical community and pharmaceutical companies would later draw upon some of these prescriptions in the use of human insulin. This chapter will therefore set the scene for future chapters. In actor network terms this chapter will define the 'script' for the use of human insulin. Then in future chapters, I will describe how this initial script was called into question.

In deriving this script, particular reference will be made to the following areas: the status of genetic engineering before and after the development of human insulin; reasons given for the need to develop human insulin; corporate involvement with the development of human insulin; and, economic influences on the development of human insulin. It is noteworthy that because interest in human insulin crossed a number of areas, such as the development of human insulin and the first use of genetic engineering, there was constant reporting and discussion of the developments of human insulin in the media. Indeed, the scientific development of human insulin was reported as a 'race' and later as a 'war' or 'battle'.

Since the sequencing of human insulin in 1960 (Nicol and Smith, 1960) attempts have been made to produce human insulin (see Figure 2-3). The successful sequencing of human insulin enabled researchers to identify some of the similarities and the dissimilarities between various types of insulin. Attempts were then made to substitute the differing amino acid(s) of animal insulins to form human insulin (Bodanszky and Fried, 1966; Obermeier and Geiger, 1976). However, the methods produced only small amounts of impure human insulin. In order for this impure human insulin to be consumed by diabetics it would have to go under extensive purification which would be expensive, and would then only yield small amounts of insulin. To enable the mass production of human insulin it would be necessary to produce larger and purer amounts of human insulin.[7]

The use of genetic engineering presented the possibility that human insulin could be

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[7] See Markussen (1977) for a description of tried methods.

produced on a commercial scale. This possibility was of interest to a number of groups, such as scientists, the media, pharmaceutical companies, diabetics and diabetic care groups. There were a number of reasons why the development of human insulin was of interest to these groups:

1) Prestige - In the development of human insulin many novel techniques were being used, namely those involving genetic engineering.
2) Application - The techniques being used would be applicable to many other areas, particularly for scarce drugs.
3) Scientific advancement - It was believed, by some, that it would be better for diabetics to use human insulin rather than existing animal insulins.
4) Shortages - There were predictions that there would be a shortage of current animal insulins.
5) Economic - By developing new insulins various insulin producers could capture the market of other insulin producers. It was also believed that the development of human insulin would mean cheaper insulin.

Between 1977 and 1981 there were three broad techniques that were under development to eventually produce human insulin. One technique, called enzymatic conversion (Figure 2-4), and was being developed by Novo Industri, aimed to replace the amino acid alanine, present in porcine insulin, with threonine, so as produce human insulin. A second, aimed to use genetic engineering to produce the whole human proinsulin gene in bacteria (cDNA approach), and was being developed by scientists at Harvard University and University of California at San Francisco (UCSF) (see Figure 3-2). A third, also used genetic engineering, but synthetically produced separate A and B chains of human insulin which were then to be combined. This approach was being developed by a new company called Genentech (see Figure 3-1). This third approach was simpler than the second, since it did not attempt to produce the whole human insulin hormone in one process.

My concentration will be on the last two approaches which used genetic engineering, although reference will be made to the approach of Novo Industri. There are a number of reasons for this. Firstly, one of the reasons for the development of human insulin was to reduce the predicted shortage of animal insulins, something that would not be achieved by the conversion of animal insulin.[8] Secondly, on a practical level, there is little written about the development of Novo Industri's insulin, except where

[8] Novo Nordisk would later develop their own genetically engineered human insulin, and stop production of their conversion insulin.

it is compared with the other approaches. Reasons for this include: the method of converting porcine insulin to human insulin was not seen as novel as those methods which used genetic engineering; the work on converting porcine insulins was being carried out 'in-house' so was not 'public' knowledge; and, it was not seen by the media as being part of the human insulin 'race'.

In this chapter I will draw on two main sources. One is a book by Stephen Hall, 'Invisible Frontiers - The Race to Synthesize a Human Gene' (1987), which describes the human insulin 'race'. This book has attempted to reconstruct the commercial development of human insulin. The other source are news reports from the popular and scientific media.

Since human insulin was to be the first human protein to be produced by genetic technology, I will first describe the meaning of genetic engineering, so that I can set the scene for the development of human insulin. I will then go on to describe one of the key points in the development of human insulin - a symposium organised around human insulin. The next section will describe the progress of the research groups, and how their respective progress was inter-related. I will then look at the process by which human insulin was commercially developed and awarded its product licence. Then, in the final section I will tie in the development of human insulin with some theoretical considerations.

3.2 GENETIC ENGINEERING AND CONTROVERSY

The techniques that were used for the development and production of human insulin employ genetic engineering. Therefore, before I begin, I would like to say something about genetic engineering, and particularly, describe some of the concerns that surrounded it.

Genetic engineering, or recombinant DNA technology, is the process by which the genetic make-up of a living organism is changed by artificial means so that it will produce foreign proteins.[9] A number of features led to the development of genetic engineering:

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[9] Genetic engineering is part of biotechnology. See Bud (1991) for an extensive review of the meaning of biotechnology.

3. The development of human insulin

> "The possibility of genetic engineering derives from three major advances in DNA technology...these are, 1, the discovery of means for the cleavage of DNA at highly specific sites; 2, the development of simple and generally applicable methods for the joining of DNA molecules; and 3, the discovery of effective techniques for the introduction of DNA into previously refractory organisms."
>
> (Sinsheimer, 1975: 52)

When human insulin was first being developed genetic engineering was a novel technique. Due to the unfamiliarity of the techniques being used, there were a number of concerns over the safety of genetic engineering, from such groups as regulatory bodies, public groups and some scientists. It seems sensible therefore, to place human insulin within this historical period.

Concerns over genetic engineering were initially voiced after Herbert Boyer and Stanley Cohen reported their work on gene splicing in 1973. Both Berg and Cohen co-signed a letter, known as the 'Berg Letter' (1974), which was published in the journal Science, amongst others. The letter expressed concerns that similar work, being carried out by other scientists, would produce "infectious DNA elements whose biological properties cannot be completely predicted in advance." (Berg et al., 1974: 1). The letter called upon scientific colleagues around the world to adopt a partial and voluntary moratorium on certain types of recombinant DNA work.[10]

As a result of the letter, a voluntary moratorium on genetic engineering experiments was adopted. However, according to McKelvey, the moratorium was internal to science, because the debate was within scientific journals and:

> "...the regulatory guidelines which most debaters had in mind would be designed, watched over, and evaluated by scientists..."
>
> (McKelvey, 1996: 94)

In 1975 a conference was organised, known as the Asilomar Conference, which attempted to codify the guidelines outlined by the Berg letter. From the Asilomar Conference came a set of general guidelines that were recommended by an international group of geneticists (Philipson, 1977)

So in looking at the develop of human insulin by genetic engineering, we have to consider the controversy that existed over genetic engineering in the middle to late

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[10] See Krimsky (1982) for a fuller account of the controversy in the USA.

1970s. In order to produce human insulin, using genetic engineering, it would be necessary for those involved to allay the concerns over genetic engineering. One way in which this was done was by stressing the reasons why there was a need to produce human insulin. Those wishing to develop human insulin also had to stress that it was only by using genetic engineering that the production of human insulin could be achieved. A key point at which the necessity of producing human insulin using genetic engineering was explicated was at a symposium held in 1976. The symposium was jointly organised by Eli Lilly and another 7 pharmaceutical companies. Although there were 8 pharmaceutical companies involved in the symposium, it was Eli Lilly who was by far the most prominent company.

3.3 ELI LILLY SYMPOSIUM

As stressed in Chapter 1, Eli Lilly are one of the main players in the insulin market. Eli Lilly often helped organise scientific meetings to enable researchers to discuss their work. The symposium held in May 1976, in Indianapolis, and sponsored by the National Academy of Science had a bias towards discussing the possible production of human insulin. Eli Lilly themselves were interested in developing a human insulin by genetic engineering. They had already established an in-house group of scientists to look into the possibilities of genetic engineering. The symposium held in May 1976 aimed to further this interest. Eli Lilly were also interested in uniting both commercial interests and academia, something that they had been doing since 1922 (Hall, 1987: 5).

At the symposium there was a strong emphasis on the benefits of genetic engineering. Irving S. Johnson of Eli Lilly pointed out that there was not a shortage of insulin at the present time, but their could be a shortage in the future. He argued that theoretically pig and cow pancreases would produce enough insulin to supply diabetics. However, he argued that there was an unpredictable supply of pancreases for a number of reasons: drought conditions caused less cattle to be raised; changes in dietary and feeding routines meant that there was a lower amount of insulin in the pancreases of slaughtered animals; some pancreases were 'snapped' up as food delicacies; and, other pancreases were too contaminated to be salvaged (Hall, 1987: 129).

The image presented by Johnson was one where supply was taken out of the control of the pharmaceutical companies and given to nature, or practices were out of the control of the pharmaceutical companies, such as farming techniques and cultural eating habits. What Eli Lilly wanted was to be able to control the amount of insulin that they could supply.

Ruth Hubbard was at the symposium as an opponent of the proposed research. She questioned what was meant by a potential benefit. She suggested that human insulin was a quick fix and would not solve the problems of diabetics. She also argued that if pharmaceutical companies were looking to reduce the cost of diabetes, they should concentrate on needles and syringes, which cost more than insulin per day (Spallone, 1992: 59). If the groups assembled at the symposium were to be successful, they would need to silence these dissenting voices (actors).

The symposium was important because it brought various research groups together. Further, it set the scene for a possible race, between Harvard University and University of California at San Francisco (UCSF). This race would be won by the first to develop and refine complicated DNA technology that could produce the *whole* human insulin structure. However, on another level, there was a battle for the first to produce a commercially viable human insulin, no matter what technique was used. Into this race would come Genentech. After the symposium it was believed that on a practical level "it seemed feasible to get bacteria to make insulin - human insulin..." (Hall, 1987: 6). It is to the outlining of this race that my attention now turns.

3.4 RESEARCH GROUPS AND THEIR PROGRESS

I would now like to describe the progress of the three research groups. Space does not permit a full in-depth look at the step-by-step scientific developments.[11] Instead, I will be concerned with how the research groups stressed the importance of developing a human insulin.

I will also refer to the interest of Eli Lilly in the work of the various research groups. Eli Lilly were interested in the work of the research groups because they wanted to commercially produce a human insulin. Specifically, they wanted this human insulin

[11] The book by Stephen Hall provides an extensive account of the scientific developments (1987).

to be produced by genetic engineering, and not by the conversion of animal insulin (as was the aim of Novo Industri). Eli Lilly also wanted to break into a number of insulin markets, so the control of human insulin technology was very important. By having control of the human insulin production techniques that were being developed by the research groups, Eli Lilly would be able to prevent others from developing the technology. By comparison, Novo Industri were only mildly interested in the research groups, since, as I have already mentioned, they were developing their own form of human insulin.

Two basic DNA approaches were to be tried by three different research groups to produce the insulin gene. Harvard University and UCSF were attempting to produce the human insulin gene by the full DNA approach (Figure 3-2), while Genentech would take the synthetic option (Figure 3-1). Human insulin consists of two chains, known as A and B chains. The DNA approach would attempt to produce both these chains in one process, while the synthetic approach would produce the two chains separately and then join them together. Both groups would have a 'test' project: Harvard University and UCSF would initially work on rat genes; while Genentech would work on somatostatin.

In the following section I will look at the development of human insulin by the three research groups. Some of the issues that I will look at are: the relevance of the human insulin work to society and how this was related to worries over the use of genetic engineering; the involvement of insulin manufacturers; and, how the various groups funded their work.

When looking at the actions of various actors in this study, it is important to be aware of the place of insulin within a number of networks. The use of insulin has long been established as the primary treatment method for Type I diabetes.

Before the advent of human insulin, diabetics injected insulin which had an animal origin. Importantly, animal insulin does not have the same amino acid sequence as that used by healthy individuals. It was suggested that this difference caused complications in diabetes, such retinopathy (damage to the retina) and nephropathy (damage to the kidneys). Further, it was also suggested that the worldwide demand for insulin would outstrip the supply of animal insulin. I suggest that by linking the

problems over existing animal insulin treatments and the necessity for insulin per se, research groups were able to negate some of the controversy over genetic engineering, such as that of Ruth Hubbard. Added to this, there was already an existing market for insulin and there were already insulin manufacturers ready to fund the development and production of 'new' and more 'efficient' insulins.

3.4.1 The Progress of the Research Groups

Due to the concerns over genetic engineering one of the questions that I wish to deal with here is: Why did the groups choose human insulin as the first project in which genetic engineering and commercial production would be incorporated? As I will show, one reason for this was the placing of insulin within society, namely that it was a well known drug. By using a well known drug the research groups were easily able to put a case forward for the development of that drug by genetic engineering.

In 1976, noted biophysicist Walter Gilbert and his research group were working on globin. Globin did not have the same medical impact as other genes so the researchers were considering other genes. They believed that it was important to have an 'interesting' gene so that funds and expertise could more easily be attracted to the project. Gilbert argued that:

> "Somewhere very early on we switched to the idea of insulin, with the argument that it was a smaller protein, and actually a more useful one, to make in bacteria..."
>
> (Hall, 1987: 19)

Herb Boyer and Robert Swanson, who would form Genentech, were also interested in producing insulin. They wanted to establish a new pharmaceutical company with research, manufacturing, and marketing all under one roof. They knew that the selection of the initial product was very important. Swanson claimed that they:

> "...looked for a product that could have a relatively short time through the regulatory hurdles. That was a key factor."
>
> (Hall, 1987: 24)

They, like Walter Gilbert, also wanted a drug that already had public recognition, and human insulin appeared as one possible candidate. In April 1976 Boyer and Swanson formed their pharmaceutical company - Genentech. They received $100,000 capital form Kleiner and Perkins, a venture capital firm. When Genentech was formed Boyer

was a professor of biochemistry and biophysics at UCSF. Prior to forming Genentech, Robert Swanson was a partner with Kleiner & Perkins.

Genentech issued their first contract to Arthur Riggs, the City of Hope Hospital, and his team for $300,000.[12] The project was to produce somatostatin, a hormone which effects the secretion of growth hormones, insulin and glycogen. It was perceived by them as a good model system and stepping stone to human insulin. Somatostatin was used as a model system for a number of reasons: it was a relatively small hormone; its chemistry was well known; and sensitive tests were available to test whether it was active in a cell (Business Week, 1977). As Arthur Riggs argued:

> "Insulin was definitely part of the contract. The plan was just to demonstrate feasibility, and obtain patents, with somatostatin, then immediately go for insulin."
>
> (Hall, 1987: 84)

One of the problems that the research groups encountered was over the ability to carry out the genetic engineering work. In order to be able to do this the research groups had to put a case forward for their research. The moratorium on DNA technology was lifted by the National Institutes of Health (NIH) on the 23rd of June 1976. It then became possible to carry out of genetic engineering work (Norman, 1976; Wade, 1975). Most planned experiments were then allowed to go ahead, but under strict safety controls.

However, Cambridge City Council in Massachusetts, where Walter Gilbert and his Harvard group would be carrying out their work, still had concerns. At a meeting held in July 1976, Gilbert put forward reasons why the work should be allowed to take place. He argued that:

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[12] The team also submitted a grant proposal to the National Institutes of Health (NIH) to produce somatostatin. However, the NIH claimed that the work was simply an intellectual exercise, and that they didn't think that it could be done in three years.

3. The development of human insulin

"One of the experiments we're interested in is putting the gene for human insulin into a bacterium. The purpose of that experiment is to make human insulin, a specific hormone, available. You probably know that insulin is used to treat diabetics. You may or may not know that the source of that insulin is from pigs or from cows, and that molecule is not identical to the one that is in all our bodies. [He added that these commercially available insulins were not perfect]...We are making something which is, beyond price. It is not that we are making cheaper medication. We are making something we cannot get by other means..."

(Hall, 1987: 53)

We see here that the idea of linking the science to wider social issues is very important. However, The Coalition for Responsible Genetic Research pointed out:

> "In spite of the pervasive effects of the atomic bomb and the increasing domination of so many aspects of life by technology, the assumption [that progress in science is progress for society] has been preserved by biologists who, to receive immediate public approval, have had to cite only the general relevance of their work to medicine."
>
> (Coalition for Responsible Genetic Research, 1977)

It is notable that one of the reasons why the research groups chose human insulin as a research project was also seen, by some, as a criticism. As I have already stressed, there was an important reason why human insulin was being developed using DNA technology. By surrounding the DNA technology with a prospective use-value for diabetics and society, it becomes more than of 'internal' interest to science. However some, such as The Coalition for Responsible Genetic Research, saw the attachment of genetic engineering technology to the prospective use-value of the resulting gene as being a way to carry out the research. From this point of view, the production of human insulin came secondary to developing genetic engineering.

Despite some of these concerns, the Harvard group was given the go-ahead to carry out genetic engineering work (Culliton, 1976: 25). Gilbert and his group were then able to carry out their work; as with the UCSF group, they would base their work on producing rat insulin.

Genentech were not restricted by the National Institutes of Health (NIH) restrictions. They were using synthetic DNA, and the NIH guidelines said nothing about synthetic DNA. Boyer stated the mounting regulation against recombinant DNA work as one of the reasons for using the synthetic option (Hall, 1987). Boyer could in effect exploit a loophole in the guidelines, in terms of physical access to laboratories,

regulation and, public concern.

Perhaps because the UCSF group were able to carry out DNA research as soon as the NIH lifted the ban on DNA research, they were the first to clone the gene for the rat insulin hormone. They put together a paper for the journal *Science* and applied for a patent. In May 1977 the paper on cloning rat insulin genes was given to the editors of Science magazine (Hall, 1987: 140).

On May 23rd 1977 the UCSF team held a press conference to announce the cloning of the rat insulin gene, and "because insulin continued to be a magic word, the response was almost overwhelming." (Hall, 1987: 142). The work received considerable attention in the press and within the scientific community. One reason for the attention was that the researchers had achieved, "much earlier than expected, the first step towards the goal of isolating the human insulin gene and using it for the manufacture of insulin protein" (Wade, 1977: 1342). Importantly, scientists could see the potential benefits of recombinant DNA technology. Great expectations were also being 'whipped up' in the public sphere for the possibilities of genetic engineering. For example:

> "Possible benefits began to sound like certain benefits. The possibility of cheaper therapeutics became the certainty of cheaper therapeutics."
>
> (Hall, 1987: 145)

At the UCSF press conference the research was described, as was some future research - the rat insulin would be expressed in bacteria within six months - but more importantly, human insulin was only a year or two down the line. The paper was published in Science on June 17th 1977 (Ullrich et al., 1977). At this point "everyone in the scientific community could appreciate the resourcefulness of the San Francisco team." (Hall, 1987: 145).

It was also pointed out that the paper in *Science* did get published quickly and suffered from an unusually significant number of typographical errors. According to some, this suggested that there were significant political overtones to the editorial handling of the work. One reason could have been that the experiment was seen as a stepping stone to public acceptance of recombinant DNA technology by the public (Hall, 1987: 142).

A few months later, the Genentech group had cloned and expressed somatostatin. With these results, Genentech burst out ahead of the biotechnology pack. Genentech moved ahead of UCSF because UCSF had only cloned a gene (rat insulin) and not expressed it. As Hall writes:

> "Somatostatin in a sense was a scientific show-and-tell; human insulin was a money-maker. Doing human insulin, and doing it first, might well establish Genentech's pre-eminence in the emerging field of biotechnology..."
>
> (Hall, 1987: 165)

A paper was written and accepted by the journal *Science* and appeared on the 19th December 1977 (Itakura et al., 1977). A press conference followed a month later, in which the results were reiterated. Subsequent press reports claimed that recombinant DNA technology would now be able to deliver on its promises. Further, it became more obvious, as the media reported the developments, that somatostatin was the gateway to human insulin.[13] The somatostatin work was seen as a model system into which human insulin could be placed. According to Arthur Riggs, "essentially the same recombinant DNA techniques were used in the somatostatin and the present insulin work..." (Gunby, 1978: 1698).

The somatostatin results added to the rat insulin work, by UCSF, in re-framing genetic engineering. It was argued that the public were able to see the possible social benefits of genetic engineering. Rather than being for science in itself, genetic engineering could be seen as having wider implications. Pfund and Hofstadter (1981) have looked at articles in the American media about industry involvement in recombinant DNA technology. They looked into seven major newspapers, ten magazines and six science/medical periodicals between 1976 and 1979. They found that before the mid-to-late 1977 reports concentrated on the controversy surrounding genetic engineering, however, towards the end of 1977 the benefits of genetic engineering were stressed instead.

With the developments in DNA technology it was becoming obvious that genetic engineering could be big business. For example, following on from the Genentech press conference, Genentech easily raised $1 million dollars to move onto the

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[13] Indeed, it was questionable whether somatostatin would ever be commercially produced (Hall, 1987: 175).

production of human insulin. With this funding Genentech would not only go for human insulin, but also other important genes, such as growth hormone, the interferons and interleukins.

Not everyone, however, was interested in these new developments. In early 1978 Genentech had approached Novo Industri about the possibilities of a R&D contract for genetic engineering (McKelvey, 1996: 128-129). Novo Industri were not interested in such a contract for a number of reasons:

1) Genetic engineering was a new technique and very uncertain, Novo Industri believed that the technology wouldn't work.
2) Novo Industri questioned the long term viability of genetic engineering techniques.
3) At the time Genentech were a new and unknown company.
4) Novo Industri were developing their own technique to convert porcine insulin into human insulin, that drew upon their existing competencies with enzymes.

There was also corporate interest in the work being carried out by the other two groups. Towards the end of 1977, Gilbert was being approached by a number of venture capitalists. T.A. Associates wanted to bring together a 'dream team' of scientists to form a pharmaceutical company. Although Gilbert was initially uneasy about uniting academia and business, after a number of meetings he became more interested. Gilbert was a well known and respected figure within the scientific community, and as a result, it appears that he was the main representative of the scientists that were gathering on this 'dream team.' Due to his standing in the scientific community other scientists saw the formation of the company in a positive light. It was also Gilbert who was helping to direct the possible research projects of the company in discussion with T.A. Associates. Gilbert admitted that his motivation was in:

> "...wanting to do something socially useful, wanting to create an industrial structure, wanting to make something grow, wanting to make money. Although the desire to make money is not that high, generally, in scientists..."
>
> (Hall, 1987: 195)

On May 6th Biogen was officially formed. Their primary targets were alpha interferon and the hepatitis B vaccine, as they promised to be large and lucrative markets. Gilbert also knew that another aim was to duplicate their work on rat insulin, but for

human insulin. Eli Lilly also attempted to gain a license to have access to the techniques developed by the Harvard University team, with the aim to develop them for use in commercial production. However they failed, with the license going to Biogen (McKelvey, 1996: 132).

Eli Lilly had also been in discussion with the UCSF research group. During the summer of 1978, the final touches to the agreement were made to develop not only human insulin, but also human growth hormone. The contract was estimated at $1.3 million dollars lasting for five years, during which time the UCSF would carry out research and retain ownership of the resulting material and techniques. In return, Eli Lilly would get first refusal as to whether they wanted to license the results (McKelvey, 1996: 131). They would also build a new laboratory in Strasbourg for the work. At the same time Eli Lilly were also having discussions with Genentech. It appears that Eli Lilly were covering all possibilities.

Looking at the two main pharmaceutical companies, both Novo Industri and Eli Lilly seem to have seen human insulin as the direction in which future developments of insulin should be headed. However, the paths by which this was to be achieved were different. Initially, Novo Industri were interested in their in-house work on converting porcine insulin to human insulin. On the other hand, Eli Lilly were interested in the new genetic engineering approaches.

One of the necessities of the work being carried out by both UCSF and the Harvard group was not just that insulin was being expressed but also that it could be secreted. When the UCSF research group reported their work in 1977 they had cloned rat insulin, but they had not secreted it. It would be necessary to secrete insulin in order to harness the process for industrial application. In August 1978 the Harvard group published a paper which described the secretion of rat pre-proinsulin (Villa-Komaroff et al., 1978). The paper was published in the *Proceedings of the National Academy of Science* (PNAS), which is the publication of choice when you have a 'hot result' (Hall, 1987: 223). Although there was no actual mention of human insulin in the paper, there was an awareness that the work was a "step toward using bacteria to

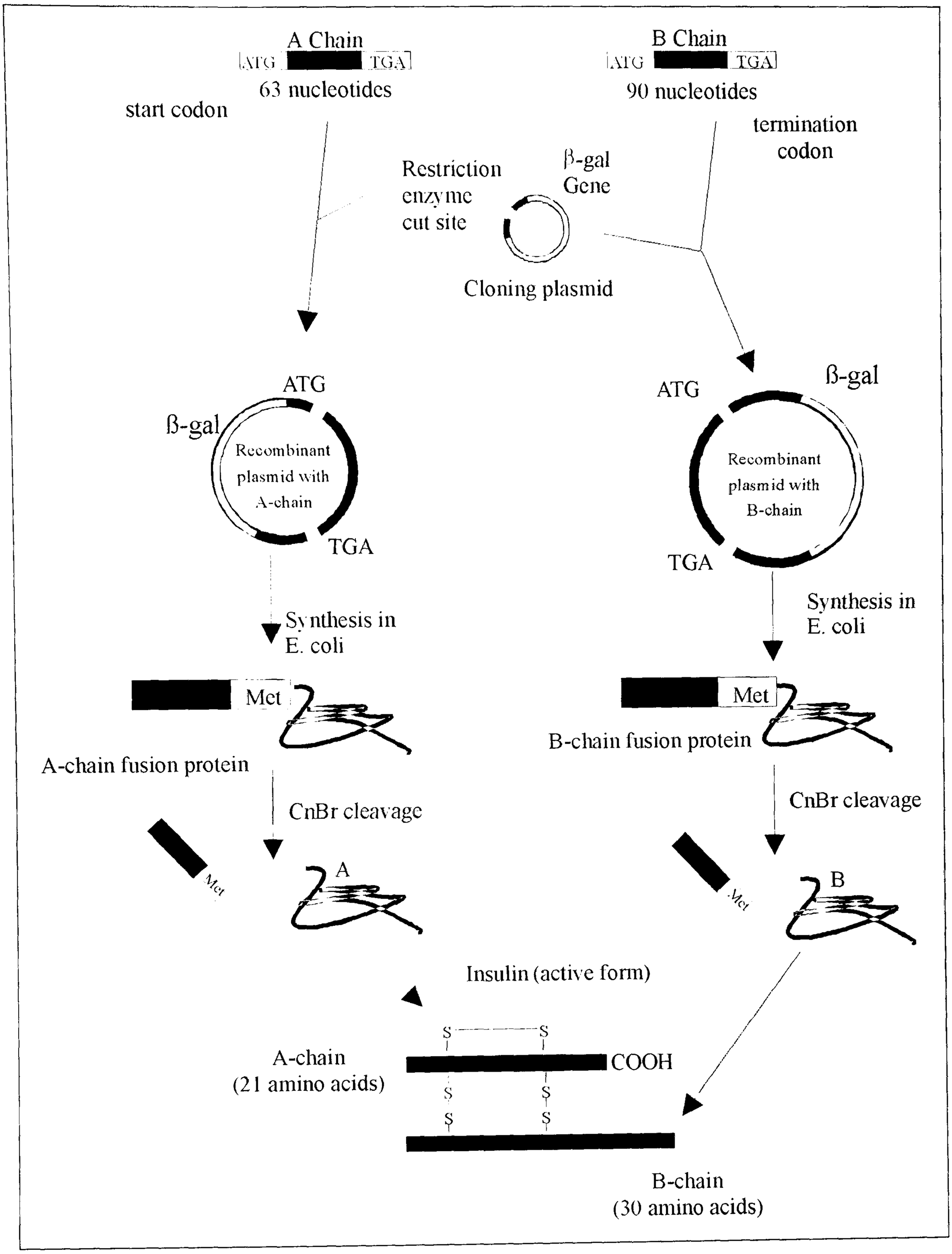

Figure 3-1: Procedure involved in the production of bio-engineered human insulin (BHI) using the two separate chains method (Taken from Chien (1996))

produce human insulin." (Gunby, 1978: 1698). The paper caused media excitement, more for the fact of the possibilities than the work in itself. It was now believed that the promised human insulin was just around the corner (Hall, 1987: 235).

With the secretion of rat insulin the group could now use a similar technique for the production of human insulin. With the backing of Biogen, Gilbert attempted to produce human insulin with the same team that synthesised rat insulin.

However, by the end of August 1978 the Genentech team had successfully produced human insulin (Figure 3-1. Taken from Chien (1996)). There is an interesting comparison between somatostatin and human insulin. Compared with somatostatin, human insulin was not as scientifically interesting to the scientific community (since the production of human insulin was basically a repetition of the techniques used for somatostatin). However, to the general public, human insulin was more exciting than somatostatin. Human insulin was more embedded within the concerns of the public. For example, most people know that diabetics need insulin. This led Spyros Andreopoulos, of the Stanford University Medical Center, to claim that:

> "...while perhaps not as glamorous as human insulin, one could have written the same story about any number of cloning experiments at the time."
>
> (Andreopoulos, 1980: 744)

On hearing the news from Genentech, Earl B. Herr, Jr., president of Eli Lilly Research Laboratories, claimed that:

> "Our agreement with Genentech was made to assure diabetic patients of the continued availability of insulin without total dependence on animal glands."
>
> (Quoted in Gunby, 1978: 1697)

Negotiations with Eli Lilly had been going on since early 1978, but with the demonstration that human insulin could be produced in the laboratory, the links with Genentech were fixed in August that year. Eli Lilly now had links with two research groups - UCSF and Genentech. Swanson, the founder of Genentech, planned to link Genentech to Eli Lilly because, Genentech knew very little "...about processing, fermentation, scale-up testing, shepherding a drug through clinical trials, winning Food and Drug Administration (FDA) approval, marketing, and sales." (Hall, 1987: 268). With the knowledge that Genentech could gather from the scale up of human insulin. they hoped to be able to follow other projects right through to commercial production.

A press conference was held on the 6th of September (Genentech, 1978) which came

before the scientific papers were published (Crea et al., 1978; Goeddel et al., 1979).[14] The press conference attracted many television and media journalists. Just as with the development of insulin by Banting and Best in 1922, human insulin became world news. Bliss writes of the Banting and Best discovery:

> "...everything connected with this discovery, the development of insulin, and its application to human beings, was read with the greatest interest...He [Banting] was in demand everywhere as a speaker...and the press was constantly seeking to interview him."
>
> (Bliss, 1983: 80)

The effect of the publicity and press conference was also to show that the recombinant DNA work was relevant to society. In the press release, for the press conference on human insulin, Swanson argued that:

> "The development of human insulin demonstrates the viability of using recombinant DNA technology to produce products with practical application."
>
> (Genentech, 1978)

This again illustrates what Pfund and Hofstadter (1981) argued, that the view of recombinant DNA technology moved, between 1976 to 1979, from controversy, over its safety to the public, to one of medical benefits to the public.

At the press conference, the experiments were outlined and the name Genentech became a 'household name.' Further, there was an outlining of the long range commercial development of human insulin (Gunby, 1978: 1697). Genentech also raised $10 million dollars, from Lubrizol Corp., to pursue other projects, such as interferon.

Andreopoulos (1980) has pointed out that critical questions that would have put the work into perspective were not asked at the press conference. The substance had not actually been tested on animals, one reason for this was that the experiments were not producing enough insulin to make this possible. This was a criticism not just of human insulin, but also of other innovative discoveries, such as the synthesis of human growth hormone and clones of interferon-producing bacteria (Andreopoulos,

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[14] A member of the research group presented their work at a seminar before the press conference, so that the work would be in the scientific domain. One reason for this was that there was a rumour that a major paper was going to be given by the Harvard group. In fact, Gilbert knew of no such meeting and had nothing to report anywhere, but hoped to try to produce human insulin in September (Medical World News, 1978: 10).

1980: 744). However, the majority of the media took it as a fact that insulin could be scaled up to commercial production, and could be used for the treatment of diabetes.

Eli Lilly were however aware of the hypothetical nature of the commercial production of insulin. They were aware that just because human insulin had been produced in the laboratory, did not mean that it could be scaled up and commercially produced. Although they agreed to fund research and development of human insulin, with the aim to scale it up, there was no commitment that human insulin would be produced commercially. Eli Lilly wanted to see whether the scale up of human insulin could be done (Hall, 1987: 276). Indeed, Eli Lilly had actually negotiated a tough deal with Genentech requiring them to meet a number of benchmarks.

Before I go on to look at the scale up of human insulin, I would like to say something about the other two research teams.

3.4.2 A Final Note on the Other Two Groups

Although I have already explained who 'won' the race, that is not the end of the human insulin story. After the agreement between Eli Lilly and UCSF was signed, UCSF successfully isolated and cloned the human proinsulin gene. This was around the time that Genentech had produced human insulin. This was not as disturbing as it seems since the UCSF research group were interested in isolating the human gene, that is, seeing the array in its entirety. Genentech's synthetic approach did not reveal such information, it simply produced human insulin.

Meanwhile, one of the members of the UCSF group moved to Genentech to continue to develop the pre-proinsulin work. By the end of 1979, with the help of the new member of the group, Genentech had successfully cloned the preproinsulin in E. coli (Frank et al., 1981). See Figure 3-2 (taken from Chien (1996)).

Eli Lilly now had two possible methods to produce human insulin. They opted to first go for commercialisation of the original procedure, the linking of the separate insulin chains, although privately they preferred the proinsulin bacterial method (Hall, 1987: 294).

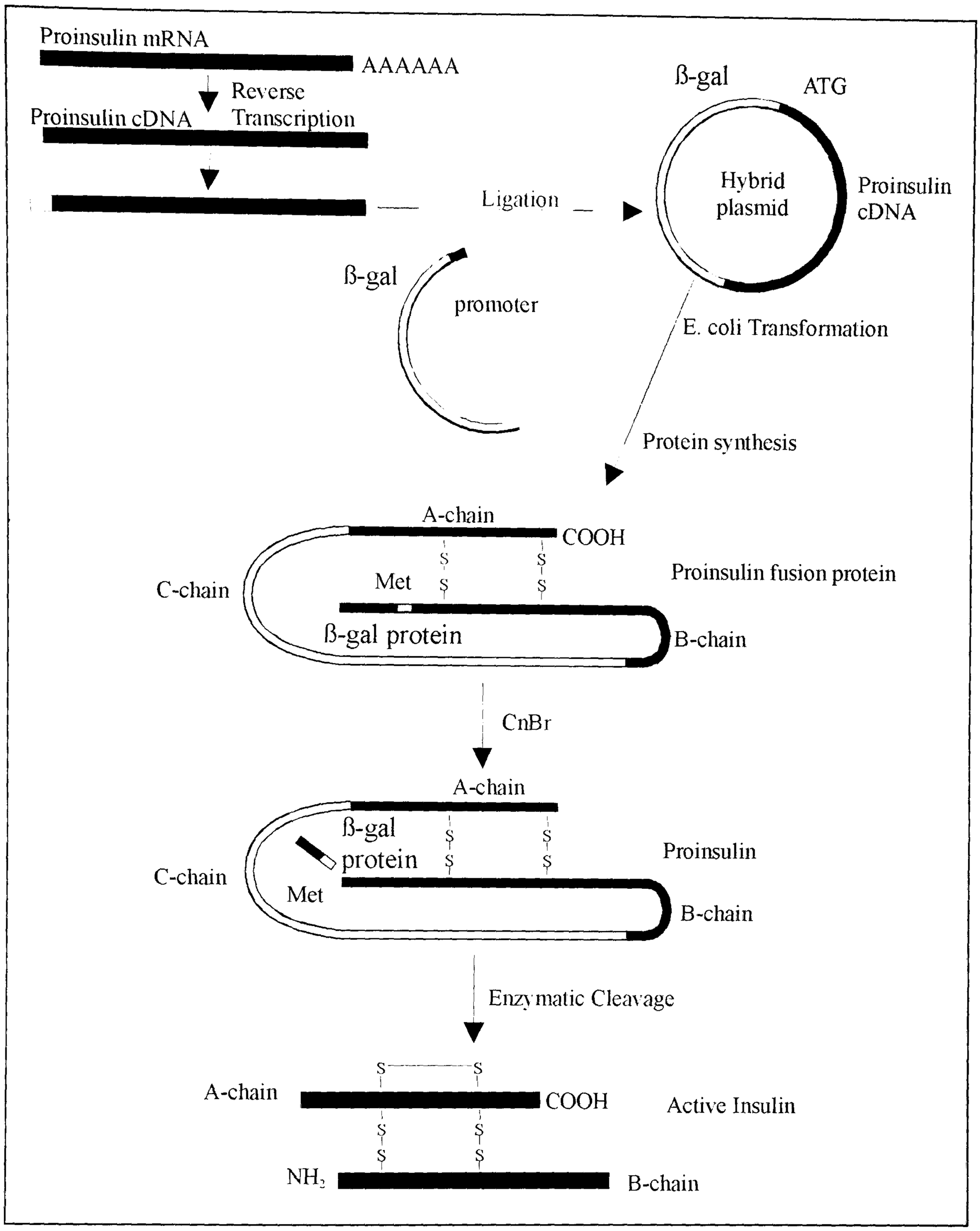

Figure 3-2: Procedure involved in the production of bio-engineered human insulin using the proinsulin method (taken from Chien (1996))

As is now clear, it was Genentech who 'won the race' for human insulin. However, in late 1979 the UCSF group found the human insulin gene, not an abbreviated version, but the full genetic structure (Bell et al., 1980). The identification of the gene gave an excellent up-to-date understanding of genes. It is interesting that Genentech's bacteria were producing human insulin over a year before the actual insulin gene was isolated from the human chromosome.

The Harvard group, with the backing of Biogen, attempted to produce human insulin. However, again, they were having problems with access to the necessary laboratory. Since the human insulin experiments were using human genetic material they had to be carried out in a more tightly controlled laboratory than was necessary for the rat insulin work. Access to such a laboratory could not be found in America, so Gilbert applied to use the British Army's Microbiological Research Establishment in Porton Down. In order to carry out the work there they had had to pack up all the equipment that they would need for the human insulin experiments. While carrying out some of the experiments for human insulin they had inadvertently cross contaminated the human insulin work with their previous rat insulin work, a type of contamination known as transtubation. Gilbert described the trip to England as a "total disaster" (Hall, 1987: 265).

So the development of human insulin led to a number of outcomes: it became possible to produce human insulin by genetic engineering in the laboratory; techniques used in the laboratory could be applied to other settings; and, more was known about the human insulin gene. In the following section I will look at some of the issues that were important in the commercial production of human insulin.

3.5 COMMERCIAL PRODUCTION

I would now like to look at the scale up and clinical testing of human insulin, what Jasanoff calls regulatory science (1990). With the movement from laboratory production to the commercial scale up of human insulin, commentators were able to see how the technology could realistically solve the predicted supply problem of insulin. The *British Veterinary Journal* argued that:

> "The benefits to be derived from this work are multiple which adds to their importance. It is predicted that during the next 20 years the demand for insulin will outstrip the production capacity of the conventional technique of isolation from animal sources. This restriction is now being removed with the advantage of producing human insulin of high purity for the treatment of diabetes in man."
>
> (British Veterinary Journal, 1980: 518)

It was also predicted that the technology would go significantly beyond the production of human insulin. For example, it was argued that a number of uses of the technology were on the immediate horizon: it could be used to produce hormones, interferon, vaccines, antibodies, enzymes and for prenatal diagnosis (Riggs and

Itakura, 1979: 537-8).

When Genentech was able to show that human insulin could be produced commercially, Genentech and Eli Lilly parted company. In the process of developing human insulin Genentech had established themselves as the first biotech company, and the one that had used gene-splicing to produce human insulin for the treatment of diabetes. The separation between the two companies was however, an amicable one. As McKelvey points out:

> "Lilly were not willing to share the insulin market or jointly develop insulin production with Genentech. Nor was Genentech overly eager to try to enter a market that was so completely dominated by a few firms."
>
> (McKelvey, 1996: 140)

By the middle of 1980 Eli Lilly had tested the insulin for purity and bacterial contamination. Human insulin was then ready to enter other clinical tests. Eli Lilly had also cleared the construction of large scale fermenters through the Recombinant DNA Advisory Commission. The fermenters would be necessary for commercial production of human insulin. Three months later, Eli Lilly announced plans for their construction, one in Indianapolis and the other in Speke, England, at an estimated cost of between $70 - $80 million dollars. The plant at Speke was expected to produce human insulin for clinical trials towards the end of 1980 (Wright, 1980). This led some to comment that:

> "Eli Lilly's investment in its insulin manufacturing facility devoted to biosynthesized human insulin should...prove a good investment - for the shareholders and mankind."
>
> (Nossal, 1980: 286)

Later, in 1980, Eli Lilly received permission to start large scale production of synthetic insulin and proinsulin, and also human growth hormone, somatostatin and theymosunalpha-1. By this time DNA technology was becoming big business, as a leading molecular biologist said, "There are millions of dollars floating around. If you claim something fancy you can raise a lot of money." (Quoted in Wade, 1980: 492).

Pharmacology	Toxicology studies in animals (efficacy, metabolic and toxicological assessments).
IND	Investigate New Drug.
Phase I	Trials to test the safety and dosage in 20-50 healthy subjects.
Phase II	Trials to test its efficacy against the targeted illness, 20-100 subjects.
Phase III	Trials to test the effectiveness against existing treatments for the same illness, 500-5000 subjects.
NDA	New Drug Application.
Phase IV	Continuation of Phase III or post-marketing pharmacovigilance survey.

Figure 3-3: Overview of clinical testing for pharmaceuticals

Before human insulin could become commercially available it had to go for clinical trials (see Figure 3-3). These clinical trials would delimit what human insulin could do, in effect, 'checking' its theoretical claims. Chance et al. (1981) outline a 'complex battery' of biochemical and animal systems (12 in all) through which human insulin was tested and compared with both pancreatic human insulin and standard pork insulin. Their conclusion was:

> "All results obtained on BHI indicate that it is chemically, physically, and biologically equivalent to pancreatic-derived insulins."
>
> (Chance et al., 1981: 149)

Once passed through chemical and animal testing, controlled trials on healthy subjects could be carried out. However, there were still some voices of caution. For example:

> "...it is still in the experimental stage and much work needs to be done before anyone can dare hope that it will be the day-to-day insulin available for human use."
>
> (Iveson-Iveson, 1980: 37)

In the middle of 1980 Dr. Harry Keen, of the Unit for Metabolic Medicine at Guy's Hospital in London, performed the initial clinical tests, on healthy volunteers, using human insulin from Eli Lilly (separate chains) (Wright, 1980: 4). It was believed that if "successful in healthy people, clinical trials on diabetic patients could start by the end of September." (New Scientist, 1980: 351).

As each new development was reported, constant reference was made to the benefits of human insulin over conventional insulins, to take but one example:

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> "Unfortunately, there is a world shortage of animal insulin. Another problem the new synthetic insulin might solve is that animal insulin sets off an immune response in the body and a large proportion of the hormone is destroyed in the blood without ever benefiting the patient. However the hormone churned out by Eli Lilly's bacteria is practically identical to that produced by humans."
>
> (New Scientist, 1980: 351)

As already shown, it was believed that the best insulin was that which most closely resembled that produced by the body. Indeed, this was one of the reasons why pork insulin had superseded beef insulin. Compared to human insulin, beef insulin differs by three amino acids, while pork insulin differs by only one (see Figure 2-3). As Galloway argued:

> "...the best insulin is that which is the purest and has a chemical structure most like human insulin - has resulted in a marked shift of insulin usage from beef containing insulins to monospecies pork. It has been an important impetus to the research and development that has led to the production of human insulin using recombinant technology."
>
> (Galloway, 1980: 615)

The results from the study by Keen (1980) were published in August 1980. The results showed that there seemed to be no demonstrable difference between purified porcine and genetically synthesised human insulin:

> "We have, therefore succeeded in demonstrating, in a small number of intensively studied healthy volunteers, the safety and efficacy of a human preparation produced in E. coli by recombinant DNA technology. This is but the first step in a longer process of investigation of its actions, validation of clinical efficacy in diabetics, and continuing vigilant surveillance for unexpected adverse effects."
>
> (Keen et al., 1980: 401)

Keen also claimed that genetically engineered human insulin may be more bioefficient than animal insulin, because it would be absorbed by the body more quickly. It was also claimed that human insulin may suppress the production of toxic substances in the kidneys (Yanchinski, 1982).

Similarly, a study carried out by Novo Industri, on diabetics using their converted insulin, found that human insulin's effect on the body was identical to very pure pig or beef insulin (Yanchinski, 1982). It is important to realise that these early studies did not show that human insulin was necessarily more efficient than existing conventional insulins, rather, they were equivalent. However, Novo Industri were

still pleased with their results. The prediction that human insulin would solve some of the complications of diabetes could not be shown, because this would require prolonged use of the new insulin. Indeed, there was some concern that no long term studies were planned (Yanchinski, 1980: 720). However, this did not prevent the hope that engineered human insulin would reduce the risk of diabetic complications, because it had the same amino acid sequence as 'natural' pancreatic human insulin. One of the biggest costs of diabetes are the associated complications (both direct and indirect) which may develop over time (Datamonitor, 1997), so any attempt to reduce these complications would be warmly welcomed by both diabetics and the medical profession.

There was also some disagreement over the interpretation of some of the experimental results. Teuscher and Diem questioned the results of skin tests, which aimed to test for adverse reactions:

> "We were surprised that Keen et al. found positive skin tests with their human insulin in some of the healthy volunteers. Although described as minor and trivial, erythema and swelling were still present 5h after intracutaneous injection..."
>
> (Teuscher and Diem, 1980: 1186)

There were also some wider concerns over the predicted benefit of human insulin. Yanchinski argued that animal insulins "have worked well until now" (Yanchinski, 1982: 697) and this was backed up by Keen's study, which concluded that:

> "...there seems to be little demonstrable difference between the purified porcine and the genetically synthesised human insulin."
>
> (Keen et al., 1980: 400-1)

Human insulin may not therefore solve some of the complications of diabetes. For example, Dr Kurt Alberti, who was instrumental in Novo Industri's clinical trials at the Royal Victoria Infirmary Hospital, Newcastle Upon Tyne and Nottingham General Hospital, claimed that most diabetic complications resulted from wide variations in blood glucose levels due to injecting insulin. High levels of glucose have been shown to damage the body's structural proteins, and subsequently, cause retinopathy (damage to eyes) and nephropathy (damage to the kidneys) (Yanchinski, 1982).

3.5 Commercial production

One solution to these complications, according to Alberti, would be the use of insulin pumps. Insulin pumps provide a continuous controlled insulin infusion. This continuous infusion of insulin would prevent variations in blood glucose, which "may be responsible for many of the most serious complications of diabetes, such as blindness, vascular disease, and kidney failure." (Sun, 1980: 1227).

External pumps were already used by several hundred diabetics, however, the aim was to develop internal pumps, similar to pace makers. There were a number of concerns in relation to insulin pumps and insulin: conventional insulins tended to clog the tubing of the pump; conventional insulin can 'go off'; the size of the pumps; the ability of the pumps to detect changes in glucose levels and adjust insulin supply accordingly; internal pumps would need more concentrated insulin to reduce the time between refills; and, there needs to be a fail-safe way to control dose, since an excess of insulin can result in death. The insulin suppliers were keeping abreast of the development of insulin pumps, and some were developing their own devices.

There is an important link here between pumps and insulin. It was reported that the question of insulin type would move from the control of the manufactures of insulin to the manufactures of insulin pumps, since the pump manufacturers would be able to specify the insulin formulations that they required for the insulin pumps. Therefore, companies that manufactured both insulin and insulin pumps would have a strong advantage. John Galloway, a scientist at Eli Lilly, argued that insulin pump makers would demand "the best insulin, and the best insulin will be human insulin, barring any surprises." (Quoted in Sun, 1980: 1227).

It is also important to look at the insulins that human insulin was intended to replace. Some medical professionals questioned the advantages, claimed by using Novo Industri, of their purified insulins. Novo Industri claimed that their purified insulins would prevent allergic reactions, which occur in 5 percent of diabetics who take conventional insulin. Reactions include skin rashes and lipoatrophy, where the fat cells around the injection site deteriorate and form 'dents' in the skin surface. There were also suggestions that purer insulins reduced antibody build up, which can block insulin action in patients.

