THE INTERNATIONAL POLITICS AND OPERATIONAL CONTROL OF POTENTIALLY DANGEROUS TECHNOLOGY: A CASE STUDY OF RECOMBINANT DNA

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FOR MY FATHER

His encouragement will be

sadly missed.

CONTENTS.

ABSTRACT.

The focus of this thesis is on the international features of the case of recombinant DNA. A transnational model of decision-making is applied to the development and implementation of safeguards which followed the authoritative public announcement by eleven leading microbiologists that certain new experimental techniques involved conjectured hazards. The case is taken, in an historical context, as an example of a new technology displaying 'low probability, high consequence' risks emphasising the international uncertainty involved.

A multilevelled systems approach is adopted to link organisational decision-making analysis to concepts of transnational political relationships (developed from K. Deutsch, R. Keohane and J. Nye, J. Burton, H. Simon, R. Cyert and J. March, W. Evans, and G.T. Allison). The study stresses the importance of operational safeguards developed in the United States and the United Kingdom, illustrating their roles as models, often borrowed and modified elsewhere. In all, some thirty-two states and eleven international organisations are covered, emphasising communications linkages and sources of information.

Uncertainty concerning potential hazards led to a transnational incremental approach to the process of decision-making as it affected the development and operationalisation of control options designed to reduce risk. Satisfactory rather than optimal strategies resulted. It was apparent that the limitations faced in 'rational' assessments assisted the growth of political debate in an overall climate of empirical uncertainty. Scientists proved to be well organised internationally, and on the whole retained a dominant input into the transnational decision-making, despite the general level of political controversy. The case stands as an object lesson in the problems associated with internationally assessing uncertain hazards (and benefits) despite the presently accepted perception that risks are somewhat less than originally conceived.

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INTRODUCTION

> "It is only by means of the sciences of life that the quality of life can be radically changed. The sciences of matter can be applied in such a way that they will destroy life or make the living of it impossibly complex and uncomfortable; but unless used as instruments by the biologists and psychologists, they can do nothing to modify the natural forms and expressions of life itself. The release of atomic energy marks a great revolution in human history, but not (unless we blow ourselves to bits and so put an end to history) the final and most searching revolution." 1

Aldous Huxley made this observation in 1946 in a foreword to his book, Brave New World, first published in 1932. Of interest is his inference of a future biological revolution capable of radically altering the quality of life, not least through its modification. Huxley brought attention to hypothetical social, political and philosophical consequences of such a revolution. In recent years some have described the developments known as recombinant DNA techniques or genetic manipulation in terms akin to Huxley's forewarnings.[2] Hailed as something of a scientific revolution, the techniques of recombinant DNA heralded a very marked advancement in the ability of man to manipulate DNA, the controlling substance of all life.[3] Whatever the long-term future holds for extrapolative developments of genetic manipulation, there will undoubtedly be philosophical, ethical, social and political questions to be addressed. Many claims relating to the interference with life through recombinant DNA techniques are perhaps premature, although one characteristic links them all. Such claims were primarily a consequence of the uncertainty that surrounded the earliest developments of *in vitro* techniques to manipulate DNA in the laboratory. In addition, the very scientists involved themselves expressed fears as a consequence of conjectured physical risks associated with the work.[4] The focus of this thesis is less towards the wider philosophical and ethical issues, than towards the political issues surrounding the initial development

and control of recombinant DNA techniques. In particular the emphasis is on international aspects of decision-making and the operationalisation of safeguard options consequent to the origin of concern.

Technological developments have long been considered a component of processes of social and political change, influencing a wide variety of literature in the field of International Relations.[5] Whether addressed from the realist state-centric mode of analysis or from perspectives disaggregating the state, technological issues have been of note. Power theorists at the inter-state level have seen technology as a component of the resources of state power, especially when linked to military capability. On the other hand, functionalists have seen technological issues as a component of the growing complexity of global activity, which engenders transnational co-operation. Most of the literature assumes the inevitability of technological change and the general advancement of science, and focuses on the means by which this occurs and the direction that research and development follows. For the vast majority of individual cases, the application of technology is not generally considered controversial. Focus has tended to be towards general processes of development, or indeed transfer, of technology.[6] It is only when considering what can be termed 'big' technology or science[7] that there has been considerable and narrower interest from the international viewpoint, most notably with regard to studies of nuclear energy (both weapons development and energy production) and international governmental co-operation in areas such as aerospace.[8] Such considerations are representative of the way technology has been addressed within the field of International Relations. It is the purpose of this thesis to examine in detail a particular set of issues arising out of a development in microbiology, which are a reflection of a technology fulfilling certain narrow conditions outlined below. That

technological development is of importance in international relations is undeniable; it is however the form of its importance that is open to interpretation.