However, some in the medical profession argued that purified porcine insulin only

benefited a small percentage of diabetics. Those who would benefit were those who experience allergic reactions to conventional insulins. Josse Roth, chief of the National Institute of Arthritis, Metabolism, and Digestive Diseases, argued that Novo Industri and Nordisk had made a big deal about the purified insulins, but that patients would not benefit from these insulins (Sun, 1980: 1226). A. M. Albiseer, director of biomedical research at Toronto's Hospital of Sick Children, put it another way, he argued that using purified insulins is like "using high octane gas in all vehicles." (Quoted in Sun, 1980: 1226).

Eli Lilly agreed that purified porcine insulins were unnecessary, although for different reasons. They argued that so much insulin was lost in the purification processes, that there would be a shortage of insulin if everyone used purified insulins. Novo Industri however, claimed that it only lost an additional 10% of insulin in its purification process. Even though Eli Lilly claimed there would be a shortage of animal insulins, they too were developing a purified porcine insulin of their own. Further, as James Smart of Nordisk claimed, the emphasis on a shortage was self serving: "It's very intelligent marketing until Lilly gets their recombinant DNA insulin." (Quoted in Sun, 1980: 1226).

So was there a shortage? The Food and Drug Administration (FDA) said that evidence of a shortage was hard to come by. A study by the FDA and the National Diabetes Advisory Board in 1978 found that there would be adequate supplies of insulin for the next 20 years. As already pointed out, the supposed supply problem may be due to distribution and availability of animal glands, rather than the number of animals that are slaughtered each year (Teuscher and Diem, 1980: 1186). Further:

> "...with use of all available pancreas, supply could easily exceed current demand. Distribution is more of a problem than supply, and efforts must be made to improve this for the benefit of developing countries where patients with diabetes still die because of 'non-availability of insulin.'"
>
> (Teuscher and Diem, 1980: 1186)

It appears that there was little evidence of predicted shortages, as John Gueriguian of the FDA pointed out, "We haven't seen a shred of data about a shortage. We get the same letters [predicting shortages] ad nauseam but no data." (Quoted in Sun, 1980: 1226).

3.5 Commercial production

Just as purity was an issue with conventional insulin, it was also an issue with human insulin. Scientific claims of purity range form 5-50%, while for pharmaceutical companies, drugs have to be almost 100% pure (Hall, 1987). The most common impurities in recombinant drugs are proteins. Protein impurities can cause allergic reactions, or alter the therapeutic effects of the drug. Such impurities are not as important in scientific experiments. Insulin had to be so pure because the body would react against any impurities. In the pharmaceutical industry, purity is finally decided when the patient doesn't show any allergic reactions or side-effects.[15] Paul Burnett from Eli Lilly claimed that, "Our product [human insulin] is equal or better than the best porcine insulin in purity." (Quoted in Yanchinski, 1980: 760). Claims of purity was even more of an issue in the case of human insulin, because the issue of purity was one of the causes of competition between the insulin manufactures. For example:

> "The reason for this expensive effort, according to Paul Burnett, who is in charge of Lilly's molecular biology unit, is that animal insulins can cause severe allergies with prolonged use. However, in reality, both companies are using their new products to poach on each other's commercial territories."
>
> (Yanchinski, 1980: 760)

The situation between the companies was defined in strong terms, with headlines such as 'Genetic engineers battle over insulin' (Yanchinski, 1980) and 'Insulin Wars: New Advances May Throw Market into Turbulence.' (Sun, 1980). The 'battle' was over dominance of the insulin supply market:

> "A battle royal is taking place between two drug manufactures to decide which will be the first to sell synthetic human insulin and so dominate a market in the United States and Europe worth billions of dollars."
>
> (Yanchinski, 1980: 760)

Eli Lilly were unable to access other insulin markets because the Federal Trade Commission (FTC) were concerned with their monopoly of the insulin market in America. Eli Lilly did not want to fight against the FTC and agreed with the FTC to "license out its existing know-how in insulin manufacture to domestic and foreign companies." (Sun, 1980: 1227). However, Eli Lilly managed to retain their insulin

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[15] A fascinating account is given by McKelvey of the initial trials of human growth hormone, where subjects in phase one of clinical trials showed allergic reactions to the hormone, even though analytical tests showed the protein to be pure. The result therefore was that the invisible, the impurities, became visible though the subjects. Later, the invisible would be shown by the development of more sensitive analytical tools, such as silver staining SDS gels or High Pressure Liquid Chromatography (HPLC) (McKelvey, 1996: 205-217).

knowledge in respect of future developments in that they only had to share their knowledge with American companies. Since Novo Industri and Nordisk are not American, they did not have access to the recombinant DNA technology, so this new knowledge was a way of by-passing the FTC ruling.

There was great competition between Novo Industri and Eli Lilly to be the first to market human insulin. There are many barriers that prevent entry into an insulin market that is already dominated by another company. One barrier is the ability to differentiate insulin products (Datamonitor, 1997). Novo Industri had done it with their purified animal insulins, and gained some success. Now both companies were attempting to do it with human insulin - human insulin represented a degree of product differentiation.

The company to market human insulin first would be the company able to negotiate various regulations. In 1981, it was argued in *SCRIP* (A journal of world pharmaceutical news) that "Novo's lead could be as much as 12 months over Lilly." (1981a: 15). One reason for this suggestion was that it was believed that Novo Industri were enjoying a relatively trouble-free development programme (SCRIP, 1981a: 15), and progress through regulations. As Scott King argued:

> "Novo Industri has chosen the more expedient route of having protocols designed to achieve approval in the minimal time, [where as Eli Lilly] has devised time-consuming protocols that are evidently designed to prove human insulin's superiority."
>
> (Scott King, a US broker, quoted in SCRIP, 1981b: 5)

Even with some kind of scientific proof of the efficiency of human insulin, there were still concerns over the investment of resources in human insulin, rather than other areas of diabetes. For example:

> "We can be justly proud of human ingenuity, which has opened another way to synthesise human insulin. However, for patients, it would be far more important for research to reveal how to reduce vascular and neurological complications of diabetes."
>
> (Teuscher and Diem, 1980: 1186)

However, as time passed, more and more data was collected and regulations passed. Henry Miller, of the FDA, claimed that Eli Lilly's insulin was on the 'fast track' for

approval.[16] Since the effects of natural human insulin were well known, and the new human insulin was the same substance, the FDA thought it was vital to pass the new drug (Yanchinski, 1980: 760). It could also be compared with other insulins, that is, "all the questions that have been asked concerning purified pork insulin will be applied to biosynthetic human insulin." (Galloway, 1980: 621). Harry Keen, who carried out the initial clinical trials, argued that the Committee on the Safety of Medicines (CSM), Britain's drug regulatory body, was committed to passing the new drug as quickly as possible (New Scientist, 1980: 351).

This paralleled the original case for conventional insulin, as Bliss wrote:

> "The clinical application of discovery often takes a long time, but in this case a bare twenty weeks had passed between the first injection of insulin to a diabetic dog to a diabetic human. The time was very short and many problems were clamouring for attention: the immediate saving of lives, the production of insulin, research and more."
>
> (Bliss, 1983: 76)

Permission was granted in early 1982 for limited sales of Novo Industri's human insulin in Malta, France and Austria (Yanchinski, 1982: 697). Novo Industri also received approval for the sale of Novolin in England and Germany. Novo Industri also formed a partnership with the US pharmaceutical firm E.R. Squibb and Sons, who were contracted to market Novolin in the United States. The link between Squibb and Novo Industri was not new, Novo Industri was already "selling exclusively finished, packaged insulin to Squibb." (SCRIP, 1981b: 5). In 1981 it was thought that, as a result of the link between the two companies, Squibb had around 15%-17% of the US insulin market. Novo Industri were also experiencing increased sales in the European market. Before the introduction of human insulin, it was claimed that Novo Industri had a "projected nominal growth rate of insulin sales of 22%-26%, excluding the impact of 'human insulin.'" (Scott King, a US broker, quoted in SCRIP, 1981b: 5).

By 1982, Eli Lilly were sending out advance publicity material for human insulin even though human insulin had not yet been licensed (Yoxen, 1983). By May 1982 Eli Lilly had filed a New Drug Application (NDA) with the Food and Drug Administration. On the 29th October 1982 the FDA passed human insulin, the insulin

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[16] In the 1980s the average R&D process took 12 years (Office of Technological Assessment, 1993).

was called Humulin and was estimated to cost twice as much as animal insulins (Shapley, 1982). By 1983 human insulin was in pharmacies. A month before it had been approved in Britain, Swanson claimed that the approval, "is a tribute to the collaboration of two great scientific teams - those at Eli Lilly and Genentech." (Genentech, 1982).

In 1981 Novo Industri agreed with Biogen to develop a genetically engineered human insulin by using yeast expression. It was hoped that it would be cheaper than the chemically altered insulin. It was reported in the media, that the work was progressing rapidly and it could be approved within 2-4 years (SCRIP, 1981b: 5). However, Biogen failed to get the technology to work in practice, even though they had the relevant technology. It was Zymo Corporation (later ZymoGenetics) who would eventually express human insulin in yeast for Novo Industri.

It is notable that the media did not report as much on Novolin as they did Humulin. One reason why Novo Industri were able to produce a human insulin quicker than Eli Lilly was because they were not using such complicated techniques, indeed, they were based on work carried out in the 1970s. The techniques were not as new and controversial as the genetic engineering methods and so the insulin passed the process of regulation quicker. Until October 1985, human insulin was the only genetically engineered product approved for sale, the second product appeared in 1985, a growth hormone produced by Genentech.

In the preceding sections I have outlined a number of factors that made the development of human insulin interesting. I have shown how the development of human insulin, by genetic engineering, entered into the debate over the first use of genetic engineering, and how research groups chose human insulin because of its existing 'social value'. I have also shown how problems were suggested with existing insulins, and that some of these problems could be solved by the development of human insulin.

3.6 APPLYING SOME THEORY

In this section I would like to relate what I have discussed above to my theoretical chapter (Chapter 2). I have two particular aims. One is to show how the process of translation can be applied to the development of human insulin. The second, is to

illustrate how some of the ideas behind the prescription (in actor network terms) of artefacts can be related to human insulin. Rather than separate these two concerns, I will deal with them together. One reason why this will be fruitful is because human insulin, as a drug in itself, and insulin more generally, already had a particular set of prescriptions, or allowances, at the time of the commercial development of human insulin. Therefore, various networks used the existing prescription of insulin to carry out translation, that is, to define the roles of other entities or networks.

Before continuing with this section, it is worth pointing out that in order to produce this chapter I have had to construct a narrative for a complex set of events. Unavoidably, I have stressed the role of some actors, at the expense of others. For example, I have not described the complex strategies used by the various research teams in their experiments. It is also important to be aware that there are problems in assigning ANT terminology to the case study. For example, it is not always easy to follow the changing links and shifts between the actors involved. This reiterates the point that this narrative is only one out of many possible narratives.

The structure of the remainder of this chapter will be as follows. I will first refer to the importance of some of the features of insulin within the insulin network. I will structure this section around the moments of translation that were outlined in Chapter 2. I will describe the way in which various groups attempted to problematize the existing insulin network, and importantly, provided their own solutions to these problematizations. I will then indicate how human insulin became a black box, with a particular set of prescriptions. This 'black boxing' required the enrolment and silencing of a number of actors. Throughout the discussion of these moments of translation, reference will be made to other elements that were discussed in Chapter 2, such as the body as a network. However, before I do this, let's recap on some of the key actors involved in the development and production of human insulin.

Throughout this chapter I have shown how various actors have dropped in and out of the story. Initially there were concerns over the use of genetic engineering, for example, over the possibility of escaping organisms such as E. coli. However, these concerns disappeared from the story, although it is likely they were still present in some parts of the network. On the other hand, Eli Lilly were initially on the sidelines. They observed what was happening within the research groups, and maintained links

with them. Over time they became more dominant actors in the development of human insulin, eventually taking over from Genentech in the commercial production of human insulin. It is also notable that Novo Industri were always on the sidelines, content with developing their own human insulin. Other actors were always present in some form or another, such as the medical profession and diabetics.

Therefore, when talking about the roles that various actors and networks played, and would later play, we have to be aware that the roles and aims are not always the same. When other actors become more dominant, others begin to disappear from the story - such as Genentech, who 'left the scene' when Eli Lilly took over the commercial production of human insulin. But as I argued, the split between these two actors was amicable. There was a temporary alliance between Eli Lilly and Genentech that existed around the production of human insulin. It was therefore a 'temporal or temporary artefactual relation'. That is, the reason for the relation between the two networks was the production of the artefact human insulin. When the artefact was produced, there was no longer any reason for the two networks to interact, and so the relationship disappeared.

There were other similar relations that disappeared once an objective, based around an artefact, had been achieved. For example, for Eli Lilly to gain a licence to market human insulin they had to have contact with various regulatory authorities, such as the MCA and the FDA. On a more general level, the relations between Eli Lilly and regulatory bodies are continual, but they revolve around different artefacts.

3.6.1 The Importance of Insulin

One of the most important references made by various groups in this chapter, was to the existing prescription of insulin as a generic substance. As noted in Chapter 2, prescription refers to the attributes that are inscribed into artefacts, and what an artefact allows from human and nonhumans. In the case of insulin, it allows healthy individuals to convert glycogen into glucose. In the days before animal insulin, the life expectancy of a juvenile diabetic was less than a year after diagnosis (Bliss, 1983). With animal insulin, the life expectancy of a Type 1 diabetic was multiplied twenty five fold. However, animal insulin did not solve all the problems of diabetes - the injection of insulin did not allow a diabetic to lead the same life as an individual

whose pancreas was working properly. Or as Bliss writes:

> "Artificially supplied insulin could not perfectly compensate for the missing pancreatic function."
>
> (Bliss, 1983: 245)

Those who developed engineered human insulin used the existing prescriptions of animal insulins and 'natural' pancreatic human insulin to interest networks to become involved in the development and production of human insulin. To put it simply, the prescription of animal insulin was drawn upon because it showed that the administration of 'non-natural' insulin worked to keep diabetics alive. The prescription of 'natural' pancreatic human insulin was drawn upon because this is what healthy individuals use, so in theory, it would be better than animal insulin.

This illustrates the 'complicity' entailed in network building, in so far as some of the features of the use of animal insulin were drawn upon, such as the ability of the body to absorb injected (animal) insulin. On the other hand, certain features of the use of animal insulin were problematized, such as the differing amino acid sequence. In the development of human insulin therefore, what could be described as an animal insulin network (consisting of animal insulin and the entities which allowed its use) was being broken apart. Certain elements were being acquired or used, and others problematized. This illustrates that just because a network was durable, does not mean it always will be. As Callon has argued, the consensus and alliances that a network relies on can be contested at any time, and the processes of translation need to be continually successful to maintain a durable network (1986).

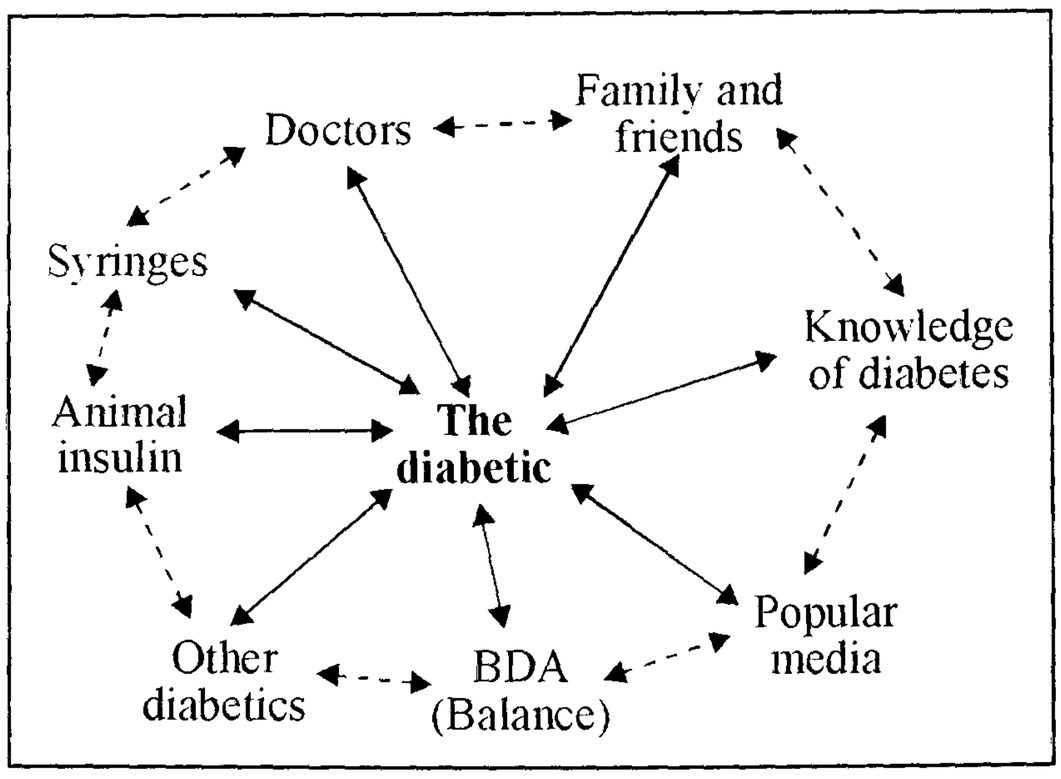

Figure 3-4: A simplified version of a diabetic network body

One of the important features of animal insulin is that it already had a place within the diabetic network body, as did some of the features of its use, such as syringes (Figure 3-4). Animal insulin had been shown to work well in a large number of cases, and formed a durable part of the diabetic network body. Since animal insulin had been shown to work well, it had become part of the institutional consumption path. That is, when a patient is diagnosed as having Type I diabetes they are prescribed insulin. Those who developed human insulin intended it to replace animal insulin in this institutional consumption path. Access to this consumption path would enable pharmaceutical companies to have a ready made market for their insulin, indeed this was one of the reasons stated by the research teams for the development of human insulin. In order for animal insulins to be replaced by human insulin, existing animal insulins would need to be problematized.

3.6.2 Moments of Translation

Those who wanted to enrol groups to adopt human insulin, whether in the development, production, regulation or prescription stages, both had to play on insulin's existing role as a life saving drug, and also to problematize existing insulin treatment. Through problematization questions were raised about animal insulin, but importantly, not about other areas of insulin administration that went with animal insulin. For example, if pharmaceutical companies were to problematize current insulin injection methods, it could be argued that the development of human insulin would not solve the problems of diabetes. Indeed, one of the arguments of Ruth Hubbard (Spallone, 1992) and the Coalition for Responsible Genetic Research (1977) was that it was the management of diabetes that should be problematized, and not the species of insulin used by diabetics.

Others have argued that we should be treating the cause of diabetes. There is persuasive evidence, from studies of developing countries, that one possible cause or trigger of diabetes is the high level of sugar and low fibre content of the Western diet. Therefore, a case can be made for alerting individuals to these possible causes of diabetes, just as it is for heart disease, in order to reduce the incidence of diabetes and the increasing need for insulin. This was not the strategy adopted by the pharmaceutical companies, instead, the pharmaceutical companies gave a particular image of the world, as Edward Yoxen argues:

3.6 Applying some theory

> "...there is a clear need to try and reduce the demand for insulin, which the advertising rhetoric of cheaper, better insulins obscures by suggesting there is no alternative - disease is fixed, it is always with us so we can only cure it."
>
> (Yoxen, 1983: 118)

Instead of problematizing these areas of insulin treatment, pharmaceutical companies and scientists chose to stress two other problems: firstly, there was the predicted shortage of animal insulins, and secondly, the claim that complications could be caused by the more immunogenic, compared with human insulin, animal insulin.

With claims of a predicted shortage of insulin the research groups and Eli Lilly were able to stress the need for alternative sources of insulin. In particular, it was human insulin that they wanted to be the alternative. However, if supply was the only problem to be solved then other sources of insulin could have been found. For example, since the development of insulin there has long been interest in using fish insulin. Indeed, the Japanese made insulin from whales briefly during World War Two (Bliss, 1983: 246). Yet it was not just because of the predicted problems in supply that researchers wanted to develop human insulin. There were also concerns over the immunogenicity of animal insulins compared with human insulin.

Obviously, the use of fish insulin would not address this concern. The research groups also wanted to develop genetic engineering techniques, and human insulin seemed a vehicle through which this would be possible.

It should be clear that Eli Lilly were carrying out more than one problematization. They were not only problematizing the supply of insulin, but also the adequacy of any insulin that did not have the same amino acid sequence as 'natural' pancreatic human insulin. Further, not all problematizations were distributed evenly to all actors. To regulatory authorities, Eli Lilly were problematizing the predicted shortage in the supply of insulin, with such a problematization Eli Lilly hoped to speed up the licensing of human insulin. To the medical profession, Eli Lilly were problematizing the adequacy of current animal insulins.

Eli Lilly did not distribute problematizations directly to diabetics, although they were present in the network by implication. Problematizations dispersed through intermediaries represented potentially 'tragic' effects, if the problematizations, defined by Eli Lilly, were not accepted by other important actors: What would happen

to diabetics if there was a shortage of insulin? Wouldn't diabetics be better off if insulins were purer? Therefore, through the problematization of various parts of the current insulin network, diabetics were being constructed as 'prospective consuming bodies' of human insulin. In order for human insulin to be consumed by diabetics, it was necessary for Eli Lilly to distribute, and have accepted, a number of different definitions and identities.

One interesting act of problematization was conducted by Eli Lilly, over Novo Industri's highly purified porcine insulin. I outlined above that Novo Industri had developed a highly purified porcine insulin - that would prevent insulin allergies. Eli Lilly claimed that a large amount of porcine insulin was lost in the process of purification, and subsequently, this would increase the predicted shortage of animal insulin. However Eli Lilly in the early 1980s, had themselves developed their own purified insulin as well as their human insulin. Although Eli Lilly may have problematized purified porcine insulins, they still wanted to have a similar range available to medical practitioners and diabetics to that of Novo Industri.

Novo Industri were playing a similar 'game' with human insulin. They were attempting to 'demote' the predicted benefits of human insulin, while also developing their own human insulin preparation. Eli Lilly claimed that one reason for developing human insulin was that porcine insulin differed by one amino acid to human insulin. Eli Lilly claimed that this difference may cause allergies. However, Novo Industri claimed that the slight difference in amino acid structure was too minor to cause serious allergies. Instead, Novo Industri claimed that the cause was contaminants present in conventional insulin preparations. As a result, Novo Industri had developed their purified animal insulins. However, Novo Industri were also developing a human insulin. The strategies of the two companies can be summarised as follows. Eli Lilly were problematizing purified animal insulins and promoting human insulin, while also developing a purified porcine insulin. Novo Industri for their part, were problematizing the benefits of human insulin and promoting their purified insulins, while also developing a human insulin.

It should be clear that the problematizations of both Eli Lilly and Novo Industri appear to have some contradictions. I would suggest that we can outline the 'surface' problematizations of an actor, but these only tell half the story (simplified in Figure 3-

5). Both companies were problematizing, on the surface, a certain area of the insulin network, whether it was the supply of animal insulin or the impurities of conventional animal insulins. Each then offered a solution to their problematizations, whether it was genetically engineered human insulin or purified animal insulin. This can be defined as an overt strategy: it is overt since it is the main strategy of the network, or the one that other networks are aware of.

Company	Surface Problematization	Overt Strategy	Covert Strategy
Eli Lilly	• predicted shortages of animal insulin. • problems with immunogenicity of animal insulins.	• development of genetically engineered human insulin.	• development of purified animal insulins.
Novo Industri	• it is conventional animal insulins that are the problem, due to their impurities.	• development of purified animal insulins.	• development of a converted human insulin. • later development of genetically engineered human insulin.

Figure 3-5: Surface problematizations, overt and covert strategies

However, we can also derive a covert strategy. The covert strategy is one that is perused in parallel with the overt strategy, but does not have the same prominence. Interestingly, a covert strategy may contradict the surface problematization. In this case, Eli Lilly had a covert strategy that was to develop purified animal insulins, and so, was in contradiction to their problematization of a shortage in supplies of animal insulin. Novo Industri, on the other hand, had problematized conventional insulins in favour of their purified animal insulins. At the same time, they were developing a human insulin, in the first place converting animal insulin, and then later a genetically engineered human insulin.

Of course, such actions are not unexpected. There are a number of reasons for this. Pharmaceutical companies need to maintain the image of innovation, for Eli Lilly it was by using genetic engineering, and for Novo Industri, it was by purifying animal insulins. By adopting overtly different innovative methods the companies were stressing their individual innovation. Pharmaceutical companies also need to look forward to the future. What would be the effect on the pharmaceutical companies if: Genetic engineering was not successful? If supplies of animal insulin were vastly

improved? Or, if predictions of a shortage in animal insulin were correct?

The movement between the overt and covert strategy also has to be managed carefully, indeed, it may only be in retrospect that the contradictions within a particular problematization became apparent. As already mentioned, within the pharmaceutical industry there is a stress on innovation. However, companies also need to 'hedge their bets' in case one innovation is unsuccessful.

With existing insulin problematized it was then necessary for the enrolling actors to define different identities and wants of different actors. Those groups who were attempting to define the key players, such as the pharmaceutical companies, wanted to define the aims of various other groups. For example, diabetics were defined as wanting a 'new and modern' insulin and the medical profession were defined as wanting an insulin that would reduce diabetic complications. In terms of the program of action, the enrolling actors wanted to define a program of action for those involved. The aim was for the defined program of action to be adopted by those networks that the enrolling actors defined as important. If they were accepted, then there would be no obvious antiprogram. In general terms, a program was defined in which human insulin was to be developed, produced and regulated. Actors, such as scientists and regulatory bodies, were to agree with this program. However, if scientists questioned the benefits of human insulin, and regulatory bodies refused to regulate it, then a antiprogram may have developed.

From the point of view of pharmaceutical companies, there were a number of reasons why they wanted to develop human insulin. Pharmaceutical companies wanted to be able to: capture particular insulin markets; control the supply of insulin; be at the forefront of medical technology; produce cheaper insulins; reduce some of the complications of diabetes; and serve diabetics better. The enrolling actors' aims were to make their aims 'compatible' with those networks that they wished to enrol.

Of course these aims did not apply to all the involved networks. Diabetics are unlikely to be concerned that some pharmaceutical companies wanted to capture another company's insulin market. Importantly, different aims were applicable to different networks. As long as the pharmaceutical companies multiple aims did not conflict with specific aims, defined as relevant to a particular network, then enrolment

was likely to be successful. For example, as long as diabetics were still receiving an insulin that they felt happy with, they would not necessarily mind who was supplying that insulin.

This suggests that human insulin had a variable geometry (Law and Callon, 1992: 24) or interpretative flexibility (Pinch and Bijker, 1987: 40) before and after its development. By this I mean that human insulin meant different things to different networks. For the pharmaceutical companies it was a way to break into new markets, for some scientists it was a means to carry out genetic engineering work, and for diabetics it was, perhaps, a more efficient insulin.

Throughout the development and production of human insulin the medical profession were defined as wanting to have pure and regular supplies of insulin. The medical profession were initially on the outskirts of the development and production network of human insulin. However, without the medical profession enrolled, human insulin would not be an option for diabetics - it would not be within the diabetics' network body. Although on the outskirts during development and production of human insulin, the medical profession would gradually become a central actor as human insulin moved from production to use by diabetics.

The medical profession became involved through the clinical trials that were necessary for human insulin to be approved as safe. Without passing through clinical trials, an obligatory passage point, human insulin could not be certified as safe. The medical profession are a crucial part of this process. As time passed the role of the medical profession was extended even further. Doctors were to be one of the crucial points by which diabetics would be able to use human insulin. As a result, advertising campaigns were directed towards doctors informing them of the benefits of human insulin.

I described above that diabetics were being constructed as 'prospective consuming bodies' of human insulin. As such, it was hoped that human insulin would easily replace animal insulins in the network body of diabetics. The important point is that there was already a group or network of people who consumed animal insulin. We can outline two types of consumption. On the one hand, there were actors who physically consumed insulin, namely diabetics. On the other hand, there were actors

within the 'consumption path', such as doctors and pharmacists. Importantly, it was believed that human insulin could be 'slotted' into the place where animal insulins were. Added to this, there would be benefits for the diabetic, and others within the network body. For example, family members would benefit as the diabetic may not suffer from diabetic complications in later life.

Of course some antiprograms to the development of human insulin by genetic engineering did exist. Ruth Hubbard for example, was worried about, "the hazards of looking for technological fixes as solutions to complicated diseases of metabolic control and other complicated problems" (Hall, 1987: 130). However, these concerns did not form a dominant antiprogram. Those who believed that the genetic engineering of human insulin was a 'quick fix', were unable to enrol the appropriate actors to be able to oppose the research groups. One reason why they were unable to do this was undoubtedly the existing meaning of insulin as a 'life saving drug'. Added to this, human insulin had been presented as the solution to a number of other problems, such as problems of immunogenicity and supply of animal insulin.

An important feature of problematization and interessement is the way in which an enrolling network is able to fulfil its own research interests. In the case of the Harvard University and UCSF groups, they wanted to carry out genetic engineering work. By attaching human insulin to this work, and defining why this was important to other networks, they were able to negate the concerns over genetic engineering. Indeed, as pointed out, much thought was given by the research teams to what would be the first genetically engineered protein. Human insulin appeared as a prime candidate, not only because a lot was already known about it, but also because of insulin's identity. It could be argued therefore, that the development of human insulin acted as a 'carrier network', or key to further research into genetic engineering. Or to look at it another way, human insulin was the obligatory passage point by which scientists could further their own goals. The genetic engineering techniques developed for human insulin would not just be used for human insulin. They would also be applied to, and were always intended to be applied to, the production of other drugs.

There is then a coming together of the aims of the enrolling actor and those whom they wish to enrol. The aim of the enrolling actor is to make themselves, or what they

can offer, the only way to achieve the wants that have been defined for the various actors. In actor network terms, actors want to become the obligatory passage point. It is notable that the research groups set themselves up with slightly different aims. Genentech defined themselves as being able to produce human insulin for commercial production. On the other hand, Harvard University and UCSF also wanted to know more about human insulin itself.

When the research groups had contact with the pharmaceutical companies, the companies were interested in what the groups' aims were. As I have pointed out, Eli Lilly were interested in all the research groups. Before the contract with Genentech had been signed, Eli Lilly had already made arrangements with UCSF to develop human insulin. UCSF had claimed that they were the obligatory passage point by which human insulin could be produced. Eli Lilly accepted this claim, and offered to build a new laboratory for them to carry out their work in Strasbourg.

However, as Genentech's work progressed, Eli Lilly believed that Genentech would be able to commercially produce human insulin quicker than the other research groups. One reason for this was that the methods that Genentech were using to produce human insulin were less complicated, since the insulin A and B chains were engineered separately.

By keeping their options open Eli Lilly were maintaining a number of multiple and simultaneous obligatory passage points. Eli Lilly wanted to have access to whichever centre of calculation would be the first to produce a commercially viable human insulin. However, they also wanted to have access to the techniques that would produce the most efficient human insulin. By maintaining the links with a number of research teams Eli Lilly were more likely to achieve these goals. It is also important to realise that by maintaining a link between themselves and the research groups, Eli Lilly were able to access the knowledge produced by both research groups. Of course these links are symbiotic. The research groups needed the financial support that Eli Lilly could offer, and Eli Lilly needed the scientific know-how from the research groups, or at least preferred to use this source of knowledge rather than develop their own research techniques.

It was therefore very important for Eli Lilly to manage a number of obligatory

passage points. In theory, other actors, other pharmaceutical companies, could have been more eager to form more concrete relations with Genentech or UCSF, or the two research teams may have decided to develop human insulin on their own.

Through interessement existing links with various actors were broken. In order to overcome the restrictions of carrying out genetic engineering work individuals presented various reasons why they should be lifted. For example, at the Cambridge City Council meeting in Massachusetts, Walter Gilbert attempted to interest and reassure various groups over the benefit and safety of genetic engineering. The links that were being broken were of a negative order, i.e. worries over the threat of genetic engineered organisms, such as E. coli, entering the environment. These links were broken through the presentation of work protocols and other inscriptions which aimed to reassure those who had negatives attitudes towards genetic engineering.

Interessement for Genentech involved proving to Eli Lilly that human insulin could be produced in the laboratory, and later, that it could be scaled up. By doing so, links that Eli Lilly had with other human insulin research groups were reduced. One reason why links were reduced is because the cost of R&D is high, and so a pharmaceutical company will be very selective over the projects they fund (Davis, 1997). During the 1980s the cost of the R&D process was put at $65 million (in 1990 dollars) (Office of Technological Assessment, 1993). This was one reason why Eli Lilly were happy to let others carry out the early developmental work. If they had originally funded one group, and that group had been unsuccessful, it would have been costly, and perhaps disastrous, for the company.

It was also necessary for the research groups to carry out interessement within the laboratory. The scientists had to enrol the methods used for the production of the insulin chains. In order to purify human insulin the scientists had to break the proteins' link with various impurities. This was done by laboratory protocol, where 'pollutants' attachment to various entities was reduced (scientific instruments, scientists and the environment). Or by removing the already attached protein impurities to human insulin, through the enrolment of other entities to form purification devices.

Interessement also occurred within the medical and scientific community. At the

symposium held by Eli Lilly , Irving Johnson presented data and graphs that showed the predicted shortages of insulin. Such inscriptions, or immutable mobiles, combined a lot of information to form clear 'proof' that there would be a shortage of animal insulin. For example, one graph that was circulating at the time showed two lines. One line showed the predicted increase in the diabetic population each year (estimated at 5%), the other line showed the predicted supply of animal insulin. The graph showed a crossover point, where demand would outstrip supply (Hall, 1987).

It is only when an actor's pre-existing associations with other entities have been severed (interessement) that enrolment, albeit temporarily, can be said to be successful. In this study this was evident when contracts were signed and regulatory bodies passed human insulin. In the case of human insulin itself, techniques and enzymes were enrolled when human insulin was actually produced. Importantly, enrolment occurred a number of times, in different situations. It was one thing to enrol the techniques to produce human insulin in the laboratory, but for the commercial production of human insulin, it was necessary to use other techniques in order to produce human insulin in appropriate commercial quantities.

Finally, mobilization referred to the way that some entities were able to silence and speak in the name of others. Indeed, I have shown how Eli Lilly silenced the laboratory development of human insulin by Genentech. It was Eli Lilly's human insulin and not Genentech's. When human insulin was finally marketed as Humulin, a large number of other networks had been silenced, such as the scientists and production processes involved in the production of human insulin.

3.6.3 The Black Boxing of Human Insulin

Throughout the process of translation there were many elements that came to be black boxed. For example, there was no mention of the regulatory procedures and clinical trials that had been carried out that enabled human insulin to be marketed. Importantly, such features are still present, it is just that they are no longer visible. However, as I will show in subsequent chapters, where there is a crisis in the current setting or network, black boxed features such as clinical trials may become visible again. For example, one response by the pharmaceutical companies to the claim that human insulin caused side effects was to refer to the successful completion of clinical

trials, that showed that human insulin was safe and efficient (Keen et al., 1980; Clark et al., 1982). In my theoretical chapter this was described as a feature of the inoculation of artefacts.

In Section 3.5 I described how human insulin had to pass a number of clinical trials and regulations (Figure 3-3) before it could be marketed for use by diabetics, and became part of the network body. It is the role of regulatory authorities to outline the tests that have to be conducted. Through this process the drug, in this case human insulin, became defined as edible. As stated in Chapter 2 the classification of a substance as edible/inedible can be applied to prescription drugs. By going through the 'ritual' of clinical trials a drug is defined as edible, although there are restrictions under what circumstances the prescription drug can be consumed.

The prescription drug does not become edible for all, rather, there are particular restrictions on who, and under what conditions, the drug can be consumed. In the case of human insulin, consumption is under the guidance of the doctor. Referring back to my theoretical chapter - the process of regulation allowed human insulin to be available at particular consumption sites (the pharmacy), through a particular consumption path (consisting minimally of the diabetic, doctor, a diagnosis and pharmacist). Crucially, the consumption path is culturally defined: it draws upon existing cultural practices and standards, in this case the authority of the doctor.

Further, human insulin became inscribed with particular prescriptions and proscriptions. It wasn't just defined as edible, but also as superior to other insulins. I argued above that throughout the development of human insulin frequent reference was made to the prescriptions of pancreatic human insulin. Through the clinical tests and regulatory procedures these claims were put to the test.

I would now like to make some comments on the regulatory procedures that I described in Section 3.5.[17] It is obvious that clinical trials cannot be carried out on all individuals. Tests are initially carried out on healthy individuals and then on the intended users of the drug. Therefore, those who used human insulin in the clinical trials were acting as representatives of a larger population. Healthy individuals were

[17] These comments will not be comprehensive, however, see Abraham (1997) for a more comprehensive discussion.

acting as representatives of 'human beings', while diabetics were acting as representatives of the larger diabetic population. I have termed such bodies 'exemplar' bodies or simplified network bodies.

It is expected that results from these 'exemplar' bodies can be generalised to the wider population. However, we have to be aware that only a small percentage of those who will eventually use a particular drug, will actually be involved in clinical trials. Furthermore, certain patients will be excluded from such trials because their multiple pathologies or their use of other medications may interfere with the scientific demands of controlled comparison (Abraham, 1997: p. 129). Therefore, the process by which results from clinical trials are extrapolated to the wider populations may be problematic.

There are not just scientific pressures on regulating new drugs. As should be clear from this chapter, the two pharmaceutical companies had a commercial interest in getting their human insulin through regulatory procedures and marketed as quickly as possible (Abraham, 1997). This was especially the case since the insulin market is very competitive, albeit only between a small number of companies. Due to the interest in human insulin, the first company to have a marketable product would have an advantage over the other. Since Novo Industri were using less controversial techniques it could be argued that their progression through the regulatory process would be quicker. Eli Lilly, on the other hand, were the first to use genetic engineering, which was in its infancy.

However, because of the interest and promise of genetic engineering, it can be argued that human insulin was a special case. According to the Food and Drug Administration (FDA), who regulate drugs in America, human insulin was on the 'fast track' for approval (Yanchinski, 1980). It was also argued that the same commitment existed with the Committee on the Safety of Medicine, the UK drug regulatory body (New Scientist, 1980). Therefore, there are many factors that effect the approval of particular drugs. If the perceived societal need and importance of a drug is great, then there is a likelihood that regulatory bodies will respond to this.[18] Of course, the issue of 'perceived societal need and importance' is the result of translation, and as in this

[18] See Epstein (1996) for an example of how activism within the AIDS community accelarated the approval of various drugs.

case, involves the enrolment of many actants.

3.7 CONCLUDING REMARKS

When the scientists at Genentech were developing human insulin they saw it as a set of exciting scientific experiments that would produce socially useful results. As Eli Lilly became involved, Genentech had deadlines to meet and finally disappeared from the commercial production of human insulin - Humulin is produced by Eli Lilly and not Genentech. However, Genentech are still present in some respects. In accounts of the history of genetic engineering, Genentech are referred to as the first to use genetic engineering to produce a human protein.

It is interesting how original definitions of problems can change. Eli Lilly had presented a picture where the supply of animal insulin was problematic, and problems existed with animal insulins. However, when one of the scientists from the Genentech group went on a tour of an Eli Lilly insulin production plant, in December 1979, he saw another side to these problematizations. He realised that: highly purified animal insulins were not impure; they did not cause allergic reactions; and there was not a shortage in animal pancreases. Although the DNA method was elegant and less messy, it was not necessarily simpler or cheaper than the method for producing animal insulin (Hall, 1987: 298). It was also complicated to produce the starting material for human insulin, compared with that for animal insulin, which was a by-product of the meat industry.

This example illustrates that translation, and particularly problematization, are variable. Power is possessed by those who are able to define a particular problematization, and have it accepted by particular networks, and so enrol a number of allies, both human and nonhuman. These definitions do not have to apply to all networks, and as such, a network may have multiple definitions of a situation which are then selectively applied to different networks. Eli Lilly had defined shortages and impurities with animal insulins, and these had been accepted by scientists and regulatory bodies. However, as the Genentech scientist found out, another interpretation of the situation was possible. It was not so much that there were problems with the supply and production of animal insulin, rather, this was the way Eli Lilly wanted others to perceive the situation.

3.7 Concluding remarks

In future chapters I will show that the constructed prescription of human insulin was called into question.

In particular, the superiority of human insulin over animal insulin was problematized. I have already shown that human insulin was not necessarily more bio-efficient than purified animal insulins, as was theoretically suggested. I will show in later chapters that some diabetics experienced adverse effects on human insulin, and a significant number returned to their 'less modern' animal insulin.

In the next chapter (Chapter 4) I will describe some of the initial reactions of diabetics, care groups, and those in the scientific and medical community, to problems experienced by some diabetics on human insulin. In particular, I will look at the change in warning signs of approaching hypoglycaemia that were experienced by some diabetics. This chapter will set the scene for future chapters, where I will look at the long term reactions of the scientific community and pharmaceutical companies (Chapter 5), and diabetics and care groups (Chapter 6).

4. INITIAL PROBLEMS ON HUMAN INSULIN - SYMPTOMS AND INITIAL REACTIONS

4.1 INTRODUCTION

In Chapter 3 I outlined the development and promise of human insulin. In this chapter, I wish to discuss some of the problems that a number of diabetics experienced on human insulin. I am particularly interested in how diabetics initially voiced their concerns regarding a change in some of the characteristics of diabetes, namely hypoglycaemia, that they (eventually) attributed to human insulin. This chapter also sets the scene for the following 2 chapters. In the next chapter (Chapter 5), I will look at the reactions of the scientific community and pharmaceutical companies in the human insulin debate. Then, in Chapter 6, I will look at what actions were taken by diabetics and care groups in the human insulin debate.

In this chapter, I will first describe the meaning of hypoglycaemia in 'normal' circumstances for a diabetic. I will then go on to address how hypoglycaemia should be seen as a disruption of the everyday activities of diabetics. Next, I describe some of the problems encountered by some diabetics on human insulin, particularly in relation to hypoglycaemia. In the next sections I examine how various groups (care groups, the scientific community and the medical profession) responded to the claims of diabetics on human insulin. Finally, I will consider how the work outlined in the previous sections can be related to my theoretical base.

4.2 WHAT IS HYPOGLYCAEMIA? ITS ROLE IN DIABETES

For some diabetics, human insulin did not fit unproblematically within the existing management of their diabetes. One particular problem reported by diabetics was that they experienced a change in the warning signs of approaching hypoglycaemia. Before I look at this change in symptoms, I would first like to describe the place of hypoglycaemia in the management of diabetes.

From the first discovery and use of insulin, diabetics have experienced hypoglycaemia (Bliss, 1983). Peter J. Watkins argues that:

4.2 What is hypoglycaemia? Its role in diabetes

> "Hypoglycaemia is the major hazard of insulin treatment...All diabetics on insulin who are reasonably well controlled will experience hypoglycaemia at some stage. At its mildest it is no more than a slight inconvenience, but at its severest, when unconsciousness can occur, it is both a hazard and an embarrassment...All diabetics must be carefully taught about the causes, symptoms and treatment of hypoglycaemia. Ideally, new diabetics should be made to experience hypoglycaemia during their initial education."
>
> (Watkins, 1982: 278)

Hypoglycaemia is therefore a very important characteristic of diabetes.

Hypoglycaemia, or low blood sugar, occurs when a diabetic's glucose level drops too low to be able to fuel the body's activity. During the digestion of carbohydrates glucose is absorbed into the blood stream, with unused glucose being stored in the body as glycogen. Blood glucose levels are measured in mmol/L (millimols per litre)[19], with a normal blood sugar level being between 3.33 to 6.66, depending on when the person last ate (see Figure 4-1). The amount of glucose in the blood stream is mainly regulated by the hormones insulin and glucagon. Too much or too little of these hormones circulating in the body, at any one time, can cause blood sugar levels to fall too low (hypoglycaemia) or rise too high (hyperglycaemia).

Classification	mmol/l	mg/dl	State
Hypoglycaemia	2.0	35	Extremely low, danger of unconsciousness
	2.8	50	Severe hypoglycaemia as defined by DCCT (American Journal of Medicine, 1991)
	3.0	55	Low, marginal insulin reaction
Normoglycaemia	3.33 | 6.66	60 | 120	Normal range for blood sugar
Hyperglycaemia	7 ↓	130 ↓	High blood sugar

Figure 4-1: Blood sugar levels

Figure 4-2 shows the approximate biological process by which the body responds to a fall in blood glucose (Gale, 1989). It is important to be aware that failure in the process can occur at any level, in which case, the diabetic may not (or may be unable to) take appropriate action. In many cases the appropriate action is eating carbohydrates, in the form of a chocolate bar or a biscuit, and in severe cases the administration of glycogen.

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[19] This is the SI (Systeme International) unit. However, the United states use mg/dl (milligrams per decilitre). To convert blood sugar from mmol/L to mg/dl, multiply by 18 and to convert blood sugar from mg/dl to mmol/L, divide by 18.

4. Initial problems on human insulin - symptoms and initial reactions

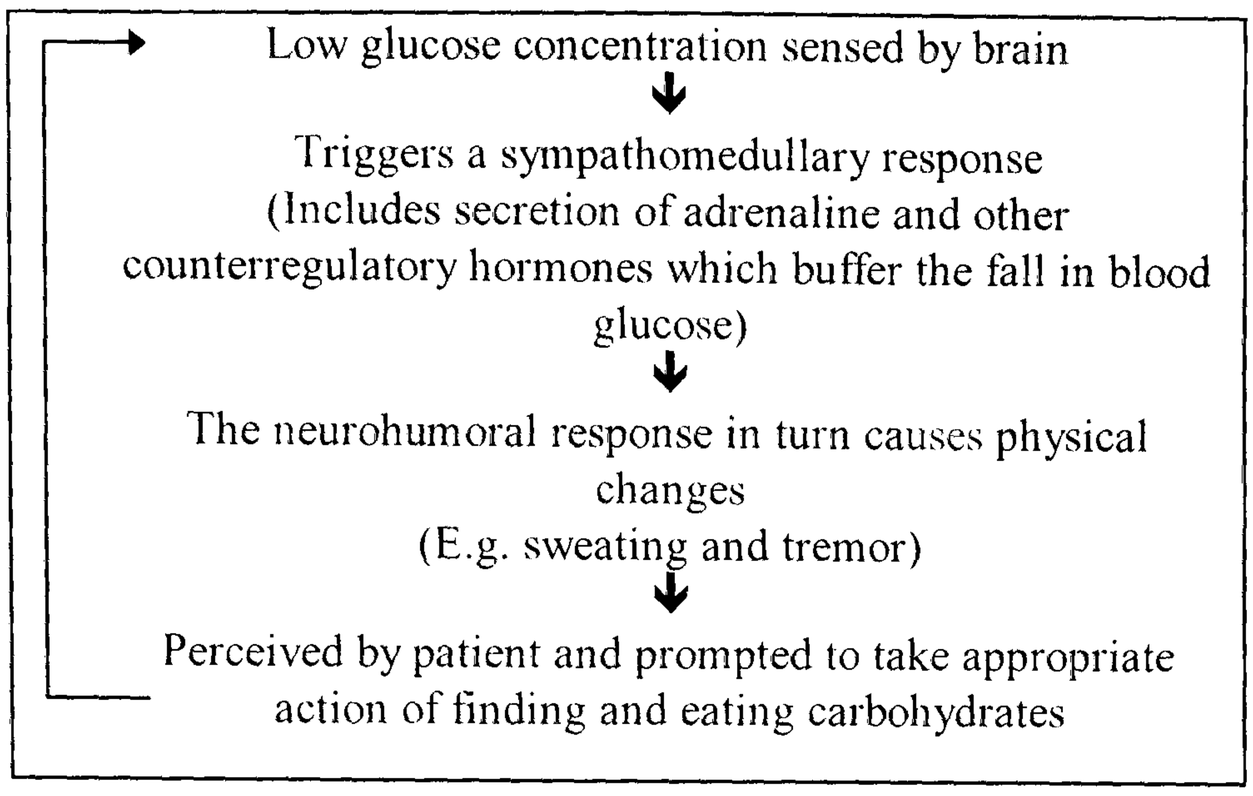

Figure 4-2: The process of hypoglycaemia

The initial symptoms of approaching hypoglycaemia are known as sympathoadrenal symptoms (Figure 4-3). When a diabetic experiences these symptoms it is likely that they will be able to take action in the form of eating carbohydrates. Neuroglycopenic symptoms come later. When a diabetic experiences these secondary symptoms, they are less likely to be able to take action themselves because they may be confused or experiencing seizure. It has been suggested that sensations of hypoglycaemia are experienced by as many as 50% of insulin-dependent diabetics, as frequently as once a month (Goldgewicht et al., 1983).