Not least is the question of whether or not technological change can be seen as an independent variable influencing political change. Emphasis has often been towards an examination of the consequences for political structures of technological or economic changes. Thus the impact of nuclear weapons and the spread of multinational corporations with their technological links may suggest political consequences. In a wider context industrialisation or modernization have been linked to transformations of political structure.[9] Alternatively, focus might be on the political factors in existence prior to the emergence of innovations, emphasising political motivations and configurations contributing to the emergence, definition and direction of new technology. Such a distinction has been made by H.R. Nau, among others,[10] but with his observation that most analysts would not too rigidly take models of such singular causality. It is argued here that technology cannot be seen as an independent variable, but rather it is one variable amongst many which collectively can be viewed as interdependent. Political processes affect technological progress and vice versa. A more telling point is perhaps to suggest that many individuals in scientific and technological fields like to view their activity as on the whole separate from politics, while many outside these fields, often from an explicitly critical stance, view technology and science as inextricably political. Science policy and the consequences of technological change are both increasingly subject to academic analysis, including political studies. Specific projects and general processes have each come under scrutiny. A substantial literature has thus developed, if not directly within the International Relations field.

Aside from studies of 'big' technology, often emphasising risks in their application, notably in the nuclear energy field, there has been a tendency in general terms for authors to examine the relationship between society and technology, often with regard to problems of control of technology.[11] Much of this work tends to be analyses of the inter-relationships between technology in the widest sense, politics, and society, often supported by case studies. For example, contributors to a book edited by Johnston and Gummett examined nuclear technology, blind landing systems, the motor industry, pesticides and, of particular interest here, recombinant DNA.[12] However, most work of this type appears to be confined to general conceptions of 'society' utilising domestic studies, whatever the country. Largely ignored from the point of view of such authors are the explicitly international political elements. An aim of this study is to take some of the concerns evident in these normative considerations of technology and examine explicitly the international dimension with regard to a specific case study, recombinant DNA.

A definition of technology is a necessary starting point, although most works referring to technological issues tend to avoid this task. It could be argued that technology is a term with many meanings, which have been summarised under three general types:[13] technology as a body of organised knowledge; as the products of organised knowledge; and as the activity of applying organised knowledge. As a body of organised knowledge, it can be distinguished from other forms of knowledge on the basis of it having an industrial utility.[14] Under the second heading there is a linkage with extending human capability through developing and applying tools or techniques, products or processes, equipment or methods. It is suggested here that the third definition enhances the conception of technology as a process rather than a static notion, thus

highlighting the links with social and political change. However, it is important to note that technology is indivisible from science, a point cogently illustrated by Steven and Hilary Rose in their now famous book, Science and Society.[15] Traditionally, they suggest science and technology were taken respectively to refer to "the way in which the observable world works", and techniques or inventions which "add to our control over the world around us" while not enhancing understanding of the laws of nature. Such a distinction they suggest cannot be long maintained in that they are interacting terms, on the basis that:

> "... discovery precedes invention, and invention in turn presages discovery - at least in our contemporary society. And because of the elision between science and technology, between scientific methodology and scientific culture, which together form the totality of science, it often becomes difficult to talk about any specific meaning for the word 'science'." 16

Further, it can be suggested that the distinctions between pure and applied research, which are often made, must not be over emphasised. 'Pure' research in nuclear physics led to the atomic bomb, while 'applied' research in the quest for new alloys has directly influenced solid-state physics. Recombinant DNA, not least, displays an interesting mix of both elements. Interest in applied research, unusually, in this instance emerged very early in the development of laboratory techniques and experiments. Indeed, industrial concerns quickly mobilised their own 'pure' research efforts directed towards eventual 'applied' ends. Finance was channelled from the industrial sector to university academic research, establishing many new alliances.[17] Such was the growth of interest in the new techniques, first established in 1973, that by 1979 the term 'biotechnology' became familiar, referring to an applied combination for industrial purposes between recombinant DNA and more traditional biologically based methods such as enzyme technology and fermenting.[18]