Sympathoadrenal	Neuroglycopenic
Sweating	Headache
Palpitations	Confusion
Tremor	Visual disturbances
Nervousness	Amnesia
Irritability	Seizure
Hunger	Focal signs, e.g. hemiplegia
Excessive heart rate	Coma

Figure 4-3: Typical symptoms of hypoglycaemia

Since hypoglycaemia is part of diabetes, diabetics are taught how to manage their diabetes in order to avoid, and cope with, hypoglycaemia. Through experience, a diabetic will also learn how to detect approaching hypoglycaemia by being aware of sympathoadrenal symptoms.

In order to prevent hypoglycaemia, diabetics are taught the possible causes (see Figure 4-4). A large part of the management of diabetes is to maintain a balance[20], in the case of hypoglycaemia, it is between insulin and glucose intake. For example, if a

[20] Indeed, the full title of the magazine of the BDA, is ' Living with diabetes - Balance a lifestyle'.

diabetic takes exercise then it is important that they also consume extra glucose.

- Taking more exercise than usual
- Delay or omission of a snack or main meal
- Administration of too much insulin
- Eating insufficient carbohydrate
- Over-indulgence in alcohol
- Mistake in sulphonylurea (tablets used to stimulate the production of insulin in the pancreas) dosage

Figure 4-4: Some causes of hypoglycaemia

There are a number of classifications of hypoglycaemia, depending on the severity. In normal circumstances these occur in the following order. Mild hypoglycaemia can easily be treated by the patient, and is often referred to as 'having a low blood sugar'. This type of hypoglycaemia will probably not be reported to the doctor. A moderate hypoglycaemic episode occurs when someone else has to intervene to bring the diabetic to normoglycaemia (normal blood glucose concentration). The diabetic may be unable to consume glucose themselves because they are confused or unconscious (neuroglycopenic symptoms). Severe reactions often cause stupor, coma, fits or focal neurological signs, such as a hemiparesis (muscle weakness down one side of the body). With such reactions hospital treatment may be needed. Indicators for hospital admission include: poor or incomplete recovery from severe hypoglycaemia; recurrent severe reactions; or poor home circumstances, such as an elderly patient living alone who has had a severe reaction for no obvious reason.

There are a number of factors that make hypoglycaemia particularly distressing for diabetics and their families, as Rajaram writes:

> "The intensity, unpredictability, and risk of physical harm of an insulin reaction, all contribute to the complexity of illness experience. Management of an insulin reaction involves an ongoing discourse between patients and their physical states, their partners, the medical professionals, and the social and ideological constraints, within a social and cultural context."
>
> (Rajaram, 1997: 281)

Hypoglycaemia is a complicated biographical disruption in the management of diabetes. Bury (1982) describes a 'biographical disruption' as a disruption of taken-for-granted assumptions of one's self concept caused by chronic illness.[21] It is worth

[21] Interestingly, the IDDT made a proposal to the World Health Organisation for an amendment to the St. Vincent Declaration. The declaration sets general goals for those adults and children with

pointing out that there has been a movement away from focusing solely on biographical disruptions. Attempts have been made to "extend the theoretical and methodological frameworks that link illness and disability with self-identity, social interaction and critical features of the life course and social structure" (Bury, 1997: 136). One particular area is the active responses that people make in order to manage the possible changes in lifestyle and identity that those with illness may experience (Bury, 1997). Bury (1991) has characterised these responses in terms of coping, strategy and style. Further, there has also been an interest in studying the changes in patterns of illness and the cultural contexts in which they occur. As a result, individuals who have the same illness, for example those with HIV/AIDS (Carricaburu and Pierret, 1995), may adopt different strategies to minimise the influence that the illness has on their identity. Moreover, strategies may change over time for the same group as societal views of a particularly group or illness change.

Moving back to biographical disruption, the taken-for-granted assumptions that are disrupted in times of illness are part of the network body. When the network is durable the body is hidden, yet, in the case of chronic illness the network body is initially opened up or becomes 'unblack boxed'. There are a number of reasons why a hypoglycaemic biographical disruption can be particularly problematic for a diabetic. Rajaram (1997) outlines five:

1) The uncertainty and unpredictability of a hypoglycaemic episode.
2) The suddenness and intensity of the onset of an insulin reaction.
3) The disorientation and loss of cognitive-motor functioning.
4) The risk of physical harm to themselves and others.
5) The possibility of death due to an accident or failure to take timely corrective medical action.

Diabetics are encouraged to understand the day-to-day management of their illness, to prevent biographical disruptions, and to be able to carry out a 'normal' life. They are encouraged to understand the importance of diet, insulin dose and self-monitoring of blood glucose levels. Through experience and education the network body may expand. A newly diagnosed diabetic network body will consist of new artefacts and knowledge. Over time, the network body will not only consist of insulin, syringes,

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diabetes, and also sets 5 year targets to improve education, general awareness, independence of those with diabetes, support facilities, and further, sets targets for the reduction of complications. The IDDT wanted to amend the declaration to include hypoglycaemia, *and* the fear of it, as a complication (1995c: 11).

blood glucose monitoring equipment, but also knowledge of diabetes and hypoglycaemia. However, because of the uncertainty and unpredictability of hypoglycaemia, a diabetic's efforts may not be enough to prevent a hypoglycaemic episode.

I have described here the characteristics of hypoglycaemia. In normal circumstances the onset of hypoglycaemia is usually recognisable. However, a number of diabetics claimed that they lost their traditional warning signs when transferred from animal to human insulin. This is where my attention now turns.

4.3 CHANGING WARNING SYMPTOMS OF HYPOGLYCAEMIA

In 1985-6 only about 6% of insulin sold in Britain was human insulin. By 1989 about 80% of insulin dependent diabetics used human insulin (Balance, 1989a: 8), even though "diabetologists agreed that human insulin in general has no advantages over highly purified porcine insulins." (Egger et al., 1992: 351). Although many studies showed that human insulin was comparable to animal insulin, they did not show that it was *better* than purified porcine insulins.

In the following sections I will outline some of the symptoms that were reported by a number of diabetics. I will also describe what effect these experiences had on a diabetics' body as a network.

4.3.1 Symptoms

The British Diabetic Association first heard about problems with human insulin in 1987 and looked at it seriously, with the Professional Advisory Committee and the Executive Council (Balance, 1991a: 22). While the Insulin Dependent Diabetic Trust (IDDT) reports, in retrospect, that within a year or so of human insulin being used people were reporting problems with human insulin (1994: 2).

The British Diabetic Association, through their magazine *Balance*, first reported possible problems on human insulin in October 1987 (1987d).[22] One possible reason for the gap between the introduction of human insulin, and reports of side-effects could be due to the steady increase in use of human insulin between 1986-89. There

[22] Another concern, that was expressed earlier, was of the possibility of catching AIDS from human insulin (Balance, 1987b: 51).

were a number of reasons for the increase in use: between 1986-87 a number of porcine insulins were withdrawn and replaced by a human equivalent; many bovine insulins were replaced with human long acting insulin zinc suspensions; there was an increasing popularity for multiple injection regimes, that used human insulin; and, there was an increased promotion of human insulin by pharmaceutical companies (Pickup, 1989). By the end of 1989, the BDA had received 60 unsolicited letters from diabetics reporting a change in the nature of hypoglycaemia while on human insulin.

It is also interesting that the pharmaceutical companies received few reports of problems on human insulin. From 1987 to the middle of 1989, Novo Nordisk, who had the largest share of the insulin market in Britain, only received reports of 28 events in relation to hypoglycaemia and hypoglycaemia unawareness. Of those 28 events, only 4 were coded as unexpected. Eli Lilly received a similar number of reports of an adverse reaction to human insulin (Pickup, 1989: 992). It is likely that such a lack of reporting to pharmaceutical companies was due to diabetics reporting their effects to other networks, such as doctors or care groups.

Although the number of reported cases may have been small, it is important to realise that the experience of unexpected hypoglycaemia has important consequences for a diabetic. Typical reported problems on human insulin were:

- Loss of hypo warnings (hypoglycaemia unawareness).
- Increase in weight especially under multiple daily injection routines.
- Extreme tiredness.
- Loss of memory.
- Change in personality.
- Less stable diabetic control, more hypoglycaemic episodes, some severe.

The most frequently reported change was in the warning signs of approaching hypoglycaemia. Teuscher and Berger termed this change in symptoms 'hypoglycaemia unawareness' (1987), or loss of warnings. Some diabetics claimed that their hypoglycaemic symptoms changed from those associated with sympathoadrenal activation (sweating, tremor, palpitations, and so on) to those of neuroglycopenia (inability to concentrate, speech and visual disturbances, headache and so on). This change in symptoms meant that a diabetic was sometimes unable to take action to correct low blood glucose levels. This is worrying for a diabetic because they may feel they are losing control of their lives. They may also feel afraid

of losing their jobs and becoming a nuisance to others (Balance, 1991b). It was not clear however, whether this change in symptoms was due to human insulin or some other cause. There was also some suggestion in the media, that human insulin could trigger neurological disorders such as multiple sclerosis (Balance, 1994).

The naming of a change in the symptoms of hypoglycaemia as 'hypoglycaemia unawareness' is important because it represents the symbolic legitimation of an ideology of expertise (Habermas, 1971: 81). Cooper (1997) describes the naming of ME, arguing that:

> "...those who wish to 'psychologise' the condition have been accused of constructing the term Chronic Fatigue Syndrome in order to sustain this belief, whilst those who wish to construct ME as a physical disease insist on calling it 'Myalgic Encephalomyelitis' (the term translates into inflammation of the brain)...the label ME has come to serve as a symbol for the usurpation of power from doctors to patients."
>
> (Cooper, 1997: 188)

However, in this case, the term 'hypoglycaemia unawareness' is used by both care groups, doctors and scientists. There are therefore no competing claims to the 'correct' terminology between the 'experts' and the 'public'. From my investigations there is no alternative term, although loss of warnings is used with 'hypoglycaemia unawareness'.[23] Yet there was not a consensus that hypoglycaemia existed in relation to human insulin. Loss of warnings however, has been found in both diabetics and non-diabetics. Hypoglycaemia unawareness has been noted in patients with insulinoma, spinal cord section and ganglionic blockade (Gerich, 1992). In insulin dependent diabetic patients, it "has been accepted as a textbook feature of diabetic autonomic neuropathy" (Ryder et al., 1990: 786).[24]

There is not, on the whole, a battleground as to whether hypoglycaemia unawareness has a biological or psychological basis, as in the case of ME. Instead, care groups and diabetics were attempting to link hypoglycaemia unawareness to a possible side effect of the use of human insulin. Importantly, the symptoms of hypoglycaemia unawareness are difficult to assess, from a medical point of view. Therefore, it is

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[23] It is interesting to note that 'hypoglycaemia unawareness' suggests that, diabetics who experienced a change in warning signs missed the sympathoadrenal symptoms. However, it should be noted that in some diabetics the sympathoadrenal symptoms existed, but were not as pronounced, or diabetics did not experience these symptoms for the same length of time, that they had previously.

[24] Although Ryder et al. (1990) call this into question.

perhaps sensible, following Cooper (1997) on ME, that when I refer to sufferers of hypoglycaemia unawareness, I am referring to those who believe that their bodily experiences should be labelled as 'hypoglycaemia unawareness'. It is the ability of various actors to have their symptoms diagnosed as hypoglycaemia unawareness that is one of the issues at hand.

When hypoglycaemia is unexpected, or action cannot be taken to correct the imbalance of glucose, it should be seen as a 'severe biographical disruption'. I use the term 'severe biographical disruption', to signify a disruption of the taken-for-granted assumptions *of the* illness. For example, the onset of hypoglycaemia[25] is usually accompanied by particular sympathoadrenal symptoms such as sweating, tremor, palpitations, and so on (Figure 4-3). A severe biographical disruption occurs when a diabetic is unaware of the initial sympathoadrenal symptoms. The management of chronic illness can be seen as an attempt to manage the biographical disruption; in severe cases, the disruption is difficult to manage because it is unexpected (even in retrospect, the diabetic may not be able to account for their hypoglycaemia). The important point is that the hypoglycaemic episode cannot be accounted for within the existing management of diabetes. To talk again in terms of the network body, the network body becomes threatened; the current network body is unable to cope with the new situation. As Rajaram argues:

> "It is through a process of communication that the significance and justification of these experiences become an integral part of the illness experience, embedded with the ideological context of everyday existence."
>
> (Rajaram, 1997: 290)

I would now like to look at the effect that these symptoms may have on a diabetic.

4.3.2 Experiencing Symptoms

The aim of this section is to indicate the ways in which diabetics were influenced to produce narratives which described their own experiences. In doing so, I will also indicate that the notion of narrative is complex since actors produce narratives and are also subject to them.

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[25] Hypoglycaemia is termed a 'non-disease' or 'illegitimate illness' because it is generally defined in terms of symptoms, with an uncertain aetiology and pathogenesis (Cooper, 1997). Also see Singer et al. (1984).

4.3 Changing warning symptoms of hypoglycaemia

When a diabetic experiences an unpredictable hypoglycaemic episode, it can affect the diabetic's identity. The diabetic may no longer see themselves as being someone able to lead a 'normal' life despite their illness. Further, when such disruptions become public disruptions, questions may be raised about the ability of the diabetic to look after themselves. Importantly here, it is not that the diabetic did something 'out of the ordinary' in their normal routine. In cases of severe biographical disruptions, diabetics have to deal with stigmatising reactions and a discredited identity, but not because there was a failed performance (Goffman, 1963). In cases of a failed performance a diabetic is able to account for the discredited identity within the network body, for example, a delayed snack or meal. However, where there is no (known) failed performance, a diabetic is likely to search for a reason for such biographical disruption in order to understand why they had the hypoglycaemic episode. This search for meaning comes through an interaction with existing and new networks that reconfigures the network body.

To reiterate, the network body includes many different entities, not only artefacts and knowledge, but also the meanings attached to these entities. For example, where a diabetic experiences problems on human insulin, they may no longer consider human insulin to be a wonderful modern drug. Where once it was viewed as a technological advancement by the diabetic, it is now viewed with suspicion. It is also important to realise that the meaning of animal insulin, the 'old' insulin, may also change. Animal insulin may now be viewed as something to be returned to, indeed, the diabetic may feel that animal insulin is better than the 'new' human insulin.

Further, "the body is not merely the location of disease but is that through which one continues to apprehend the world and oneself in it" (Radley, 1989: 232). Therefore, we cannot separate 'the body' from 'the world'. The experience of hypoglycaemia can be seen as being mediated, and justified, through a number of networks. Rajaram (1997) argues that the management of a hypoglycaemic episode involves an ongoing discourse between:

a) Patients' relationships with their illness.
b) Patients' relationship with their intimates.
c) Patients' relationships with the medical profession.
d) Relationship of diabetic partners to the world at large.

In the case of a severe hypoglycaemic biographical disruption these networks are even

more important. Moreover, because reasons for the episode cannot be easily found within the existing relationships, the diabetic may draw upon other networks. Therefore, in the case of a severe biographical disruption, we should also add:

e) Patients' relationships with other diabetics.
f) Patients' relationships with care groups.
g) Patient and family relationship with the media.

It is through interaction with these networks that sufferers' generate narratives. As Somers has argued, it is "through narrativity that we come to know, understand, and make sense of the social world" (1994: 606). Importantly, narratives are intimately related to identity. There is a stress here on the plurality of narratives; it is not the case that we simply pick from one narrative and that defines our identity. Rather, it is important to stress "the embeddedness of identity in overlapping networks of relations that shift over space and time" (Somers, 1994: 607). Identities change because our relations between various networks change. These networks include not only family, friends, care groups and the medical profession, but also the body itself.

In keeping with ANT, narratives will be seen as an intermediary or inscription (in the form of letter or conversation) that passes from one network to another (for example, a diabetic may tell a doctor that they are feeling ill on human insulin). In this case study, narratives are the way in which diabetics share their experience of hypoglycaemia: that is, how they describe their symptoms. More specifically, it is through narratives that diabetics describe the state of their network body. Importantly however, it is possible that as a result of becoming aware of narratives, a diabetic may then produce new or altered narratives describing their own experiences. As a result, narratives and experiences are closely related, not only because they are used to describe experiences, but also, because they may have a role in prompting actors to describe their own experiences.

It is also interesting to look at the point where narratives meet. As such, in what follows, I explore what happens when a diabetic reports problems to their doctor, or writes to the BDA. This is important because a diabetic, who reports their problems to their doctor, may be satisfied with the solution presented to them, and as a result, will be unlikely to direct a narrative towards the BDA or IDDT. However, a diabetic who is dissatisfied with the solution presented to them by their doctor may then direct

narratives to other actors, such as care groups.

Different narratives also have a different authority. Those networks that already have a large measure of authority are likely to produce powerful narratives. This stresses the relational nature of power. For example, a warning from the medical profession over the efficiency of a particular drug will probably have more of an effect than from a care group. Indeed, it is interesting to look at how one narrative can produce others, which become more authoritative, either because they are backed up by other networks, or because the number of similar narratives increases. This will be illustrated in Chapter 6, where I describe how care groups were able to collect many similar narratives of those who were having problems on human insulin.

It is possible to outline at least two broad forms of narrative. Narratives produced by patients, which relate to their illness, can be classed as 'illness *as* narrative' (Hydén, 1997). This form of narrative should be seen as personal experience, since it comes from the body, and it is about the body. This should be contrasted with 'narratives *about* illness' (1997), which refers to those narratives that convey knowledge and ideas about illness. The concept of narratives *about* illness stresses that actors, who do not have a particular illness, can produce narratives about illness. The source of these narratives includes not just doctors, but also family members, care groups and the media.

It is not just the origin of narratives that is important: there are both different forms of narrative (such as oral or written forms) and different types (such as interviews, letters or magazine articles and formal reports). The form of narratives are important because written narratives have the possibility of possessing greater immutability compared with oral forms. The type of the narrative is also important because they may be received in different ways. Letters, published in Balance, from diabetics may not have the same authority as magazine articles or formal reports.

It is also possible to outline an 'institutional context', which refers to narratives that are produced and shared in a medical environment, such as within the doctor-patient relationship or where professionals talk about the symptoms of their patients (Agar, 1985). Early points to illness narratives that occur in 'everyday contexts', such as when a patients tells another person about their illness (1984). In this situation, the

type of narrative produced may be variable, depending on the shared experiences of those involved, or the 'others' positioning. There are likely to be different narratives produced when one diabetic talks to another, compared with a diabetic talking to a non-diabetic. Similarly, narratives produced through contact with sympathetic care groups are likely to be of a different order to less sympathetic care groups. Hydén points to another context, called 'elicited contexts', where a researcher interviews subjects about their illness (1997).

It is also important to understand that narratives are rarely stable, as Hydén argues:

> "...illness narratives are constantly changing and being renegotiated, depending on changing perspectives and other changes in the illness process."
>
> (Hydén, 1997: 61)

This again stresses that narratives do not exist in isolation from other factors. Not only are narratives dependent on the context in which they are expressed, but also on changing perspectives. For example, a diabetic who is experiencing problems on human insulin may feel that they are alone, or through interaction with their doctor they may feel let down. Narratives at this point are likely to be 'down beat'. However, through interaction with others who have had similar experiences, future narratives may be more positive. These issues will be dealt with in Chapter 6.

The notion of narratives is therefore complex. Importantly, narratives do not simply pass from one actor to another. Instead, narratives may have an influence on actors, indeed, this is the aim of many of the narratives that are passed between actors. Narratives become even more complex when they become collectivized, since choices have to be made as to what information is included in the collectivized narratives. Through collectivization actors have a degree of flexibility as to which experiences are included within narratives, and as a result, what they wish to represent. For example, there were differences in the narratives that the BDA and the IDDT collectivized. In particular, the IDDT was far more hostile towards human insulin than the BDA. This will be explored in Chapter 6.

It seems sensible at this point to give an illustration of how meanings come to be generated through the network body. A diabetic may produce a narrative about themselves to their doctor, for example, that they are experiencing a change in

hypoglycaemic symptoms on human insulin. The doctor may then tell the patient about possible side effects of human insulin, or possible causes of their change in symptoms. Through this interaction, a diabetic is likely to experience a shift in self-identity, perhaps from a diabetic coping with their illness, to one that is not. However, it is very rarely the case that the doctor-patient relationship is isolated from other networks. For example, part of the reason for a diabetic talking to the doctor may be due to encouragement from close family members or from contact with other diabetics. Of course, there is continual feedback here, the diabetic may not agree with the doctor and produce other narratives to other networks, such as care groups.

When a diabetic experiences a change in the symptoms of hypoglycaemia, either through self-monitoring or because they were unable to take action themselves, they may reassess a number of meanings. They may reassess their own identity, the role of others, and of their diabetic management, as well as the meaning of objects within the network body. As Good (1994) has pointed out, a central problem with illness narrative is often a lack of an ending. That is, how will the situation develop in the future. For a diabetic, the new characteristic of their diabetes, 'hypoglycaemia unawareness', increases the feeling of a lack of an ending because the diabetic has to redefine what it means to be a diabetic.

When an existing network breaks down there may be both a motivation to re-engage with existing networks and to engage with new ones. This motivation may come from individual experiences, or from other networks, such as close family members encouraging the diabetic to search out information.

I would now like to look at how diabetics initially interacted with other networks.

4.4 INITIAL REACTIONS

I have dealt above with a number of rather abstract issues concerning the experience of some diabetics on human insulin. In this section I would like to look more closely at the way diabetics expressed their experiences on human insulin. I have a number of broad aims. Firstly, to look at the initial responses of various groups to patients' experiences, their illness *as* narrative. Secondly, to look at how patients' narratives were initially represented within certain groups, that is, narrative *about* illness (Hydén, 1997). This type of narrative deals with situations in which doctors and

professionals talk about patients' illness.

Frank (1994) argues that modern illness narratives are based around three central tensions: to gain a public voice that relates a private experience; to sustain the primacy of one's own voice in relation to the voice of medicine; and, to balance the illness experience against the scheme of one's own life. This section aims to illustrate how diabetics gained a public voice.

One important area of study is how a private narrative becomes public, and how private narratives come to be collectivized into a coherent narrative. By collectivized I mean the process by which individuals come to realise that they are not the only one experiencing a particular problem. Part of this process entails how individuals come to be supported and represented by other networks. This collectivization occurs through the production and accumulation of narratives, and becoming aware of narratives already in circulation, such as news reports of the experiences of others. One particular type of 'other' narrative is what we can call a grand narrative[26], such as those printed in the 'popular' diabetic press (e.g. Balance) and the popular press (e.g. national newspapers). Grand narratives differ from other narratives by their diversity and density. That is, their content will come from a range of networks (e.g. scientific community, care groups and regulatory authorities), and from a variety of sources from within these networks (e.g. those scientists who felt that human insulin did cause negative side effects and those who did not). For example, the media may bring together diabetics who have experienced problems on human insulin and narratives from doctors and care groups.

This collectivization of narrative is intimately tied to the ways in which 'issues' arise. Cobb et al. (1976 taken from Scambler, 1998) outline three models through which political issues emerge. They distinguish between:

[26] Apologies to Lyotard (1984).

1) The inside access model - where the initiative is generated and pursued by office holders or political leaders, while the broader public is either excluded altogether or able to exercise only scant influence.
2) The mobilization model - again the initiative is taken from within the political system, but where the support of a mobilized public sphere is required to effect change.
3) The outside initiative model - where it is a mobilized public sphere, or pressure of public opinion, that promotes an issue to the point of salience and concern in the political system.

Rather than looking at the political system, these models may be generalised to look at other groups or networks, such as scientists and care groups. For example, the inside access model would refer to an issue generated by scientists, while the outside initiative model would refer to 'lay' sufferers or interested individuals taking the initiative. Pictured on a continuum doctors may be placed nearer to scientists, while care groups nearer to interested individuals or patients. Since scientists are already within the generalised institution of medicine, they are able to take the initiative from within this network. This is also the case for doctors. However, we have to be aware that single scientists are unlikely to be able to start an initiative, unless backed by part of their institutional network. Patients on the other hand, are outside of this institutional network. Patients are likely to have to go through care groups in order to take some form of initiative. Importantly, some care groups act as a bridge between patients and doctors. However, some care groups are able to do this more than others. For example, the BDA are more able to bridge this gap than the IDDT because of their existing links with a variety of medical actors. Although rather simplistic, this continuum may be a useful tool to look at how various issues are generated, and dealt with, within wider society.

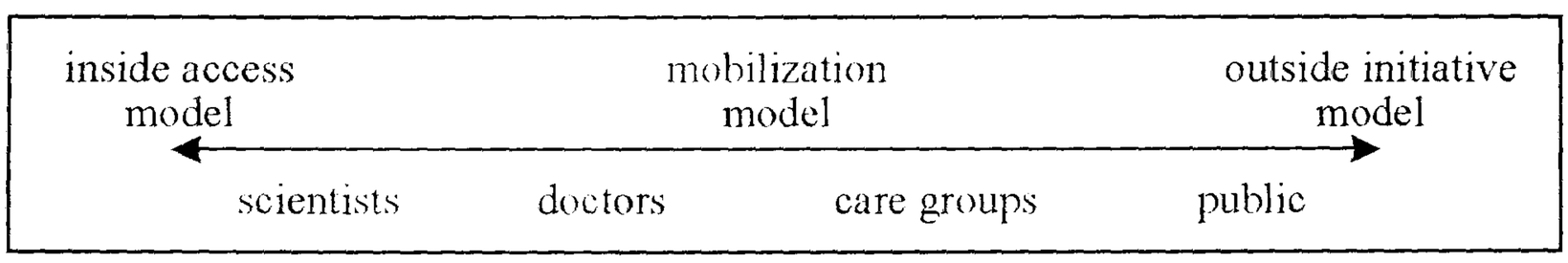

Figure 4-5: Initiative types and various groups

In the next sub-sections I will deal with three areas. In the first sub-section I will look at help groups, and how they became aware of some of the problems experienced by some diabetics on human insulin. In the second sub-section I will deal with the scientific community, and look at how interest in human insulin and its possible

problems arose. In the third sub-section, I will look at why the medical profession drastically increased the prescription of human insulin between 1986 and 1989. For clarity these areas have been separated, however, as will be shown in each sub-section they are not distinct. These sections are important because they will 'set the scene' for the following chapters, which will describe the long term actions of some of the key actors in the human insulin debate.

4.4.1 Help Groups

In this section I will look at some of the reactions of the popular diabetic press. I will first describe and compare the two main groups that are of interest in this study, the British Diabetic Association (BDA) and the Insulin Dependent Diabetes Trust (IDDT).[27] I will then look at some of the initial reactions of these groups. Comparisons between these two groups will be made in greater depth in Chapter 6. A comparison will not be made in this chapter because, in the initial stages of the human insulin debate, the IDDT did not exist.

Throughout this thesis the two main patient help groups, the British Diabetic Association (BDA) and the Insulin Dependent Diabetic Trust (IDDT), will be collectively referred to as 'care groups'. My justification for this is that although both these groups include diabetics, they also include non-diabetics, such as members of the medical community. It could be argued however, that the term 'patient group' could be used to describe the IDDT. Indeed, they describe themselves as a 'patient/carer organisation' (1995c) or as a 'patient-centred organisation' (1994). However, both groups aim to 'care for' diabetics, it therefore seems sensible to use the term 'care groups' to apply to both groups.

4.4.1.1 British Diabetic Association (BDA)

The British Diabetic Association (BDA),[28] founded in 1934, was the first medical self-help charity in Britain, and also the first to have both lay and professional members. The Association was founded by R.D. Lawrence, a diabetologist who had diabetes himself, and the author, H.G. Wells who is famous for books including The

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[27] It should however be noted that the IDDT started over 10 years after the introduction of human insulin.

[28] BDA, 10 Queen Anne Street, London, W1M 0BD, UK.

Time Machine and War of the Worlds. The aims of the BDA are: to help and care for people with diabetes and those close to them; to represent and campaign for their interests; and, to fund research into diabetes.

The association produces a magazine called *Balance*, once every two months.

4.4.1.2 The Insulin Dependent Diabetes Trust (IDDT)

The Insulin Dependent Diabetes Trust (IDDT)[29], a registered charity, was started in 1994 with its first newsletter being printed in April of that year (1994). It was set up to be a ''patient centred' organisation based on true self-help', and had the following aims:

- To offer care and support to people with diabetes and their carers, especially those experiencing difficulty with 'human insulin.'
- To influence appropriate bodies to ensure that all insulin users have a continued supply of their chosen insulin.
- To ensure all patients/carers are properly informed of the alternative treatments available to them.
- An equal choice of injection devices, including a pen injection system for animal insulin.
- To collect information and experiences from those with diabetes and their carers, to use the results of this, to help others in the same situation and to pass it to professionals to create a greater understanding of 'life with diabetes.'
- To inform its members and others through a quarterly newsletter.
- In the longer term, to promote research and surveys into 'human insulin' and its effects.

With the exception of the trust's medical advisor, Dr Laurence Gerlis, the initial trustees all lived with diabetes - 3 had diabetes and 3 were carers. They came together because they had experienced problems with 'human' insulin, either directly or indirectly. Further, the problems appeared to disappear when they changed back to animal insulin. Interestingly one of the co-founders, Jenny Hirst, was a former vice-chairman of the executive council of the BDA (Rogers, 1995). One of the reasons why Jenny Hirst and Dr Matt Kiln formed the IDDT was because they felt that the BDA were not representing and supporting diabetics adequately, in respect of differences between animal and human insulin (personal email). In particular, they were aware that the BDA were receiving a large number of letters from diabetics who

[29] IDDT, PO Box 294, Northampton, NN3 2BN, UK.

were experiencing problems on human insulin. Jenny Hirst claims that the BDA had up to 3,000 letters of complaint (IDDT, 1997).

Due to their experiences, the initial IDDT trustees, wondered how many more people were experiencing problems on human insulin. They were especially interested in those who had not thought about moving back to animal insulin, to see if that helped remove the problems. They also wanted to ensure that animal insulins continued to be available for all who wished to use them.

The IDDT is different from the BDA in so far as it was set up specifically because of the problems diabetics experienced on human insulin. As a result, it had a particular set of concerns for those diabetics who used human insulin. Their concerns can be summarised as follows:

- Those who have only used human insulin have no comparison to make about how they feel. They may accept erratic diabetic control as the best they can achieve, and may also put how they feel down to just being diabetic.
- Those who have symptoms that appear gradually may not think about changing their insulin species.
- Although scientific evidence shows no difference, anecdotal evidence is valuable, and people with diabetes do know how they feel and their carers are valuable observers in any changes. Those who live with diabetes, need to be assured that the professionals looking after them are fully aware of this.
- Those who want to change insulin species should be able to do so.
- Those living with diabetes should feel secure that their chosen insulin will continue to be produced, and that animal insulins will not be withdrawn in the UK.
- People should not be dissuaded from using animal insulins because they are not available in cartridges for pen-injection devices.

(IDDT, 1994)

Although some of these concerns are the same as those of the BDA, it is obvious that the IDDT took a more aggressive stance towards the introduction and use of human insulin than the BDA. One example is the naming of human insulin. The IDDT claimed that the naming of human insulin was "clever and misleading" because "It is NOT human insulin" (1995a). The BDA did not have such a concern.

I will return to these groups throughout this work.

4.4.1.3 Reactions from the care groups

In 1987 the first letter on problems with human insulin was published in Balance, the magazine of the BDA. A family member explained the change in symptoms of their mother. When she was changed to human insulin from bovine insulin, the family felt that she was getting more 'hypos' without warning, and often felt confused and disorientated. The letter also asks if Balance had received any other such reports, which they had. In reply to the letter, Balance describes the study by 'two Swiss doctors' (Teuscher and Berger, 1987). The study showed that 66 out of 176 people, who were switched from animal insulin to human insulin, claimed that their symptoms had changed. Some of the 66 were not aware of their low blood sugars, and a few experienced hypoglycaemic coma.

The reply in Balance concludes:

> "Clearly this report means that anyone changing from beef or pork to human insulin should be very careful, monitoring their blood sugars frequently and reporting any changes immediately to their diabetic clinic. For those who prefer to stay on animal-derived insulin, we can reassure you that beef and pork insulins will continue to be available for the time being."
>
> (Balance, 1987d: 50)

At the end of 1987, Balance (1987e) requested that diabetics who had been transferred to human insulin from animal insulin, in the last year, should contact them if they would be willing to fill in a confidential questionnaire. The results were published 8 months later (Balance, 1988c).

Another letter asks readers for their help. A mother tells of how her son was experiencing problems on human insulin, on which:

> "Not only did he become ill physically his whole personality changed, becoming aggressive, tearful and lethargic."
>
> (Balance, 1988d: 7)

The letter describes how it took nearly a year for her son to be diagnosed as being unable to use human insulin. She asks that other parents and diabetics contact her if they were experiencing similar problems.

This suggests that it is possible to outline two broad types of help groups. One organised on a large scale, and another on a more personal level. Katz and Bender

(1976) suggest that help groups can be divided into two basic kinds:

1) Inner-focused, groups primarily aimed at providing an arena where members can share their personal problems with fellow sufferers, likely to be organised on a local level and meet regularly.
2) Outer focused, groups that are likely to act as pressure groups, who represent the needs of many. They act to disseminate information to district authorities, professionals and suffers, and also carry out fundraising.

My focus here is on outer focused care groups. Both the BDA and the IDDT act as pressure groups that disseminate information. Although the above letter, asking for others to contact the author if they were experiencing problems, can be allocated to the inner-focused group, to a large extent the BDA took over the role of helping those with problems.

The issue of a loss of warnings was generated by diabetics themselves, what Cobb et al. would allocate to the outside initiative model. Such initiative, through the interaction of the public and help groups, enables a 'popular epidemiology' to form. A popular epidemiology is defined by Williams and Popay (1994) as:

> "...situations in which lay people conceptualise and gather information on health problems and risks about which orthodox experts are silent or unreliable...lay knowledge moves beyond individual complaint to develop a public voice and provide the basis for collective action for change in policy."
>
> (Williams and Popay, 1994: 120)

However, we also have to be aware that the nature of medical knowledge has changed. For example, Comaroff and Maguire (1981) point out that as explanations become more biologically sophisticated, patients find it more difficult to relate scientific knowledge to their experience of illness. They become more alienated from that knowledge compared to their experiences (Williams and Popay, 1994)

If this is the case, self-help groups play an important role in bridging feelings of alienation. Self help groups give patients a degree of comfort, since patients become aware that they are not the only ones suffering a particular illness or set of symptoms. The important point is that self help groups place value on experiential knowledge. Added to this, outer-focused groups share scientific knowledge. Help groups are likely to bring one (sanitised) form of scientific knowledge into their publications. For example, Balance referred to the 1987 study by Teuscher and Berger in one of their letters (1987d) and to other studies in a number of other articles (1992b; 1994).

Balance also have a regular 'research round up-section'. The IDDT also refers to studies (1996), although not as regularly. Help groups then, reduce an individuals feeling of alienation that may exist as a result of differences between their experiences and scientific knowledge.

In outer-focused groups knowledge is disseminated to diabetics (amongst others). The BDA, for example, acts to raise issues that are of general concern to diabetics, that are usually suggested by diabetics themselves. They frequently discussed the problems that were experienced by diabetics on human insulin in Balance. In 1988 the BDA, via their magazine *Balance*, asked for diabetics to contact them and complete a questionnaire on their experiences of using human insulin (1987e). They also set up, and funded, various pieces of research and working groups. For example, in October 1989, the BDA set up the Human Insulin Working Group (HIWG) to look at the issue of human insulin and deaths in young people. Many questioned the make-up of this group because it was medically biased, and did not contain any patients who experienced difficulties on human insulin (Balance, 1994: v). This was corrected in 1991, when the BDA set up the Loss of Warnings (LOW) Task Force to help and support those who had been experiencing a loss of hypoglycaemia warning signs (Balance, 1991a).

Outer-focused groups act as a channel of knowledge by producing press releases. For example, the LOW Task Force printed 40,000 copies of a special leaflet, mailed professional advice sheets and a copy of the leaflet to all the medical professionals on the BDA's mailing list. Leaflets were also sent to BDA branches; adverts of the new leaflet were placed in many national newspapers; a press conference was held; and, extra resources were made available to the Diabetes Care Department and the BDA telephone helpline (Balance, 1991a: 46).

Before I end this section, I would like to say something more about the experiences of diabetics on human insulin. In particular, I would like to look at 'semi-legitimised' symptoms and those reported by diabetics. Semi-legitimised symptoms are those frequently reported in the media. The most frequently reported symptom was hypoglycaemia unawareness. However, if we look at symptoms that have been reported by patients on the whole, rather than the semi-legitimised symptoms, we can produce a longer list. For example, the IDDT (IDDT, 1995b) listed the symptoms

that had been reported by its members (Figure 4-6). Most patients experiencing 3 or 4 symptoms.

Loss of warnings	Depression
Extreme tiredness or lethargy	Blood sugars dip and peak wildly
Sleeping all the time	Not the same person
Weight increase of 1.5 stones or above	Mood changes - difficult to live with
Feeling unwell all the time	Pains, especially in legs
Memory loss/confusion	Late or irregular periods

Figure 4-6: Reported problem on human insulin

Although loss of warnings and changes in blood sugar levels are in the list, the other 8 problems were not regularly associated, by non-diabetic actors such as medical commentators and doctors, with human insulin. It is possible to outline a number of reasons for this. On the one hand, the label 'hypoglycaemia unawareness' is simple (although its diagnosis is not) and can be used as a 'catch all' term. Hypoglycaemia unawareness has also been shown to be related to other factors of diabetes, and so already had a degree of 'facticity' and credibility. According to Turner (1990), some health disorders (such as anorexia nervosa) are more socially constructed and over-determined than others (such as goitre and gout). As a result, it may be possible to outline a continuum (Arksey, 1998) with 'troubles' on one end of the line and 'well-established, respectable' illnesses on the other end of the line (Turner, 1992: 106).

Taking a lead from Arksey (1998), there are also differences in the extent to which particular conditions have been taken up by professional bodies. Although hypoglycaemia unawareness is not necessarily well established in physiological terms, it has been taken up by medical professionals. Therefore, for those who wished to claim that problems existed on human insulin, it would be less of a political struggle if the claim was based on an established category.

Another reason could be that, in theory, hypoglycaemia unawareness could be tested and assessed in the laboratory, whereas the other symptoms could not. Perhaps then, the division between hypoglycaemia unawareness and other symptoms, can be compared against 'expert' and 'lay' classifications. That is, by referring to hypoglycaemia unawareness, media articles could refer to scientific studies and patient experiences. However, by referring to other symptoms, the media could only draw upon 'lay' knowledge. Another important consideration is that the original

study looking at human insulin, claimed that, in some cases, human insulin caused hypoglycaemia unawareness.

I would argue, then, that the problems experienced by some on human insulin had been simplified and 'black boxed'. Through the simplification of the problems experienced by some diabetics, the media were able to 'deal' with particular positions. For example, in most discussions in the human insulin debate there were just two questions, related to the negative symptoms experienced by diabetics on human insulin, that needed to be answered. These questions were: Does human insulin increase an unawareness of approaching hypoglycaemia? and, Does human insulin cause sharp changes in blood glucose levels?. When the media dealt with scientific evidence and the negative symptoms experienced by diabetics, they talked in terms of these two questions.

In this section I have aimed to outline some of the initial concerns of care groups, particularly the BDA. Rather than look in-depth at some of the issues, I have mainly concentrated on describing some of the features of help groups. In Chapter 6, I will look more closely at a number of concerns that existed around the use of human insulin, such as increased unawareness of hypoglycaemia and the withdrawal of a number of animal insulins.

4.4.2 Scientific Community

As implied above, one of the questions that I am interested in is the origin of issues, in particular, whether human insulin caused a change in the warning signs of approaching hypoglycaemia. More generally, I am asking the question: Where did the pressure to look into human insulin come from? I explained in Chapter 3 how human insulin was shown to be a safe alternative to animal insulin (Clark et al., 1982). However, other studies were carried out that called this into question. Others still agreed with the original findings. The original studies were carried out before the drug was marketed as a requirement of regulatory bodies. Later studies, however, were carried out due to an interest in the possible side-effects experienced by some diabetics.

In this section I would like to describe some of the initial reactions from the scientific community. I do not intend to look at the results of specific studies; rather, I will

illustrate how possible problems with human insulin entered the scientific community. In the next chapter (Chapter 5) I will discuss some of the studies and their results in detail.

The first study to look at the link between human insulin and a change in warning symptoms, was carried out by two Swiss investigators in 1987 (Teuscher and Berger, 1987). The study described 3 case studies, and then a follow up study, in which 176 patients who had switched to human insulin were questioned. This study was prompted by an awareness by the investigators that their patients were experiencing problems on human insulin. Further, in response to a criticism of their study, Teuscher and Berger, argued that one reason for publishing the study was to inform physicians of the decreased awareness of hypoglycaemia, experienced by some patients, who were transferred to human insulin. They also wanted to show that hypoglycaemia unawareness was a potentially important clinical problem (Egger et al., 1988). Letters in the medical press were also prompted by doctors' experiences of patients transferring to human insulin (Turner et al., 1988).

Studies were carried out by insulin manufacturers who were concerned about the suggested negative effects of human insulin. For example, Eli Lilly carried out an assessment study in 1988 (Lancet, 1989). Another insulin manufacturer, Novo Nordisk, started clinical trials in co-operation with the BDA in 1989 (Prentice, 1989).

The BDA, through the Human Insulin Working Group, also recommended that studies be carried out to see if there were any differences between animal and human insulin. An article in *Balance* pointed out that normally research takes a long time to set up, but this research was commissioned and set up within three months of an advertisement appearing in the medical press (Balance, 1991b). In total, the BDA would spend over £250,000 on funding research into the effects of human insulin (Hope, 1995). The studies aimed:

> "...to meet the concerns shown by members about the loss of hypoglycaemia warnings following the change to human insulin."
>
> (Balance, 1994: iv)

In one study funded by the BDA, a research group from the Royal Infirmary in Edinburgh (Hepburn et al., 1992), studied the differences in the symptoms of

hypoglycaemia experienced by diabetics on human and porcine insulin. In another, Dr Simon Heller (1992) was given £53,000 to cover a two year research project to look at the switch to human insulin, especially a diabetic's ability to detect hypoglycaemic reactions (Balance, 1992b). Another study led by Dr A Swerdlow looked into diabetic death, especially in relation to insulin type. The study aimed to follow more than 30,000 patients with diabetes throughout the UK (Balance, 1994).

In this section I have described some of the initial actions taken by the scientific community as a result of concerns over possible side effects of human insulin. I have outlined a number of influences on the scientific community in bringing problems on human insulin to the attention of the scientific community. I have also described how a number of studies were carried out, some funded by the BDA. I would now like to sketch the role that the medical played in the use of human insulin.

4.4.3 Medical Community

Obviously the medical community play an important role in this study. In this section I would like to look at their position within the evolving human insulin network. In the first sub-section I will suggest a number of reasons why doctors transferred diabetics to human insulin. Then, in the sub-second section, I will look at some of the initial responses of doctors when diabetics reported problems on human insulin.

4.4.3.1 Transferring to human insulin

As prescribers of human insulin, doctors have a crucial role in the consumption path of human insulin. Therefore, it seems wise to look at some reasons why large numbers of diabetics were prescribed human insulin between 1986 and 1989. It has been argued that, from the point of view of doctors, there were three main reasons for transferring a diabetic to human insulin (Wolff, 1992). Firstly, promotional literature claimed that human insulin was far less immunogenic than animal insulin. Secondly, advertising campaigns made the new insulin sound superior to existing insulins, so patients asked for human insulin. Thirdly, physicians and pharmacists were under the impression that animal insulins were being discontinued.

As already pointed out in Chapter 3, one of the claims made about human insulin was its reduced immunogenicity. In Chapter 5 I will look at this claim in more detail.

4. Initial problems on human insulin - symptoms and initial reactions

However, it may be useful to point out that, in retrospect, it has been argued that the transfer to human insulin was not necessarily for clinical benefit, rather it was for commercial reasons (Egger et al., 1992). In Chapter 3 I described how by developing a new insulin Eli Lilly would be able to 'break into' European markets. I also argued in Chapter 3 that the marketing of human insulin began before it was available for sale (Yoxen, 1983). Indeed, new drugs need to be energetically promoted to doctors if pharmaceutical companies are to recuperate their development costs (Burstall, 1990).

Although for Eli Lilly human insulin may have been a way to 'break into' other insulin markets, this was obviously not the identity of human insulin presented to doctors and diabetics. Instead, human insulin was defined as being superior and 'healthier' than existing animal insulins. Indeed, the exact amino acid sequence of the human insulin produced by the pharmaceutical companies to natural pancreatic human insulin was used as a marketing tool by the pharmaceutical companies (Datamonitor, 1997).

On the issue of advertising campaigns it should be pointed out that insulin is not widely advertised. For example, when an advert was placed in the *British Medical Journal* for Humulin, claiming that it was less immunogenic than other insulins, there was some concern over its accuracy. However, another concern was over the advert's language. It was argued that:

> "The advertisement, which is written as though directed to the patient rather than to the doctor, is rich in emotive innuendo and lacks any explicit experimental or clinical basis."
>
> (Collier and Pilkington, 1984: 191)

However, in reply it was argued that:

> "The advertisement has been placed in journals whose contents are aimed at doctors. It has never been placed in any journal to which patients have access."
>
> (Knight and Gennery, 1984: 191)

Others have argued that it is more likely that patients may have asked for human insulin due to news reports in the popular media (Drug and Therapeutics Bulletin, 1989). This is an example of the public consuming the public representation of science. As Lambert and Rose have argued, "The public representation of science is

generally mediated through its application or its promised application" (1996: 74). In the case of human insulin, there was a representation of human insulin based on its promised application and benefits. In actor network terms, diabetics were aligning themselves with the prescription of human insulin, that is, what it was claimed that human insulin would allow.

On the third point of animal insulins being withdrawn, the results of a BDA survey found that some patients had been changed to human insulin with the explanation that 'Your old insulin is no longer being made. This is the modern one' (Redmond, 1988). Other doctors were under the impression that all animal insulins were soon to disappear, so began to change their patients over to human insulin (Drug and Therapeutics Bulletin, 1989). The survey by the BDA also found that a number of patients had simply been given the new insulin without any guidance from their doctor. In such cases, patients may not have been alerted to possible changes in their sensitivity to the new insulin (Pickup, 1989).

4.4.3.2 Responding to problems

In this section I will look at some of the initial responses from doctors when patients reported problems on human insulin. The reports come from patients' accounts and those reported in the media. The aim here, is to outline some of the responses, given by doctors, to diabetics who reported ill effects on human insulin. In Chapter 6 I will look more closely at this area.

When a diabetic presents themselves to their doctor, claiming that they are having problems with human insulin, the doctor could do one of three things:

1) Accept the patient's view, and change them back to animal insulin.
2) Reject the patient's view, and maintain the same insulin regime.
3) Change some part of the insulin regime, but not the insulin species.

A consistent complaint from diabetics was that doctors refused to acknowledge that they were having problems on human insulin (Pickup, 1989: 993). When patients asked to be changed back to animal insulin, many doctors replied that: pork insulin was no longer available; human insulin is better for you, it would be a step backward to use animal insulin; you've been on human insulin too long to change; and, the different species cannot be used in the same syringe (IDDT, 1995b: 9).

4. Initial problems on human insulin - symptoms and initial reactions

In relation to this final point, it was argued that diabetics should not be dissuaded from using animal insulins because they are not available in cartridges for pen-injection devices (IDDT, 1994: 2), Insulin pens are small pen like injection systems which use cartridges to deliver a set amount of insulin. Insulin pens remove the need to take insulin into a syringe from an insulin vial. As well as being small and convenient, it is also possible to adjust the administered dose by use of a selector at the top of the pen. The development of insulin pens went hand-in-hand with the development of human insulin, and initially, were only available for use with human insulin.

Before a diabetic could ask to change insulin they had to attribute changes in their diabetic management to human insulin. One possible reason why patients may have attributed a change in the management of their diabetes to human insulin, could have been media publicity. It has been argued that the media worried many diabetics on human insulin, and as a result, even though a diabetic did not have particular problems, they requested to be put back on animal insulin (Balance, 1992b: 18; Gale, 1989).[30] Wolff points out that some television programmes featured articulate and concerned diabetics who presented their symptoms as caused, without doubt, by human insulin (1992: 376).[31] Motivation to change insulin therefore, may not come from a 'real' side effect of human insulin, but rather the perception, by a diabetic, that human insulin is the cause of their problems. Gale points out that some diabetics have run in to problems:

> "Some unlucky patients have run into trouble at the same time of changing to human insulin, but it seem likely that many have simply attributed all their problems to it."
>
> (Gale, 1989: 1266)

I have looked here at some of the reasons for the change to human insulin and some initial responses to problems experienced by some diabetics, from the point of view of

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[30] Gabe et al. describes a similar case for tranquilliser dependence. They argue that some users of tranquillisers are influenced by the media to such an extent that they define themselves as dependent on tranquillisers simply because they use them (Gabe et al., 1991: 334). Also see Montagne (1988).

[31] Interestingly in August 1991 it was reported that lawyers were putting together a case to represent 400 diabetics who claimed to have experienced negative effects on human insulin (Hall, 1991a). By September, it was reported in *The Times* that the number had risen to 700 (Times, The, 1991). Indeed it was argued that the number could rise to 25,000. Some argued that the press coverage over the case enormously increased the numbers who felt injured or litigious. Indeed, it was argued that the 'real' cases of human insulin related hypoglycaemia unawareness would be hidden under a large number of 'me-too' complaints (Wolff, 1992: 376).

doctors.

4.5 CONCLUDING REMARKS

In the previous sections I outlined the process by which a number of issues were brought to the attention of various groups. I have utilised the concept of narratives to illustrate that it is not only a matter of producing narratives, whether it be illness as narrative or narratives about illness, but of gaining support for a particular narrative. Diabetics were crucial in producing the initial narratives of a change in symptoms on human insulin; narratives were then (re)produced by other actors, such as the BDA.

In this final section I intend to bring together some of the issues outlined in the previous sections. I intend to relate the previous sections to work outlined in my theoretical chapter (Chapter 2). I will also provide some pointers to the content of the next two chapters.

As I illustrated above, the BDA acted to gather information on the possible symptoms of human insulin, through questionnaires and the funding of studies. Relating this to ANT, the BDA became the representatives of diabetics who were experiencing problems on human insulin. However, some were unhappy with the way that the BDA were representing them, and so started their own alternative network - that eventually took the form of the IDDT.

Through the production of various narratives the prescription of human insulin was being changed for some. Rather than seeing human insulin as a 'safe alternative to animal insulin' (Clark et al., 1982), a number of diabetics saw human insulin as a less effective insulin than animal insulin. Indeed, some actors, such as doctors and diabetics, were beginning to form an antiprogram against human insulin. Further, some diabetics not only developed an antiprogram to human insulin but also to other elements of the diabetic network, such as doctors and the pharmaceutical companies. It is important to note however, that these responses were not universal. For many diabetics human insulin was still a safe alternative to animal insulin. I will look at this more closely in the next chapter, when I consider the many scientific studies that were prompted by the experiences of those on human insulin.

There are many reasons why some diabetics may have claimed to experience negative

effects on human insulin. An obvious cause is that they were experiencing side effects. However, diabetics do not use insulin in a vacuum: as argued in this, and in Chapter 2, we can conceive of the diabetic as living through a number of other networks, such as family, the media, doctors and various artefacts. These other networks will influence the actions of diabetics, just as these networks are influenced by the actions of diabetics.

Through interaction with other actors, such as the media and other diabetics, diabetics may have linked human insulin with their current experiences. There may then be a breaking of the identification of human insulin as 'modern' and 'healthy'. These 'other' actors may therefore affect perceptions of risk.

It is also important to realise that these 'other' actors can be enrolled by diabetics themselves. For example, by making issues 'newsworthy', delegitimated actors are able to bring their perspectives into the public eye (Epstein, 1996). As Klandermans has described, by diffusing particular beliefs various groups are able to gain credibility that they would not have been able to gain on their own (1988). The ways in which diabetics enrolled other actors will be expanded in Chapters 5 and 6.

As I have stressed throughout this chapter, the key actors/networks should not be seen as discrete actors/networks, rather there is constant interaction between these actors/networks. Further, groups or networks may need to balance a number of relationships between different groups. For example, the BDA felt that the reports in the media about possible litigation by those experiencing problems on human insulin caused difficulties for the BDA. They argued that they needed to support and represent those who were having problems on human insulin, but did not want to cause unnecessary distress to people who did not have problems with human insulin (Balance, 1994: v).

Before I end this chapter, it is worth making reference to what I have called the network body. If we remember, the network body consists of all those entities that make up the experience of illness, whether it be doctors, the media or artefacts. Over time patients come to a negotiated settlement with their illness. This settlement involves the coming together, and an understanding of, the features of the network body. Yet, where new symptoms emerge new relationships need to be formed with

parts of the network body. In some cases new entities or networks may need to be introduced.

Human insulin was introduced into this network body with the aim that it would replace existing animal insulin. Further, at the same time other artefacts may have been introduced into the network body, such as pen injection systems which further re-shaped the network body. As already noted, in some cases diabetics were discouraged from changing back to animal insulin because it could not be used with pen injection systems - now not only an integral part of the network body, but also closely linked to human insulin.

Therefore, the selection of one entity, in this case the convenient insulin pen, is closely tied to the use of human insulin: it is not possible to use an insulin pen without also using human insulin. This led care groups to pressure pharmaceutical companies to ensure the supply of animal insulins, so that doctors and diabetics had a choice of the insulin species they wished to use with the insulin pen.

In sum, when human insulin was introduced into the network body, it was initially believed that there was no need to change other parts of the network, such as insulin dose. However, over time it was realised that a number of changes had to be made to existing networks within the network body.

In the next two chapters I will look at the long term actions taken by a number of important actors. I will begin Chapter 5 by giving a chronological outline of some of the issues that were discussed in the human insulin debate, which will encompass both institutional and patient centred points of view. I will then go on to discuss the ways in which various institutional actors attempted to position themselves as central actors in the human insulin debate. Chapter 5 will therefore look at the scientific community and pharmaceutical companies. Then, in Chapter 6, I will look at the way patient centred actors attempted to define certain issues as important in the human insulin debate.

5. AFTER THE INITIAL REACTIONS - SCIENCE AND THE PHARMACEUTICAL COMPANIES

5.1 INTRODUCTION

In this, and the following chapter, I intend to describe how various actors attempted to render meaningful, the claims by diabetics, that they were experiencing problems on human insulin. I am interested in such groups as: pharmaceutical companies, the scientific community, the medical profession, care groups, and diabetics themselves. Outlining and describing these actors will not be an easy task since there are a great number of strands and interconnections between these groups.

If we take a look at Figure 5-1 we can see that the key actors are linked to, and through, each other. By this I mean that actors are dependent on each other. For example, in order for pharmaceutical companies to have a relation with GPs, pharmaceutical companies and their products need to be registered and cleared through a number of regulatory bodies. As another example, GPs are likely to gain information from the scientific community through the scientific and medical media. GPs may also report to regulatory bodies, and report observations to both the medical and popular media.

It will not be possible to deal with all the possible connections and strands in this study. As such, this chapter will inevitably be comprised of a constructed narrative, since it is not possible to do justice to all the 'moments' linking the numerous actors involved. I have therefore had to make choices as to which moments to describe, and thus, which to leave out. Consequently, I do not consider this to be the only possible account of the issues within the human insulin debate.

What I will attempt to do, in this and the following chapter, is to bring out some of the key issues of the human insulin debate in order to form one possible narrative. In the first section of this chapter I have chronologically outlined some of these key issues and moments. The aim of this outline is to provide a grounding for future sections. I have also summarised the key issues, and how they related to various central actors, in a chronological table (Figure 5-2).

Once I have provided an account of some of the key issues in the human insulin

debate, I will then go on to look at the roles of a number of important actors. To bring some structure to the narrative I have divided them into two thematic chapters. This chapter can be seen as being institutionally centred, in that I will look at the scientific community and pharmaceutical companies. Chapter 6 on the other hand, can be seen as being patient centred. That is, I will look at issues that are of direct concern to diabetics, such as: patient knowledge; the doctor-patient relationship; the role of care groups; and, factors in the choice of insulin species.

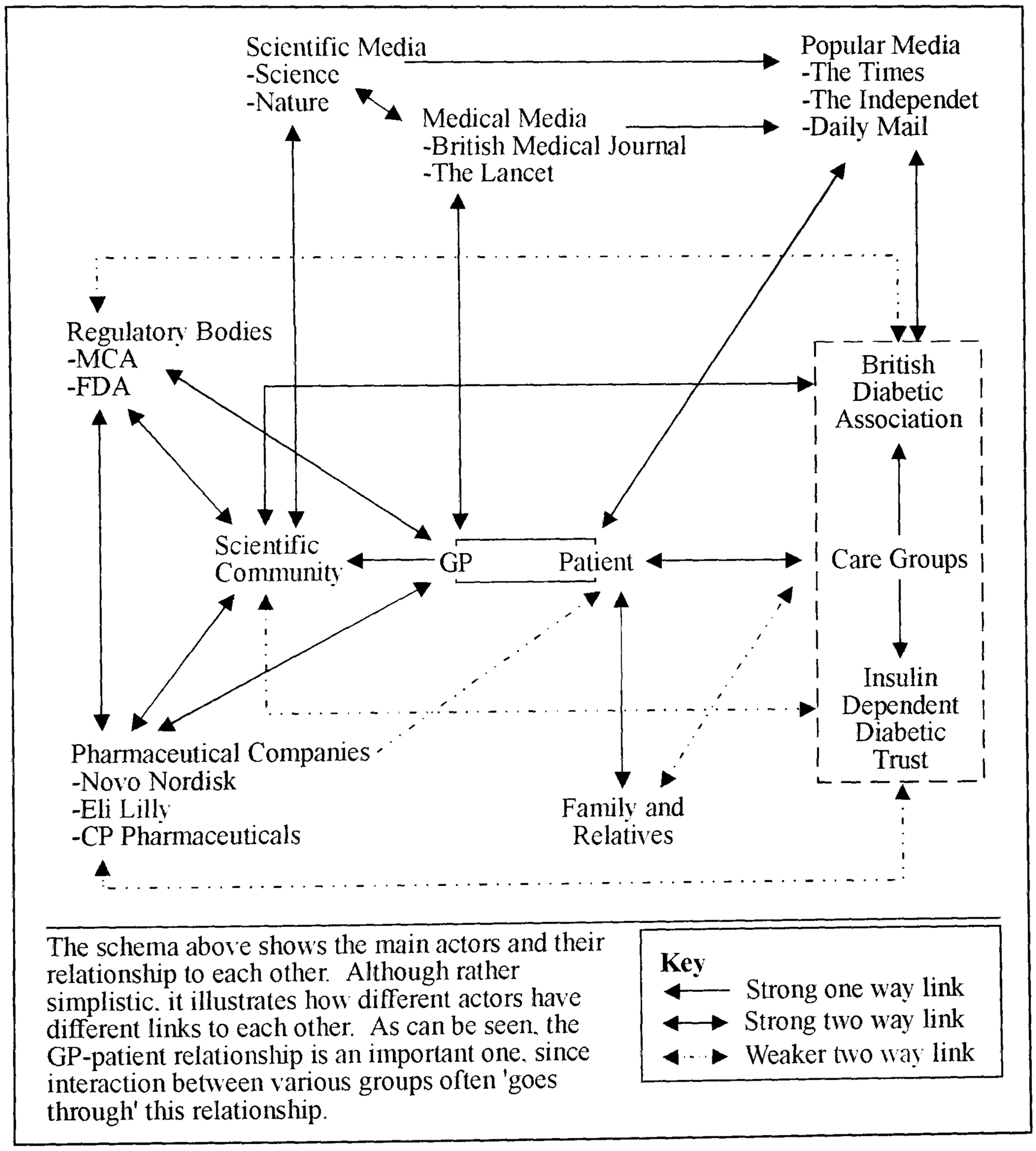

Figure 5-1: Schematic to show how the various actors are linked to each other

Although I have separated these two broad areas, this does not mean that the institutional and patient centred chapters are not linked in their content. Looking at Figure 5-1, we can see that care groups do have some link to pharmaceutical

companies. For example, care groups, through their publications, will pass on information about current medical thinking to diabetics.

In order to bring these two chapters together, in Chapter 7 I will bring out some of the linkages between the actors described in these two chapters. There are two areas that I am particularly interested in. Firstly, the different ways in which a multiple of actors attempted to bring some form of closure to the human insulin controversy. Secondly, I am interested in how the various forms of knowledge discussed in the following chapters can be related to each other.

Date	Science	Care Groups	Patients	Companies
1981	•Human insulin approved for sale			
1982				
1983				•Novo Laboratories are to discontinue the production of some porcine insulin
1984				
1985	•Investigation of diabetic deaths begin		•Only 6% of insulin sold of human type	
1986				
1987	•Teuscher and Berger's paper on unawareness of hypoglycaemia	•Questionnaire request printed in Balance	•Diabetics first start to report problems	
1988		•Questionnaire results published		
1989		•The Human Insulin Working Party (BDA) meets for the first time	•About 80% of diabetics using human insulin	•Nordisk Wellcome in Britain introduce a warning for the first time in connection with marketing of a new human insulin. Followed discussions with the British government's Committee on Safety of Medicines
1990		•BDA issue first statement on human insulin, being the result of more than two years scientific and clinical study		
1991	•Interest in outlining the ideal study •First study on diabetics who had experienced problems on human insulin •Pair of studies by Egger et al	•Interest in outlining the ideal study •BDA set up the Loss of Warnings (LOW) Task Force •Leaflets produced and sent to medical profession •Letters written by the BDA to pharmaceutical companies asking for better labelling of their insulins	•First news of possible legal action	
1992	•Study by Colagiuri et al •'For Debate' summaries •Liverpool Symposium on human insulin and hypoglycaemia held	•BDA still receiving letters from patients about their experiences on human insulin		
1993			•Court case collapses	
1994		•First newsletter of the Insulin Dependent Diabetes Trust •BDA's Insulin Campaign petition presented to pharmaceutical companies •The BDA produces a special supplement on human insulin - 'The Insulin Debate'	•BDA petition started	•Novo Nordisks Insulin Simplification Programme •Novo Nordisk stated that animal insulin will remain in production at least until the turn of the century
1995	•Study by Meneilly et al on NIDDM subjects		•84% of people with diabetes use human insulin	
1996				
1997			•Number of diabetics on animal insulins put at 50,000	•CP Pharmaceuticals Ltd announce they are extending their range of animal insulins to include cartridges
1998	•Insulin becomes a prescription only drug			

Figure 5-2: Chronological outline

5.2 A CHRONOLOGICAL OUTLINE

In the previous chapter I outlined a number of reasons why the prescription of human insulin rose from 6% in 1985 to about 80% in 1989. I suggested that advertising aimed at the medical profession, media attention toward human insulin, and the belief that animal insulins were being withdrawn, all affected the transfer of diabetics from animal to human insulin.

Soon after the initial introduction of human insulin in 1982, various animal insulins were also being withdrawn, and a number of these were being replaced with equivalent human insulins. For example, in 1986 it was announced that beef Ultratard was to be withdrawn in July (Balance, 1987a: 5). In December 1986, Novo Laboratories announced that they were replacing two of their Monocomponent (MC) pork insulins[32] with human equivalents (Balance, 1986: 4). As the use of human insulin increased the BDA received many letters regarding the withdrawal of these insulins. As a result of these letters the BDA were constantly seeking reassurances from the pharmaceutical companies over the availability of animal insulins (Balance, 1987).

In Chapter 4 I also described some of the initial reactions of diabetics who were experiencing problems on human insulin. In particular, I pointed to the request by the BDA, in 1987, for those diabetics who were experiencing problems on human insulin to contact them. Another important date was the publication of the first study, in 1987, that showed that human insulin did cause a change in the warning signs of approaching hypoglycaemia. I ended that chapter by describing some of the initial reactions of diabetics and doctors, to claims of a change in the warning signs of approaching hypoglycaemia.

The initial study by Teuscher and Berger in 1987 (1987) prompted many other studies. These tested two main hypotheses: 1) whether human insulin caused a change in the warning signs of approaching hypoglycaemia, and 2) whether human insulin increased the number of severe hypoglycaemic episodes. Although there were many studies that were carried out, it is possible to pick out a number that were important. These studies were important for a number of different reasons: a new study design was used

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[32] The initials 'MC' signify highly purified insulins.

that improved on a previous study; two papers were published close together that showed different sides of the argument; and, as a result of a published study, the medical media received, and published, letters.

What is important about these studies is that they were not carried out to satisfy regulatory bodies, as were the initial studies but were, rather, prompted by concerns within the medical community over problems experienced by some diabetics who were using human insulin. Reports were then published in the medical press, which fed back to the medical community.

Some studies that looked at the issues that surrounded the possible negative effects of human insulin showed contradictory results. Studies showed both that human insulin did, and did not, effect the awareness and number of hypoglycaemic episodes, compared with animal insulin. From a clinical point of view, there were a number of suggested reasons for the effects experienced by some diabetics who were on human insulin. It was suggested that the cause of the experiences may have something to do with the natural biography of diabetes or to some other therapeutic change, rather than human insulin (Pickup, 1989).

Throughout the human insulin debate there were a number of reasons suggested for the problems experienced by some diabetics that were not strictly scientific or medical. For example, there was a concern that some diabetics were changed to human insulin without proper advice and monitoring. Turner et al. argued that:

> "Advertisements have led general practitioners to alter the insulin brand their patients receive without the diabetic clinic knowing about the change and therefore being unable to monitor or adjust the dose."
>
> (Turner et al., 1988: 1150)

This was backed up by the BDA's survey of diabetics:

> "[one group of people]...who have had difficulties are those transferred, unknowingly, from pork to human by the pharmacist."
>
> (Alexander, 1989: 157)

Despite the fact that by 1989 there was still no scientific 'proof' that human insulin caused a change in the nature of hypoglycaemia, insulin manufactures printed warnings on their human insulin packaging. The warnings stated that some diabetics

had experienced problems on changing from animal to human insulin. These warnings were produced in consultation with the Committee on the Safety of Medicines.

As would be expected, the BDA were aware of the problems that some diabetics were experiencing on human insulin. However, it was only in 1989 that they investigated the problem by setting up the Human Insulin Working Party (HIWG). The HIWG's task was to monitor the human insulin situation, gather data, and keep abreast of any new developments. The group comprised a number of recognised experts on hypoglycaemia, a number of BDA staff members, and representatives of the insulin manufacturers.

One criticism of the HIWG was that there were no diabetics in the group (Balance, 1994: v). In response to this criticism, the BDA set up a Loss of Warnings (LOW) Task Force in 1991. The task force aimed to bring to the attention of doctors some of the problems that diabetics were experiencing on human insulin (Balance, 1991b). They also wanted to encourage better communication between patients and doctors. They took a number of practical steps in order to achieve this. For example, they produced a special leaflet - People with Diabetes and Changes in Hypoglycaemic Warnings - which outlined some of the problems experienced by diabetics (see Appendix 2). This leaflet was circulated to medical professionals, placed in various national newspapers and printed in an issue of Balance. At the end of 1991, Dr Ward of the BDA, wrote to the insulin manufacturers asking them to clarify the labelling of their insulin types (Balance, 1991b).

Requests for further information for diabetics and doctors did not just come from diabetic care groups. In a study that showed no difference in awareness of hypoglycaemia between porcine and human insulin, the researchers concluded that:

> "Clear advice is urgently required for the many patients who are anxious about the possible risks of hypoglycaemia with human insulin."
>
> (Patrick et al., 1991: 531)

One problem in obtaining clear advice was that the scientific community were in disagreement over the possible negative effects of human insulin. One solution to this would be in designing an ideal study. It was in 1991 that there was the most interest

in outlining an ideal study capable of determining definitively the impact of human insulin, and so resolving the human insulin debate. However, within the scientific community there was no agreement as to the size and format of such a study.

Also in 1991, a steering committee was formed in which lawyers and diabetics had got together in order to look into the possibility of taking legal action over the side effects that they had experienced on human insulin. There was a lot of interest from diabetics and solicitors over the possibility of legal action. However, it was unclear who the action would be against, and in March 1993, the legal case was dropped since claimants were unlikely to get legal aid, and there were insufficient scientific grounds for the claim.

Although there had been warnings and advice over the possibilities of problems on human insulin for over 5 years, the BDA were still receiving letters from diabetics concerning the negative effects of human insulin. In particular, letters from diabetics described how, despite experiencing problems on human insulin, their doctors were refusing to change them to back to animal insulin (Balance, 1992c). However, it is important to point out that the number of letters of complaint had fallen considerably since the activities of the LOW Task Force had begun (Balance, 1992c).

As already pointed out, there had been some confusion over the availability of animal insulins. In order to clarify the situation the BDA began their animal insulin campaign in 1994. The aim of the campaign was to make animal insulins available indefinitely (previously the BDA had argued that any withdrawal of animal insulins had to be accepted). In September and October 1994, the BDA presented a petition, with 140,000 signatures, to the three main insulin manufacturers. Novo Nordisk said that they remained committed to animal insulins, and assured the BDA that they would be available until the year 2000. However, they could not commit themselves after this, since it would depend on the economic viability of animal insulins. Although Eli Lilly had never marketed animal insulins in the UK, they expressed their support for a choice of insulin species for diabetics. As for CP Pharmaceuticals, they made an ongoing commitment to the production of beef insulin.

Also in 1994, the BDA produced a special supplement on human insulin. The

supplement outlined some of the issues that surrounded the human insulin controversy. The supplement was printed in an issue of Balance.

One important moment was the setting up of the Insulin Dependent Diabetic Trust (IDDT) in 1994. One of the prime aims of the trust was to offer care and support to diabetics, particularly those on human insulin. Indeed, one of the reasons for the setting up of the trust was because its members felt that the BDA, and other organisations, were not offering adequate support to diabetics who were experiencing problems on human insulin.

Between 1995 and 1996 Novo Nordisk began their Insulin Simplification programme. The aim of the programme was to simplify the number of insulins that the company supplied, as many of the insulins were duplicated. Throughout the simplification programme the BDA had frequent contact with Novo Nordisk over the structure of the programme. In particular, they were influential in gaining a number of concessions, such as assurances that clinical trials would be carried out looking at how diabetics dealt with the switch from the discontinued insulins.

In 1997 CP Pharmaceuticals announced that they were extending their range of animal insulins. Some of their existing beef insulins would be produced in cartridges, for use with insulin pens. Insulin pens are pen like devices that carry set insulin doses that can be administered quickly and conveniently. They were also going to produce some new porcine insulins in cartridges. For the BDA and the IDDT this was a major boost. The BDA felt that their 1994 campaign had helped persuade CP Pharmaceuticals that there was a market for animal insulins in pen form.

Both the BDA and the IDDT had argued that since human insulins were available for use with both syringes and insulin pens, this should also be the case for animal insulin. Some had argued that since human insulins were available in cartridges, many diabetics had been dissuaded from transferring back to animal insulin, despite experiencing problems, because they wanted to use this convenient method of insulin administration (IDDT, 1996a: 10). With animal insulins available in pen form, diabetics and the medical profession, had a full choice of insulin and administration devices.

At present, the human insulin debate is still unresolved. However, through greater awareness by both the medical profession and diabetics, it can be argued that human insulin is less of an issue than it was. The IDDT does still exist, and receives many letters from diabetics who are still experiencing problems on human insulin. The IDDT has established strong links with diabetic populations in other countries who are experiencing problems on human insulin.

In this overview I hope that I have adequately outlined some of the important points in the human insulin debate. There are a number of particular elements that I intend to bring out in future sections, these will be organised under the thematic chapters institutionally and patient centred. In this institutionally centred chapter I will first look at some of the studies that have been carried out to look into whether human insulin is to blame for the problems experienced by some diabetics. I will then go on to consider the argument for other possible causes for these experiences. I will then address attempts, by both sides of the debate, to outline the criteria of the ideal study that would close the human insulin debate. I will also refer to some non-scientific elements of the human insulin debate. Finally, I will look at how the pharmaceutical companies responded to concerns over human insulin, in particular, warning diabetics of problems on human insulin.

These issues are important for a number of reasons. By describing the studies that took place within the scientific community, and claims that it was not human insulin that caused negative effects but an unrelated therapeutic change, I hope to illustrate the complexity of assessing whether the use of human insulin does cause negative effects. Discussion of the ideal study is also important because it is an illustration of how scientists attempted to close the human insulin debate, and this should be contrasted with the following sub-section, which describes more rhetorical attempts at closure. The final sub-section, on the pharmaceutical companies, is interesting because it describes actions taken by human insulin manufactures that were not forced upon them by the scientific community.

5.3 SCIENTIFIC COMMUNITY

The scientific community had an important role in the regulatory process by which human insulin was certified as 'safe and efficient'. The trials which were organised

and funded by pharmaceutical companies, enabled human insulin to be approved for use by diabetics. After the introduction of human insulin other trials were still carried out, however, these trials were more interested in assessing the benefits of human insulin, rather than its safety. In the majority of cases, rather than being funded by pharmaceutical companies, the studies were organised within the scientific community, prompted by the experiences of some diabetics on human insulin. In this section I am interested in these latter studies. Before I look at these however, it might be helpful to give some background to the introduction of human insulin from a scientific standpoint.

When human insulin was first introduced there were concerns over the commercial versus scientific aspects of human insulin. In 1983 it was pointed out that there were a large number of commercially sponsored symposia, unreviewed papers and reports in books and supplements to well-known journals. By comparison, there were only a small number of original papers on human insulin that had passed a peer review system (Sonnenberg and Berger, 1983: 458). Indeed, as noted in Chapter 3, some have argued that the introduction of human insulin was very speedy compared with other drugs. Hall has argued that the time frame, in which human insulin was regulated, was very short because there was pressure from a number of areas to have human insulin available for use as soon as possible (Hall, 1987). The interest in, and speed by which, human insulin passed through the regulatory authorities was due to the ability of key actors, such as scientists and the pharmaceutical companies, to define other insulins as problematic, and human insulin as the solution to these defined problems.

When human insulin was introduced there were a number of suggested benefits, such as it being less immunogenic than animal insulin. When an insulin is less immunogenic it means that there are less circulating insulin anti-bodies. The reduction of insulin antibodies is important because insulin antibodies can cause lipoatrophy (pock marks) at the site of injection, and insulin resistance.[33] Studies have shown that human insulin is less immunogenic than conventional animal insulins (Fineberg et al., 1983; Collier and Pilkington, 1984). However, when human insulin

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[33] However, insulin resistance is rare now that purified porcine insulins are now in common use (Pickup, 1989).

is compared with highly purified porcine insulin the picture becomes less clear (Peacock et al., 1983; Pickup, 1986). Therefore, looking at the issue as a whole, there seemed to be little justification for the massive transferral of diabetics to human insulin. This led Sonnenberg and Berger to argue that, in 1983 that the "present vogue for human insulin is not matched by comparable benefits in clinical practice" (1983: 458).

Since human insulin had not been shown to be clinically advantageous, it was argued in the scientific community, that there was no reason to transfer diabetics to human insulin who were well controlled on animal insulin (Amiel, 1995: 258). Indeed, it was argued that only those who suffered from insulin allergy or who needed insulin treatment intermittently would benefit from human insulin (Pickup, 1986). However, it was argued that human insulin should be the logical choice for newly diagnosed diabetics (Pickup, 1986).

The first trial to suggest that human insulin had particular side effects, rather than being comparable with porcine insulin, was that carried out by Teuscher and Berger in 1987 (1987). As I described in the previous chapter, Teuscher and Berger claimed that human insulin caused 'hypoglycaemia unawareness'. That is, some diabetics lacked the early warning signs of approaching hypoglycaemia that they usually experienced when they were on animal insulin. After the study by Teuscher and Berger there were a large number of studies, letters and editorials printed in the scientific press concerning the possible problems that some diabetics experienced on human insulin. Therefore, I would argue that it was the paper by Teuscher and Berger that, at least in part, initiated the 'scientific controversy'.

Although for purposes of exposition I have separated out some of the important actors in this and the following chapter, it is important to be aware that they should not be seen as entirely distinct. For example, work carried out within the scientific community influenced how the medical profession treated the issue. Care groups also draw upon work carried out by scientists.

In order to bring some structure to this section I will base it around a number of key studies that have been carried out. I will look at these studies and the letters that

resulted from their publication. I do not claim that the studies that I will deal with are the only possible key studies. However, by keeping to a relatively small number of studies and responses to, and criticisms of these studies, I hope that I will be able to clearly outline some of the issues involved. For example, I will show how there was some debate over which type of study would be able to show whether human insulin did or did not cause negative effects. I will also show how, over time, the selection of the study population was reassessed.

So, in the following sections, I will consider a number of scientific studies that looked at the possible side effects of human insulin (as initially suggested by Teuscher and Berger). In the next section, I will look at other possible causes for an increase in the frequency of severe hypoglycaemia and a change in the symptoms of hypoglycaemia. Whereas the first section will look at causes that can be 'studied scientifically', the second section will be concerned with claims about a number of more 'wide-ranging' causes. Explanations in this section put the experiences of diabetics down to either the 'natural' biography of diabetes or to problems in the management of diabetes. From this point of view, it is not human insulin per se that is to blame, but rather aspects of clinical practice. I will then go on to look at how scientists attempted to define the 'ideal study', that would, in theory, be able to show whether human insulin did or did not cause side effects. In the final section, I will draw together some of the points made, in particular, how the scientific community perceived the human insulin debate.

5.3.1 The Studies

The first study to look specifically at the possible side effects of human insulin, rather than looking at its benefits, was published in 1987 by Teuscher and Berger (1987). The study was the first in which the term 'hypoglycaemia unawareness' was used to refer to some of the symptoms experienced by some diabetics on human insulin.

The conclusion of the study by Teuscher and Berger was that the use of human insulin can effect the onset of the classic early warning signs of approaching hypoglycaemia. They argued that warnings signs of approaching hypoglycaemia tended to be of an neuroglycopenic nature, rather than the classical sympathoadrenal warnings. If we remember from Chapter 4 (Figure 4-3), with sympathoadrenal symptoms (sweating,

hunger and irritability) a diabetic is likely to be aware of approaching hypoglycaemia, and be able to take appropriate action. Neuroglycopenic signs on the other hand, are secondary signs, and due to their nature (confusion and seizure) they may prevent a diabetic from taking appropriate action.

Teuscher and Berger stressed that, for the majority of diabetics, there would be no benefit in transferring patients from animal to human insulin. They further stressed that they were concerned over the "apparent marketing effort of manufacturers to influence physicians and patients to switch from animal to human insulin" (Teuscher and Berger, 1987: 385). As a result of their findings, they stressed the need for the continued availability of beef and pork insulins.

Type of study:
- the study was looking at frequency of hypoglycaemic episodes and not unawareness of hypoglycaemia.
- studies carried out on healthy subjects not diabetics.
- 'one-off' laboratory studies may not be powerful enough to detect differences between insulins.
- retrospective studies - relies on accounts of diabetics after the fact.

Failure to exclude certain subjects:
- those who experienced a loss of warnings before being transferred to human insulin.
- those with long duration of diabetes.

Problems with studies:
- the study was too small to detect a statistically relevant result.
- variations in recall periods.
- lack of a control group.
- varying criteria in the definitions, assessment and classification of 'severe hypoglycaemia'.
- issues of variability of biological responses within subjects when hypoglycaemia is induced.
- incomplete records.
- statistical validity.
- comparing results from various studies is difficult.
- selective transfer of patients to human insulin.

Figure 5-3: Summary of possible problems with human insulin studies

There were however, a number of criticisms of this study (see Figure 5-3 for a summary of various criticisms of studies carried out looking into human insulin). Hepburn and Frier (1989) point out that Teuscher and Berger did not exclude those patients who experienced a loss of warnings before being transferred to human insulin. By not excluding these subjects, the study would exaggerate the prevalence of the problem of hypoglycaemia unawareness in the study population. The study also consisted of diabetics with a long duration of diabetes (Gale, 1989). This is important

because long duration of diabetes has been shown to increase the occurrence of hypoglycaemia unawareness in diabetics (Drug and Therapeutics Bulletin, 1989: 22). Again, this would affect the prevalence of hypoglycaemia unawareness in the study study population.

Another criticism was that the study was designed to reach a particular conclusion, and did not warrant statistical analysis (Lean, 1987). An editorial, written quite a few years after the study, cast strong aspersions on the original paper by Teuscher and Berger, claiming that it was 'evidently unscientific' and should never have been published (Home, 1991: 799). Although Wolff responded to the editorial by arguing that it was "an interesting and publishable preliminary study" (1992: 376).

As already indicated the paper written by Teuscher and Berger was the first to associate hypoglycaemia unawareness with human insulin.[34] Although there had been concerns over the marketing and clinical benefit (compared with purified animal insulin) of human insulin, there had not been concerns over a negative effect of human insulin. Looking at all the subsequent scientific papers, they all referred to the paper by Teuscher and Berger. Therefore, if we wish to define a 'starting point', at least in a codified way, of the human insulin controversy, this would be it.

A possible cause, suggested by Teuscher and Berger, for a change in the classic warning signs of approaching hypoglycaemia, was due to decreased neurotransmitter secretion. One type of neurotransmitter that has interested scientists are catecholamines. As Pickup points out:

> "...absent or reduced release of catecholamines in response to hypoglycaemia correlates with unawareness of hypoglycaemia, a well established and extremely hazardous complication of insulin dependent diabetes."
>
> (Pickup, 1989: 991)

Studies that have investigated the size of catecholamine response to hypoglycaemia induced by porcine or human insulin have found conflicting results. Some studies have found that there is a decreased catecholamine response in healthy subjects (Heine

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[34] However, Teuscher and Berger argued that some other studies should be reassessed. They point to a study by Clark et al. (Clark et al., 1982) which claimed that biosynthetic human insulin was a safe alternative to porcine or bovine insulin. However, Teuscher and Berger (Teuscher and Berger, 1987), point out that 6 out of 94 patients withdrew from the study due to severe hypoglycaemia.

et al., 1989). Others have found that there is no difference (Kern et al., 1989). In 1989, Tattersall and Macdonald reviewed the issue of human insulin and the release of neurotransmitters and concluded that the issue remained controversial (1989).

Another suggested reason for the difference in warning signs of hypoglycaemia was due to the absorption rates of human insulin compared to pork insulin - their pharmacokinetics. It has been found that the pharmacokinetics of pork and human insulins have indistinguishable biological actions after intravenous administration (Pickup, 1989). However, when human and porcine insulins are injected subcutaneously, human insulin is absorbed slightly faster than the equivalent pork insulin (Sonnenberg and Berger, 1983). Both human and porcine insulin are absorbed faster than bovine insulin. This means that although human insulin has a faster onset of action, it has a shorter duration of action. It has been argued that this difference in absorption may be more noticeable in some patients, which results in a hypervariability of glycaemic control in these patients (Pickup, 1989).

It has also been suggested that because porcine insulin is slightly more lipophilic than human insulin, it is able to cross the blood brain barrier faster than human insulin (Heine et al., 1989). This effect may lead to high concentrations of insulin in the brain, and so have a differential effect on the central nervous system.

What is noticeable at this stage is that there are only a small number of suggested possible causes for a change in the symptoms exhibited by some diabetics on human insulin. Although future studies would look into these possible causes, the main concentration was in assessing whether human insulin did cause negative effects, rather than the origin of the effect. There were two effects or hypotheses that were investigated by researchers. One hypothesis was that human insulin increased the occurrence of severe hypoglycaemia in diabetics. A second was that human insulin altered the warning signs of approaching hypoglycaemia.

As I will show, some studies agreed with the findings of Teuscher and Berger, and others showed no negative effect of human insulin. However, some studies have found that diabetics have experienced an increased awareness of hypoglycaemia on human insulin (Hepburn et al., 1989). For this very feature, some diabetics preferred

human insulin to animal insulin.

There were other reasons why some diabetics preferred human insulin. In a follow up study to the original study by Teuscher and Berger (1987) 59 (89%) patients were available for re-examination. From these 59, 25 had remained on human insulin. Reasons given by these 25 diabetics for their continued use of human insulin were: insulin type "'does not matter' (n=12); human insulin 'must be [a] better insulin' (n=7); human insulin can be used in an insulin pen, but animal insulin can't (n=3); and, 'no sweating in hypoglycaemia' (n=3)" (Teuscher and Egger, 1989: 1072).

Berger et al. also noted that some patients saw the lack of sweating, which is normally experienced as a warning of approaching hypoglycaemia, as a positive feature of human insulin. They argued that:

> "...a few patients preferred human insulin because they found the symptoms of sweating (common on porcine insulin) disturbing."
>
> (Berger et al., 1989: 1044)

However, we have to be careful to distinguish between the frequency of severe hypoglycaemia and the quality of warning signs. Tattersall and Macdonald have pointed out that, "in early trials some patients reported feeling better because they did not get the unpleasant hypoglycaemia symptoms, and the conclusion was that the risk of hypoglycaemia was lower" (1989). However, it may be the case that these diabetics were clinically hypoglycaemic, but due to the lack of warning signs, they were unaware of their low blood sugars. In such cases, the diabetic may have felt able to carry out normal activities, such as driving, however, this would have been dangerous for the diabetic and others.

None of the studies described so far have studied diabetics who had reported a loss of awareness of hypoglycaemia after the change from animal to human insulin. However, in August 1991, a paper was published that studied this population (Patrick et al., 1991). The researchers compared the awareness of acute hypoglycaemia symptoms for diabetics on porcine and human insulin. They concluded that symptomatic responses to hypoglycaemia were not impaired by the use of human insulin.

5.3 Scientific community

As would be expected this study was criticised. Egger et al. argued that the study was too small to be able to conclude any clinically important result. They also argued that there may have been some misclassification of symptoms as either symptomatic or neuroglycopenic (Egger et al., 1991). Another criticism was that the subjects had not been treated with each insulin for long enough. David Kerr argued that, "Comparisons between insulin species should be made after patients have been treated for a reasonable time with each type of insulin" (1991: 951). Although this study was supposed to help close the controversy, since it was carried out on those very diabetics who were experiencing problems on human insulin, Kerr concluded that: "The human insulin/perception of hypoglycaemia debate is unresolved" (1991: 951).

A pair of studies that attempted to resolve the human insulin debate were carried out by Egger et al. in 1991 (1991c; 1991b). These studies are interesting because they tested the two hypotheses that I outlined earlier. One study showed that human insulin was associated with an increased risk of hypoglycaemia (Egger et al., 1991c). The second study concluded that human insulin could impair a diabetic's ability to take appropriate steps to avoid severe hypoglycaemia (Egger et al., 1991b).

In response to these studies, a whole string of letters were published in the *British Medical Journal*. In one letter, Matthews wrote:

> "The two papers by Dr Matthias Egger and colleagues on the risk of hypoglycaemia associated with treatment with human insulin reopen a debate that British doctors with diabetic patients had hoped was closed."
>
> (Matthews, 1991: 1265)

In particular, Matthews points out that it should not be a particular concern of scientists and the medical profession to seek to "prove or refute potentially litigious differences between porcine and human insulin" but to make sure that patients and families are aware of the possibility and educate them accordingly (1991: 1265). Others argued that, just because some studies showed that there was a rise in hospital admissions, for severe hypoglycaemia in the area of study, and the increased use of human insulin, it did "not necessarily impute a causal relation" (Frier et al., 1991: 1667). Indeed, as I will show in a following section, there are a number of other possible causes of hypoglycaemia unawareness and increased frequency of severe hypoglycaemia. These other causes include such factors as the movement towards

tight blood glucose control, that occurred at a similar time as the transferral to human insulin, and features of the 'natural' biography of diabetes.

Another criticism was put forward by Frier et al. (1991). They pointed out that the patients in the studies were transferred from animal to human insulin at equivalent doses. Yet, research had shown that a dose reduction may be necessary when diabetics were transferred to human insulin from animal insulin. They especially point out that:

> "Because of an expected reduction in insulin requirement after transfer from animal to human insulin diabetic patients in the United Kingdom were instructed to reduce their dose by at least 10% and few subsequently experienced increased hypoglycaemia."
>
> (Frier et al., 1991: 1667)

As outlined above, there were some strands that were continually present through the human insulin controversy. One such strand was the transferral of diabetics back to animal insulin if they experienced problems on human insulin. Even those studies that showed that there were no negative effects for diabetics on human insulin, did not advocate that human insulin should be the only insulin available to doctors and diabetics. This was also expressed by authors of editorials. For example:

> "In our opinion the balance of available evidence does not suggest that human insulin specifically impairs perception of hypoglycaemic symptoms or that its use predisposes to severe hypoglycaemia...[however]...we have no hesitation in transferring patients back to animal insulins if they so wish..."
>
> (Williams and Patrick, 1992b: 356)

Indeed, at the Liverpool Symposium on Human Insulin and Hypoglycaemia (Patrick and Williams, 1992), held in January 1992, there was general agreement, from both sides of the human insulin debate, that a number of guidelines should be followed (see Figure 5-4, taken from Williams and Patrick (1992b)). Those at the symposium included, Dr Matthias Egger, Professor Arthur Teuscher, Dr Alan Patrick and Dr Gareth Williams who have all been prominent in the human insulin debate.

1) Patients who are satisfactorily treated with animal insulin should not be transferred routinely to human insulin. If transfer is indicated on medical grounds (for example hypersensitivity to animal insulin) the doctor should discuss this fully with the patient and monitor the change over carefully. It is not acceptable for patients to be transferred to human insulin by pharmacists.
2) Patients receiving human insulin should be transferred back to animal insulin if they so wish.
3) Animal insulin preparations must therefore remain available, they should include cartridges for the pen injection devices which are increasingly popular with patients (only human insulin cartridges are available for the most widely used devices).
4) Adequately designed studies should be performed as a matter of urgency to determine conclusively whether human insulin has specific adverse effects.

Figure 5-4: Suggested strategy for managing diabetic patients with insulin

In a quite well received study by Colagiuri et al, the research group found that human insulin did not have a negative effect (1992a). This study was particularly crucial because it involved diabetics who had been referred by their doctors because they experienced ill effects on human insulin. The study was therefore similar to that carried out by Patrick et al. (1991). However, one criticism of the study by Patrick et al. was that the findings were not applicable outside of the laboratory setting (Egger et al., 1991). The study by Colagiuri et al. attempted to correct this criticism.

The study found that there was no difference between porcine and human insulin in glycaemic control or the frequency, timing, severity, or awareness of hypoglycaemia (Colagiuri et al., 1992a: 1434). For Colagiuri et al. it appears that any change in warnings in the diabetic population are slight. Indeed, they conclude their paper by arguing:

> "Hypoglycaemia is the most common and distressing side-effect of insulin therapy. Hypoglycaemia unawareness is frequent and deserves more attention in clinical practice. It is common during treatment with both human insulin and porcine insulin."
>
> (Colagiuri et al., 1992a: 1435)

As with the majority of papers published concerning the human insulin debate, subsequent letters were printed in the scientific and medical press. Egger and Davey Smith (1992) for example, argued that the study did not match a number of standards that have been defined as important for clinical trials (Altman and Dore, 1990). These are based on the calculation of: sample size; method of randomisation; and, statistical analysis which explores any discrepancies between different treatment groups. Egger

and Davey Smith argued that "Colagiuri and colleagues' report fails on all three counts" (1992: 301). As a result, they concluded that the study was of little help to the human insulin debate. Colagiuri et al. responded by arguing that Egger and Davey Smith, "...make spurious comments on the design of our study and inappropriate reanalysis of our data" (1992b).

Such comments can be seen as typical rhetorical moves in scientific controversies (Collins, 1985). In addition to criticising the methodology of a study, the criticisms are directed towards the credibility and authority of an individual author. Similar to above, when Dr. Kiln (1992) dismissed the study by Colagiuri et al. (1992a) as 'worthless', due to serious flaws in the design of their study, they replied:

> "Mr R Kiln dismisses our study on insulin species and awareness of hypoglycaemia as worthless. Kiln's comments reflect a less than careful reading of our paper."
>
> (Colagiuri et al., 1992c: 957)

Other responses would state the current state of the controversy. Again, this should be seen as a kind of attempted rhetorical closure. For example, Von Kriegstein argued that:

> "...Colagiuri's study should neither end the scientific debate, nor end the need for porcine insulin to be kept available for our patients who, we remain convinced, have difficulties with human insulin."
>
> (Von Kriegstein, 1992: 302)

In 1992, an editorial (Gerich, 1992) and a pair of discussion papers (Egger et al., 1992; Williams and Patrick, 1992b) were published in the *British Medical Journal*. As may be evident so far, the authors Egger, Davey Smith and Teuscher were frequently having material published in the scientific press concerning problems on human insulin. Similarly, but to a lesser extent, Williams and Patrick frequently had articles published in which they claimed that human insulin did not have any negative effects. Therefore, the publication of these two discussion papers is interesting since it puts the 'for and against' groups in a space in which they can easily be compared. I should point out that the formulation of two sides in human insulin debate is not just mine, but was quite prevalent in the scientific and medical media (Patrick and Williams, 1992).

5.3 Scientific community

No new evidence was presented in either of the discussion papers. Rather, each paper reviewed other studies that had been carried out in order to assess whether human insulin had any negative effects. They came to the following conclusions:

> "...a different symptom pattern seems to exist in at least one important group of adult insulin-dependent patients - those with tight glycaemic control and a history of diabetes of several years."
>
> (Egger et al., 1992: 354)

> "In our opinion the balance of available evidence does not suggest that human insulin specifically impairs perception of hypoglycaemia symptoms or that its use predisposes to severe hypoglycaemia."
>
> (Williams and Patrick, 1992b: 356)

So, although both sets of authors had the same material to review, since they were published at the same time, they came to different conclusions. From the outset the two groups of authors came from different stand points, indeed, this is probably why they were chosen. There are however a number of differences in the content of the two papers.

The paper by Egger et al. (1992) provides a comprehensive review of the studies that had already been carried out. They argued that, from their reading, a number of these studies had shown that human insulin does act differently compared with animal insulin. In particular, they point to a change in the symptoms of hypoglycaemia. The review by Williams and Patrick (1992b) points more to other possibilities, such as a diabetic's change to tight glycaemic control, which may have occurred at a similar time to the transferral to human insulin; Williams and Patrick point to the complexity of diabetes in general, rather than human insulin.

There were however some points of agreement. The authors of the two discussion papers agreed that future studies should be aimed at those who have experienced a change in the warning signs of approaching hypoglycaemia, which have returned when patients were transferred back to animal insulin. The papers also reiterated that those patients who experienced problems on human insulin, and wished to change back to animal insulin, should be able to do so.

Another point of agreement was that both sets of authors proposed the need for a large multicentre randomised trial (Gerich, 1992). However, the specifics of such a trial

were not outlined. One important criterion would be the size of the study. Egger et al. talk of a study of 'adequate size', while Williams and Patrick defer the decision of the size and duration of the study to the statisticians. On the other hand, John Gerich, the author of the editorial, rejected the need for a large trial. Instead, he argued that the study by Colagiuri et al, which showed "no statistically significant differences between insulin species" (1992a: 1432), should be repeated, as their "combined power could exclude a clinically important effect" (Gerich, 1992: 325). From looking at articles in the scientific media it does appear that 1992 was a period when there was a great deal of interest in the outlining of an ideal study. Since this is an important part of any attempt to scientifically close the human insulin debate, I have dealt with issues concerning the 'ideal study' in a following section (5.3.3 The Ideal Study).

In 1995 a new study was carried out by Meneilly et al. (1995), that looked at the effect of human insulin on non-insulin dependent diabetics. This study is important because, although human insulin had been administered to healthy subjects and diabetics, it had not been given to non-insulin independent diabetics. This study then, had the possibility to extend the human insulin debate into a different area (Amiel, 1995). The study found that "...beef/pork insulin results in greater awareness of hypoglycemic warning symptoms than does human insulin in elderly patients with NIDDM" (Meneilly et al., 1995: Abstract). Indeed, these results were similar to many others in the debate that showed a difference in symptoms of hypoglycaemia on human insulin.

As part of the review of the study by Meneilly et al, Amiel (1995) considers some of the literature on human insulin in general. She argues that the majority of formal investigations have shown that human insulin does not specifically alter the psychological responses to hypoglycaemia induced in a laboratory setting. In terms of clinical practice, she also argued that there seemed to be no increase in the frequency of severe hypoglycaemia.

In the editorial Amiel also asks the question: Is the debate now to be rehearsed for patients with NIDDM? (1995: 258). She points out that due to a number of reasons, such as the treatment period being rather short, the clinical significance of the study was not clear. This is especially the case since a large number of studies on insulin

dependent diabetics have shown conflicting results. Indeed, Amiel calls for another similar study to be conducted where preceding glycaemic experiences of the patients is known, and so can be compared over the study.

In this section I have illustrated how attempts to close the human insulin debate by clinical trials have largely failed. As each study was published, various criticisms were lodged (Figure 5-3). However, as each new study was carried out it was hoped that it would improve on previous studies. Indeed, looking at the criteria by which subjects were selected, we can see that they were narrowed down from an unselected population, consisting of diabetics with a long duration of diabetes, to one where subjects were selected because they claimed to be experiencing problems on human insulin. This is important because long duration of diabetes has been shown to reduce a diabetic's awareness of approaching hypoglycaemia. As a result, by including such a sub-population in a study, it would not be possible to assess whether the occurrence of hypoglycaemia unawareness was due to human insulin or to a long duration of diabetes.

In the next section I will look at other explanations for the experiences of some diabetics on human insulin. Here, the issue is no longer whether human insulin is, or is not, the cause of the negative experiences of diabetics. Rather, the focus shifts to other areas of the network body, such as therapeutic changes.

5.3.2 Other Possible Causes

In this section I would like to look at claims for other possible reasons for the effects experienced by diabetics on human insulin. These are factors that have already been shown to affect the perception of hypoglycaemia. What will emerge are the difficulties in apportioning blame to human insulin. Indeed, since one of the symptoms exhibited by some on human insulin is an unawareness of hypoglycaemia, it is important to realise that an estimated 1.5% of diabetics lose awareness of hypoglycaemia each year under 'normal' circumstances (Colagiuri et al., 1992a; Gale, 1989).

5. After the initial reactions - science and the pharmaceutical companies

Summary of other possible causes of a perception of increased severe hypoglycaemia or hypoglycaemia unawareness

- One hypoglycaemic episode may prejudice responses to subsequent episodes.
- Part of the 'natural' biography of diabetes.
- Perception of hypoglycaemia can be dulled by alcohol and medications.
- Tight glycaemic control may increase the chance of hypoglycaemia.
- Perception of hypoglycaemia is notoriously difficult.

Figure 5-5: Summary of causes of hypoglycaemic

For those who believed that human insulin was not to blame there were many other possible causes for the change in awareness (see Figure 5-5). Indeed:

> "It could be argued that hypoglycaemia is fairly common in insulin dependent diabetes, whatever the treatment, and that on a few occasions patients could well attribute a chance increase in hypoglycaemia to come recent therapeutic manipulation."
>
> (Pickup, 1989: 992)

In the past a number of changes in the management of diabetes have resulted in claims by patients that their hypoglycaemic symptoms had changed. Changes were noted when patients have switched from beef to pork insulin (Gale, 1989); when patients were changed from conventional animal insulins to highly purified animal insulins in the 1970s (Home, 1991); when insulin strengths were changed from U40 and U80 insulin to U100 in the early 1980s[35] (Pickup, 1989); with the introduction of insulin pump therapy (Home, 1991); and even changes in colour coding of insulin vials (Dejgaard, 1991).

In many cases, at the time of transfer to human insulin, the chance was also taken to alter a patients management of diabetes. Many doctors and clinics implemented changes to a diabetic's routine; there were attempts to improve overall glycaemic control; intensified injection regimes were introduced; diabetics were encouraged to increase self monitoring of blood glucose concentrations; and, there was also a renewed program of diabetes education for patients.

The importance of glycaemic control was shown in the Diabetes Control and Complications Trial (DCCT) where tighter glycaemic control was shown to reduce the chance of diabetic complications in later life (Drug and Therapeutics Bulletin, 1989).

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[35] Pickup notes that the extent of any such change due to insulin strength is poorly documented (Pickup, 1989).

However, these measures also increase the chance of low blood sugars occurring, and subsequently, there is an increased risk of hypoglycaemia (Lesser, 1989a). It has been suggested that strict control in itself can reduce the warning signs of hypoglycaemia, possibly by lowering the glycaemic threshold at which catecholamines are released (Amiel et al., 1987; Amiel et al., 1988; Pickup, 1989: 992). As noted above, one suggested cause for some of the negative effects experienced by some diabetics on human insulin was that human insulin reduced the release of neurotransmitters, such as catecholamines (Teuscher and Berger, 1987).

Since the management of diabetes can be complicated, it is important to be aware that even slight changes in routines may affect the health of a diabetic. Pickup has argued that, "on a few occasions patients could well attribute a chance increase in hypoglycaemia to some recent therapeutic manipulation" (1989: 992). That is, a diabetic may devise a common-sense aetiology, based on knowledge of the change to human insulin (or any other therapeutic change). For example, in some studies no clinical difference has been found in patients who reported hypoglycaemia unawareness, although they themselves had attributed their unawareness to human insulin (Maran et al., 1993; Patrick et al., 1991). Also, in studies that showed no significant differences between human and porcine insulin, patients still remained convinced that human insulin interfered with their awareness of hypoglycaemia and chose to be treated with animal insulins (Williams and Patrick, 1992b: 356).

It is also known that one hypoglycaemic episode may prejudice responses to subsequent episodes (Ovalle et al., 1998; Amiel, 1995: 258). Therefore, no matter what insulin is used, if a diabetic is already badly controlled, then human insulin will make little difference to the management of diabetes. Linked to this are the findings that hypoglycaemia unawareness is known to occur in diabetics as part of the general biography of diabetes. For example, as a feature of a diabetic's age, duration of diabetes and the presence of autonomic neuropathy (Drug and Therapeutics Bulletin, 1989: 22). These are all factors that are part of the biography of diabetes, with or without human insulin. Therefore, any study that looks at hypoglycaemia unawareness must take into account the nature of the study population. Indeed, some studies were criticised because they did not exclude particular diabetic sub-populations, such as those diabetics with a long duration of diabetes (Teuscher and

Berger, 1987).

On a much more general front, it is known that the perception of hypoglycaemia can be dulled by alcohol and other medications, such as beta blockers used for treatment of high blood pressure and angina (Williams and Patrick, 1992b: 355). Therefore, before apportioning blame to human insulin, it is important to consider a number of factors which may cause 'hypoglycaemia unawareness'. Everett and Kerr (1994) have suggested a number of practical steps that should be taken before changing a diabetic back to animal insulin (Figure 5-6).

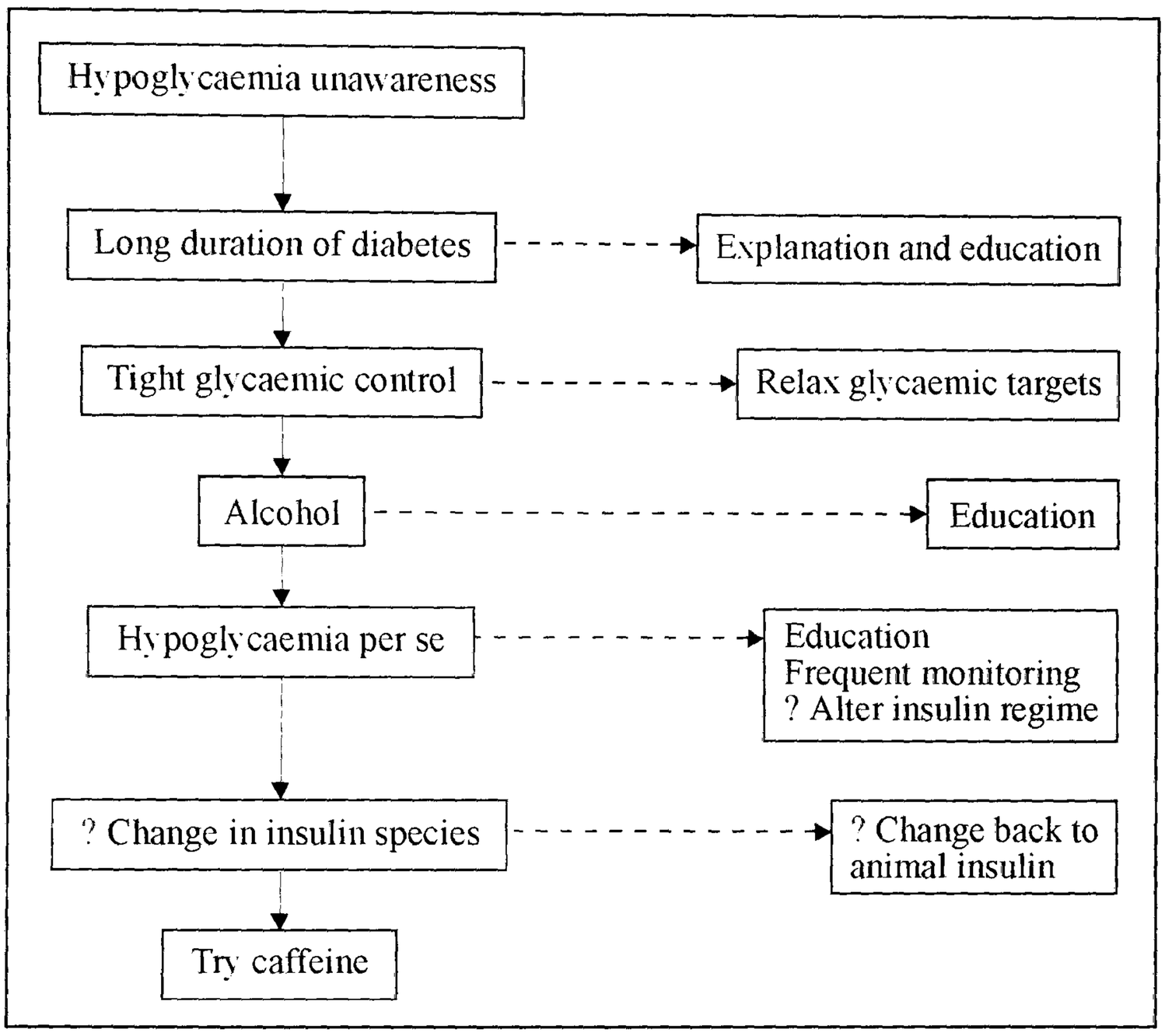

Figure 5-6: Treatment options for patients who experience hypoglycaemia, but lack awareness of its occurrence

One important finding that has an effect on apportioning blame to human insulin, is that when diabetics, who are experiencing problems on human insulin, are transferred back to animal insulin, the changes in the management of diabetes that they experienced on human insulin disappear. Teuscher and Berger in 1987 (1987) found that for a "...substantial number of diabetic patients there is a substantial loss of the classical warning symptoms, which is reversible after transfer back to animal insulin despite improved diabetes control" (Teuscher and Egger, 1989: 1072).

Therefore, it has been argued that it is not the case that diabetics who have experienced negative effects on human insulin, have experienced chronic and irreversible unawareness of hypoglycaemia (Patrick et al., 1991; Maran et al., 1993). In such cases then, the argument would be that the experience of diabetics on human insulin, cannot be part of the biography of diabetes, i.e. due to the long duration of diabetes or a diabetic's age. Neither could it be due to a therapeutic change, as long as the same conditions exist before and after the transfer back to animal insulin.

However, not all diabetics that were on human insulin and had experienced problems, and were then transferred back to animal insulin regained their original warning signs (Home, 1991). It has also been found that a loss of warnings of hypoglycaemia could be reduced over time on human insulin, what is known as desensitisation (Cranston et al., 1994). In another study, it was found that only a very small number of diabetic patients could identify the species of insulin that had been administered. This led the researchers to conclude that:

> "The fact that only two of 50 patients could do so [identify insulin species] is convincing evidence against a species effect on hypoglycaemia awareness."
>
> (Colagiuri et al., 1992c: 957)

This adds to some of the evidence outlined in the previous section that showed that studies of patients who have reported a change in the warning signs of approaching hypoglycaemia on human insulin, have not shown any scientific reason why this may happen (Patrick et al., 1991; Maran et al., 1993). This was my argument in the previous section: although scientific studies have suggested reasons why diabetics may have experienced problems on human insulin they could not be 'proved'.

It is also important to be aware that the perception of hypoglycaemia is problematic. There are a whole number of possible symptoms of hypoglycaemia and these vary between individuals (Figure 5-7). One study found that well educated and motivated patients wrongly judged that they were clinically hypoglycaemic in a quarter of episodes (Egger et al., 1991c). There is then, a divide between what may be defined as clinically hypoglycaemia and what signs of approaching hypoglycaemia exist in practice. In day-to-day life it is a diabetic's experiences that will affect the way they conduct themselves. It is these experiences that will be the subject of Chapter 6.

Symptoms of mild to moderate hypoglycaemia may occur suddenly and can include:

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- irritability
- abnormal behaviour
- unsteady movement
- personality changes

Signs of severe hypoglycaemia can include:

- disorientation
- unconsciousness
- seizures
- death

Figure 5-7: Signs of hypoglycaemia from Eli Lilly

I hope that in this section I have indicated how the scientific assessment of whether human insulin is the cause of some of the problems exhibited by some diabetics has been problematized. It is not only the case that many of the studies that have been carried out have been criticised for their methodological flaws, there have also been claims that there are other possible causes of the relevant symptoms. In order to apportion blame to human insulin it would be necessary to filter out this noisy background; this can be very difficult (Williams and Patrick, 1992b: 355). One attempt to do this was through the discussion of an ideal study. This discussion is interesting because it involves both sides of the human insulin debate, who discussed the structure of a possible study before it was carried out and published, rather than after publication, as is usually the case.

5.3.3 The Ideal Study

With all these problems then: What is the ideal study? Further, if there is an ideal study: Why has not it been carried out? As already described there are a number of problems in assessing the possible negative effects of human insulin, such as the selection of subjects, methodology used, and the applicability of results in clinical practice. Although, as Williams and Patrick point out, "previous work has been useful in identifying important pitfalls which must be avoided in future [studies]" (1992b: 356).

As already mentioned, two main hypotheses need to be tested when looking at possible negative effects of human insulin. The first, is that human insulin impairs the

warning signs of hypoglycaemic symptoms. The second, is that human insulin increases the risk of severe hypoglycaemia. It has been argued that previous studies have not been powerful enough to test one or both of these hypotheses, and have thus not produced valid conclusions (Williams and Patrick, 1992b). During 1991/92 there was a large degree of interest in outlining what would be the ideal study by which some resolution of the human insulin controversy could be achieved, and this is where my attention now turns.

Discussion of the ideal study was not just restricted to the medical and scientific community. The BDA also looked into what the ideal study would be. They asked the question: Why don't scientists get together and carry out one big study to sort the problem out once and for all? (Balance, 1992a). As part of the BDA's Loss Of Warnings (LOW) Task Force, which was set up in 1991 to look into and clarify issues around human insulin (Balance, 1991b), a special workshop was organised to consider the feasibility of carrying out a large scale study.

The BDA point out that one of the factors that has added to the confusion over human insulin, is the inability of scientists to decide clearly whether or not human insulin is in any way to blame for the loss of hypoglycaemia warnings (Balance, 1992a). Although many studies have been carried out to compare the way diabetics react to human and animal insulin in terms of warning symptoms, these studies have usually been small in scale. As already mentioned, some of these studies have shown that there is a difference, while others have shown that there is no difference between animal (especially pork) and human insulin. The BDA suggest that there are two main reasons, which I have already indicated above, for the inconclusive results over the possible negative effects of human insulin:

- Warning symptoms are very personal and vary between diabetics, as a result, they are difficult to measure.
- There are many possible reasons for experiencing a loss of warnings of hypoglycaemia.

So what type of study should be conducted to deal with these problems? There appeared to be a general acceptance that the hypotheses that human insulin increases the frequency of severe hypoglycaemic episodes could only be tested in field studies (Williams and Patrick, 1992b: 356). It had been argued that field studies would be

necessary since 'one off' laboratory studies are not powerful enough, due to individual differences, to detect a genuine effect. But if this is the ideal study, there are still a number of questions that need to be answered.

One of the crucial factors in any study is the selection of subjects. It had been suggested that the selection of diabetics should be restricted to those diabetics who had experienced problems on human insulin, and when returned to animal insulin, their awareness returned (such as that by Colagiuri et al. (1992a)). This would reduce the number of subjects that would be needed if taken from an unselected population, since the selection would be based on those very subjects that were exhibiting problems on human insulin, and not as part of the 'natural' biography of diabetes.

Another problem is that there is already a 'background' occurrence of severe hypoglycaemia. On any type of insulin species, the average number of diabetics having a severe hypoglycaemic episode is estimated at about 5% each year (Balance, 1992a). Looking at new cases of hypoglycaemia unawareness, Gale has argued that if 100 patients were followed for 20 years, 30 patients would be expected to develop signs of hypoglycaemic unawareness - a rate of 1.5 per year. If 100,000 patients switched to a new insulin preparation, 1500 can be expected to develop altered symptoms, even if the new insulin was blameless (Gale, 1989). Therefore, any study would have to be able to look beyond this background rate of hypoglycaemia.

Background rate of severe hypoglycaemia per annum (%)	Size of study	Size of year follow up
1	6200	3100
5	1160	580
10	540	270

Figure 5-8: Size needed to detect a doubling of the risk of severe hypoglycaemia

It has been argued that for a study to pick up a small increase in hypoglycaemia, say from about 5% up to 6.25%, would require 10,000 insulin dependent volunteers, if they could be found (Balance, 1992a). Earlier in 1988, Egger et al. (1988) had also looked into the size of any possible study. They considered the number of subjects that would be needed to detect a doubling of the risk of severe hypoglycaemia when assuming 5% (1%, 10%) of unexposed patients, having at least one episode per year

(see Figure 5-8).

Although Egger et al's figure is not as large as that of the BDA (since this was for an unselected population), it is still a large figure. Such large numbers of subjects are needed due to the background rate of severe hypoglycaemia experienced by diabetics. Indeed, even the background rate of severe hypoglycaemia is not certain. Balance claimed it is 5%, while others have claimed that it is 10% (Egger et al., 1988; Gale, 1989). In an overview by a group of scientists, the estimated frequency of severe hypoglycaemia in daily life ranged from 4% to 29% (Amiel et al., 1991).

Williams and Patrick argued that because of the rarity of patients, who matched their criteria (those suffering from hypoglycaemia unawareness which abated after transferring back to animal insulin), it may be necessary to carry out a multi-centre survey (1992b). Although they do not give an idea of the size of such a study, they do say that:

> "No doubt the statisticians, who have been vocal in the debate so far, will be able to give precise details of the necessary size and duration of such a study."
>
> (Williams and Patrick, 1992b: 356)

The BDA agreed that multicentre field studies would be needed. However, they were more precise over its details. I have already pointed out that the BDA believed that they would need 10,000 diabetics, although again, it should be noted that these subjects would be from an unselected population. The BDA point to a number of logistical problems with such a study:

- Estimated that it would need to be a 3-5 year study.
- Data would have to be analysed in over 100 centres, with a person employed in each centre.
- Both on practical and ethical grounds it would not be possible to carry out the study in the UK (or Australia).
- The cost of carrying it out in North America or Asia would be high.
- One possibility would be Eastern Europe, however in this part of the world health care is generally poorer.
- Estimated that it would cost a minimum of £1.5 million to carry out the study, over half the BDA's annual research budget.

The BDA and the LOW Task Force concluded that such a study would not be possible, and that even if it was, the current cost would make it impractical (Balance,

1992a).

Some have also argued that the "manufacturers who profit from the sale of human insulin should fund this enterprise: this is surely an ethical imperative." (Egger et al., 1992: 354). However, the pharmaceutical companies were not keen to do this. In another article, Egger and Davey Smith point out that it is up to those who propose a therapeutic change, in this case the pharmaceutical companies, to demonstrate the complete safety of what they propose before it is implemented (1992). This had been done, at least to the satisfaction of the regulatory bodies.

Egger et al. (1988; 1992) argued that there was a need for a large randomised trial of adequate size.[36] Although small scale studies had been carried out, they had not been specifically designed to test for an increased risk of severe hypoglycaemia (Egger et al., 1992). The trial would need to be a randomised double-blind trial, with carefully constructed questionnaires and case control studies, with the aim of determining the relative risk of severe hypoglycaemia and human insulin (Egger et al., 1988). Williams and Patrick also stressed that the study would have to be 'blinded' in some way. They argued that:

> "Because of general awareness of the debate and (regrettably) the possible motive of compensation claims insulin species can now be compared only under at least single blind conditions."
>
> (Williams and Patrick, 1992b: 356)

However, there was not total agreement that a multi-centre study would be needed. John Gerich argued that many studies have shown there to be no clinically significant differences between human and porcine insulin. As a result, he questions the need for an expensive large scale multicentre study (1992). Instead, he argues that the double blind crossover trial carried out by Colagiuri et al. (1992a) should be repeated. The study by Colagiuri et al. consisted of 50 diabetics who had been selected because they had reported reduced awareness of hypoglycaemia after transferring to human insulin. The group found that human insulin did not reduce the risk of hypoglycaemic unawareness, neither did it increase the incidence of severe hypoglycaemia. Although this study was criticised on a number of levels (see Teuscher, 1992; Von Kriegstein,

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[36] This was also recommended during a symposium on human insulin and hypoglycaemia in Munich in 1990 (Von Kriegstein, 1992).

1992), Gerich argued that with an additional study, with a design identical to that used by Colagiuri et al, "their combined power would exclude a clinically important effect" of human insulin having negative side effects (1992: 325).

Indeed, it was argued by some that a large study would not be needed since, according to Dr Matthias Egger and his team, unawareness of hypoglycaemia was a common occurrence. As Patrick and Williams argued:

> "If affected patients are as common in Switzerland as the work of the Berne group suggest the group should be able to test its hypothesis easily in a rigorously controlled setting, rather than simply adding to the existing confusing reports."
>
> (Patrick and Williams, 1991: 1266)

In summary then, there was interest in looking at the ideal study from both sides of the human insulin debate. Since previous studies could always be criticised on a number of points, such as the selection of subjects or the assessment of hypoglycaemia, there was discussion over the organisation of the ideal study. However, all researchers did not agree on the size or method of this ideal study. As a result an 'ideal study' was never carried out, although as shown above, many studies were carried out after the main interest in outlining the 'ideal study'.

5.3.4 Some General Strands

In this final section I would like to make some general comments on how the scientific community perceived the human insulin debate. As with many scientific debates, issues do not simply remain in one area, in this case human insulin. Some have argued that the debate over human insulin has helped to illustrate the problems with hypoglycaemia (Teuscher, 1992; Wolff, 1992). It has been argued that due to the human insulin debate, a lot more has come to be known about diabetes, hypoglycaemia unawareness, and human insulin, than would have been the case otherwise.

On the other hand, some authors felt that the human insulin debate was drawing attention away from other areas of the management of diabetes. Colagiuri and colleagues argued that the "continuing focus on insulin species distracts attention from the serious clinical problem of hypoglycaemia unawareness." (1992b: 303). Gale

argued that the "real problem is the inadequacy of current insulin therapy, not the insulin species in use" (Gale, 1989: 1266). Another concern was over the image that the development of human insulin gave to diabetics. As Sonnenberg and Berger argued

> "...there is a risk that the mere change to human insulin might lead some physicians and patients to the superficial and wrong impression that everything possible has been done to optimise the treatment of diabetes..."
>
> (Sonnenberg and Berger, 1983: 458)

As should be evident in the above sections, there were continual attempts to 'limit' the effect of a particular study. By this I mean that when a study was published scientists criticised particular elements of the study, such as the selection of subjects, treatment periods, or the statistical tests that were used. Some editorials were also criticised in this way. After the publication of an editorial concerning human insulin in 1992 (Wolff, 1992), which had the general tone that the human insulin controversy was to some extent 'created', one subsequent letter argued that "we are still sitting on a human insulin timebomb" (Kiln and Sugarman, 1992 :p. 10). This led Williams and Patrick, in reply to Kiln and Sugarman, to argue that:

> "...it is now time to turn attention to the many other pressing problems of diabetes. Kiln and Sugarman are worried that 'we are still sitting on a human insulin timebomb'. If they listen carefully, they may well discover that this particular timebomb has stopped ticking."
>
> (Williams and Patrick, 1992a: 355)

Some authors, who were sceptical of any possible case against human insulin, were accused of being in the pay of human insulin manufacturers (Wolff, 1992: 376). On a wider level, reports in the medical press have made some strong claims. Home argued that some journals encouraged the controversy by giving space to articles about the controversy with the aim of serving their "own interests before those of patients and the medical community" (1991: 799). In particular, Home points to the Lancet:

> "Even journalists and media commentators have been led to ask whether some of the heavily criticized contributions in the field, and in particular the self-evidently unscientific study which began the controversy, should have been published in reputable medical journals at all."
>
> (Home, 1991: 799)

Throughout the debate various groups attempted to claim some form of closure in the

human insulin debate. On the one hand, reports from authors such as Arthur Teuscher and Matthias Egger, showed that human insulin did cause some change in the warning signs of hypoglycaemia. On the other, studies showed that human insulin did not impair a diabetics control of their diabetes. Instead, a diabetic's experience on human insulin was seen to be due to a parallel change in the management of diabetes or to some part of the 'natural' biography of diabetes.

As usual in scientific controversies, closure was attempted through the use of rhetorical criticisms or claims. As outlined above, some authors were criticised for their lack of understanding of the methods used in a particular study or due to their less than careful reading of the study. In other cases, some authors claimed that the controversy was still open or closed, without necessarily fully supporting their claim.

Although there was no agreement between the two sides of the debate, over the possible side effects of human insulin, there was agreement that those diabetics who wished to change back to animal insulins should be able to do so. Studies had shown that when diabetics, who had claimed to have experienced problems on human insulin, were transferred back to animal insulin their awareness returned (Patrick et al., 1991; Colagiuri et al., 1992a). There was therefore a general agreement that animal insulins should be available for those diabetics who wished to change back to them (Maran et al., 1993: 171: Figure 5-4). Obviously then, those within the scientific community supported the availability and choice of different insulin species.

Therefore, although scientifically no 'proof' could be demonstrated either way, and no clinical consensus reached, the scientific and medical community did reach general agreement that animal insulins should remain available for those diabetics who wished to remain on animal insulin (Egger et al., 1992: 354).

In Chapter 7 I intend to bring some of the issues discussed above together, while referring to theoretical work. In particular, I am interested in the ways in which scientists attempted to 'close' the human insulin controversy, both on a scientific (clinical studies) and non-scientific (rhetorical claims) level. The scientific community were attempting to define the grounds under which closure would be achieved, whether this was through an experimental study or the continued availability

of animal insulin. Those scientists attempting to do this can be seen as being part of the core set (Collins, 1985). However, other groups were attempting to enter this core set. These included pharmaceutical companies and care groups. This complicated matters, since these other groups were competing with others to define the grounds under which closure of the human insulin debate could be achieved. These grounds may not be the same for all groups. One complication was the involvement of the pharmaceutical companies, and this is where my attention now turns.

5.4 THE PHARMACEUTICAL COMPANIES

As argued in Chapter 3, describing the commercial development and production of human insulin, the pharmaceutical companies were able to pass human insulin through regulatory bodies relatively quickly. I argued in Chapter 4 that one reason for the mass transfer of diabetics from animal to human insulin was due to pressure from the pharmaceutical companies. The pharmaceutical companies argued that there were benefits to patients in using human insulin, usually because of the claimed reduced immunogenicity of human over animal insulin.

However, the choice by doctors and pharmacists between animal and human insulin could not always be made on a 'level playing field', since some animal insulins were being withdrawn. The withdrawal of some animal insulins occurred in parallel with the introduction of human insulin. As early as 1986, it was announced that beef Ultratard was to be withdrawn (Balance, 1987a: 5). In December 1986, Novo Laboratories announced that they were replacing two of their Monocomponent (MC) pork insulins with human equivalents (Balance, 1986: 4).

The BDA warned that although Novo Laboratories were the first pharmaceutical company to discontinue animal insulins, and replace them with a human equivalent, they would not be the only ones to do so. Balance believed that diabetics had to accept that some insulin manufacturers were going to standardise their insulins because it made commercial sense (Balance, 1986: 4). The BDA's medical advisor wrote:

> "...it is likely that all manufacturers will 'rationalise' their insulins to human only in the near future, and we have no choice but to accept this."
>
> (Balance, 1986: 4)

5.4 The pharmaceutical companies

Although pharmaceutical companies' strategy of withdrawing animal insulins continued through the 1980s and into the 1990s, the reasons behind the marketing of human insulin, and the withdrawal of animal insulins, did seem to change. Gale has argued that, as the lack of a clear benefit of human insulin, especially its immunogenicity, over purified animal insulins (especially porcine insulin) became apparent, claims by pharmaceutical companies for the superiority of human insulins were quietly dropped (1989). The argument then became one in which, since both human and porcine insulins were so very similar, porcine insulin was no longer needed (Gale, 1989).

So was it the case that pharmaceutical companies argued that human insulin did not cause noticeable side-effects in diabetics? One way in which this can be gauged is through patient information leaflets. Since original studies showed that human insulin was 'safe and efficient', no warnings were originally placed on human insulin patient information leaflets. However, it has been noted that warnings appeared as early as 1983 on Eli Lilly human insulins that were marketed in the United States (Dejgaard, 1991). These warnings alerted diabetics to possible changes in the signs of approaching hypoglycaemia (Drug and Therapeutics Bulletin, 1989).

In the United Kingdom there were initially no such warnings. This led Teuscher and Egger to write:

> "...we are disturbed that insulin manufacturers have not yet produced more precise information on this important issue [the change in warning signs] in the inserts of their human insulin packages, both for physicians and diabetic patients."
>
> (Teuscher and Egger, 1989: 1072)

However, as concern began to grow in the United Kingdom, pressure was exerted on the pharmaceutical companies to put some warning on their human insulins. In August 1989, Nordisk Wellcome in Britain, announced that they were to introduce warnings with the marketing of their new genetically engineered human insulin (see Figure 5-9. Taken from Novo Nordisk). Nordisk said that the warnings followed discussions with the Committee on the Safety of Medicines (Lesser, 1989b: 22).

Changing to human insulin

- You should only change to human insulin on your doctor's advice.
- Transfer from porcine to human insulin of the same type, does not normally require a change in dose.
- Transfer from bovine or mixed bovine/porcine insulins to human insulin may require a dosage adjustment; follow your doctor's advice on this.
- A few patients have reported that after being transferred to human insulin, the early warning symptoms of hypoglycaemia were less pronounced than they were with animal source insulins.

Figure 5-9: Example of a Novo Nordisk human insulin insert

The British Licensing Authority also wrote to all insulin manufacturers:

> "...suggesting that the patient leaflets and the data sheets for human insulin should contain a specific warning that some patients have noticed less pronounced symptoms of hypoglycaemia on transferring to human insulin from animal insulin."
>
> (Pickup, 1989: 993)

All manufacturers made this change in their insulin packaging, which the BDA welcomed (Balance, 1989a). However, Frank Lesser pointed out that it was unclear whether diabetics themselves would be aware of the warnings. He argued that many pharmacists remove manufacturers inserts before passing the insulin on to diabetics. He also argued that the leaflets seemed to be aimed more at specialists than at patients (Lesser, 1989b: 22).

Although the BDA initially accepted the withdrawal of a number of animal insulins, in 1994 the BDA began a campaign to maintain choice for diabetics as to the species of insulin they wished to use. They collected 140,000 signatures that were then presented to three UK insulin manufacturers in September and October 1994 (Hope, 1994). The aim was to ensure that animal insulins were made available indefinitely, and to secure the availability of animal insulin pen devices.

The Insulin Campaign petition was presented to Novo Nordisk on the 29th of September 1994. Novo Nordisk reiterated their commitment to animal insulins into the next millennium, indeed, they pointed out that new investment was being made to ensure this. They also stated that this did not mean that animal insulins would be discontinued after the year 2000, rather, no indefinite commitments could be made. With regard to pen devices, Novo Nordisk said that they had no plans to produce porcine insulin pen cartridges as it was not economically viable to do so (Hope, 1994).

5.4 The pharmaceutical companies

The petition was presented to Eli Lilly Industries on the 13th of October. Eli Lilly have never marketed animal insulins in the UK, but expressed their support for a choice of insulin species for diabetics. However, they pointed out that more than 80% of insulin users were on human insulin, which had been proved scientifically, to be safe and effective. As to the future, they said that they had no plans to apply for an animal insulin product licence, but would keep the situation under review (Hope, 1994).

On the 26th of October the petition was presented to CP Pharmaceuticals Ltd who only manufactured beef insulin, after having recently discontinued the production of human insulin for commercial reasons. They made a substantial commitment to the ongoing availability of beef insulins (Hope, 1994). So while other companies were withdrawing their animal insulins, CP Pharmaceuticals had withdrawn their human insulin. CP Pharmaceuticals were therefore becoming a specialist in the market of animal insulin production.

One important point in the withdrawal of animal insulins was Novo Nordisk's insulin 'Simplification Programme'. The Simplification Programme aimed to reduce confusion that occurred due to the merger between two Danish Companies, Novo and Nordisk in 1989, to form Novo Nordisk. When these companies came together they kept all their insulins, which led to a duplication in many insulins.

The programme consisted of two phases. The first phase began in 1995, with the second beginning in April 1996. When the BDA became aware of the simplification programme they began discussions with Novo Nordisk to gain a number of alterations in the programme.

The first phase is not of great interest to this thesis, since it only concerned the withdrawal of some duplicate human insulins. However, it should be pointed out that the BDA managed to: lengthen the timetable of implementation of the changes; improve the content of information provided to diabetics and health care professionals concerning the changes; and, set up a telephone helpline to deal with queries (Balance, 1995: 42).

In April 1996 Novo Nordisk announced the second phase of their simplification

program, in which the naming of some insulins would change and some insulins would be withdrawn. The BDA said that they were particularly concerned that other such commercial decisions may be made, even though only a year ago the BDA gained a commitment from the company that they would continue to produce animal insulins (Balance, 1996). Again, the BDA had meetings with Novo Nordisk and gained a number of assurances:

- They would continue to produce their 'core group' of animal insulins as long as there was demand.
- They would re-invest in an animal insulin manufacturing plant.
- Clinical trials would be conducted in different parts of the country looking at the switch from the discontinued insulins. The data gathered would be used to help others make the change in the future.

The renaming of some animal insulins, where they had human equivalents, took place in April/May 1996. Patients were warned of the forthcoming change through a flash on the insulin packaging, and after the change, the insulin had different packaging to reflect the change. The production method of two of these insulins was also going to be changed, and patients were advised to carry out more frequent blood glucose testing (Balance, 1996).

Those insulins that were withdrawn were two of Novo Nordisk's lesser used MC animal insulins. The packaging of these insulins incorporated a flash saying that they would not be available after September 1997. Novo Nordisk was also carrying out studies to find an appropriate alternative (Balance, 1996).

In 1997 CP pharmaceuticals announced that they were extending their range of animal insulins, to include cartridge administered ones (to be used with pen devices). The BDA claimed that this was a major victory for them (Balance, 1997). CP pharmaceuticals were not only going to produce some of their existing bovine insulins in cartridge form, but also some new porcine insulins. I will return to this in Chapter 6.

The campaign by the BDA had aimed to ensure the availability of animal insulins and to ensure that animal insulins were available in pen devices, to some extent then, this campaign had been successful. CP Pharmaceuticals said that they were committed to supplying animal insulin in vials and cartridges indefinitely.

In conclusion, there was a tendency for pharmaceutical companies to withdraw a number of animal insulins. However, CP Pharmaceuticals Ltd began to expand their animal insulins and also developed animal insulin pen cartridges. Those producing human insulins did include warnings on their human insulins, however some were concerned with the wording of these warnings. In general, the production and use of human insulin increased after its initial introduction.

5.5 CONCLUDING REMARKS

In this chapter I have looked at some of the issues that were of concern to the scientific community and pharmaceutical companies. Work carried out within the scientific community was unable to show whether human insulin was or was not the cause of changes in the awareness of, and number of, hypoglycaemic episodes. However, there was an agreement that those diabetics who wished to be transferred back to, or stay on, human insulin should be able to do so.

Pharmaceutical companies wanted to maintain human insulin as the primary insulin. The two main players, Eli Lilly and Novo Nordisk, had withdrawn a large number of their animal insulins, and replaced them with human equivalents. CP Pharmaceuticals on the other hand, had increased the range of animal insulins that they were manufacturing and had invested heavily in animal insulins.

There is then an element of choice. The scientific community argued that animal insulins should be available, and CP Pharmaceuticals were manufacturing animal insulins. I also pointed out that the other two pharmaceutical companies did support a choice of insulin species. However, these pharmaceutical companies were not going to provide the opportunity for choice themselves. I will return to the idea of 'choice' in Chapter 6.

There was some interaction between the scientific community and pharmaceutical companies, with one result being that the pharmaceutical companies had produced warnings on their human insulins about a possible change in the nature of hypoglycaemia. Other actors also had links with these two main actors. For example, the BDA had consulted with the pharmaceutical companies, and some patients did write to the pharmaceutical companies about their experiences. In Chapter 6 I will

look at some of these other actors in more detail.

It is in Chapter 7 that I will bring some of the key actors together under a theoretical framework. In particular, I will be interested in attempts by various groups to bring some form of closure to the human insulin debate. When I have dealt with issues from a patient centred point of view I will then be in a position to compare the differing attempts at closure, between those actors that may be defined as being institutionally centred and those being patient centred.

6. AFTER THE INITIAL REACTIONS - DIABETICS AND CARE GROUPS

6.1 INTRODUCTION

In Chapter 5 I gave a chronological outline of some of the key moments in the human insulin debate. I then went on to describe in more depth some of the important moments in the human insulin debate from an institutionally centred point of view. In this chapter I would like to look at human insulin from the perspective of the patients. Rather than being interested in large organisations or communities, this chapter will look at what role patients and care groups had to play in the human insulin debate.

I will first describe some of the experiences of diabetics on human insulin. I have already described some of these initial experiences in Chapter 4, but it will be helpful to summarise these experiences here in order to set the scene for future sections. Then, in Section 6.3 I will look at the role of two mediating actors, families and the media, and their role in the human insulin debate. The following section will look at the interaction between doctors and diabetics. In particular, I am interested in how solutions and resolutions, presented by doctors, were accepted or rejected by diabetics themselves. Section 6.5 will then go on to look at issues around the 'choice' of insulin. Finally, in Section 6.6 I will compare the way in which the BDA and the IDDT approached the human insulin debate.

6.2 SOME EXPERIENCES

Before I go on to look at issues in the human insulin debate that can be seen as patient centred, I will first set the scene by recalling some practical experiences of diabetics on human insulin.

Some diabetics described how, when transferred to human insulin, they no longer felt that they were in control of their diabetes. I described in Chapter 4 how some diabetics found that on human insulin they no longer had the usual warning signs of approaching hypoglycaemia. A number of diabetics described how these changes, in the management of their diabetes, had a detrimental effect on the conduct of everyday life. Diabetics described how it was only due to paramedics, neighbours, family members and the casualty department at the local hospital that they did not suffer

detrimental effects on human insulin (Balance, 1991d).

The experience of diabetics on human insulin therefore affected a number of areas of their social life. For example, one diabetic describes how:

> "...since starting on Human Monotard Insulins around 1986, I have suffered many embarrassing and dangerous hypos, with doctors being called to treat me on several occasions."
>
> (Balance, 1991c)

As a result of these problems, the diabetic describes how, when on an animal insulin mixture, he was employed in a position of responsibility, being able to manage his diabetes through an in-built 'early warning system' of threatening hypoglycaemia. Due to problems on human insulin, he asked for, and was given, early retirement. His experiences were therefore impinging on his 'normal' life (Balance, 1991c).

I described in Chapter 2 how those who have recently been diagnosed with an illness, in this case diabetes, come to a negotiated settlement over their illness. In this negotiated settlement, new relations are set up with doctors and family members, and with artefacts such as syringes. However, in times of 'new' biographical disruptions, this newly configured network body comes to be questioned. Many diabetics described how a change in their diabetes not only affected their employment, but also their relationship with their families. Indeed, as Alexander has pointed out:

> "Hypoglycaemia, especially if it is severe or without warning, can be most frightening, and can threaten normal living and employment."
>
> (Alexander, 1989: 156)

There are plenty of examples of this from the diabetic literature, for example:

> "My memory loss has been particularly distressing because it affects my job."
>
> (IDDT, 1995b: 5)

> "In my job, work with which I had been familiar for nearly ten years became a major task; as my memory began to fail, each piece of work required much more time as I had to spend so much time trying to remember how to deal with it. Not surprisingly, within a year, I was retired on ill-health grounds. By virtue of this I lost my home that I was buying and was forced to return to my parents'."
>
> (IDDT, 1996c: 9)

Another area that caused concern for diabetics on human insulin was driving. The

results from the BDA questionnaire (Redmond, 1988) of those on human insulin, found that a typical response to a change in the symptoms of hypoglycaemia, on human insulin, included the statement:

> "I find the lack of symptoms of hypoglycaemia a bit worrying, especially regarding driving, as I no longer get the early warning symptoms."
>
> (Redmond, 1988: 67)

Indeed, two respondents claimed to have been involved in road traffic accidents as a result of losing their usual warning signs of approaching hypoglycaemia (Redmond, 1988: 67). In their original study, Teuscher and Berger described the case of a diabetic who had had a car accident while on human insulin, even through he had eaten half an hour before and so should not have experienced low blood sugar (1987). Others also stressed caution for diabetics who were on human insulin and drove (Drug and Therapeutics Bulletin, 1989). Indeed Pickup argued that:

> "It is particularly necessary to warn patients of the danger of hypoglycaemia while driving and remind them of the need for checking blood glucose concentrations before the journey and at about two hourly intervals during long periods of driving."
>
> (Pickup, 1989: 993)

In the following sections I will describe the ways in which diabetics sought to remove the uncertainty that existed around their problems on human insulin. In Chapter 5, I described this 'reduction of uncertainty' from an institutionally centred point of view. I did not, on the whole, look at how the reactions, both physical and cognitive, to human insulin affected the practical management of diabetes. In this patient centred chapter, I will look at the ways in which patients attempted to bring some form of resolution to their problems on human insulin. Obviously, any attempt at resolving problems on human insulin involves interaction with the medical profession, and again we should refer to the schema in the previous chapter (Figure 5-1).

6.3 MEDIATING OTHERS

In this section I would like to look at the role played by two important groups in mediating the experiences of diabetics. Referring back to my schematic (Figure 5-1) we can see that the family and the popular media have a direct link to the patient. I also refer to care groups as a form of media in this section, since I will be talking

about the way information was passed from care groups to diabetics through newsletters and magazines.

My interest here is in the way that these two groups mediated the experiences of diabetics. I am therefore interested in a number of questions: What role did carers play in the management of 'another's' diabetes? Did family members notice a change in the symptoms of hypoglycaemia, while the diabetic did not? How did the popular media influence diabetics? What issues did the popular media bring up? How was the popular media 'used' by diabetics to influence others?

6.3.1 Family

The IDDT point out that carers are observers in any change in the management of diabetes, and therefore, have an important role to play in the management of diabetes (1994). This is especially the case for changes in the warning signs of hypoglycaemia, since some of the symptoms (such as confusion) may inhibit the diabetic from being able to take notice of, and appropriate action to correct, approaching hypoglycaemia. In a number of cases, it was family members who noticed changes in diabetics. One letter printed in an IDDT newsletter says:

> "The real problem is that these conditions are subjective and gradual - meaning that a slow descent over many years appears quite normal. It is only when somebody remarks on this personality change 'you were never like that before'."
>
> (IDDT, 1995b: 5)

Another letter, written by the mother of a diabetic in her early twenties, tells of how her daughter was getting more frequent episodes of hypoglycaemia and had become moody and depressed. Although the mother noticed these changes the daughter didn't. More importantly, the mother could not make her daughter to see that her personality had changed (IDDT, 1996c: 10). Another diabetic, through blood glucose monitoring, was aware that he was experiencing low blood sugar, however, he was unable to spot the warning signs himself, but his wife could. He writes:

> "Soon after changing to human insulin, however, I noticed the absence of those symptoms [clear warning signals of low blood sugar]. I seem to be able to function quite normally on very low blood sugar levels. Although my wife can spot my warning signals, I am unable to do so."
>
> (Balance, 1991e)

6. After the initial reactions - diabetics and care groups

A recurring theme in letters received by the BDA and the IDDT was that relatives noted that patients no longer recognised hypoglycaemia, and so did not report a change to their diabetic clinic. This led some to request that:

> "We would urge doctors to question relatives rather than rely on self reports when trying to decide whether a patient does or does not get adequate warnings of hypoglycaemia."
>
> (Tattersall and Macdonald, 1989: 1338)

As well as arguing that doctors should take notice of carers, it was also suggested that carers may be able to add to the scientific body of knowledge. One doctor suggested that:

> "Now that the validity of previous studies looking at problems experienced with human insulin have been questioned we must rely on the hundreds of case reports about human insulin from patients and their carers. These suggest that many patients have problems when using human insulin. The patients and their carers confirm an improvement when the patients change to animal insulin."
>
> (Kiln, 1995: 1407)

It can be extremely dangerous for a diabetic if they are not aware that they are approaching hypoglycaemia. In such cases the importance of 'others' is even more dramatic. For example, a diabetic may feel that they are able to carry out normal activities, like drive and operate machinery, however they may actually be unable to do so safely. Indeed, this is one reason why Pickup stressed that diabetics should be warned of possible problems on human insulin, and encouraged to carry out more frequent blood glucose monitoring, especially when driving (1989: 993).

The observations from others are not just important at particular times, such as approaching hypoglycaemia, but also in the long term. From observations of a diabetic, family members may encourage and motivate a diabetic to consult their doctor. Therefore, knowledge from family and friends can play an important role in a diabetic's understanding of their own diabetes.

On a wider front, family and friends may come across information that they feel will be useful to the diabetic and/or their family. For example, a mother of a diabetic describes how a friend had telephoned her after watching an edition of *Newsnight*. The programme featured the IDDT, and described symptoms that mirrored those of

the daughter. In particular, it was the first time that the mother had heard of animal insulin (IDDT, 1995d: 7). Such information may also be useful in enabling 'choice', since diabetics may become aware of what options are available to them. This is something that I will return to in a later section.

As I will show in the next section, the media, especially the diabetic media, played an important role in collectivising issues around human insulin.

6.3.2 Media

Throughout the human insulin debate articles and news items were published in the popular media which described the problems experienced by some diabetics on human insulin. Some articles were concerned with the portrayal of the human insulin issue. One article, in *The Independent*, described how a diabetic smashed up his home, which was put down to being on human insulin (1991). However, a subsequent letter from a physician, argued that the article made a 'serious factual error', in saying that those on animal insulin 'invariably' retain appropriate warning signs. The letter further states that:

> "It would be wrong to suggest, as your article does, that the problem [lack of awareness of approaching hypoglycaemia] has come about solely as a result of the introduction of human insulin."
>
> (Watkins, 1991: 18)

There were other articles that caused distress. In 1992, an article was published in *The Sunday Times* entitled, 'The Cure that Went Wrong' (Shannon, 1992). The article recounted the experiences of one diabetic who was on human insulin. In particular, the article alleged that the BDA was funded by major pharmaceutical companies, so wouldn't speak out about the problems. The BDA responded by pointing out that their funding comes entirely from legacies, donations, and fundraising efforts (Balance, 1994).

A news item in *The Sunday Times* in 1995 linked the deaths of a number of diabetics with the use of human insulin (Rogers, 1995). Again the BDA responded, referring directly to the article, they wrote that they wanted to "reassure the very large number of people who may have been caused stress by the contents of this article" (Independent on Sunday, 1995). The statement and advert - Human Insulin - reality

and myths - was placed in a number of newspapers. *The Sunday Times* refused to include the advert, but they did include a letter from Michael Cooper, the BDA's Director General, which was an edited version of the advertisement (Cooper, 1995). The hope was that the advert would reduce the anxieties raised by *The Sunday Times* article. However, other letters in response to the original article, commented on the 'informative nature' of the article (Norton, 1995), and that it highlighted an important issue (Hill, 1995).

Letters and articles in the media made diabetics aware that their experiences of problems on human insulin were not isolated instances. This was especially the case for the IDDT. Many letters from diabetics, printed in the IDDT newsletter, described how they felt reassured after reading letters or articles in the newsletters. For example:

> "Dear Jenny [a member of the IDDT], Many thanks for talking to me on the telephone and for your useful Newsletters. It made me realise that I really had to do something about my diabetes..."
>
> (IDDT, 1995c: 10)

> "After reading your letter in our local paper I finally raised the courage to approach my doctor and he agreed to put me back on pork insulin."
>
> (IDDT, 1996b: 11)

> "Dear Jenny, Thank you for your letter. I am pleased to say I've now benefited from changing back to pork insulin. I'm feeling much more comfortable and happy. Many thanks for your help and for the Newsletter which is most interesting and well put together."
>
> (IDDT, 1996c: 11)

> "Dear Jenny, Thank you for all your newsletters. I could hardly believe my eyes when I read them because I now know that I am not making a fuss."
>
> (IDDT, 1997: 9)

As can be seen from the above quotes, the IDDT also encouraged diabetics to take action over the symptoms that they were experiencing. In particular, the IDDT made constant reference to the Patients Charter. The charter states that patients have the right to be aware of alternatives and to a second opinion. In one letter, the mother of a diabetic tells of how, after speaking to the IDDT, she became aware that she had the right to a second opinion. After a second opinion, her child was changed to animal insulin (IDDT, 1995d: 7).

As should be obvious, there was frequent two-way contact between the media and diabetics, this was not only the case in the specialised diabetic media, but also in the popular media. Importantly, what I have tried to show in this section is that diabetics do gain their information from a number of sources, whether it be family and friends, or the media. Therefore, when a diabetic forms narratives about their experiences, in whatever context, they are drawing on a range of emergent sources and resources, such as biographical accounts and larger 'factual' claims (grand narratives), that come from both the family and the media. These 'other knowledges' may have an important impact on what choices are accepted by diabetics, in the resolution of problems on human insulin. It is this set of issues that I now wish to turn to.

6.4 SOLUTIONS WITHIN MEDICAL PRACTICE

As implied in Chapter 4, there are a number of responses that can be made by the medical profession in resolving problems exhibited by some diabetics on human insulin. Moreover, it is not just the resolution of problems by the doctor that is important, but also the acceptance of these resolutions by patients. In this section therefore, I am interested in the ways that individuals resolved the problems that they were experiencing on human insulin. The focus is in the ways that patients accepted or rejected solutions given to them by the medical profession. One of the important features here will be the possession of knowledge by diabetics, not just of their experiences, but also of the experiences of other diabetics.

In the following sections I will describe some of the explanations and resolutions that were given to diabetics when they reported problems to their doctor, while on human insulin. By looking at these 'suggested' resolutions, I also intend to bring out further some of the experiences of diabetics. I intend to look at the following resolutions: psychological explanations; the experiences were part of the 'natural' biography of diabetes; a dose reduction would correct any problems; increased blood glucose monitoring would help the diabetic correct any problems; and, a change back to animal insulin would resolve the diabetic's problems.

It is important to note that these 'resolutions' should not be seen as being distinct from each other. In some cases one resolution may have been tried and may have worked, in other cases, many possibilities may have been tried. The resolutions that I will

describe should also not be seen as being in any particular order. Some diabetics, claiming a change in their symptoms of hypoglycaemia, may have been transferred back to animal insulin with little or no negotiation with the doctor. On the other hand, others may have had to battle hard to have their own wishes met. Again, one of the important features is the knowledge that is possessed by both the diabetic and the individual doctor.

6.4.1 Psychological Explanations

In some cases, when a diabetic reported problems on human insulin, their experiences were not put down to any feature of diabetes, but rather to a psychological cause. There were a number of complaints from diabetics that their experiences were being ignored (Balance, 1994). Indeed, there were a number of cases in which diabetics were told, after seeing their diabetic consultant or GP, that they "must have been imagining it [their unawareness of hypoglycaemia]" (Balance, 1991a: 20. Also see IDDT, 1995a: 5). One mother describes the experiences of her daughter. After being prescribed human insulin the daughter experienced an increase in the number of severe hypoglycaemic episodes, and also a change in her personality. The mother writes:

> "After over nine changes of human insulin I was told 'there is nowhere else to go' and we were advised that her problems were due to her hormonal changes and something she was doing - it was 'suggested' she was drawing up large doses of insulin so she could eat chocolate in large amounts and that the aggression accompanying the hypo was pretence."
>
> (IDDT, 1995d: 7)

Such replies are interesting because they are neither based around the 'natural' biography of diabetes, in which case the exhibited symptoms may 'naturally' occur, nor are they put down to human insulin, in which case some change in the management of diabetes would be needed. Rather, they are directed at the individual, it is he/she that is to blame, rather than some other part of the body network. In such cases, resolution of the experiences of diabetes can not be carried out by a change in the management of diabetes, but rather to changes in some psychological facet of the individual. Indeed, in the case above, the whole family were sent off for psychological assessment (IDDT, 1995d: 7).

In the majority of cases however, reasons for, and resolutions of, the experiences of diabetics on human insulin were put down to causes within the management of diabetes. I will now look at a number of these resolutions in turn.

6.4.2 A Part of the 'Natural' Biography of Diabetes

One well known complication of diabetes is that the awareness of hypoglycaemia can diminish over time. In such cases then, the problem is not the insulin species, but rather, part of diabetes itself. One diabetic writes:

> "All I got from my diabetic consultant was 'it's your age and you can't go back onto animal insulin'."
>
> (Balance, 1991d)

The important feature is the acceptance of diagnosis. In some cases a diabetic may accept these explanations and so adapt their own lifestyle to cope with these changing circumstances.

A similar situation existed for newly diagnosed patients. Human insulin is generally accepted to be the standard treatment for newly diagnosed diabetics (Gale, 1989: 1266). However, one of the concerns of the IDDT was that newly diagnosed diabetics may experience problems on human insulin, but accept it as part of diabetes (IDDT, 1994). In such cases, a diabetic may not place their experiences as part of the 'natural' biography of diabetes or due to some therapeutic change, but rather as part of diabetes in general. Although existing diabetics may have been aware that diagnosis of diabetes does not have to affect the way that they carry out their social life, newly diagnosed diabetics on human insulin may not be aware of this. To put it more simply, diabetics transferred to human insulin from animal insulin have past experiences to compare their current experiences with. Newly diagnosed diabetics on human insulin only have the experiences of being healthy to compare their current experiences with. For newly diagnosed diabetics, there may also not be an awareness of possible options that are available to them. The IDDT point out that some diabetics claimed that they were not aware that animal insulin existed (IDDT, 1995b: 8-9). Newly diagnosed diabetics may therefore lack the knowledge of the traditional warnings signs of approaching hypoglycaemia, and of the existence of animal insulins. These are all features of the network body for a long term diabetic.

Therefore, one of the criteria for the acceptance or rejection of a diagnosis, by a diabetic, may be the knowledge that is possessed by the diabetic. As I have already indicated, the family, help groups, and media play an important role in this.

6.4.3 Dose Reduction

Another suggested resolution was a reduction in dose. By reducing the amount of human insulin taken, compared with animal insulin, some problems on human insulin were reduced. One reason for this is that using animal insulins causes the body to produce insulin antibodies, which are specific to the insulin species. These antibodies reduce the efficiency of the specific insulin, and as a result, more of this specific insulin is needed. When diabetics change to another insulin species, in this case human insulin, there are no human insulin antibodies, and so the body has potentially more insulin than it needs.

However, it has been claimed that early guidelines from Wellcome and Nordisk suggested that, "transfer of patients from Wellcome beef insulins to Wellcome/Nordisk human insulins [can occur] on a unit-for-unit basis, as advised in the promotional literature" (Turner et al., 1988: 1150; Pickup, 1989). This advice may have led to some confusion.

However, Nordisk argued that the full guidelines suggest that:

> "(1) Most patients may be transferred on a unit-for-unit basis. Those who make dosage adjustments according to the results of blood or urine tests should continue to do so. (2) A minority of patients currently on a high daily dose of beef insulin...may require dosage reduction."
>
> (Harrison and Nick, 1988: 1305)

As already noted, many studies have shown that a dose reduction would be necessary, especially for the more immunogenic bovine insulin (Gill and Jones, 1988). Some manufacturers suggested reductions by up to one fifth (Pickup, 1989). Yet there was still some concern. Manufacturers warned that although a dose reduction may be necessary for those changing from bovine to human insulin, the impression given was that this would only be necessary for those on high doses (Drug and Therapeutics Bulletin, 1989). Indeed, from letters received by the BDA, it appears that many diabetics had not been warned that they might have to alter their dose (Balance, 1994).

6.4 Solutions within medical practice

The results of the BDA survey, carried out in 1987-8, found that a number of patients appeared to have been changed to human insulin by their pharmacists and not their doctor (Redmond, 1988). Robert Tattersall recommended that prescribers should not change insulins without good reason, and that patients should know that it may be necessary to fine tune their insulin dose and that their warnings of hypoglycaemia may change (Lesser, 1989a). Indeed, Amiel points out that some patients were transferred en masse and without consultation (1995: 258). It was also found that, when diabetics were transferred to human insulin in their pharmacies and without any medical supervision or information, there was an increased risk of severe hypoglycaemia during the transition to human insulin (Egger et al., 1992).

Frier et al. (1991) point out that when patients were transferred from animal to human insulin with a dose reduction, complaints of unexpected severe hypoglycaemia reduced. They argued that:

> "Because of an expected reduction in insulin requirement after transfer from animal to human insulin diabetic patients in the United Kingdom were instructed to reduce their dose by at least 10% and few subsequently experienced increased hypoglycaemia."
>
> (Frier et al., 1991: 1667)

However, for some, the reduction in dose was not the answer. The argument that 'few subsequently experienced increased hypoglycaemia' would be questioned by a number of researchers and diabetics, such as Berger and Teuscher, and members of the IDDT. For example, after being transferred to human insulin one diabetic experienced leg cramps. His doctor suggested a reduction in dose. However, the diabetic writes:

> "When I reduced the dose of insulin I became very lethargic and my urine and blood tests showed my diabetes was no longer under control."
>
> (Balance, 1988a)

Where doctors refused to acknowledge that human insulin was the problem, many patients felt let down by their doctor. A consistent complaint was that doctors refused to recognise that patients were having problems on human insulin despite adjustments in dose (Pickup, 1989: 993).

6.4.4 Increased Monitoring of Blood Glucose Levels

One suggested alteration to the diabetic regime, for those experiencing problems on human insulin, was to increase the monitoring of their blood glucose levels. Typically, when diabetics are changed to a new insulin (no matter what the species) or to a new insulin regime, they carry out more blood glucose monitoring. Of course, if diabetics were not told that they were on a different type of insulin, they would be unaware that they should carry out more frequent blood glucose monitoring. This led Amiel to argue that the recommendations of the early studies, that conversion to the use of human insulin should be carefully monitored and changes in doses and/or injection times should be considered, were not followed (Amiel, 1995: 258).

Although it was argued that when diabetics transferred to human insulin they should carry out more frequent blood glucose monitoring, in the early days, this was usually only stressed when changing from beef to human insulin (Balance, 1987a: 5; Muir et al., 1988). This is because there is more difference in beef insulin's amino acid composition than pork insulin.

So problems could have existed where diabetics did not keep a close enough eye on their blood glucose levels. Interestingly, some diabetics did lay the blame for a change in the warnings of hypoglycaemia at the door of diabetics themselves. A letter from a diabetic of 35 years argued that:

> "Before we blame the drug companies too strongly, maybe the individual diabetic needs to take some responsibility for not checking the possibility of their symptoms changing when they were first put on the new insulin."
>
> (Balance, 1991d: 49)

This letter is interesting because the author of the letter was involved in the clinical trials of human insulin, in which they were frequently monitored. Further, he did experience some change in symptoms, but because of the regular testing, this could be detected. Of course, in everyday life this is not always possible, and it is likely that more care will be taken by both the medical care team and the diabetic, while they are under observation.

Through the use of human insulin therefore, new objects may have come to be involved within the network body. I have already described how diabetics were

encouraged to carry out more blood glucose monitoring, either at the time of transferral to human insulin or because they were having problems. There were other changes that may have also occurred. For example, one diabetic tells of how glucagon became a regular prescription for him (Balance, 1991c). Glucagon is a protein that when injected into the body increases blood glucose levels. It is used when a diabetic has become unconscious due to hypoglycaemia, and so is unable to consume food. Glucagon has to be injected and is supplied in kit form, to be injected by a family member. After the injection of glucagon the diabetic is likely to regain consciousness.

Glucagon therefore, becomes inserted into the network body in order to help maintain health. However, rather than preventing hypoglycaemia as blood glucose monitoring does, glucagon is used when the network body breaks down, or, in other words, diabetic coma. Of course this is not satisfactory. Glucagon is supposed to be used for emergencies, rather than on a regular basis. If glucagon is used frequently then this should be reported to a diabetic's doctor, so that changes can be made to the patient's management of their diabetes.

The three explanations/resolutions described above can be seen as accommodations in which there is a continued use of human insulin. These ranged from a simple dispelling of any problems that a diabetic described, to changes in the management of diabetes, whether through a reduction in dose or greater blood glucose monitoring. What is important is a diabetic's reaction to a particular resolution. Although a change in dose or increased blood glucose monitoring resolved some diabetics' problems, others were still not happy with the control of their diabetes. Where diabetics were still not happy, another possible resolution involved a return to the original species of animal insulin.

6.4.5 A Change Back to Animal Insulin

As already mentioned, the changes above should be seen as being within the context of treatment with human insulin. However, in a large number of cases, more was needed than simply a change in dose or increased blood glucose monitoring. As outlined in Chapter 5, it was found that when diabetics changed back to their original animal insulin the majority regained their awareness of approaching hypoglycaemia (Maran et al., 1993). However, there were a number of reasons why diabetics would

not be automatically returned to animal insulin. These reasons ranged from an unawareness of the availability of animal insulins on the part of either the doctor or the diabetic, to a disbelief that human insulin was to blame for the problems.

When looking at controversies there is a temptation to see only the negative cases, where less 'powerful' individuals are marginalised by a more powerful group or individual. However, it is important to be aware that doctors were not always unsympathetic to the experiences of diabetics. For example, one diabetic writes that when she went to the diabetic clinic 'determined to return to animal insulin':

> "We [her and her husband] were prepared to dig our heels in but, surprise, surprise, I made the request and the doctor was most co-operative and immediately found a pork insulin he thought would suit me."
>
> (IDDT, 1995a: 11)

Another diabetic describes how, after experiencing an increase in severe hypoglycaemia on human insulin, he reported his problems to his doctor, who dismissed his concerns. However, after falling down a pair of concrete stairs, he had 'had enough' and went back to his doctor. He writes:

> "That was it, I had had enough! I went to the clinic and 'the boss' was there, not my usual doctor. I explained my problems and within two minutes he changed my insulin back to pork."
>
> (IDDT, 1995a: 5)

However, there were many cases where diabetics were unable to change back to their original animal insulin. Letters to the BDA's Diabetes Care Department, from diabetics, spoke of doctors who refused to change them back to animal insulin, even though their letters suggested they had problems (Balance, 1992c: 18). Many diabetics described how they had to fight to be able to change their insulin species. For example:

> "After many requests to the consultant at the diabetic clinic, he has changed me back onto bovine insulin and after a short settling in period, I am now back to the way I was before, with hypos detected sufficiently early for self treatment."
>
> (Balance, 1991c)

As well as the scientific evidence, there was much anecdotal evidence that when

diabetics returned to their original insulin, their symptoms returned.[37] For example:

> "I have clear cut, recognisable diabetic warnings of hypos. The warnings are not quite a early as I remember them on soluble insulin, but there is no doubt about them and I have quite enough time to react."
>
> (O'Nions, 1988)

> "Now I feel wonderful; no longer do I have a fuzzy head and my husband tells me I am back to how I used to be before human insulin. I never want to use human insulin again."
>
> (IDDT, 1995a: 11)

> "I have now changed my insulin from human to pork and feel much better! The hypos have stopped, my mood-swings have stopped and my skin cleared up. I feel as if a heavy 'cloud ' has been removed and that I am now back in control of my life again! My family has commented that I now seem more like I used to be - I am delighted at this, but also angry that my family, friends, and colleagues should have had to 'put up' with my character changes."
>
> (IDDT, 1995b: 10)

Although one diabetic was aware that some diabetics would not regain their warning signs, when returned to animal insulin, he also points out that it becomes more compelling when added to other evidence:

> "I feel as sure as I can be that human insulin has materially adverse effects in terms of the warning signals of the approach of hypoglycaemia. Although I cannot definitely prove this from my own experience, I believe that the coincidence is simply too strong to ignore even in my case alone. When it is added to the anecdotal evidence, which I have heard and which you must have collated from diabetics and their doctors throughout the country, I believe that the case becomes compelling."
>
> (IDDT, 1995c: 11)

From the view of doctors, there were a number of reasons why diabetics were not automatically changed to another insulin species. Some doctors believed that existing animal insulins were being discontinued. For example, one diabetic wrote to *Balance* (1988a) saying that they had been transferred to human insulin because their doctor said that their existing animal insulin was being discontinued. On human insulin he had experienced problems, despite an adjustment in dose. As a result, the diabetic wanted to return to their existing animal insulin, and wanted to know if it was still possible to obtain supplies. *Balance* responded, saying that they had been in touch

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[37] Although this was not always the case (Home, 1991).

with the medical advisor of Novo Laboratories, and they had responded saying that Lentard insulin was still available.

This example suggests that some doctors were not fully aware of the situation regarding animal insulin, although we do have to be aware of the possibility that the doctor was lying. One source of information for doctors is the British National Formulary. It is produced jointly by the British Medical Association and the Royal Pharmaceutical Society and gives information on drugs, their costs and details of adverse effects. In the September 1995 edition, it gave the following information on human insulin:

> "Preparations of human sequence insulin should theoretically be less immunogenic, but in trials no real advantage has been shown...some patients have reported a loss of warnings of hypoglycaemia after transfer to human insulin . Patients should be warned of this possibility and if they believe that human insulin is responsible for their loss of warnings it is reasonable to transfer them back to porcine insulins."
>
> (British National Formulary, 1995: 280)

As well as the belief that some animal insulins were no longer available, the IDDT found a number of other reasons why doctors would not return diabetics to animal insulin when they reported problems on human insulin. These included claims that: human insulin was a better insulin; that using animal insulin would be a step backwards; and that they had been on human insulin too long to change. With this last point, the IDDT asked the question: Why was there then a change to human insulin? (IDDT, 1995b: 9).

One option available to those who wanted to obtain animal insulin, but where their doctor would not sanction it, was through the named patient system. In special circumstances drugs that are not available in the UK can be obtained through the NHS with a 'named patient prescription' that is obtained through a doctor. Of course such an option would require the doctor to accept that a particular (animal) insulin is necessary for the health of the diabetic.

Where diabetics were unable to obtain animal insulin through their doctors, another way of obtaining animal insulin was by going outside of the existing doctor-patient relationship. One letter, printed in an IDDT newsletter, described how a diabetic was

concerned with the "blinkered attitude of some of the medical profession" (1995a: 5). He was particularly concerned, as happened with him, that doctors simply dismissed any problems that diabetics were having on human insulin. The diabetic encourages others, who have problems on human insulin and where their doctor does not accept their problems, to go over the doctor's head until they get a sympathetic hearing.

Another way of going temporarily outside of the existing doctor-patient relationship was by obtaining animal insulin independently from the doctor. For example:

> "Dear Jenny, My husband did very badly on both animal and human insulins when he was forced to change from 40 strength concentration to the U100 strength. He managed thanks only to the imported 40 strength insulin which he uses to the present day.
>
> (IDDT, 1995a: 11)

> "I have recently secured porcine insulin U 40 u/cc strength from France and over a few weeks my old well known visual warning signs of hypos have returned."
>
> (IDDT, 1996d: 11)

Prior to August 1998, insulin was a 'class P drug', which meant that it could be bought over the counter without prescription, it was however, expensive, and pharmacists were expected to only sell it to diabetics.[38] The IDDT gave advice on how to obtain animal insulin from a source other than their own doctor. They also printed the name and address of a pharmacist who would sell animal insulin to diabetics (IDDT, 1996d: 11). However, diabetics were always warned that they should consult their own doctor before any change of insulin. We should also be aware that the diabetic would have to pay for the cost of the animal insulin, since it was not acquired through the legitimised consumption path. A months supply of pork insulin costs between £7-8 from pharmaceutical companies (Prescription Pricing Authority, 1997).

The IDDT also pointed out that animal insulin pens were available before 1994 in other countries, but were not available in the UK for an unknown reason. They

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[38] From August 1998 insulin became a prescription only drug (POM) (Statutory Instrument, 1998). There were a number of reasons for this change. One was due to concerns over the use of human insulin by non-diabetics such as body builders (Hall, 1998). The change also brought the United Kingdom in line with the European Union (Balance, 1998).

describe how to obtain the pens and cartridges through a 'named patient prescription' or, failing that, from IDIS World Medicines (a global supplier of internationally licensed medicines) (IDDT, 1994: 3). Although they do point out that such equipment is expensive. However, some insulin pens were also being withdrawn in other countries. As shown in Chapter 5, they were however, introduced into the UK in 1997.

In the next section I would like to relate further some of the experiences of diabetics to the doctor-patient relationship. In particular, I am interested in how the relationship between the doctor and the patient can change over time, and how, in some cases patients can be motivated to search out further information when they are dissatisfied with their treatment.

6.4.6 Some Notes on the Doctor-Patient relationship

Clearly, then, some diabetics sought information from sources other than their immediate medical practitioner. Importantly, there were various triggers to seeking more information both from existing sources, and also through 'new' and 'alternative' sources. One diabetic wrote that after having problems on human insulin, and not receiving much information from her doctor, she decided to search out information herself (IDDT, 1995d: 10). After 5 or 6 months of feeling more and more ill every week, and her doctor not taking any notice of her, she writes:

> "I HAD HAD ENOUGH and having continuously researched information about diabetes I decided that human insulin could be the cause and I asked the clinic if I could change to pork insulin to which they said fine."
>
> (IDDT, 1995d: 10)

Whether an individual searches out further information will be based on a number of different criteria. It is what both the patient and the doctor bring to the doctor-patient that is of importance. It is possible to outline a number of beliefs or positions that doctors and diabetics may hold with regard to human insulin. For example:

- The doctor may not believe that human insulin is the cause of symptoms exhibited by their patient.
- The doctor may not be aware that animal insulins are still available.
- The patient may not be aware that animal insulins are still available.
- The patient may not attribute their problems to human insulin.
- The patient may not be aware that other diabetics are exhibiting similar problems that have been put down to human insulin.

The approach taken by both the doctor and the patient, will affect the outcome of any negotiation between the doctor and the patient. In some cases a doctor may accept that the diabetic is experiencing problems on human insulin and change them back to animal insulin. In other cases, the doctor may believe that human insulin is not the cause of any side effects. The diabetic may accept this assessment, however in other cases, through a belief that human insulin is to blame, a diabetic may search out further information themselves. I will return to analyse this array of possibilities within a theoretical framework in Chapter 7.

However, just because an individual gathers knowledge, does not necessarily mean that it will be put into practice, and this brings me to issues of the doctor-patient relationship. It is unlikely that there is only one formulation of the doctor-patient relationship. Stewart and Roter look at the doctor-patient relationship in terms of the degree of control exhibited in the encounter by each party (1989). A paternalist one occurs where the doctor is in control, and a consumerist relationship where the patient is in control. Tuckett et al. argue that a mutual control relationship is desirable (1985).

Of course, the nature of any relationship can change over time. Gabe et al. (1991) point out that when patients experienced tranquilliser dependence, the doctor-patient relationship changed from a Parsonian model of reciprocity (Parsons, 1951) to one based around a Freidsonian conflict model (Freidson, 1970). In such cases the patients may the feel let down by the doctor, who was supposed to maintain their health. The patient may then search out further knowledge. Cooper (1997), looking at sufferers of ME, describes their experiences of the medical profession. She tells of how, in some cases, individuals were dismissed and disbelieved, and were often labelled as bored housewives or depressed adolescents, when they attempted to gain a diagnosis. As a result of this 'rejection', Cooper describes how:

> "...acting no longer as passive agents when their needs were not met, respondents actively pursued their own paths to knowledge and challenged the authority and status of their GPs and consultants."
>
> (Cooper, 1997: 190)

There are similarities here with some of the psychological explanations that I outlined above, where diabetics were told that they must be imagining their problems (Balance, 1991a; IDDT, 1995a) and as with above, such responses encouraged diabetics to search out other information.

One of the important features of all the responses outline above is that those who are exhibiting problems on human insulin want to be diagnosed 'adequately'. Therefore, if the response from the doctor was adequate for them, a diabetic may not pursue the matter further. Thompson[39] has looked at how doctors are 'idealised' by patients when they give the 'correct' diagnosis to the patient, that is, it matched with their own diagnosis. However, where doctors denied the existence of 'the illness', and were unable to name and heal the disease, and so legitimate it, then patients 'demonised' these doctors.

As I have shown, it was argued that some problems on human insulin could be solved by a reduction in the dose of human insulin. For others, it was felt, by either diabetics or doctors, that a change to animal insulin was the answer. In looking at chronic fatigue syndrome (CFS), Woodward et al. found that patients were much happier after a diagnosis of CFS. They argue that after diagnosis, sufferers were provided with a rational and structured meaning system for their experiences of disability and illness (Woodward et al., 1995). The important feature is the acceptance of a particular diagnosis. For example, some diabetics may accept that their experiences are part of the biography of diabetes and others may believe that such a diagnosis is inadequate. Now, these are individual choices and strategies. However, that there is choice at all is arguably because of the efforts of care groups. It is to their role that I now turn.

6.5 CHOICE OF INSULIN

As indicated in Chapter 5, animal insulins were withdrawn as early as 1986 by Novo

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[39] Reference unknown, although see Cooper (1997: 200) for original reference.

Laboratories. Initially, withdrawal was accepted by the BDA. The BDA argued that companies would want to standardise their insulins since it made commercial sense (Balance, 1986: 4). They also argued that diabetics and care groups had "no choice but to accept this" (Balance, 1986: 4).

The BDA did however give advice to their readers. When Novo Laboratories were replacing their MC pork insulin with a human equivalent, the medical advisor to the BDA said that people should be able to transfer from pork to the human insulin without any problems. However, the advisor pointed out that if diabetics noticed a significant change in the action of the insulin, which could not be corrected by dose adjustments, or were not happy about the principle, they should contact their doctor (Balance, 1986: 4).

A number of articles, that dealt with the withdrawal of animal insulins, also stressed which animal insulins were still available. The BDA often sought reassurances from pharmaceutical companies on their current animal insulin policy. In August 1987, CP Pharmaceuticals Ltd announced that they would continue supplying their Hypurin range of highly purified beef insulins for the foreseeable future while demand existed. Evans Medical Ltd also stated that their range of beef insulins would remain available as long as economically viable for them to be produced (Balance, 1987c: 4). During the late 1980s the BDA acted to gain reassurances of the availability of animal insulins from the manufacturers. Also through their magazine, the BDA acted to inform diabetics of the continued availability of various animal insulins.

Throughout the late 1980s and early 1990s, other animal insulins were also withdrawn from production. Some, however, argued that reducing the number of insulins available would be beneficial. Robert Tattersall pointed out that between 1983 and 1989 the number of branded human insulin preparations increased from 4 to 17, which was a source of confusion to medical staff, pharmacists and patients alike (Lesser, 1989a). Some argued that in the UK the classification of insulins as short, intermediate, and long was too confusing and should be simplified (Bonn, 1996). Others however, disagreed with this (Kreigstein et al., 1997). *The Drugs and Therapeutics Bulletin* claimed that there was an argument for reducing the number of insulins available, however a range of pork, beef and human insulin should always be

available (Drug and Therapeutics Bulletin, 1996).

Whenever the diabetic media reported that an insulin was being withdrawn it was always stressed that there were similar animal insulins available for diabetics. However, this did not always mean that diabetics would be given the appropriate insulin. Various letters were printed in *Balance* telling of cases where diabetics had been given the wrong insulin (Balance, 1988b) or where patients had been transferred to another insulin without their knowledge (Redmond, 1988). I referred to this above, where diabetics were more likely to experience problems when they were not told of the change of insulin species.

As a result of some of these concerns over the transferring of some diabetics to human insulin, the BDA's medical adviser gave advice to all diabetics - see Figure 6-1 (Redmond, 1988).

Advice given to diabetics when receiving their insulin:
1) Be sure you are aware what insulin you are using.
2) Note the manufacturer, species and the name of your insulin, as well as your doses.
3) Always take sample vials with you whenever you see your doctor, nurse or chemist.
4) NEVER LET A CHEMIST GIVE YOU DIFFERENT INSULIN, unless your doctor has explained it.
5) Read the paper insert that comes in the box with your insulin.
6) Find out whether it is likely your insulin will need to be changed.
7) Ensure any change is adequately explained by your diabetes medical advisor.
8) If you do have your insulin changed and you experience problems, make an appointment to see your doctor so that you can discuss the problems fully.

Figure 6-1: Advice given to diabetics when receiving their insulin

In 1991 the BDA set up the Loss of Warnings Task Force which had the aim to bring to the attention of doctors some of the problems experienced by some diabetics (Figure 6-2). Due to criticisms of the Human Insulin Working Group (HIWG), that was set up in 1989, the LOW Task Force also included diabetics, particularly those grappling with hypoglycaemia unawareness. The HIWG had included health care professionals and members of insulin manufactures, but did not include diabetics (Balance, 1994). The LOW Task Force wished to encourage communication between the patient and the doctor on the issue of problems with the use of human insulin. The BDA felt that it was important that doctors were flexible to the wishes of diabetics, especially if they wanted to change back to animal insulin (Balance, 1991b).

6.5 Choice of insulin

There are many factors therefore, that are important in the choice of insulin - not just concerning the availability of animal insulins. On the one hand it is based around the knowledge and desire of the doctor. Some doctors changed patients over to human insulin because they were not aware that there were other animal insulins available, or that they were under the impression that existing animal insulins were being discontinued. It also seems that many diabetics were transferred to human insulin, by their doctor, due to the marketing techniques of the pharmaceutical companies. On the other hand, diabetics themselves may have needed information on the availability of animal insulins in order to 'push' for animal insulin.

Steps taken by the BDA's LOW Task Force

- A special leaflet - People with Diabetes and Changes in Hypoglycaemic Warnings - was printed and reproduced in an issue of Balance (see Appendix 2).
- A copy of the leaflet and professional advice sheets were sent to all the medical professionals on the BDA mailing lists
- A copy of the leaflet was sent to all BDA branches
- An advertisement for the new leaflet was placed in many national newspapers. Local branches were also encouraged to put adverts in their local newspapers.
- A press conference was held, and a press statement and copies of the leaflet were sent to national newspapers
- Extra resources were made available to help the Diabetes Care Department answer queries on hypoglycaemia and human insulin. In particular extra resources were made available to the BDA telephone helpline.

Figure 6-2: Steps taken by the BDA's LOW Task Force

Before 1994 the BDA had simply sought reassurances for the continued availability of animal insulins from the pharmaceutical companies. However, in 1994 the BDA attempted to stem the flow of withdrawals of animal insulin by beginning its campaign to maintain a choice for diabetics, as to the species of insulin they wished to use. They collected 140,000 signatures that were then presented to three UK insulin manufacturers in September and October 1994 (Hope, 1994). The aim was to ensure that animal insulins would be available indefinitely, and to make animal insulin available for pen devices.

As outlined in Chapter 5, Eli Lilly have never marketed animal insulins in the United Kingdom, but supported the availability of animal insulins. Novo Nordisk, said that they would continue to produce some animal insulins as long as it was economically viable. CP Pharmaceuticals only manufactured beef insulins and made a continued commitment to them (Hope, 1994).

6. After the initial reactions - diabetics and care groups

Later, in 1996, the BDA embarked on a European wide survey to check out the strength of market demand for animal insulin, and so monitor the user patterns that influence insulin suppliers (Balance, 1996: 12). It was also hoped that greater links with European partners would help groups campaign more efficiently.

Although some animals insulins were being withdrawn, and others simplified, we have to be aware that there was a general agreement that there should be a continued availability of animal insulins. As I showed in Chapter 5, scientists also agreed with this. Simon Hope, of the BDA, argued that the Insulin Campaign was underpinned by freedom of choice, so that people with diabetes may use the insulin that suits them (1995: 10-11). The pharmaceutical companies also seemed to support choice, at least while demand made it economically feasible (Hope, 1994).

The IDDT did have some concerns about the Simplification Programme that was being carried out by Novo Nordisk in 1995/96. Although changes were only being to human insulins, they were concerned that other changes may also be carried out by doctors, they frequently argued that:

> "This programme only affects human insulins and there will be no changes in the animal insulins, so don't let anyone persuade you otherwise!
> (This has already started to happen to some of our members - perhaps an excuse to change them to human insulin!)
> The changes will not affect animal insulins."
>
> (IDDT, 1995a: 4)

Again, from the point of view of the IDDT, it was the knowledge that was possessed by diabetics that was important. If diabetics were unaware that the simplification programme was only aimed at human insulins, and did not affect animal insulins, they may have accepted that their animal insulins were being withdrawn.

The IDDT also believed in the availability of choice so that doctors and diabetics could choose which insulin species they wished to use. However, from reading some of their newsletters the point was not always made clear. For example, one letter printed in the newsletter began:

6.5 Choice of insulin

> "Please remove my name from your mailing list. I originally joined IDDT because of my belief in choice. However I find some of your articles alarming and unnecessarily frightening."
>
> (IDDT, 1997: 15)

In answer to the letter, the editor pointed out that they did believe in choice, but that they were concerned that choice was only possible if diabetics had all the information. As the editor writes:

> "An INFORMED choice means having sufficient information to be able to look at the pros and cons of an action or decision and, when this applies to diabetes, it sometimes means having information which may be upsetting or frightening."
>
> (IDDT, 1997: 15)

Choice, according to this perspective, is not just about the availability of different insulin species, but also knowledge of the available insulins. In other cases choice is tied up with other actants. From the view of diabetics, one reason why they may have wanted to continue to use human insulin was because it was available for pen injection systems, but animal insulin wasn't. Care groups argued that diabetics should not be dissuaded from using animal insulins just because they were not available in cartridges for pen-injection devices (IDDT, 1994: 2). This is especially the case if a diabetic had been on human insulin and used an insulin pen. If a diabetic used this convenient method, then they may have been reluctant to change back to animal insulin, and so lose this method. As this quote illustrates:

> "After trying pork insulin I am convinced that the human insulin has a definite detrimental effect on my moods causing deep, dark (sometimes suicidal) periods whereas the same thoughts whilst on pork insulin are almost insignificant. I have switched back to human insulin twice during the 3 months, initially because I wasn't convinced it was the cause of the difference and then, because of the convenience of the pen. Both times I noticed the 'moods' return within a week."
>
> (IDDT, 1996c: 11)

However, in April 1997 CP Pharmaceuticals announced that they were going to produce some animal insulins (both pork and beef). Victory for the change was claimed by both the BDA (Balance, 1997) and the IDDT (IDDT, 1997c). The IDDT also gave credit to the directors of CP Pharmaceuticals (IDDT, 1997e). The IDDT argued that the development of the animal insulins gave diabetics equal choice of insulins, totally uninfluenced by the lack of an insulin pen. From the point of view of

doctors, the IDDT argued that doctors would not now be 'forced' into prescribing human insulin as a first line treatment (IDDT, 1997e).

As would be expected, the IDDT newsletters, after the announcement that animal insulins were going to be available in cartridges, contained a number of letters about animal insulin cartridges.

"Good news about CP Insulins . Nice to know we no longer have to succumb to the `take it or leave it' attitude and the hide bound refusal to listen by the `human' insulin school'."

(IDDT, 1997c: 5)

"I just wanted to congratulate all of you on your success with CP Pharmaceuticals. It is reassuring that pressure can persuade common sense to prevail. Keep up the good work. Although my daughter appears to have no particular problems with `human' insulin I feel for those who do."

(IDDT, 1997c: 5)

"My specialist nurse ordered 30 pens - her estimation of how many she would need for the clinic and within 2 or 3 days she had to make a second list because that wasn't enough. She couldn't understand where all the people were coming from."

(IDDT, 1997c: 5)

> "My specialist nurse told me they were discovering patients in the area they didn't know existed until CP introduced their pen cartridges for animal insulins."
>
> (IDDT, 1997c: 5)

Although animal insulin pens and cartridges had been introduced, the IDDT were concerned that diabetics may not know about them. They argued that since pharmaceutical companies can only directly advertise to the medical profession, a diabetics knowledge of new products is dependent on the medical profession (IDDT, 1997d). The IDDT point out that since they are only a small organisation, there is no way that they can reach large number of diabetics, but the BDA could. However, the initial introduction of animal insulin cartridges did get quite a lot of attention in the diabetic media.

Throughout this section I have indicated how the IDDT believed that diabetics needed more information in order to be able to make choices over the species of insulin that they wished to use. However, as already indicated elsewhere, some diabetics were

transferred to human insulin without their knowledge (IDDT, 1995b). In order to counter this possibility, the IDDT produced stickers which said, 'This patient does not give consent for human insulin to be administered' (IDDT, 1995d). The idea was that these stickers could be stuck on medical notes, so that human insulin was not 'mistakenly' given to diabetics against their wishes. Although some diabetics thought these were a good idea (IDDT, 1997) others felt that they were 'adversarial' (IDDT, 1997).

In this section I hope that I have indicated the various actions that were taken by both the BDA and the IDDT, in the maintenance of choice of insulin species. The main difference between the BDA and the IDDT is that while the BDA lobbied pharmaceutical companies over the availability of animal insulins, the IDDT worked on an 'individual' level. The IDDT were more concerned with giving information to individual diabetics, so that they themselves could utilise the choice of insulin.

6.6 COMPARING THE BDA AND THE IDDT

It should be obvious that there are a number of differences between the BDA and the IDDT. In this section I would like to expand on some of these differences. One difference between the two groups is in the way in which they were set up. As outlined in Chapter 4, the IDDT is a relatively new organisation, being set-up in 1994. One of the reasons why the IDDT was set-up was to offer help and support for diabetics and carers, who were experiencing problems on human insulin.

Another difference between the two groups was the resources that they had available. The BDA is a larger group than the IDDT, and was able to fund a number of research studies into human insulin and its possible negative effects (Balance, 1992a: 16). They were also able to carry out more country wide publicity, as shown by the BDA's letter to medical professionals (Balance, 1991b). They were also able to afford adverts in the popular press (Independent on Sunday, 1995).

The IDDT were less powerful in this sense. Rather than attempting to place adverts in national newspapers, which they themselves admitted they could not afford, the IDDT trustees wrote letters to national and local newspapers. In one case, Jenny Hirst, of the IDDT, wrote a letter to a number of local and national newspapers describing the

experiences of her husband and daughter, who both had problems on human insulin (IDDT, 1995b: 8). In an article, entitled 'No big advertising campaign - just one letter', Jenny Hirst describes how the letter had been printed in a large number of these newspapers (IDDT, 1995b: 8).

The IDDT also encouraged other diabetics, who were having problems on human insulin, to write to their own local newspapers (IDDT, 1995d: 7). Further, they managed to publicise themselves through news programmes (IDDT, 1995d: 7). From reading the IDDT newsletters, such methods did seem to get themselves noticed, with some diabetics contacting the IDDT after reading or hearing about their work from the media (IDDT, 1996b: 11). The IDDT also had a number of letters published in the medical press (*British Medical Journal*, *Diabetologia*, *Diabetic Medicine* and *The Lancet*) which outlined some of the problems that were experienced by some diabetics. Some of these letters were by non-medical members of the trust (Hirst and Hill, 1996a; Hirst and Hill, 1996b; Hirst, 1998) and other by medical members (Kiln, 1995; Kiln, 1996a; Kiln, 1996b).

Another difference between the BDA and the IDDT was in the content of the material that each group produced. The BDA produced material that was less antagonistic than that of the IDDT. Indeed, the IDDT were so antagonistic towards human insulin that some were under the impression that the IDDT wanted human insulin to be totally removed (IDDT, 1995d: 5). As a result, in July 1995, the IDDT issued a press release that re-stated their aims, particularly that they wished for the continued availability of animal insulins, and that human insulin shouldn't automatically be seen as the first choice of insulin treatment (IDDT, 1995d: 5).

The IDDT were also very keen for those diabetics experiencing problems on human insulin to speak with the media and write letters, they also encouraged diabetics to report problems on human insulin through the Yellow Card Scheme. Indeed, the IDDT were very critical of the current way in which adverse effects of drugs were reported.

In the UK, part of post-marketing surveillance, is the Yellow Card Scheme. In the scheme, adverse drug reactions are reported to the Committee on Safety of Medicines

(CSM). The IDDT described how a new drug is on trial from its discovery to its final demise, and that it is through pharmacovigilance (watching over drugs in use) that adverse reactions can be reported (IDDT, 1995a). The Yellow Card Scheme is however, based on spontaneous reporting by doctors, and as a result, is dependent on the vigilance and enthusiasm of doctors. Studies have shown that in any one year 11-13% of all UK doctors sent in at least on Yellow card, with the cumulative number over four years being about 35% (Medicines Control Agency, 1997). The IDDT pointed out that in 1994, very few adverse drug reactions on human insulin had been reported to the CSM, with the consequence that the CSM had not been sufficiently alerted to the frequency of problems on human insulin (IDDT, 1994).

Although patients are unable to report problems direct to the CSM, the IDDT encouraged patients to ask their doctor to report their problems. They gave the following advice:

> "Simply book a long appointment with your GP and ask him or her kindly to report your case. Say that you know he or she is very busy but please could they do it especially if you have changed to animal insulin and things have improved."
>
> (IDDT, 1994: 2)

In 1995 the Royal Pharmaceutical Society and the Patients Association had talks with the MCA about the possibility of expanding the Yellow Card Scheme to allow pharmacists, and possibly patients, to report adverse drug reactions.

This is not to say that the BDA were not keen that diabetics should be well informed. For example, the Hypoglycaemia Workshop, which met in 1994 and was organised by the BDA, argued that knowledge for people with diabetes, and those who care for them, leads to empowerment (Balance, 1994: vi). This was not just knowledge of their bodies and their diabetes, but also of their current treatment.

It is also notable that initially the BDA began by informing health care professionals of some of the concerns of diabetics, and asked these care professionals to be aware of possible problems on human insulin. The BDA were concerned not to "invoke undue distress to people who were not having problems by publicising a matter on which there was only anecdotal evidence" (Balance, 1994: xi).

6. After the initial reactions - diabetics and care groups

However, in retrospect, Suzanne Redmond, who was the Director of the BDA Care Division, believed that:

> "Our experiences since then have led us to believe that we should have taken the risk of provoking anxiety and made the considerations and responses of the BDA more public."
>
> (Balance, 1994: xi)

Suzanne Redmond went further and argued that the BDA were aware that many diabetics, who were having problems on human insulin, felt that they were not being listened to, because they did not see their problems being discussed in issues of Balance.

The IDDT on the other hand, had always had an approach in which they were more 'open' in their discussion of human insulin. However, for some, the content of the IDDT newsletters was too "alarming and unnecessarily frightening" (IDDT, 1997: 15). Some doctors thought that the IDDT were a bunch of 'eccentrics'(IDDT, 1996c: 2). In a book written by doctors, and to be used by GPs, the IDDT was described as having "set out to raise fears about human insulin which may increase the insecurity of GPs" (Fox and Pickering, 1995). However, others took a different view:

> "I, like many of your readers, look forward to reading your Newsletters. I love reading them, you are so outspoken and tell the truth, which some people in authority do not like; we who are unfortunate to have diabetes know you and your colleagues are doing your utmost to ease our burden and to assist us in any way you can."
>
> (IDDT, 1996c: 11)

Others saw the IDDT as a body that was campaigning against larger more powerful bodies. For example, one diabetic wrote:

> "Dear Jenny, I would just like to say how much I look forward to reading the newsletters; the ongoing story of your battle against drug companies and BDA and the professional way in which you edit the paper...I feel that the Trustees are unsung and unpaid heroes."
>
> (IDDT, 1998: 10)

In response, the editor of the newsletter points out that they do not see themselves as being in a battle with the BDA. That is not to say that they agreed completely with the BDA. The IDDT argued that the BDA did not use their resources in a way that would

benefit diabetics who were having problems on human insulin. They argued that:

> "The BDA has the power, the information amongst its members and the funds to really ensure that animal insulins remain available, if it chose to use that power."
>
> (IDDT, 1998: 10)

The IDDT also argued that they wished that the BDA "had a more open attitude to the 'human' vs animal insulin issue and that they would truly recognise that some people with diabetes are better using natural animal insulins" (IDDT, 1998: 10).

In summary then, there were a number of differences between the BDA and the IDDT. The main difference related to the two groups attitude towards human insulin. The BDA believed that, although human insulin may cause some adverse symptoms, on the whole human insulin should be the insulin of choice. On the other hand, the IDDT believed that human insulin did cause adverse effects, and that these effects should be widely publicised.

6.7 CONCLUDING REMARKS

In this chapter I have described some of the concerns of diabetics and care groups in the human insulin debate. I described the important role played by two mediating others: the family and the media. The family had an important role to play in alerting some diabetics to changes that they observed in the diabetics behaviour. Crucially, due to the nature of some of the symptoms exhibited by some diabetics on human insulin, diabetics themselves were sometimes unaware that their behaviour changed on human insulin. The media, and to a lesser extent family members, had a role to play in circulating information about the experiences of some diabetics on human insulin. In many cases, it was through the media that diabetics became aware that other diabetics were experiencing problems on human insulin.

A large part of this chapter has described the different solutions that were presented to diabetics, by doctors, when they reported problems on human insulin. What was important about the presentation and acceptance of solutions to diabetics was the knowledge that both doctors and diabetic possessed. In particular, I stressed that a diabetic may have been presented with a number of different solutions before they came to a settlement with their network body. I will theorise this issue in Chapter 7.

6. After the initial reactions - diabetics and care groups

One important issue that was dealt with in this chapter was the availability of animal insulins. In particular, I argued that there was some agreement that doctors and diabetics should have a choice of insulin species. However, it was not just the availability of animal insulins that was important, but also, that doctors and diabetics were aware that animal insulins were available. Again, the issue of insulin choice will be theorised in Chapter 7.

I concluded this chapter by looking at the differences and similarities of the two main care groups in this study: the BDA and the IDDT. The main difference between these two groups was that the IDDT saw human insulin as the cause of some of the experiences of diabetics who were using human insulin. However, the BDA were less confident on this score. This main difference reflected and influenced the way that the two groups conducted themselves in the human insulin debate. The IDDT were vocal in informing diabetics of their rights, and the problems experienced by some diabetics. On the other hand, the BDA produced material that was less antagonistic, with much of their work being carried out 'behind the scenes' in scientific studies and within research groups.

In the following chapter I will bring together some of the issues discussed in this and the previous chapters.

7. THEORETICAL PERSPECTIVES AND HUMAN INSULIN

7.1 INTRODUCTION

One of my central concerns in this thesis is the application of a number of theoretical approaches (actor network theory, the public understanding of science and the sociology of the body) to the development, introduction and use of human insulin. It is now time to draw out some of the theoretical implications of the present case study. However, before I do this, it will be beneficial to provide an overview of the thesis.

In Chapter 3 I described the development and commercial production of human insulin. There were a number of features of the development and production of human insulin that made it interesting. Human insulin was the first protein for human use to be produced by genetic engineering, and as a consequence, it generated a lot of scientific and media interest. Before 1982 diabetics used animal insulin to control their diabetes. However, there were two main concerns (or problematizations) within some areas of the scientific and medical community concerning animal insulin. The first concern was that the demand for insulin would outstrip the supply of animal insulin. Secondly, it was suggested that animal insulins may be the cause of some of the complications of diabetes, due to the differences in the amino acid sequence of animal and human insulin (Figure 2-3).

In the latter half of the 1970s work began on producing a human insulin that would allay both of these concerns. It was hoped that through genetic engineering it would be possible to produce endless amounts of pure human insulin. Between 1976 and 1979 the development of human insulin was represented by the media as a 'race' between three research teams - to be won by the first to produce human insulin within the laboratory using genetic engineering. In 1979 Genentech successful produced human insulin using genetic engineering and so 'won' the human insulin 'race'. Eli Lilly had for a long time been interested in the work being carried out by the research teams, and when it became obvious that human insulin could be commercially produced, they took over the development of human insulin from Genentech.

It was also pointed out in Chapter 3 that Novo Industri were also interested in developing a human insulin, although their method originally converted animal insulin

to human insulin. With both Eli Lilly and Novo Industri attempting to commercially produce human insulin the media reported that there was a 'battle' or 'war' as to which company would be the first to market human insulin. It was Novo Industri who won this 'battle', with Eli Lilly not far behind. It was also noted that human insulin passed through clinical trials relatively quickly, with human insulin being available in pharmacies by 1982.

One notable finding of Chapter 3 was that both Eli Lilly and Novo Industri carried out multiple and 'contradictory' strategies towards new developments in insulin (Figure 3-5). Although Novo Industri were claiming that their purified animal insulins would prevent diabetic complications (their overt strategy), and so human insulin would not be necessary, they were themselves developing a human insulin (their covert strategy). On the other hand, Eli Lilly were claiming that there was a shortage of animal insulins, and so human insulin was necessary (their overt strategy), yet they were also developing a purified animal insulin (their covert strategy).

As human insulin passed through the regulatory process it became endowed with particular characteristics, specifically, that it was superior to existing animal insulins. It was believed that human insulin could be inserted into a diabetic's existing network body without the need for changes in their network body. In terms of a program of action, pharmaceutical companies presented a program of action to doctors, who subsequently presented it to diabetics, in which human insulin was to be unproblematically used.

Once passed through regulatory bodies, human insulin was forcefully marketed by both pharmaceutical companies, with many diabetics being transferred from animal insulin to human insulin in a relatively short period of time. There were other reasons, apart from the marketing of human insulin, that caused many diabetics to be transferred from animal to human insulin. These included: claims that human insulin was superior to animal insulin; the withdrawal of a number of animal insulins; and, as a result of media interest, some diabetics requested to be transferred to human insulin (Chapter 4).

By 1987 the BDA had become aware that some diabetics were experiencing problems

on human insulin. Two particular problems arose: some diabetics felt that their 'traditional' warning signs of approaching hypoglycaemia were no longer present when using human insulin; and, some diabetics experienced an increased incidence of severe hypoglycaemia.

It was in Chapter 5 that I described some of the scientific studies that were carried out to study the possible adverse effects of human insulin. What was interesting (although in the context of SSK, very typical) about the findings in this chapter was that although some studies showed that human insulin did not have any negative effects, other studies, carried out by different researchers, showed that human insulin did have some negative effect.

At the present time there is still no definitive scientific evidence as to whether human insulin does or does not cause adverse effects in some diabetics, in SSK terms there has been no 'closure' of the debate. However, it is accepted that a number of diabetics have experienced problems while using human insulin (although human insulin may not have been the cause). As a result of the human insulin debate, there is now a consensus within the scientific and medical community (and care groups) that diabetics should have a choice of the species of insulin they wish to use.

In Chapter 6 I began to describe in more detail the experiences of diabetics, not just in using human insulin, but also their experiences within the doctor-patient setting. What particularly came out in this section was that doctors differed in the solutions that they presented to diabetics, with some doctors being sympathetic to a diabetic's experiences, and others being much more dismissive of similar experiences. Depending on the medical 'solutions' offered, some diabetics came to a re-settlement with their network body while others did not. Those who were unable to come to a negotiated settlement, that is, those whose negative symptoms on human insulin continued, contacted other actors, such as care groups and the media.

As the number of diabetics using human insulin increased, care groups became aware of a significant number of diabetics who were experiencing problems on human insulin. As textual evidence (of possible adverse effects) mounted , care groups began to circulate intermediaries through a number of different networks. For example, the

BDA sent a number of letters to the medical profession and began their animal insulin campaign, which asked for assurances from pharmaceutical companies for the continued availability of animal insulins. It was through the actions of care groups and those in the medical profession that the identity of human insulin began to change. For some diabetics and members of the medical community, the use of human insulin was no longer seen as unproblematic. In some cases changes would have to be made to a diabetic's existing network body in order to enable human insulin to 'fit' within the network body. These changes, e.g. increased blood glucose monitoring, enabled a diabetic to come to a re-negotiated settlement with their body. In other cases, it was only by transferring a diabetic back to animal insulin that the body could once again become settled.

One particular finding of Chapter 6 was that the two care groups - the BDA and IDDT - treated the human insulin issue differently. The IDDT was formed as a result of dissatisfaction with the way in which the BDA initially conducted itself in the human insulin debate. The original members of the IDDT were concerned that diabetics were not being represented adequately by the BDA, and that diabetics were not being given enough information about the possible adverse effects of human insulin. As brought out in Chapter 6, the main difference between the two groups was that the IDDT were more critical of the place of human insulin within the treatment of diabetes than the BDA.

Now that I have presented an overview of the thesis, it is now time to draw out some of the key theoretical implications of this thesis.

7.2 CONSTRUCTING A TENTATIVE THEORETICAL FRAMEWORK

I now wish to bring together, within a tentative theoretical framework, the issues that I have dealt with in the previous chapters. This section will be structured around the ways in which actors produced and circulated texts within a number of networks. As a starting point we have to keep in mind the initial identity of human insulin as brought about by the development of human insulin. I will then look at the circulation of texts by diabetics to a number of actors, in particular, care groups. The circulation of texts by diabetics is important because they were one way in which a diabetic was able to 'represent' their experiences. I will then move on to the circulation of texts by

other actors, such as care groups and the scientific community, to diabetics and those within the medical community. As noted in Chapter 2, texts are important because they can (sometimes) easily move from their point of origin, and as they move from one actor to another, their (possible) immutability allows them to align actors to (re)produce a network - they are able to act at a distance.

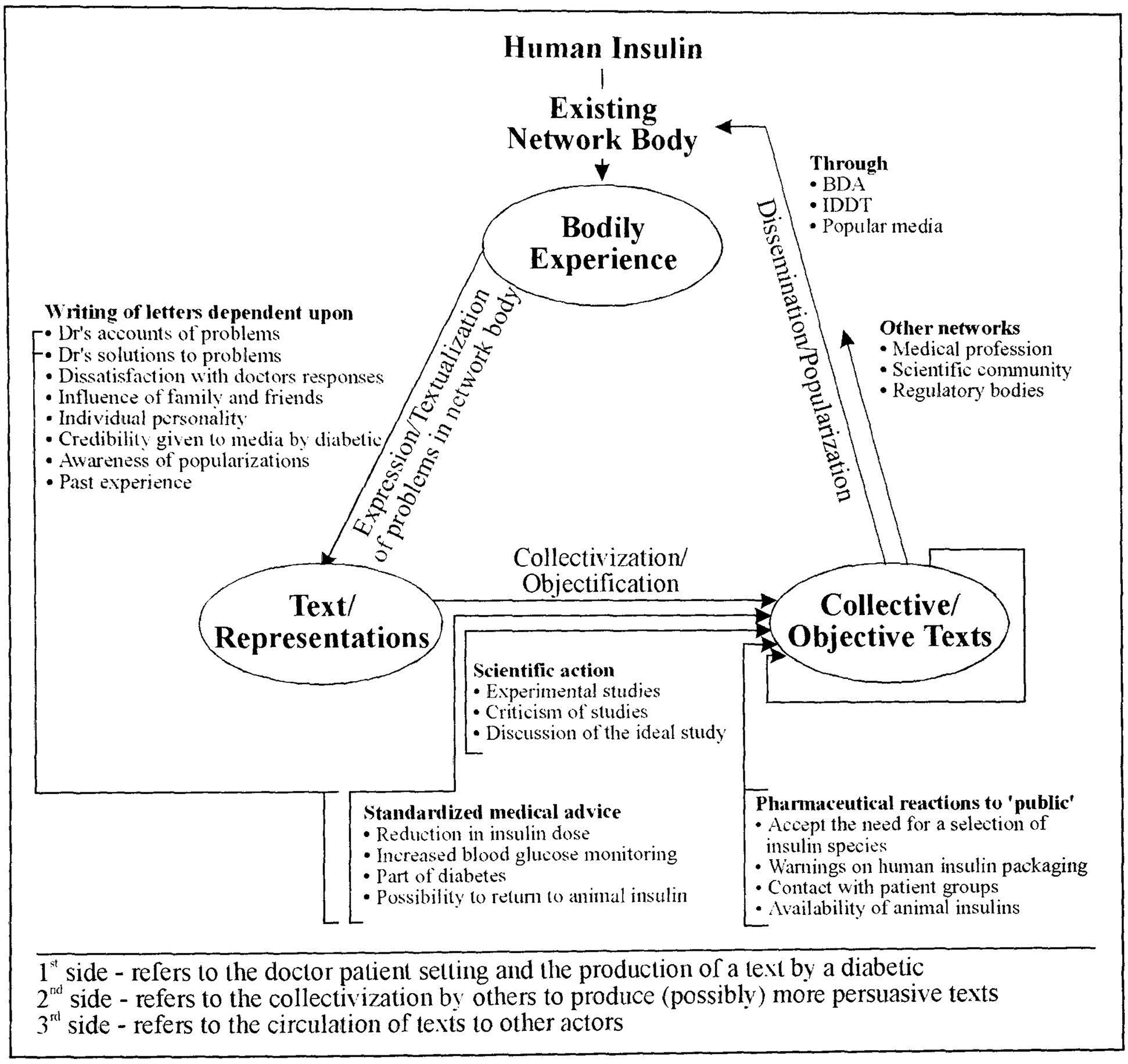

Figure 7-1: Schematization of the production, collectivization and dissemination of texts on human insulin

In order to conceptualise the circulation of texts it will be helpful to refer to Figure 7-1. Inevitably, given the complexity of the case, this is a tentative and simplified schematization. However, by beginning with the first intimation of a problem, in this case from the individual diabetic body, and 'building up', I hope to be able to bring out these complexities. Although the schematization represented in Figure 7-1 will provide the backbone to the theoretical discussion, a number of issues need to be

brought out of the discussion of Figure 7-1. Although these issues will be alluded to in the discussion of the circulation texts, they will be dealt with in greater depth in separate sections (see Section 7.3).

7.2.1 Initial Identities of Human Insulin

In Chapter 3 I described how, throughout the development and production of human insulin, existing animal insulins were problematized, and at the same time, human insulin was presented as the solution to these problematizations. Identities were also being distributed, through the circulation of texts, to a number of actors. For example, human insulin was defined as the solution to the complications experienced by some diabetics on animal insulin. Other actors were also defined: diabetics were defined as what I have called 'prospective consuming bodies' of human insulin and doctors as those who would prescribe human insulin.

However, diabetics were not just defined as 'prospective consuming bodies'. They were also defined as being able to transfer from animal to human insulin without the need for changes in the management of their diabetes. One of the concepts that I used to illustrate this was the network body. To recap, the diabetic network body includes such artefacts as insulin (originally animal insulin), syringes, doctors and other diabetics. It is the makeup of this network body that affects how an individual acts towards other networks. Although all bodies, not just 'ill' bodies, should be seen in this way, it is when a body is in crisis that elements of the network body become particularly visible. Over time, 'ill' bodies come to a negotiated settlement as new artefacts are incorporated into the network body and existing ones are redefined. The network body of a newly diagnosed diabetic comes to a negotiated settlement through the use of insulin, care over their diet, and other management techniques. These features then come to re-constitute the settled network body.

In terms of the network body, human insulin was defined as being able to slot into the existing (settled) diabetic network body - the starting apex of Figure 7-1. In ANT terms, it would not be necessary to enrol new actors within the network body, or re-inscribe existing ones, in order for human insulin to be 'successfully' used by diabetics. Further, the existing pre-inscriptions of diabetics were expected to be sufficient to enable the unproblematic use of human insulin. Referring to my

schematization, it was not believed that the use of human insulin would directly lead to adverse bodily experiences. The bodily experiences would be 'hidden', since it was expected that there would be a more or less 'straight substitution of animal insulin with human insulin. As a result of this straight substitution, there would be no need for a diabetic to represent these experiences in either talk or texts.

Referring directly to human insulin, it was believed that the prescriptions and proscriptions of human insulin would be no different to those for animal insulin. Further, it was suggested that human insulin would 'prescribe' or 'enable' more than animal insulin, since it was predicted that human insulin would reduce the occurrence of diabetic complications, which would then lead to an increase in a diabetic's quality of life. Human insulin was therefore inscribed with characteristics that gave it an identity of being superior to existing animal insulins.

It was also expected that the program of action, defined by pharmaceutical companies, would be accepted and followed by those involved with human insulin. Through the development and production of human insulin, human insulin had become black boxed, and was presented unproblematically to doctors, care groups and diabetics. A program was presented to doctors, by the pharmaceutical companies, that human insulin should be the insulin of choice, due to its claimed superiority over animal insulin. In turn, doctors prescribed human insulin to diabetics, claiming that human insulin was the 'modern' and 'best' insulin. These initial identities of doctors, as prescribers of human insulin, and diabetics as users of human insulin, were accepted. This was shown by the 'speedy' increase in the use of human insulin from 6% to 80% between 1985-1989 (Balance, 1989).

Those diabetics who used human insulin, without experiencing any changes in the management of their diabetes, accepted, perhaps unknowingly, the program of action that human insulin was superior, or at least equal to, animal insulin, and used human insulin without experiencing any change in the management of their diabetes. Referring to my schematization (Figure 7-1), a diabetic did not experience a change in the way that their diabetes was managed.

However, many actors did not accept these distributed identities. Using my

schematization (Figure 7-1) as a basis, I will describe the means by which diabetics expressed their concerns over human insulin. However, it is not just the rejection of these identities that has been my interest in this thesis. I have also been interested in the way in which one particular actor, such as a diabetic, attempted to re-inscribe the meaning of human insulin, and in turn, how other actors, such as doctors, responded to this complication. At this point it is worth recalling that Akrich and Latour described re-inscription as defining the drama (Akrich and Latour, 1992), and Latour has argued that re-inscription is the transformation of a silent artefact into a polemical process (Latour, 1992). One of the aims of this thesis has been in describing this drama.

7.2.2 Textualization of Problems in the Network Body

For a significant number of diabetics human insulin did not fit unproblematically within their existing network body. As a result of a 'fitting' artefact[40] being replaced by a 'non-fitting' one, many diabetics produced intermediaries which expressed their new bodily experiences. Looking at Figure 7-2, diabetics have a varying degree of experiential knowledge depending on their duration of diabetes. It was because a diabetic's existing experiential knowledge was unable to accommodate changes in the management of their diabetes that a diabetic produced and circulated intermediaries. These intermediaries expressed the nature of the artefact's 'non-fittingness'.

When experiencing problems on human insulin, it was likely that a diabetic would have initially consulted their doctor. The doctor-patient setting is a good place to start because the medical practice is the legitimised source from which diabetics are encouraged to seek solutions to problems in the management of their diabetes. However, within this site of expertise, the actors involved have different knowledge bases from which they draw. A diabetic's primary source of 'knowledge' comes from interpreting their own experiences. On the other hand, a doctor's primary source of 'knowledge' comes from institutional sources, in particular the British National Formulary.

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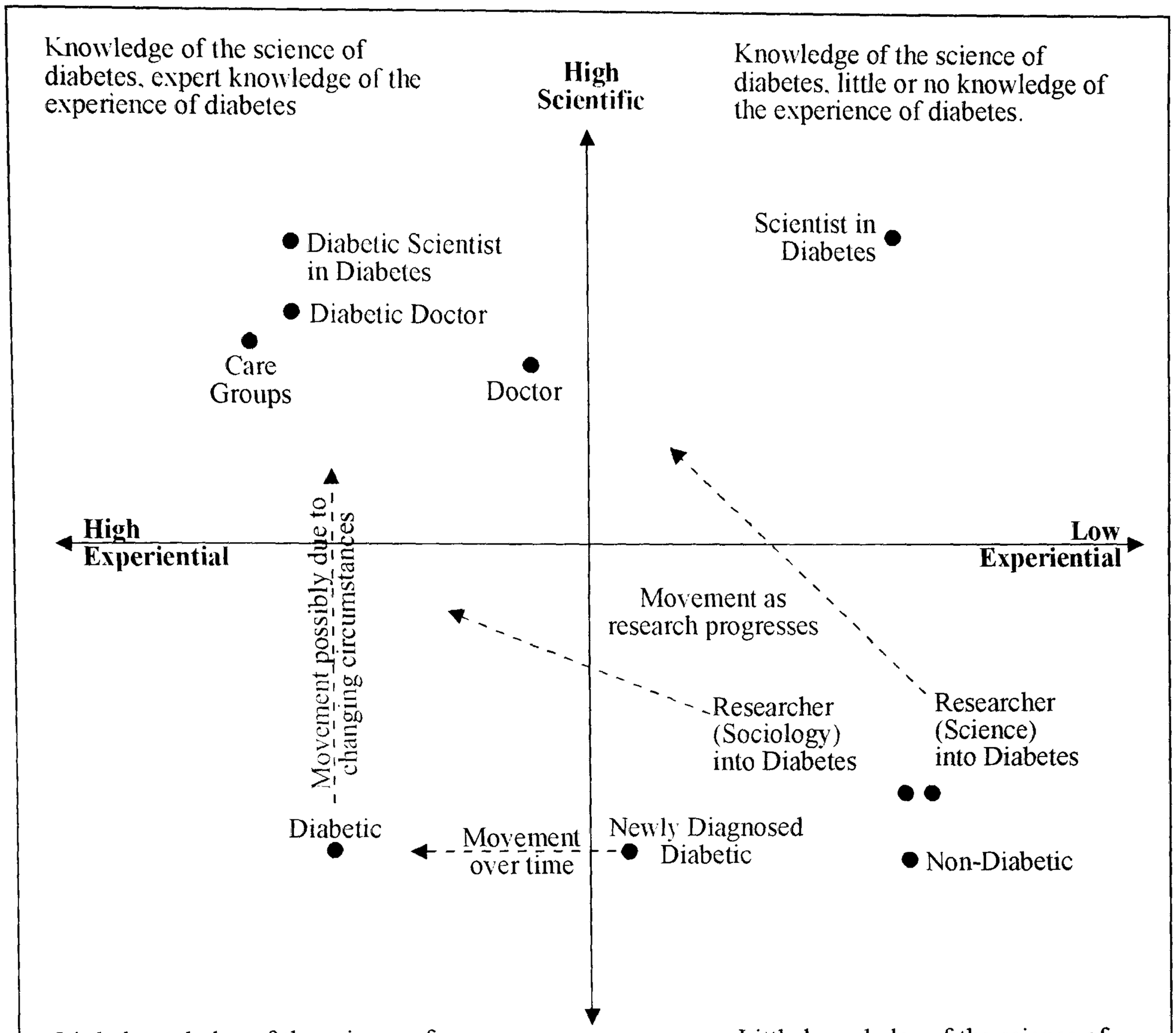
[40] Importantly, 'fitting' artefacts may have at one time been 'non-fitting'. As illustrated in chapter three, there were a number of reports of diabetics experiencing problems on animal insulin when they changed from porcine insulin to highly purified porcine insulin.



The bottom right part of the figure shows those actors that have little or no scientific or experiential knowledge of diabetes, such as a newly diagnosed diabetic. However, as a newly diagnosed diabetic learns, through experience, about their diabetes they begin to gain experiential knowledge, and move into the bottom left part of the figure.

The top right part of the figure shows those actors who have knowledge of the science behind diabetes, but are not diabetic themselves, so lack experiential knowledge. However, a scientist who is a diabetic, will have both the experience of living with diabetes, and may know something about the science behind diabetes.

Figure 7-2: Illustration of the dimensions of experiential and scientific knowledge

Within the doctor-patient setting the doctor has often been classed as an 'expert', while the patient is 'lay', that is belonging to a group referred to as the 'public'. The label of an actor as an 'expert', refers to the classification of that actor, as an acknowledged professional in their field, "by virtue of formal accreditation, knowledge, training and experience" (Arksey, 1998: 15). On the other hand, 'lay' actors are those who are not seen as professionals but nonetheless may be interested by a particular topic. As described in Chapter 2, one of the important differences

between these two actor types is the main source from which knowledge is drawn. An 'expert' relies on those texts that have been deemed legitimate within their medical field. By contrast, 'lay' actors largely, although certainly not always, draw from their own experiences and from those sources that have textualized the experiences of similar actors with which they identify.

I noted in Chapter 2 that the divide between 'expert' and 'lay' knowledge is problematic. As Davison et al. have argued:

> "The two strands [lay and scientific], though, are rarely if ever entirely separable, indeed the range of thought and belief in both the professional and public domains is so broad that the traditional lay/scientific dichotomy may well have outlived its usefulness."
>
> (Davison et al., 1991: 5)

So, if the distinction between 'lay' and 'expert' is too simplistic, what other dimensions are there? I suggest that we should view this case as based on two criteria, the 'scientific' and 'experiential' (Figure 7-2). The term 'scientific' refers to those actors who possess what is termed scientific or expert knowledge within a particular field. By contrast, the term 'experiential' refers to knowledge that is gained by experiencing illness in the first person, or by being in contact, and identifying with, those who are experiencing illness. Experiential knowledge will draw upon cultural representations, just as scientific knowledge does, but, and this is the key point, these are not 'accredited' or seen as 'scientifically objective'.

In any particular situation, and around any particular issue, actors within a site of expertise will possess differing degrees of 'scientific' and 'experiential' knowledge (classified as low and high). The importance of this classification is that actors can possess both types of knowledge simultaneously. Through the doctor-patient setting, a doctor may gain an understanding of what a diabetic is experiencing. On the other hand, a diabetic may gain an understanding of the scientific basis for their experiences. Actors will attempt to persuade other actors of the validity of the knowledge that they possess, and it is the value that actors give to both their own, and the knowledge of others, that is important to the outcome of the doctor-patient setting.

It was negotiations that took place within the doctor-patient setting that may have

affected whether a diabetic produced texts for networks outside of the doctor-patient setting. Importantly, there were many possible influences that may have affected whether a diabetic was satisfied with solutions presented to them by their doctor (first side of schematization).

These influences include: the popular and diabetic media; family and friends; and other diabetics. For an antiprogram to exist, however preliminary, towards a particular program, a link has to be made between artefacts, actors and networks. In many cases, it is the circulation of texts that enable actors to link what are possibly disparate actors and experiences. For example: What caused some actors to link hypoglycaemia unawareness to human insulin, and not to the long duration of their diabetes? The observation that actors are influenced by a large number of texts, shown throughout this thesis, illustrates that actors are subject to the influence of a multiplicity of networks (Singleton and Michael, 1993).

When a diabetic reported problems with the management of their diabetes to a doctor, whether or not they had attributed it to human insulin, the doctor had a number of possible actions s/he could take (see Section 7.3.1). The possible actions included: a dismissal of the problems; changes made to the management of diabetes, within the use of human insulin; and, a transferral of the diabetic back to animal insulin. As outlined in Chapter 2, it is through the circulation of intermediaries that actors attempt to enrol other actors into a particular program of action. The circulation of various intermediaries, realised in these different options, defined the frontline of the controversy. The negotiations that took place within this site of expertise had an influence on whether a diabetic produced texts which articulated their condition.

Many diabetics who had not attributed their symptoms to a particular origin, accepted solutions which brought them to a re-negotiated settlement with their network body. Some diabetics, who had attributed their hypoglycaemia unawareness to human insulin, also came to a negotiated settlement as doctors presented solutions to them which they in turn accepted. In ANT terms, the intermediaries that were circulated by doctors, in order for a diabetic to continue to use human insulin, had been successfully accepted by diabetics. As a result, diabetics were still enrolled within the human insulin network. This group of diabetics were unlikely to have contributed to the

production of texts which criticised human insulin. It has to be remembered however, that some diabetics originally accepted solutions presented to them, and later, possibly due to other critical texts, questioned these initial solutions.

However, if a diabetic was unhappy with the solutions that were presented to them in the doctor-patient setting, they may have produced texts which expressed their experiences. In many cases, doctors did not accept that human insulin was the cause of the symptoms exhibited by patients. Other doctors, who attributed human insulin as the cause, were nevertheless unwilling to return patients to animal insulin. In both these cases, doctors expressed counter narratives to those of the patient, and it is as a result of these counter narratives that diabetics may have written to newspapers or the diabetic media, in other words, produced texts that expressed their experiences. Importantly, the production of these texts may have been due to a dissatisfaction with a number of different solutions or negotiations within the doctor-patient setting. A diabetic may have visited their doctor on a number of occasions, reporting their problems, without the diabetic feeling that an adequate solution had been found - the intermediaries that were being circulated, to reduce the frontline, were unsuccessful.

When a doctor was unable to bring a diabetic to a satisfactory negotiated settlement, a diabetic may have produced texts for other networks. From the diabetic's point of view, it is the doctor who has the identity of being able to solve bodily problems. However, if an actor, in this case the doctor, is no longer able to maintain a particular identity then it is likely that there will be some crisis between the actors involved, in this case, between the doctor and the diabetic. Therefore, for those diabetics who did not come to a negotiated settlement within the doctor-patient setting, there was a 'personal necessity' (Lambert and Rose, 1996) to understand their unsettled network body. One way in which this understanding could be gained was through seeking out other actors.

For a diabetic experiencing problems with the management of their diabetes, and wishing to understand their experiences, an obvious starting point was to seek information from care groups. Initially, diabetics wrote to the BDA (since the IDDT wasn't yet formed) describing some of their experiences. These experiences were not just those on human insulin (such as an unawareness of hypoglycaemia), but also

describing their contact with doctors (such as claims that doctors were unsympathetic or that they denied the existence of particular animal insulins). From this body of texts care groups chose which to include within their magazines and newsletters.

7.2.3 Collectivization of Texts

With regard to my schematization (Figure 7-1), the collectivization of texts is key in showing the discussions around the human insulin debate. When texts become 'collectivized' they may include texts from a number of different sources. These sources may not be just from a similar type (letters describing the experiences of diabetics or reviews of the scientific literature) but also from different types of sources (evidence of the experiences of diabetics from both scientific studies and diabetic reports). This is one of the points where texts from other networks, such as scientific evidence, comes into contact with other sorts of understanding; that is, where different types of knowledge are differentiated and/or combined. Such differentiation and combination rests, at least in part, on the relation between 'expert' and 'non-expert' actors. This is because, what texts become collectivizable within other texts depends on the sort of trustworthiness that is attached to the initial texts. Such trustworthiness (or authority) will reflect the relation between different actors, such as experts, doctors, scientists, care groups and diabetics etc.

Before I continue, it is worth differentiating between Latour's idea of the combination or integration of texts (Latour, 1987), and my notion of collectivization. Latour talks of the process by which texts of a similar kind are integrated, and then reduced to form an immutable mobile. Take for example the calculation of gross national product (GNP). In order to calculate a countries' GNP it is necessary for statisticians to accumulate data relating to income earned by domestic citizens, regardless of the country in which their services were supplied. As a result, statistical data will be gathered from a number of sources and then reduced to a final figure. However, collectivization involves the accumulation of texts of different types and content. For example, editorials included quantitative texts (e.g. scientific studies), qualitative evidence (e.g. case studies) and biographical texts (e.g. personal accounts). The resulting narrative did not attempt to reduce the data, rather, the data was juxtaposed without integration.

The two concepts should not however be seen in opposition. Instead, they should be viewed as existing on a spectrum, with combination at one end and collectivization at the other. Although the texts dealt with in this study are the result of collectivization, they may also involve elements of combination. For example, some editorials presented data from many scientific studies, which was then reduced to a prediction of how many diabetics may be experiencing hypoglycaemia unawareness. As well as this data however, editorials also included biographical evidence.

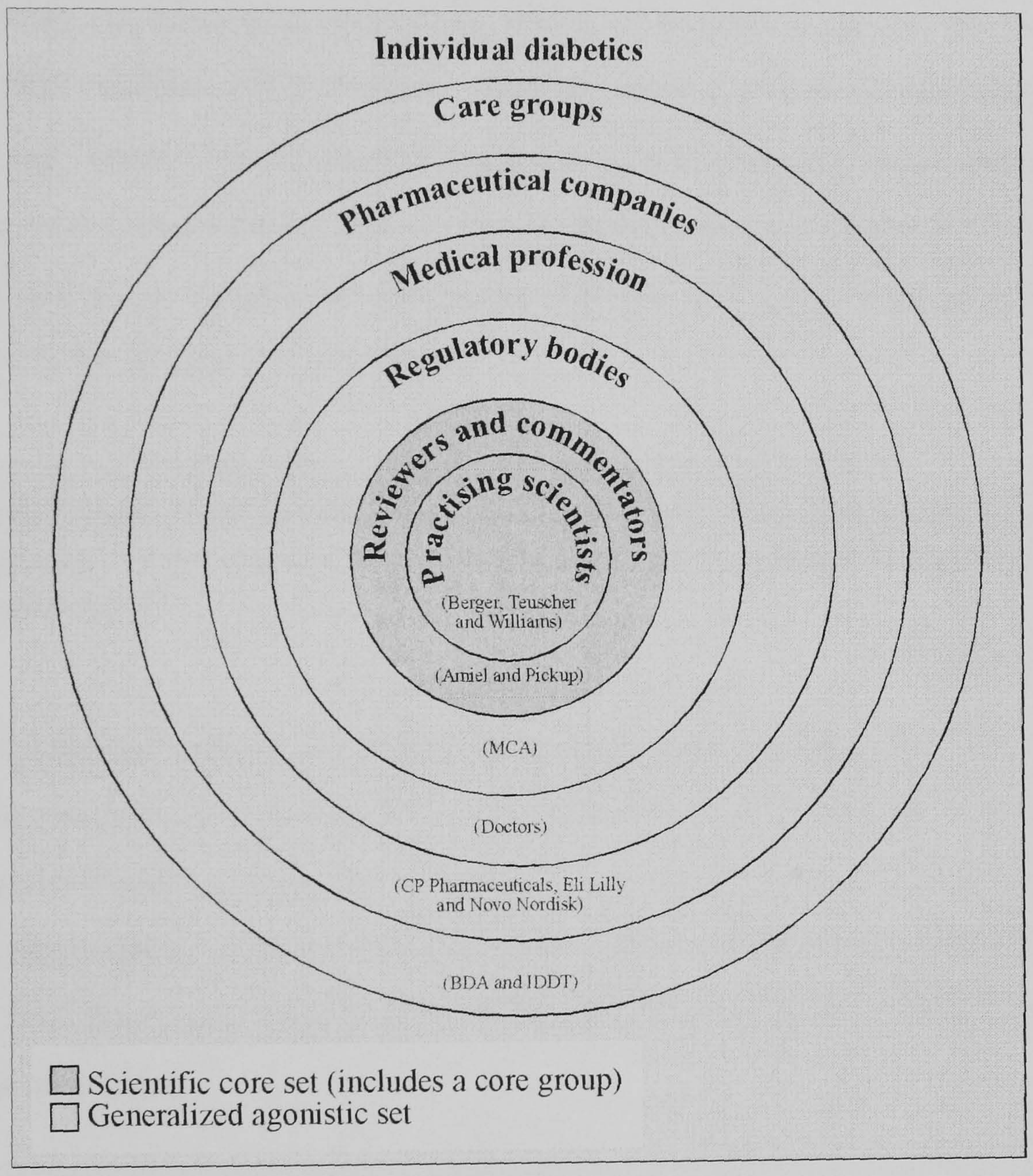


Figure 7-3: Extending the core set

It should also be stressed that collectivization is not about sharing texts. Instead, through collectivization, texts are integrated with others. It is not the case that whole texts are collectivized, rather, particular issues, within texts, are 'pulled out' and then (re-)interpreted by actors. Texts will be (re-)interpreted in terms of the network that the collectivizing actor is part.

Returning to collectivization, it is important to be able to formalise the relations between members of the scientific community and other actors (such as care groups and individual diabetics). One way to do this, is through the notion of the core set (Collins, 1981; Collins, 1985; Collins, 1988). It is necessary therefore, to take a slight detour from Figure 7-1 and describe the core set, before returning to Figure 7-1.

7.2.3.1 *The core set*

Those scientific actors, who were attempting to produce facts within the human insulin debate, can be seen as comprising what Collins calls a core set. Collins (Collins, 1981; Collins, 1985; Collins, 1988) describes a core set as consisting of 'insiders' and 'others'. In a scientific controversy, according to Collins, there is an elite group of insiders who possess the necessary technical and practical knowledge to formulate and judge competing truth claims. Of course, in a particular controversy the 'experts' will be different. For Collins:

> "...the core-set of scientists are those who are actively involved in experimentation or observation, or making contributions to the theory of the phenomenon, or the experiment, such that they have an effect on the outcome of the controversy."
>
> (Collins, 1981: 8)

Within the core set there is also a penumbra of would-be contributors. Work carried out by this group is not significant to the controversy as far as the core set members are concerned (Collins, 1981: 11). Collins has argued that it is an actor's association with the less prestigious institutions and actors which prevents them from entering the core set. As a result, the experimental material produced by these actors is seen as being of a 'low level'.

One important feature of the core set is that it includes both 'allies' and 'enemies'. That is, within a core set there is likely to be animosity and conflict, especially if members come from different scientific disciplines. Indeed, Collins points out that some members of the core set may be intent on destroying a particular interpretation of 'truth' that others have staked their scientific reputation on (Collins, 1985). This was shown in Chapter 5, where many researchers did not accept the claims of 'facticity' put forward by other researchers. Many studies were criticised on scientific grounds, and the authors of letters, written in response to these studies, were criticised

for their reading and understanding of the studies they were commentating on. These criticisms attempted to problematize the texts that were being circulated by scientists.

Another important feature of the core set is that actors within it need to maintain a degree of 'privacy' or exclusivity. By doing so, experts can maintain the illusion that they are able to produce relative certainties. When knowledge is then produced from within the core set it becomes purified (Latour, 1993). Any social, political or economic interests that once existed within the set are 'removed', and only a version of the 'science' conducted within the core set is produced. It is the use of this 'purified' knowledge, within wider circles, that feeds back into the core set and so justifies its authority (Arksey, 1998). What is at stake within core sets is the ability of actors, within the core set, to claim 'facticity' about some part of nature. Within the core set there is also a core group which embodies what comes to be known as the dominant view (Collins, 1999). In this study, the core group claimed that human insulin was safe as long as certain considerations were observed. One such consideration was that there may be a need for a reduction in insulin dose compared with animal insulin.

Those on the outside of the core set can be described as the 'lay' public. According to the notion of the core set, this 'lay' public are unable to appreciate the complexity of the science that is discussed within the core set, and as a result, can be justifiably marginalised. In one article, Collins has argued that: "it would be a strange world if there were no experts. It would be a strange world and one I would not welcome if 'the public [had] its own and legitimate interests in the very content of science'" (Collins and Pinch, 1994: 335).

In some instances, lay individuals are invited, if only in a restricted sense, to be members of the core set. In Collins' case study of the UK's Central Electricity Generating Board's demonstration of the 'safety' of its nuclear fuel flasks, members of the public were invited to attend, through the media, an experiment which demonstrated the safety of the flasks (Collins, 1988). The members of the 'public', who were invited to be observers, were temporarily defined as 'experimenters' who were able to judge the science that they were observing - in this case the testing of nuclear fuel flasks. In reality, it was not an open experiment that the public were

observing, but a display of post-closure knowledge (Michael and Birke, 1994). By accepting the identity defined for them, the actors had become allied to the work of the experimenters.

However, in this example actors were also being given other identities, as well as the temporary identity of 'experimenter'. They were also given the identity of someone interested in 'Britain's economic well being' (Michael and Birke, 1994). Without this supplementary identity, the demonstration may be rejected, on such grounds as: 'What happens when the flasks reach the power station? What are we doing with the nuclear waste?' With these other identities, the 'experiment' could have been rejected on broader political, ethical or economic grounds, rather than simply on technical grounds. With these other identities the core set can potentially be extended to encompass any actor with a view on the relevant subject, whether the view is politically or morally based (Michael and Birke, 1994).

Another problem with the conception of the core set, as outlined by Collins, is that not all disputes are confined to scientists and scientific institutions. The work of Collins has mostly been concerned with scientific controversies that involve experimentation and observation (Collins, 1981). As indicated above, Collins would oppose extending the core set beyond 'expert professionals'. However, a large number of controversies involve a public element. In such cases, Collins would argue that the public should be represented by their own experts. In such cases these 'experts' will still be using the existing pathways to knowledge - the scientific method. Collins offers no "discussion of the process by which laypeople can construct alternative ways of knowing or new varieties of expertise that-sometimes-alter the pathways of knowledge construction" (Epstein, 1996: 17). In this case, looking at a 'simplistic' core set does not help us: "where who get to count as an expert is one of the issues at hand and which set of characteristics qualify one as such" (Epstein, 1996: 17). It is not just important to look at which 'experts' are able to claim facticity, but also how 'non-experts' are able to claim that their knowledge is just as credible as scientific knowledge.

As shown throughout this study, other actors were involved within the scientific debate. As a consequence, the boundaries of the debate were more problematic than implied by the work of Collins. As Arksey has argued, when the 'public' are involved

in a scientific debate, there is a need for more politicking in order to stabilise the enquiry, that is, in deciding what the central issues are to be (Arksey, 1998). In this study, it was not just scientists that were attempting to define the important issues, but also other actors, such as care groups. In Section 7.3.3 I will look more closely at how this was done.

In this study, the traditional core set consisted of researchers such as Teuscher, Berger and Williams. There was also a group of commentators who did not carry out experimental work themselves, but wrote review articles and interpreted findings. To this groups, we can add authors such as Pickup and Amiel. However, we need to extend the notion of the core set further (Figure 7-3).

Michael and Birke (Michael and Birke, 1994) claim that by developing the concept of the core set it can become more useful to understanding scientific controversies. They argue that scientists are increasingly aware that there is a need for 'non-scientists' to be involved within scientific debate, at least on the surface. These 'other' actors comprise what they call a 'generalized agonistic set', which is open to anyone wishing to express a view. However, there is a censoring of those who are allowed into this newly constructed core set. Michael and Birke used the term 'envelopment' to describe how "target actors are invited and manoeuvred into an argumentational envelope in which there is space for a limited number of opposing or antagonistic positions" (Michael and Birke, 1994: 92). These actors are not enrolled, since the identities of the actors are not being definitively formulated, rather the associations are flexible or agonistic.

Actors within the scientific core set, define a set of minimal characteristics that groups within the 'generalized agonistic set' must follow to be part of a debate - to become part of the argumentational envelope. In the case of the anti-vivisection debate, these characteristics were: rationality, non-violence, civility, and so on (Michael and Birke, 1994: 84). I will look at the minimal characteristics for the human insulin agonistic core set in Section 7.3.2.

Figure 7-3 shows one way in which the 'new' core set can be represented. Those that are further away from the inner ring are less influenced by the texts that are circulated

from within the scientific core set. Importantly, those actors in these outer rings are influenced much more by other texts, such as those from 'lay' individuals. A comparison can also be drawn between the penumbra in Collins' version of the core set and these outer rings. Work carried out by the outer rings, particularly when it is 'non-scientific', is not seen as significant by members of the scientific core set. As I will show in Section 7.3.3, care groups attempted to break this boundary, by stressing the value of their own knowledge.

Returning to Figure 7-1, the collectivization of texts does not just include texts of a similar kind, but can include a whole variety of texts from different networks - different parts of the core set (both scientific and lay). For example, one set of texts that were produced by diabetics described how they were told by their doctor that animal insulins were no longer available. Care groups then contacted pharmaceutical companies to discover which animal insulins had been withdrawn. In a significant number of cases equivalent animal insulins were still available, and care groups reported this fact through their magazines.

In other acts of collectivization, actors had a degree of flexibility to which texts they selected. As pointed out above, one of the important features of the scientific core set is that not all actors within this set will agree. As a consequence, when an actor attempts to collectivize texts, which include those from within the scientific set, they have a degree of flexibility to which scientific texts they use and collectivize. As Epstein has argued, the definitiveness of a study is "a negotiated outcome and one that may be actively resisted by some members of the controversy" (Epstein, 1996: 334). Similarly, Shapin and Schaffer (Shapin and Schaffer, 1985) argue that scientists negotiate what counts as evidence and which experiments represent the accurate testing of a hypothesis.

When an actor is collectivizing texts, they do not just have a degree of flexibility of which experiments adequately represent reality. There is also a degree of flexibility of which texts within the rings of the core set represent reality. For example, pharmaceutical companies stressed that the majority of diabetics on human insulin did not experience any problems. On the other hand, the IDDT stressed that there were a

significant minority who had experienced problems.

As part of the collectivization of texts, the IDDT tended to draw on scientific texts that backed up the possibility of adverse effects on human insulin. This reflected the IDDT's initial position, gained from experiential evidence, that human insulin did cause adverse effects. On the other hand, pharmaceutical companies, who had invested a large amount of resources in human insulin, selected texts which backed up their position that human insulin was safe and efficient. Importantly, from the point of view of the pharmaceutical companies, the dominant view within the core set, what Collins calls the core group (Collins, 1999), was that human insulin was the insulin of choice. This was important because it allowed the continued regulation of human insulin (had the dominant view been that human insulin did cause negative effects then it may have resulted in the withdrawal of human insulin). Since the pharmaceutical companies had invested a large amount of resources into human insulin, this would have been a major upset for them.

The selection and collectivization of texts by actors is therefore shaped by the wider networks of which an actor is part: the IDDT were representing those diabetics that were having problems on human insulin, and it was those studies that 'reified' these experiences that were seen as credible. On the other hand, the BDA had built up links with pharmaceutical companies and the medical profession. These links may have been one reason why, when the BDA were contacting other actors (such as the pharmaceutical companies), they did not keep their readers informed of their actions. It may have been the case that they did not want to strain their relationship with these other actors when the negative effect of human insulin was unproven. The IDDT had no such links with other actors.

7.2.4 Dissemination of Collectivized Texts

Collectivized texts should be seen as describing the relation that the producing actor has to other actors. These collectivized texts are then disseminated with the aim of persuading others of their 'facticity'. Different texts (scientific reviews, care group articles and medical reviews), produced by different actors (scientists, IDDT and the BDA), were directed towards different actors (doctors, diabetics and regulatory bodies) within any part of the core set. The important point is that actors can, in

theory, collectivize texts from any part of the core set, whether from the scientific set or the generalized agonistic set, and disseminate these texts to any other part of the core set.

In many cases, it was through receiving disseminated texts, from care groups and the popular media, that diabetics became aware of the human insulin controversy and the problems experienced by other diabetics. The importance of these texts is that it may have enabled a diabetic to link their own experiences to those of others. For example, a diabetic experiencing a change in their warning signs of approaching hypoglycaemia may have attributed it to their duration of diabetes, perhaps through consultation with their doctor. In this situation, there may be no antiprogram to human insulin even though a diabetic is experiencing some form of biographical disruption, or 'crisis', in their network body. However, as a diabetic became aware of popularized texts that described the experiences of others, they may have re-interpreted their original diagnosis and solution, and linked their symptoms to human insulin. In such scenarios a diabetic may have formed an antiprogram towards human insulin.

When a diabetic accepted and used disseminated texts the 'knowledge' contained within them then became part of the diabetic's network body. It is this knowledge that may have been used to bring themselves to a negotiated settlement. In Chapter 6, I described how some diabetics used information about the availability of animal insulins to 'persuade' their doctor to transfer them from human to animal insulin. In some cases, using texts from the IDDT, diabetics went outside of the doctor-patient setting to gain animal insulin independently. Other diabetics used texts which described the experiences of other diabetics. These texts attempted to reduce the frontline between the doctor's dismissal of problems and the diabetic's experience of problems on human insulin. However, rather than the doctor presenting solutions, to enrol the diabetic into their program, it was the diabetic who was attempting to enrol the doctor to their program of action.

Care groups also directed texts towards other networks. For example, the BDA's petition was directed towards pharmaceutical companies, while the IDDT often wrote to the regulatory bodies about the experiences of diabetics on human insulin.

7.2 Constructing a tentative theoretical framework

I have already stressed that texts were used by diabetics to bring themselves to a negotiated settlement. However, there was another function of texts that were circulated by care groups. The IDDT encouraged diabetics to produce and circulate texts themselves. In particular, they asked diabetics to contact their local media and describe their experiences on human insulin. They also informed diabetics of their patient rights.

We must not forget that doctors also received disseminated texts. The main source of these texts was of an institutional nature, that is, the bedrock of any diagnosis is based upon certified knowledge (Collins, 1985) produced from within the scientific core set. This includes such texts as those from the British National Formulary and prescription guidelines. However, Phillips has argued that "the direct transmission of information in the medical literature...is enhanced or amplified by secondary amplification in the lay press..." (Phillips et al. (1991) quoted in Epstein, 1996: 22). Therefore, it may be through the 'lay' or non-medical media that doctors are provided with a sense of which scientific findings are important (Epstein, 1996). In the case of human insulin, doctors may have read about the experiences of some diabetics on human insulin.

Doctors may also have come into contact with other diabetics who had experienced problems. These other experiences may have been tacitly influential in the way doctors treated subsequent patients. As doctors built up their experiential knowledge, it may have become a more credible challenge to their institutional knowledge. It may have even been the case that they themselves had experienced problems with human insulin, such as Dr. Kiln.[41] As a result of these other influences, it is possible that 'institutional' knowledge will be re-interpreted within local conditions. Having an amalgamated notion of lay and expert knowledge (Figure 7-2), enables us to accommodate for the fact that actors are influenced by both 'expert' and 'lay' knowledge. Indeed, it is questionable whether actors ever possess solely 'expert' or 'lay' knowledge.

As actors disseminated texts they attempted to move themselves into more credible

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[41] As Dr Kiln admitted, he found it difficult to comprehend that while scientifically there should be no problem with human insulin, through his own experience, he felt there was a problem with human insulin.

positions, both in relation to members of the scientific core set, and with members of the 'generalized agonistic set'. For example, the pharmaceutical companies wanted to be seen to be acting on the problems experienced by some diabetics, and as a result changed their patient information leaflets. Both the BDA and the IDDT wanted to be seen to be acting in the interests of diabetics, and as a result to be seen as the obligatory passage point by which diabetics sought information. However, as shown in Chapter 6, the method by which this was done differed between the two groups. Initially the BDA directed texts towards the medical profession. This led to the claim that the BDA were not actually doing anything for the benefit of patients, when in fact, they were working behind the scenes. On the other hand, the IDDT were very open about what they were doing, in particular that they were very interested in empowering diabetics. For example, they aimed to 'educate' diabetics regarding their rights. In particular, they explained how diabetics could obtain animal insulin, without going through their own doctor.

As the debate over the safety of human insulin progressed, those carrying out scientific work attempted to give the texts that they were disseminating credibility by mixing both scientific and experiential knowledge. Studies that were carried out later in the debate included not only biological evidence (such as changes in blood glucose levels), but also experiential evidence (such as a diabetic's awareness of approaching hypoglycaemia). By carrying out such work, it was hoped that care groups would view the studies with more credibility since they were taking account of the experiences of diabetics, albeit in artificial conditions. Scientific studies are to some extent artificial because they are unable to duplicate all the possible influences that a diabetic may experience in everyday life. Care groups also disseminated scientific evidence that used to give support to experiential evidence (this will be studied more closely in Section 7.3.3).

It should be clear therefore, that through the dissemination of texts an identity of the producing actor, and its relation to other actors, is formed. For example, some diabetics and doctors felt that the IDDT was too aggressive, while others believed that the BDA wasn't aggressive enough. It was due to these different identities that diabetics and other actors (scientists and doctors) allied differently with the two groups.

7.2 Constructing a tentative theoretical framework

As well as the identity of the actor who is disseminating texts, there are other factors which determine whether a text will be accepted. Michael (Michael, 1996) talks about ignorance, represented discursively, as a result of a division of labour. This kind of ignorance is constructed due to a belief that 'credible' others are 'looking after' and protecting one. Ignorance as a division of labour then, refers to elements of the cultural (and institutional) backdrop, and how they affect the interpretation of texts - these texts may include those that represented the ill-fitted network body. For example, although diabetics may have been aware that other diabetics were experiencing problems while on human insulin, there may have been a belief that the problems were not directly related to human insulin. Some actors believed that other actors (regulatory bodies) would not allow a dangerous drug to be marketed. Indeed, some diabetics claimed that the responsibility for problems on human insulin may rest with the diabetic, since they may not be carrying out adequate blood glucose monitoring.

Before I go on to look at some particular issues, it is worth pointing out that once texts are disseminated to actors, it is by no means the 'end of the life' of the text. I have already stressed that some texts that were circulated to diabetics, by the IDDT, were used by diabetics to illustrate to doctors that other diabetics were having similar experiences to themselves. Certain scientific texts were also drawn upon time and time again, such as the initial paper by Teuscher and Berger (1987). The collectivization of texts is therefore a continual process, in which texts are chosen to support an actor's position within the debate.

Once texts have been circulated, they are added to a body of texts which may be drawn upon by other actors in the process of collectivization. Collectivization is therefore always a dynamic and unfinished process. At any time actors may draw upon disseminated texts. Importantly, the texts that are seen as credible by actors may change as other texts are circulated. For example, as texts were circulated criticising the paper by Teuscher and Berger (1987) on methodological grounds, scientists tended to draw less (collectivize less) on this study. However, the IDDT still drew heavily on this study as it was, for them at least, the study that 'proved' that human insulin did cause negative effects.

In this section I have suggested one way in which the collectivization and dissemination of texts can be theorised. As an initial starting point I looked at the way a diabetic, experiencing disruption in their network body, produced texts to care groups which expressed their own experiences. These texts were then collectivized by care groups in order to formalise a position within the human insulin debate. Although I began with the collectivization of texts by care groups, I also stressed that other actors, such as those within the scientific and medical community, also collectivized texts. These collectivized texts, which may have included both experiential and scientific evidence, were then disseminated to other actors (e.g. diabetics and doctors) with the hope of persuading these actors of their 'facticity'.

At a number of points in this section I indicated that there were issues that I would deal with separately, it is to these issues that I now turn.

7.3 OTHER ISSUES

In this section I would like to deal with three issues that were alluded to in the previous section. In Section 7.3.1 I will look at how the various solutions presented to diabetics can be related to the network body. Then in Section 7.3.2, I will look at the set of minimal characteristics that allowed actors to be members, and remain within, the agonistic core set. Finally, in Section 7.3.3, I will look at some of the actions of care groups with members of the scientific core set.

7.3.1 Solutions to the Problems Experienced by Diabetics

I argued in Section 7.2.2 that the negotiations that took place within the doctor-patient setting affected whether a diabetic textualized their experiences. I argued that within the doctor-patient setting intermediaries were circulated which attempted to bring the diabetic to a negotiated settlement. In this section I would like to theorise these various solutions in terms of ANT and the concept of the network body.

There were a 'stock of solutions' that were available to the doctor in order to bring a diabetic to a negotiated settlement over human insulin. One approach was to redefine the 'state of' a diabetic's network body. In the regulation of human insulin various scientific studies were carried out to assess the safety and efficiency of human insulin. I argued in Chapter three, that these studies were carried out on subjects that could be

called exemplar bodies, since these bodies were acting as representatives of the diabetic population. These studies showed that human insulin was safe and efficient. However, in some cases individual diabetics did not act in the same way as the exemplar bodies. Since exemplar bodies should be seen as 'normal' diabetics, some doctors attempted to redefine those diabetics, who were having problems with human insulin, as being 'not-normal'. There were many examples of this in the literature. For example, where diabetics were defined, by their doctor, as having psychological problems or imagining their problems. In this case, doctors did not accept the 'facticity' of a diabetic's experiences, and denied the existence of a diabetic's symptoms. It may be possible, as Arksey (Arksey, 1998) has suggested, that such actions to 'discredit' patients, are a way in which a doctor attempts to disguise their own lack of knowledge.

In other cases, symptoms were verified and the 'facticity' of a diabetic's experiences accepted, but the symptoms were defined as being part of diabetes, in particular, that changes in an awareness of approaching hypoglycaemia were due to a patient's long duration of diabetes. These experiences were defined as 'natural', in terms of diabetes, and independent of the species of insulin being used. In these cases human insulin was still defined as unproblematic.

Another group of solutions was based on the verification of a diabetic's symptoms, and an attribution of these symptoms to human insulin. In this approach, solutions were taken in which the diabetic's network body was reconfigured within human insulin treatment. Approaches taken here included such actions as, reducing the dose of human insulin administered and encouraging a diabetic to carry out increased blood glucose monitoring. In this case, there was an acceptance that the existing pre-inscriptions of the diabetic, generated through the use of animal insulin, were inadequate for the healthy use of human insulin. These pre-inscriptions needed to be changed, or in ANT terminology, re-inscribed.

In these cases, it was through the circulation of intermediaries (such as medical advice) that the frontline was to be reduced (Akrich and Latour, 1992). Importantly, human insulin was still to be used, by accommodating it within the network body - the use of human insulin was being re-inscribed. Although human insulin may have been

problematized, it was by reconfiguring the user, to use human insulin 'properly', that a solution was to be found. Further, any changes that were made were defined as being those that may have been necessary with any therapeutic change, not just human insulin. For example, in Chapter 5, I described how reports of a loss of awareness were made when diabetics were changed from conventional animal insulin to highly purified animal insulin. In this case, as with the transferral to human insulin, changes were defined as 'fine-tuning'.

In these two cases, the intermediaries that were circulated by the doctor, in order to continue the use of human insulin, had been accepted by diabetics. However, as indicated in the previous section, it was by no means certain that the solutions presented by doctors would be on-goingly accepted by diabetics. Through coming into contact with other texts, such as from the IDDT, a diabetic may have questioned the solution presented to them, and thus may have questioned the management of their diabetes.

A third solution was to transfer the diabetic back to animal insulin. In this case, there was a verification of a diabetic's symptoms which were then attributed to human insulin, but the solution was not seen to lie within the human insulin network. Instead, human insulin was to be removed from the network body and replaced with animal insulin - it was not the user that was being reconfigured, but one artefact was being replaced by another within the network body. In this case, the pre-inscriptions gained through the use of animal insulin were accepted as still being credible and it was human insulin that was seen as problematic.

In the other solutions, the program that human insulin was superior may not have been accepted, but the diabetic did not have the resources to be aware of alternatives. In this final solution however, a diabetic may have had the resources to reject the program that human insulin was superior.

The fact that there were a number of possible solutions emphasises that actors, especially doctors, are subject to a number different texts. Some doctors were more likely to change their patients to animal insulin than others. This also suggests that there may have been an extended process through which a diabetic may have gone

through in order for their network body to come to settlement. Over time, as an actor, whether a diabetic or a doctor, received disseminated texts they may have become aware of diabetics who were experiencing similar problems on human insulin. This awareness may have altered the solutions presented by doctors, and the solutions accepted by diabetics.

In conclusion then, the circulation of intermediaries by a doctor may have brought a diabetic to a negotiated settlement with their body. Some diabetics did not have an antiprogram to human insulin, and accepted one of the solutions which brought them to a settlement with their body. Those diabetics who had an antiprogram to human insulin, as a result of disseminated texts, also came to a settlement with their body. the solutions however, rather different, entailing either a switch back to animal, or an 'extended' switch which included further textualization, the circulation of intermediaries, and the collectivization of texts within the human insulin network.

7.3.2 Agreement within the Core Set

As described in Section 7.2.3.1, actors within the scientific core set, define a set of minimal characteristics that groups within the 'generalized agonistic set' must follow to be part of a debate. In the case of the anti-vivisection debate, these characteristics were: rationality, non-violence, civility, and so on (Michael and Birke, 1994: 84).

In this study, the characteristics for entry into the core set are not easy to define. One possible criterion for inclusion into the core set can be deduced: members of the 'generalized agonistic set' had to act 'responsibly' towards diabetics. Yet what is meant by 'responsible' is not set. For the IDDT, responsible meant the general and uncensored spread of information about human insulin; for the BDA, 'responsible' meant not sharing all the information at their disposal, due to a concern of causing stress to diabetics. Yet it is possible to outline one specific meaning of 'responsible' that all appeared to agree on - that diabetics should not change their insulin without consultation with a medical practitioner. The doctor was seen as having a central role in the management of diabetes, because of their direct access to medical texts. To question whether the doctor had a role at all would bring castigation not just from the medical community, but also from the scientific community and governmental bodies, and importantly, from other care groups. For both the care groups then, negotiations

over solutions to a diabetics problems were to take place within the doctor-patient setting. Importantly, the IDDT did encourage the inclusion of various texts into these negotiations. For example, the IDDT suggested that diabetics bring evidence of possible side effects, in the form of the IDDT newsletter, to the doctor-patient setting.

This illustrates how some texts are 'channelled' back. In particular, it stresses that by using collectivized texts diabetics were able to illustrate to their doctor that there were other diabetics experiencing similar adverse effects on human insulin. It was hoped that through the use of such texts, diabetics would be able to illustrate to their doctor that there were other solutions than those that they were currently using.

The pharmaceutical companies can also be seen as acting responsibly. When scientific evidence was mounting that human insulin may cause adverse effects, but it was by no means conclusive, pharmaceutical companies changed their patient information leaflets to warn of possible changes in awareness of hypoglycaemia. Pressure to make this change had come from care groups and regulatory bodies. The companies can be seen as attempting to reduce any potential *frontline* with members of the core set, in particular, the regulatory bodies. Further, since this strategy kept the pharmaceutical companies in a 'favourable' position within the core set, it allowed them to claim that they were doing everything they could to warn diabetics of possible adverse effects. The stress here is on the 'possible', since the view of the dominant group was that human insulin was safe. There was no pressure from regulatory bodies to withdraw human insulin, and so pharmaceutical companies only had to advise on possible adverse effects.

Membership of the generalized agonistic set also necessitated that actors believed in the principle of a choice of insulin species. For example, the IDDT were concerned that the wrong impression was being given that it wished for all human insulin to be withdrawn. They clarified their belief that human insulin should not be seen as the insulin of first choice, but that human insulin should still be available. There were no scientific grounds for human insulin being withdrawn, and for an actor to claim that human insulin should be withdrawn, would give the impression that an actor was acting irrationally.

Pharmaceutical companies also accepted the need for the continued availability of animal insulins, and consequently, for insulin choice. However, Eli Lilly did not market an animal insulin in the UK, and Novo Nordisk were discontinuing a number of their animal insulins. Therefore, both Eli Lilly and Novo Nordisk left the 'possibility' of choice, that is the production of animal insulin, to other actors. Importantly in the issue of choice, pharmaceutical actors did not have to enable choice themselves, that is produce animal insulin, rather just support choice.

What is interesting about the issue of insulin choice is that the criterion for inclusion into the debate over human insulin was mutual. The core set consisted of scientists, commentators, regulatory bodies, doctors, pharmaceutical companies and care groups. It was not the case that those within the scientific set, such as scientists and commentators, were defining the criteria for inclusion into the generalized agonistic set, which consisted of care groups and pharmaceutical companies etc. Instead, the criterion of choice was agreed upon by all members of the core set. Any actor who disagreed with this criterion would not just be rejected by the scientific set, but by members of the generalized agonistic set as well. Therefore, on the issue of insulin choice, all actors can be seen as forming, what we might tentatively call, a 'generalized consensus-orientated set', where the consensus is focused on choice.

7.3.3 Actions of Care Groups with Members of the Core Set

In a number of instances, the care groups in this study attempted to question the boundaries between themselves, and the scientific and medical community. One way in which the boundaries were questioned was through the collection and dissemination of texts, as illustrated in Figure 7-1. Many texts questioned the authority of the studies that were carried out, or the exclusivity of scientific knowledge. Figure 7-4 shows three basic strategies of how care groups attempted to blur or question the boundaries between care groups and the scientific and medical community. These strategies were: care groups stressed the value of experiential knowledge; they became actively involved in how scientific work was conducted; and, they gathered scientific knowledge and enrolled scientific actors.

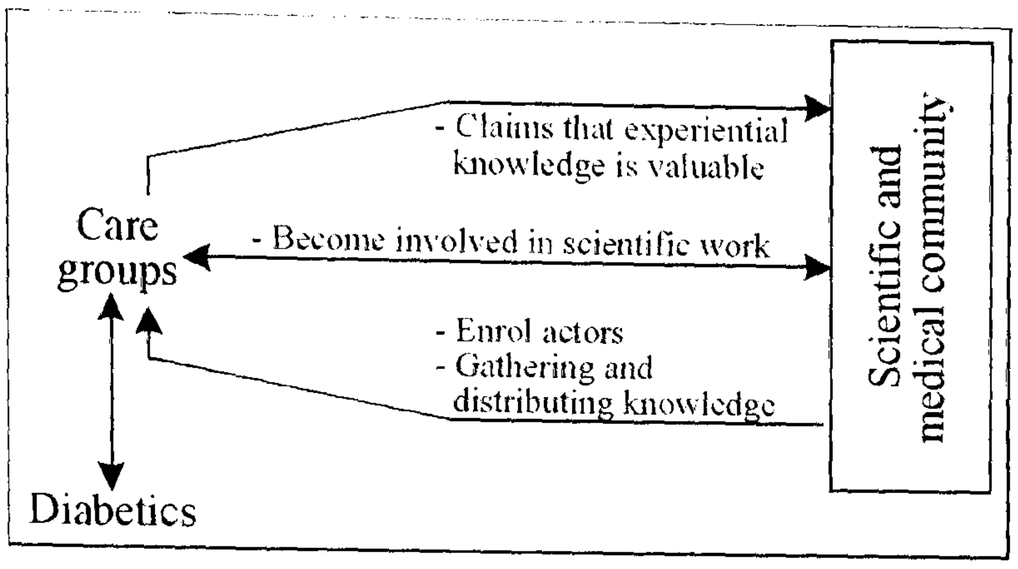


Figure 7-4: Care group strategies

In the concept of the core set outlined by Collins, the public are not seen as having the credentials to enter the scientific core set. However, in the new formulation of the core set the public do have a greater role. In controversies where the public are involved the public themselves should be seen as 'experts' (Arksey, 1998). This study can be seen as illustrating 'popular epidemiology', defined by Brown as:

> "...the process whereby laypersons gather scientific data and other information, and also direct and marshall the resources of experts in order to understand the epidemiology of disease."
>
> (Brown, 1992: 269)

It is not a simple task to be able to carry out scientific work. As Latour points out, dissent is not possible without "a huge accumulation of resources which permits the collection of relevant inscriptions" (Latour, 1987: 70). Although it is possible for care groups to collect scientific inscriptions, through reading scientific literature, it is less likely that care groups will be able to gather the many devices, artefacts and people (and the many other intermediaries) that enable the production of scientific knowledge. However, one way to counter this 'lack', is to stress and champion the credibility of other types of knowledge, in this case experiential expertise. By collectivizing and stressing the value of experiential narratives, it was hoped that patients' narratives would stand against the narratives from biomedicine (Hydén, 1997). Evelleen Richards has argued that the myth that clinical trials can produce definitive knowledge primarily serves the interests of professional legitimation. Instead, she argues for a more prominent role for the public in the decision making process (Richards, 1991). In this case study care groups were attempting to bring about this more central role, by claiming the value of experiential knowledge. As the IDDT pointed out, even if patients don't have scientific and medical knowledge, they have something valuable to offer - the experience of living with diabetes (IDDT,

1995a).

So care groups attempted to give a central role to experiential knowledge, by circulating collectivized texts detailing the experiences of diabetics on human insulin, to the scientific and medical profession (Figure 7-1). It was hoped these texts would 'educate' doctors, and ensure that patients suffering on human insulin would be 'properly' treated. Care groups were attempting to 'move' doctors into a position of higher experiential knowledge (Figure 7-2). Not only did the texts circulated by care groups describe the experiences of diabetics' network bodies on human insulin, they also described the experiences of these bodies within a number of networks. For example, they described how the experiences of some diabetics were dismissed by some doctors, and how other doctors claimed that animal insulins had been discontinued.

Care groups also attempted to affect the way in which devices, artefact and people were gathered to produce scientific work - they wanted to become actively involved in how scientific work was conducted. For example, the BDA funded a number of research projects and investigated the possibility of an ideal study. The IDDT had questioned the characteristics of the exemplar body that was used in various studies, arguing that, subjects were removed from the network in which they would normally be placed, meaning that the studies were 'overly artificial'. The IDDT also had letters published in the scientific media, criticising studies and suggesting how future studies should be carried out. The groups were therefore accepting the place of science as a key resource, but not accepting its "automatic authority in framing what the issues are" (Irwin and Wynne, 1996: 9). In relation to the core set, care groups were attempting to have active involvement in the work being carried out with the scientific core set.

Care groups also had contact with scientists. Actor network theory argues that just as scientists are able to enrol the public, so the 'public' are, in theory, able to enrol scientists.[42] Indeed, some groups set up by the BDA, consisted of scientists, as well as care professionals, members of the pharmaceutical companies, and diabetics. In a

[42] Although, as some have argued, these implications have not been fully developed (see Epstein, 1996).

similar way, Arthur Teuscher, one of the main members of the scientific core set, but not one of the core group, was closely linked to the IDDT. Such activities conferred a measure of scientific credibility to these care groups. The care groups were attempting to gain access to the core set.

As well as having contact with members of the scientific core set, care groups, and to a lesser extent individual diabetics who were experiencing problems on human insulin, also gathered and distributed knowledge that was produced within the scientific core set. By assessing these texts, care groups not only attempted to become in some degree competent themselves, but by distributing versions of these texts to other diabetics, they attempted to confer competence onto other diabetics. The 'other' versions, distributed by care groups, 'selectively' mixed both scientific and experiential knowledge. Importantly, it was because a group of actors felt that the BDA were not adequately representing diabetics, that they constructed their own network to form the IDDT. They then became competent themselves. This is one element of popular epidemiology, where medical and scientific knowledge is tested by bringing it out into the public sphere for debate (Habermas, 1989). In particular, scientific work was compared with the 'real life' experiences of diabetics. The articles produced by the IDDT were therefore comparing scientific knowledge with experiential knowledge.

These actions, by the care groups, were an attempt to reduce the exclusivity of scientific knowledge. On the one hand, care groups were arguing that experiential knowledge was valuable, and on the other, they were selectively utilising elements of science. The aim was not only to break the boundary between 'lay' and 'expert' knowledge, but also to reassess the value of exclusively relying on scientific knowledge.

7.4 DRAWING OUT THE MAIN FINDINGS

It is now time to draw out some of the main findings of this thesis. As human insulin was being developed, existing insulins were problematized and the links that various actors, such as the medical profession, had with these existing insulins were broken. In the most part, the translations that occurred through the development and production of human insulin were successful, and human insulin came to be seen as

the superior insulin.

It was initially argued that human insulin would be able to slot into the existing diabetic network body. It was believed that for human insulin to be unproblematically used by diabetics, there would be no need to change the existing pre-inscriptions that a diabetic had gained through the use of animal insulin.

However, for some diabetics existing pre-inscriptions were not adequate for the unproblematic use of human insulin, and as a result they experienced severe biographical disruptions in their once settled body. These disruptions led to a crisis in the identity of human insulin. This demonstrated that the identity and meaning of an artefact, in this case human insulin, is never fixed. Negotiations are constantly taking place in which the meaning of an artefact is re-negotiated by a number of actors. For example, for some diabetics human insulin was not a 'modern' and 'superior' insulin, instead animal insulin was superior to the more 'technologically advanced' human insulin. Similarly, individual doctors and scientists also questioned the superiority of human insulin.

Another important finding concerned the ways in which actors attempted to have their own program of action accepted by those actors who had a contradictory program of action. For example, when a diabetic wished to transfer back to animal insulin, it may have been necessary for the diabetic to circulate intermediaries in order to reduce the frontline that existed between the doctor and the diabetic. Similarly, when a doctor believed that human insulin was the 'best' insulin, the doctor may have circulated various intermediaries, such as educating the diabetic, in order to reduce the frontline in which the body was unsettled while on human insulin.

Hopefully I have also demonstrated that the body should be seen as being 'made up of' many different actors. I used the concept of the network body to illustrate this point. In particular, I have shown that there are many influences on the way in which a diabetic, or any actor, makes sense of the world, and in particular, makes sense of biographical disruptions. For example, as a diabetic became aware of the experiences of other diabetics, they were able to understand their own experiences.

Importantly, it is negotiations within the network body that brings the body to

settlement. In many cases, diabetics rejected certain knowledges used in negotiations that attempted to bring the body to settlement, not least because their network body was in possession of alternative knowledges. For example, some diabetics rejected the claim, by their doctor, that animal insulins had been discontinued because they were aware that some animal insulins, in fact, were still available. However, other diabetics would have accepted that animal insulins were no longer available, because their network body was comprised of different actors and relations.

Within this thesis I have also shown that texts from individuals become collectivized, and it is these texts that are circulated to key actors. Within this study there is a sense in which texts become accumulated by care groups, who then generalise from these texts. Care groups very rarely quantified the texts which they received, instead care groups claimed that they had received 'many letters', but not the exact number. Arguably, the vagueness of such statements is not problematic because of care groups' authority as the representatives of diabetics.

The texts that actors circulate attempt to persuade others, within the core set (both the scientific and the agonistic set), of their facticity. For example, the IDDT were attempting to persuade the medical profession, particularly regulatory bodies, that human insulin produced adverse effects in some diabetics. On the other hand, some scientists circulated intermediaries which claimed that human insulin did not cause adverse effects. For the IDDT, the reality was that human insulin was unsafe for some diabetics, but for the scientists, the reality was that human insulin was equal to animal insulin.

For actors, the collectivization of texts did not just involve the use of texts from within their own ring of the core set. Instead, in order for an actor, within one ring, to persuade an actor in another, it is necessary to bring texts together from different parts of the core set. The potency of texts therefore lies in the ability of actors to combine texts from a number of sources, such as results from scientific studies and texts which describe the experiences of patients. This relates closely to the argument in ANT that durable networks are composed of actors from a number of disparate networks. However, the texts that are being collectivized have to be perceived by the receiving actors as important and authoritative.

7.4 Drawing out the main findings

It is also important for those actors in the agonistic set to form allies with members of the scientific core set. For example, the IDDT formed links with Arthur Teuscher. Actors within the agonistic core set also form links with other members of the agonistic set, for example, the BDA had links with the pharmaceutical companies. However, these links are reciprocal. Arthur Teuscher was able to gain much needed anecdotal evidence from the IDDT to support his scientific claims, and the pharmaceutical companies, through the BDA, were able to represent themselves to diabetics as being concerned and flexible actors.

As a result, the formulation of the core set, as outlined in Figure 7-3, is (inevitably) simplistic. Actors do not simply exist in one ring and one ring only. Instead, actors move between rings depending on who they are attempting to persuade. The other important point is that actors within rings of the agonistic or scientific set are not necessarily homogeneous. For example, some actors within the scientific set identified with the IDDT and others didn't.

One important finding of this study was that the notion of the core set should be supplemented by a 'consensus-orientated set'. This new set not only crosses the scientific and agonistic set, but it is a precondition of membership of the core set that all members support a particular position. In this case the precondition was that actors should support a choice of insulin species, although actors did not have to be actively involved in the production of animal insulin.

As a final note, throughout this study I have been aware that it is not possible to produce hard and fast descriptions of the actors involved. Not only are actors constantly slipping and merging, but actors simultaneously belong to a number of different networks. For example, doctors are members of different networks; the general view within the medical community was that human insulin is safe and efficient, yet due to contact with diabetics, doctors may be led to think otherwise. Another example is the position of some medical scientists. On the one hand they carry out medical work, and at the same time may have close links with care groups, such as Teuscher and the IDDT. As a consequence of this movement, the core set should be viewed as having a degree of fluidity.

7.5 SOME IMPLICATIONS OF THE HUMAN INSULIN CASE

In this section I would like to suggest some possible practical implications of my research. As argued in Chapter 3, the regulation of human insulin occurred relatively quickly compared with other drugs. There were a number of reasons for this: a great deal was already known about insulin; human insulin was the first drug for human use to be produced using genetic engineering and so human insulin was seen as 'trial run' for the genetic engineering of other drugs; and, there were concerns that supplies of animal insulin would not meet demand. It can be argued therefore, that regulatory bodies were under social pressure to regulate human insulin quickly. In retrospect it can be argued that adequate clinical trials had not been carried out, before human insulin was regulated. More careful consideration should be given to how drugs are to be used in 'practical' or 'real' situations. Criticisms of some of the studies that were carried out during the clinical testing of human insulin claimed that the studies were 'overly artificial'. The main criticism was that the majority of the clinical studies concentrated on biological factors, rather than the experiences of diabetics.

I would therefore suggest that more careful assessment of the claims of 'interested' actors be made by regulatory bodies. However, we live in a commercial world where companies do compete to be able to produce the most technologically advanced drugs, so there are bound to be pressures from these actors to produce and regulate 'novel' drugs. It is my belief that this commercial pressure affected the speed by which human insulin passed through clinical trials. Although perhaps impractical in the commercial world, it may have been more prudent for a small number of diabetics to have been prescribed human insulin as a 'trial run', instead of the mass transfer that actually occurred.

Of course, just because a particular drug is available it does not mean that doctors have to prescribe these drugs. However, since it is likely that pharmaceutical companies have invested large amounts of resources to produce new drugs, they are likely to advertise these new drugs to doctors above existing ones. In the case of human insulin, some doctors were also under the impression that existing animal insulins had been withdrawn, and so transferred their patients to human insulin. Due to these factors, it may be wise to reconsider the ways in which doctors become aware of current treatments.

7.5 Some implications of the human insulin case

On transferring patients to new, but similar, pharmaceutical drugs it should not be taken for granted that the treatment will go smoothly. This is particularly the case when the new drug bears a close resemblance to 'natural' bodily products. One of the important points in this study was that when diabetics were transferred to human insulin, after using animal insulin for a long period of time, many diabetics experienced problems. In these cases, closer attention should be given to these patients. Linked to this, is a warning that just because a drug appears to be more technologically advanced, does not mean that patients will feel the same.

Another consideration is the information that is available to patients. Although patients receive basic descriptive information on the drugs they are following, through patient information leaflets, this is often of a very low level. Indeed, in this study, it was claimed that the information warning of possible side effects was more aimed at professionals (and in some cases removed from drug packaging by pharmacists). Patients should also be clearly warned when changes are made to their drug treatment, or when changes are made to patient information leaflets. In this study, some diabetics believed that they had not changed their insulin species when in fact they had. In some cases diabetics were not told of these changes by their doctor, and in others their pharmacist had changed then without consultation with either the patient or the doctor. One reason for this was the similarity in the names of the insulins. Many insulins simply had 'human' placed in front of their existing name. This evidently caused some confusion. Although Novo Nordisk made changes to the names of their human insulin in 1996 to avoid this confusion, it would have been preferable for this change to have been made when human insulins were first marketed. Where changes in drugs are made it may also be prudent to issue clearer warnings that the drug has changed. For example, similar drugs could be colour coded, in this case so that diabetics would be aware that they were using human and not animal insulin.

Diabetics also received information from the BDA and the IDDT. However, one criticism of the BDA was that it did not appear to be representing diabetics who were experiencing problems on human insulin, when in fact they were carrying out work 'behind the scenes'. The BDA claimed that it did not want to worry diabetics unnecessarily, and so refrained from describing their actions. In retrospect, the BDA

have argued that this policy was mistaken. I would suggest that other care groups should learn from this mistake, and inform others of the work that they are carrying out. Care groups should give more credit to 'interested publics' when outlining any possible controversy. By doing so, it may avoid actors being subjected to 'sensationalist accounts' from the popular media, which may only be reported when there is a greater body of evidence against a particular drug. Such sensationalist accounts are far more likely to worry interested publics, than evidence that is presented, by care groups, as a particular debate is unfolding. This is particularly the case with the management of diabetes, since diabetics are encouraged to become actively involved with the management of their diabetes.

One of the notable findings of this study was that doctors differed in the solutions that they presented to their patients. For some doctors, changes were made to a diabetic's management of diabetes within human insulin treatment, for others the solution was to transfer their patients to animal insulin. It was not necessarily the fault of doctors that patients were not transferred back to animal insulin, since the dominant view was that human insulin was safe. It may therefore be useful to consider changes that can be made to the way adverse reactions on drugs are reported. If the pathways by which doctors became aware of adverse reactions were more flexible, then it is likely that so too would the dominant view.

When those diabetics who were experiencing problems on human insulin reported their problems to their doctor, the diabetic was then treated as an individual case. Although doctors had the ability to report the adverse effects of human insulin to the Medicines Control Agency, through the Yellow Card Scheme, this was very rarely done. However, it has been suggested that patients should be able to report these adverse effects themselves. One effect of this suggestion could be that patients feel that their experiential knowledge becomes valued. Although there may be some problems with this suggestion, such as what the definition of a negative effect is, it appears to me that this suggestion should be taken seriously.

On a more practical level, I would also suggest that in future research groups should join together to carry out an 'ideal study' early on in a controversy. However, the notion of the ideal study should be broadened, not just to include those actors within

the scientific set, but also those within the agonistic set. The criterion by which an ideal study is conduct should include contributions from a range of experts, such as from care groups. The knowledge possessed by care groups is important since they will be able to inform research teams of the practical implications of any study. In this case study, an ideal study was only suggested late on in the controversy. Although speculative, I suggest that an ideal study may have brought the human insulin debate to closure more quickly. One reason for this is that members of the insulin debate would more likely to be in agreement as to the way diabetics should be treated when on human insulin. This may then have avoided diabetics being presented with a number of solutions, before an adequate one was found. Such an approach may have also helped the credibility of science, since care groups would have been aware that scientists were doing their best to help sufferers.

However, one word of warning has to be voiced before we accept that an 'ideal study' would have conclusively 'proved' whether human insulin did or did not cause negative effects. A study is conclusive when actors agree that a particular study is definitive. As indicated in Chapter 5, there was much disagreement on the nature of an ideal study, such as the size and method of the ideal study. Therefore, although, in theory, an ideal study may have brought some closure earlier on to the human insulin debate, an ideal study is, inevitably, elusive.

7.6 SHORTCOMINGS AND RECTIFICATIONS

As with any piece of research, there are a number of shortcomings of this work that I have become aware of. In this section I would like to describe some of these shortcomings.

In terms of the collectivization of texts, it may have been useful to study, in more depth, the process by which collectivization occurred. In particular, it may have been productive to study the choices that were made by the BDA and the IDDT when they were deciding which texts, in particular letters, were to be included in their magazines. It would also have been useful to look at the choices made by care groups as to which 'scientific data' was to be included in their magazines.

Early on in the beginning of this research I took the decision to use published texts as

my data source (see Appendix 1). Therefore, any conclusions made, are dependent upon those diabetics who produced texts. However, it may have been useful to conduct interviews with diabetics who had experienced problems on human insulin. With data from these interviews, it would have been possible to compare the 'textualized controversy' with these very personal accounts.

Interviews could also have been carried out with doctors. An image may have been presented in this thesis that doctors were one of the 'villains' in the human insulin debate, because they did not always transfer diabetics who were experiencing problems on human insulin back to animal insulin. However, as pointed out in this thesis, doctors were subject to pressure from the pharmaceutical companies to prescribe human insulin. By interviewing doctors, I would also have been able to study in more detail the differing information that was available to doctors. These interviews would have revealed the factors which affected the prescription of human insulin, and the presentation of solutions to diabetics.

7.7 FUTURE RESEARCH

As I have carried out this case study there have been a number of areas that I could have investigated further, however due to limitations of space and direct relevance, I have refrained from doing so. In this section I would like to point to these areas, and to other wider areas where future research could be carried out.

One particular direction of future research is looking at the human insulin debate in different countries. For example, in America it was argued that there was not a controversy over human insulin, even though there was a similar transferral to human insulin. This led one author to ask:

> "In the United States, the 'land of litigation,' the problem does not seems to exist, or if it does it is of little consequence and not reported. Why should there be such a transatlantic difference? There is no obvious answer...The lack of an American experience of this problem calls into question its true validity."
>
> (Walker, 1991: 1265-1266)

One suggested reason for the difference was that in America there were warnings printed on human insulin packaging in 1989 (Wolff, 1992). However, some have argued that diabetics in America are experiencing problems, but the authorities do not

admit that there is a problem. It is also argued that another reason why there is not a debate in some countries (such as Holland, Australia and America) is because these countries do not have a method of collecting evidence of adverse effects, or that patients are not being listened to (Kiln and Sugarman, 1992).

Another area of future research could be in looking more closely at the role of mediating others. In this study I have only briefly indicated that other actors, such as family and friends, do have a role in making diabetics aware of changes in their personality, while on human insulin. In some cases, family and friends, became aware, through the media, of other diabetics who were experiencing similar problems on human insulin to their relative or friend. It would be interesting to study the role of these actors more closely.

One of the interests of this thesis has been in looking at what happens when diabetics meet with doctors. Future research could be carried out looking more closely at what happens within the doctor-patient setting. In particular, it will be interesting to look at how doctors re-interpret expert knowledge due to coming into contact with experiential knowledge. Work in this area would extend my formulation of scientific and experiential knowledge (Figure 7-2), to map the process by which movement from one quadrant to another occurred.

One interesting feature of this case study was that when human insulin was introduced it was expected to replace existing insulin treatment. Importantly, this was to be done without the need for changes in the way a diabetic carried out the management of their diabetes. By looking at similar cases, where one drug was replaced by another, I would be able to see how ideas behind the network body could be applied further. It would particularly interesting to look at other genetically engineered drugs.

Human insulin also aimed to benefit patients by reducing complications. It was therefore seen as a technological advancement. It would be interesting to look at other drugs that are seen a technological advance, for example, the MMR vaccine.

There are also some specific theoretical areas that could be elaborated. In Chapter 3 I argued that the two main pharmaceutical companies, Eli Lilly and Novo Industri, had multiple strategies concerning the development of new insulins. Eli Lilly were

stressing the need for human insulin (overt strategy) while also developing a purified porcine insulin (covert strategy), and Novo Industri were arguing that their purified porcine insulin prevented diabetic complications (overt strategy), while also developing a human insulin (covert strategy). It would be interesting to study whether this was the norm within pharmaceutical companies.

Another area of further theoretical interest would be in developing the idea of the core set. I described above that within the core set there was evidence of a 'generalized consensus-orientated set' which revolved around the issue of insulin *choice*. Rather than the scientific core set defining what characteristics were necessary to be a member of the` agonistic generalized set, there was a mutual consensus by all members of the core set. It would be interesting to investigate whether this was the same in other controversies, in particular what happens when some members of the core set veer from this mutual consensus. It would also be interesting to study what conditions ensure that choice of a particular drug is maintained. In particular I would be interest in looking at cases where the availability of an 'old' drug is maintained, even though a new drug is supposedly superior. We could outline a number of factors: commercial viability, scientific necessity or patient demand.

Finally, it would also be interesting to study more closely the disagreements within the rings of the core set. I have already argued that there were differences in the way in which the BDA and the IDDT conducted themselves in the human insulin debate. It may be productive to look at how certain actors, within the rings of the cores set, become marginalised.

8. APPENDICES

APPENDIX 1 - METHODOLOGY

By glancing at any handbook on methodology we soon become aware that there are a large number of possible approaches that a researcher can adopt. Approaches that can be used include: observational methods, interviews, questionnaires and unobtrusive methods (Robson, 1993).

In this thesis I opted to use an unobtrusive method. My main body of evidence was in the form of documented evidence. The evidence that I collected related to two periods. The first was between 1976-1981, which texts detailed the development and introduction of human insulin, and a second, between 1982 to 1999, which described the problems experienced by diabetics on human insulin. However, it should be pointed out that after 1992 the number of scientific articles published on the human insulin debate did diminish significantly, since the scientific community had come to some agreement.

The documented evidence can be divided into two broad types: scientific/medical and 'lay'/experiential. Scientific and medical evidence came in a range of scientific and medical journals, such as the *British Medical Journal* and *The Lancet*, and were in the form of formal studies, review articles and letters. Experiential and 'lay' evidence came from those documents that were aimed at diabetics, mostly from *Balance* - the magazine of the British Diabetic Association - and the Insulin Dependent Diabetic Trust's newsletter. Experiential/'lay' evidence also came from newspaper articles. What all the sources had in common was that they were, in theory, public documents, that is, they could be accessed by anyone. Most libraries hold copies of the major science journals, and anyone can subscribe to *Balance* or obtain copies of the Insulin Dependent Diabetic Trust's newsletter.

When initially approaching the human insulin debate my first step was to form a database of articles. Using two bibliographic databases (Bids and Medline) I gathered references to a large number of scientific and medical articles. By reading abstracts I identified documents that were relevant to my case study, and then, using the university library I photocopied the important articles. This systematic search formed the backbone of my scientific evidence. While reading the selected articles I familiarised myself with the human insulin debate and I identified which of my

selected articles were most important. While reading the articles I also identified articles that were not included in my initial reference list, but appeared to be important. In the process of this, I soon became aware of the key authors, papers and issues within the human insulin debate.

In order to collect experiential and 'lay' evidence I contacted two care groups. I made an appointment to meet with members of staff at the BDA, and was also able to read through, and photocopy, articles and letters in back issues of *Balance*. I also contacted the Insulin Dependent Diabetic Trust and obtained back issues of their newsletter. Added to this source, I referred to newspaper indexes.

Since my interest was in the human insulin debate within the United Kingdom, all experiential and 'lay' evidence related to the debate within the UK. In terms of scientific and medical evidence some studies were conducted in other countries, notably Switzerland, but because their content was relevant to the human insulin debate, this evidence was referred to in the study.

By using these two types of documentary evidence, scientific/medical and 'lay'/experiential, I was able to build up a picture of the human insulin debate. The use of multiple documentary sources meant that I was able to corroborate certain features of the human insulin debate. However, as well as corroborating 'facts', the use of multiple sources allowed me to draw out conflicting features of the human insulin debate. In all this, my aim was to build up a picture that was not biased toward one particular point of view, whether of the medical community or care groups. The other important point was that I was able to assess which issues were important to which actors, and further, how actors responded to the issues that were deemed important by other actors.

Throughout the study I kept in mind that the documents that I was studying were written with specific purposes in mind. For example, evidence from the IDDT aimed to stress the 'reality' of diabetics' negative experiences on human insulin. It was also important to identify the position of authors within the human insulin debate. For example, Teuscher and Berger believed that human insulin caused negative effects in some diabetics, and as a result, any scientific paper written by them had to be read

with this in mind.

My analytical strategy was to examine critically evidence from different networks. By investigating the evidence, in the form of documents produced by different networks, I have been able to reconstruct the human insulin debate. When approaching the documented evidence I adopted a principle of symmetry, that is, I used the same conceptual tools to explain 'true' and 'false' beliefs. The principle of symmetry is one of the guiding principles of the sociology of scientific knowledge, and requires researchers to "bend over backwards to consider the arguments of scientific 'underdogs'" (Epstein, 1996). However, my approach to symmetry went further. In keeping with ANT, I adopted a neutral vocabulary to understand the conflicting roles of the actors, both human and nonhuman, involved in the debate.

The thesis shows the ways in which actors attempt organised the important issues in the human insulin debate. It could be argued that an interest-based conceptual framework (Shapin, 1979; Barnes and MacKenzie, 1979) would have been appropriate for this study. The interest approach argues that, "knowledge-claims made by scientists will embody or be informed by certain social, sometimes political interest" (Webster, 1991: 16). Space does not allow a full discussion of the interest approach here, but see Woolgar (1981), Barnes (1981) and MacKenzie (1981) for two possible positions. Rather than go into the intricacies of the interests approach I wish to indicate why an actor network approach was more appropriate for this case study.

One strong objection to the interest approach is that it pre-defines a set of 'background' interests. By ascribing interests to groups, which are then used to explain the actions of actors, researchers attribute a 'special (stable) status' to a backcloth of prior interests (Callon and Law, 1982). Importantly, social interests are "temporarily stabilized outcomes of previous processes of enrolment" (Callon and Law, 1982: 622). At any time an actor's interests are subject to change since other actors may be attempting to enrol actors. From this point of view, interests (and other categories such as desires, motives and wishes) are not in the background, but rather, are used to define the roles of actors within a particular social world (Callon and Law, 1982). The role of a researcher should be to describe the ways in which some stability, however temporary, is achieved through the process of enrolment.

This then, is the main analytical difference between an interests and actor network approach. Whereas an interests approach begins with a predetermined 'backcloth' and set of interests, an actor network approach studies the way in which the interests of actors are transformed. As a result, the interests of actors are revealed in the action of actors, and thus, researchers need to 'follow the actors' of every new case study.

The aim of my analytical strategy was to gain an in-depth understanding of the human insulin debate in order to understand the key events in the debate. Rather than using quantitative data analysis, my approach was to immerse myself within the data rather than reduce it to abstract codes and clusters. The method is therefore one in which I followed the actors and their negotiations, even if this was at a distance, through their texts. In Chapter 3 this was carried out in a more or less chronological manner: I first outlined the reasons behind the development of human insulin; I then went on to describe the progress of the research groups; and then the commercial development and introduction of human insulin. The aim of Chapter 4 was to set the scene for future chapters by outlining the initial use of human insulin, and was therefore presented in a descriptive manner. Chapters 5 and 6 on the other hand, were organised around a comparative structure, where I described issues of the human insulin debate from two perspectives: Chapter 5 concerned itself with issues within science and the pharmaceutical companies, and Chapter 6, looked at issues deemed important by diabetics and care groups.

Although published sources may only tell part of the story, by using a variety of sources, from the influential to the less well known, I believe that I have been able to produce a reasonably comprehensive and accurate representation of the human insulin debate. Further, by using different forms of narrative, such as scientific studies, editorials, articles and published letters, I have been able to produce an account of the human insulin debate from a number of positions.

Problems do exist with documentary evidence, and as a result, it could be argued that, in order to produce a rounded account of the human insulin debate I should have carried out interviews to add to the documented evidence. Some of the problems associated with the use of documented evidence include: their retrievability may be low due to access being blocked; the documents may be biased; or, the documents

may be inaccurate. On the whole, these problems did not arise in this study since I was interested in how the human insulin debate was played out in the 'public' domain - that is, it is possible for any individual to access the documents. The other important point is that there was an abundance of documented evidence from a large number of resources, and as a result, any possible document inaccuracies could be overcome by using multiple sources.

Another reason why documented evidence was preferred was that, on the whole, the human insulin debate was played out between 1982-1992. Within the scientific community some closure of the debate had occurred in that scientists, and those in the medical community, had come to an agreement that diabetics expressing problems on human insulin should be transferred back to animal insulin. One of the potential problems with using interview data is that retrospective accounts might be directed to issues in the present, though of course, it could be argued that with time, more 'rounded' or less 'charged' accounts from the main actors might have been forthcoming.

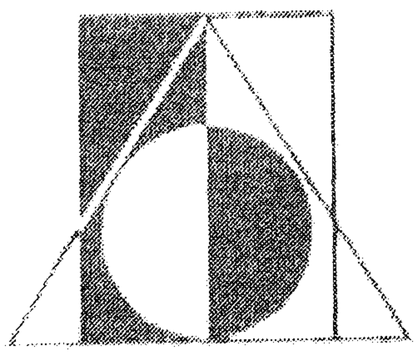
Finally, it is worth assessing the advantages and limitations of using textual analysis to explain the network body: that is, using textual analysis to decide what 'makes-up' the network body. Some of the main advantages have already been discussed in this appendix, namely those associated with the accessibility of texts. The other important point is that this study focuses on the circulation and textualization of texts, and as a result, the make-up of the network body that is represented in texts. Ironically, this leads me to a limitation of using textual analysis to explicate the network body. I have described the network body as represented in texts, and is therefore, to some extent, a sanitised version of the network body. Direct contact with diabetics, scientists and doctors may have produced another formulation of the network body. In particular, such an analysis may have revealed the different emphasises that different actors place on entities within the network body. For example, diabetics may place more emphasis on the role of close family members than scientists would, especially when a diabetic is experiencing problems with the management of their diabetes. One way in which such an analysis could be approached is by talking to individuals, and bringing out the elements that they feel are important to them in the management of diabetes.

APPENDIX 2 - LEAFLET - 'PEOPLE WITH DIABETES AND CHANGES IN HYPO WARNINGS'

• BRITISH DIABETIC ASSOCIATION •

People with Diabetes and Changes in Hypo Warnings

There has been a lot of publicity in the newspapers and on TV recently about human insulin. This has understandably caused a lot of distress for people living with diabetes. We hope that this leaflet will be helpful and reassuring.



WHAT ARE THE PROBLEMS?

Some people are saying that their hypo symptoms have changed. Instead of having their usual symptoms of sweating, trembling, hunger, weakness, anxiety and palpitations they find their symptoms have changed to lack of concentration, confusion, and personality change, and it takes some while to learn to recognise the new symptoms. Others find that they have no or very little warning of hypos or that they happen so quickly they do not have time to take action. As a result they wake up and find themselves being given sugary food or drink. They cannot remember going into the hypoglycaemic.

This is an extremely worrying and frightening situation for anyone living with diabetes because people feel they are no longer in charge of their lives. They are afraid of losing their jobs and becoming a nuisance to others. It should be emphasised that all these problems with hypoglycaemia can occur in people on any type of insulin.

WHY SHOULD THESE PROBLEMS HAPPEN?

Loss of warning symptoms of hypos is not a new problem. Even before human insulin was introduced some people with diabetes had this problem. Many research studies have been carried out in Europe during the past 3 years, but no one can explain exactly what is happening or why some people are affected when others are not. Improving control of diabetes can cause changes in hypo warnings. This is because if blood sugars are usually kept at a low level there isn't far to go before a hypo occurs, and there may be loss of hypo symptoms. Some people who have had diabetes for a long time unfortunately lose their warnings anyway, partly because of the effects of long term diabetes on their nervous system.

WHAT IS THE DIFFERENCE BETWEEN HUMAN AND ANIMAL INSULINS?

Animal insulins are extracted from the pancreas of pigs or cattle and they do not have exactly the same chemical make up as the insulin which is normally produced in the human body. Human insulin is not prepared from the human pancreas. Scientists have been able to find a way to get bacteria to make insulin which is chemically exactly the same as the insulin made in the human body. So when this type of insulin was first produced it was natural to expect that it would suit people better than animal insulin. About 8 in every 10 people who use insulin are on human insulin.

IF I HAVE LOST MY HYPO WARNINGS WHAT CAN I DO ABOUT IT?

Do not stop your injections! Remember that insulin keeps you alive and there is no substitute for it.

Check out your diabetes control by doing frequent blood tests and discuss the results and management of your diabetes with your doctor or diabetes specialist nurse. If adjustments to management do not help THE ANIMAL INSULINS ARE STILL AVAILABLE, and if you need to change back to them you can do so. Discuss this with your diabetes doctor or diabetes specialist nurse. The BDA can tell you which animal insulins are available and the correct name for them if necessary. Many people with diabetes who are treated with human insulin and have been experiencing no problems are concerned that their warning symptoms may change in the future. There is no guarantee that your warning symptoms will not change with time. However, only a small percentage of people experience this problem and it is unlikely that human insulin will be the cause so there is no reason to change your insulin.

WHAT HAS THE BDA DONE TO HELP PEOPLE ON HUMAN INSULIN WHO ARE HAVING PROBLEMS?

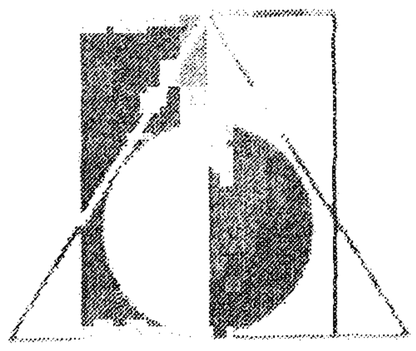
1) In 1989 the BDA set up a Human Insulin Working Party of experts in diabetes. Some are people with diabetes and others are doctors and scientists or diabetes specialist nurses. The Committee on Safety of Medicines has a representative on the Working Party. The Working Party has listened very closely to the problems and studied them, and recommended carrying out research into how people react to human and pig insulin to see if there is any difference. Normally research takes a long time to commission and set up but this research was commissioned and set up within 3 months of an advertisement appearing in the Medical Press. The BDA is paying for the research.
2) Companies who make insulin have assured us that animal insulins will not be withdrawn.
3) BDA staff have answered many thousands of enquiries from insulin users and their families and from doctors and nurses about human insulin and its effects. In 1988 the staff sent a questionnaire to people who had been put on to human insulin and the results were published in the BDA magazine Balance. Quite a lot of people had had some difficulties over the transfer. In many instances these were due to a lack of understanding of the change to a new insulin or to other in the way diabetes was managed. At that time BDA Medical Advisor advised that people should be aware of the insulin they are using and that any change in insulin should be fully explained by their medical adviser.

PROPOSALS FOR FURTHER ACTION

Because mounting uncertainty felt by so many people with diabetes the BDA is redoubling its efforts to answer important questions about hypoglycaemia and loss of warning symptoms outlined in this leaflet.

The BDA Executive Council has pledged £100,000 to be made available to fund a Loss of Warnings (LOW) Task Force which will allow for:

1) Further resources to be given to the BDA helpline
2) Preparation of information sheets for all professionals involved in diabetes care - consultants, general practitioners and diabetes specialist nurses - containing information about the background to hypoglycaemia warning symptoms and proposed treatment schedules;
3) The possibility of future research studies to be examined.



A charity helping people with diabetes and supporting diabetes research

BDA, 10 Queen Anne Street, London W1M 0BD Telephone: 071-323 1531
October 1991

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