In sum, the interest here is with certain issues surrounding both the initial laboratory breakthroughs commonly referred to as recombinant DNA techniques and the subsequent interest shown in their potential industrial applications. As defined above, these developments are sufficient to label recombinant DNA techniques as a technology. In terms of International Relations, technology in general has always been of some interest. To many social scientists a common assumption, shared here, has been that although technological advance is intrinsically desirable, it should not be uncontrolled. However, such is the complexity of linkages between the technical and socio-political sides in causal terms, that control itself is a difficult issue. This problem is difficult enough from a national perspective, but as the case here will show, there are further problems when taken to the international, or more accurately, transnational, levels. However, the categorical parameters of the nature of recombinant DNA as a technology do need some further elaboration, in order to locate its specific relevance to International Relations.

As an example of technology, the techniques of recombinant DNA are quite different from post-war 'big' science which involved massive bureaucratic and governmental involvement in order to manipulate very high energies, typical of nuclear energy development and, more recently, space research. More appropriately, recombinant A research could be taken as an example of a new sort of science, which J.R. Ravetz terms 'high-intensity' science. He sees it as a natural successor to 'big' science characterised by the essential attribute that it is impossible to isolate the small research laboratory from entanglements "on three general fronts", notably industry, the environment and politics.[19] It is the lack of explicit internationally oriented study of phenomena under this category which in part prompts the analysis here. It is important to be clear from the very

start that the case of recombinant DNA is seen as quite different in structural terms from that of nuclear energy, although many have associated the two technologies. This is important in that as far as conjectured low probability risks were perceived to exist in the development of methods of manipulating and joining DNA from diverse sources, there is a logic in looking for similarities with nuclear energy. These similarities may be relevant to a degree, but the difference between 'big' and 'high-intensity' science necessitates differing conceptions of types of social control, and indeed levels of analysis. Harold Green has argued that both technologies displayed characteristics of low probability, high consequence disaster as a result of the activities of scientists and technologists. Many others have made similar links.[20] Such similarities at this level are valid as long as the differing elements associated with 'high-intensity' science are allowed for in analysis of the precise nature of the control and politicisation of the technologies. Operationalisation of procedures for decision-making and implementation of options are for example quite different in the two types of technology despite the superficial similarity in risk perception.[21]

From an International Relations point of view, the levels of analysis applicable to these types of science are quite different. 'Big' science issues are better considered from the point of view of the state, while it is argued here that this is not the most appropriate level for a 'high-intensity' science. Although such state-centricity can in general be challenged, in this case study it is more applicable to deem it irrelevant.[22] The appropriate level of analysis is considered in more depth in Chapter One, below, at this stage it being sufficient to note that issues of 'high-intensity' science involve many actors within the state, and, as it will be shown here, across state boundaries. The

recombinant DNA debate, however, deserves academic analysis from the point of view of International Relations as it represents a case with the following features: potential disaster, if not catastrophe, was conjectured as possible, if unlikely even to the infinitesimal extreme; effects of such events would have international consequences; control and safeguards required international response; the nature of the politics with such conceptions of risk displayed transnational characteristics; the potential benefits would accrue internationally and would develop within an international economy; and the case, if justified, supports certain academic approaches within International Relations. Another issue of note was that from an early date the possibilities of utilising the techniques for biological warfare purposes were considered by scientists involved.

The case is taken, therefore, as one example of low probability, high consequence risk, superficially similar to the dangers of radiation release from nuclear plant, but related to activity at levels quite different from such earlier science. A full description of the origins of concern is presented in Chapter Four, it being of note here that in examining responses to conjectured risks, the risks themselves were authoritatively announced by involved scientists. This study rests on an analysis of the transnational responses to these fears prior to subsequent information which lessened that perceived risk.

Thus there is an important historical context to the case of recombinant DNA which calls for a differentiation between the perceptions of actors at the start of the case (the early 1970s) and at the time of writing. Uncertainty which underlay the conjectured fears reduced over time. Yet it is precisely the political nature of the original consequences of <u>early</u> uncertainty that is at the heart of this thesis. It does not matter

what is thought today, in the sense that it was the early actions under beliefs or rather fears of the time that, in particular, deserve attention. There was in addition a political process involved in the change in perception and this in its own right is of interest. Current relevance derives from the consequences for future technological developments displaying characteristics tentatively the same on discovery, which over time do not lead to a perceived diminishing of risk. Uncertainty is, therefore, a key factor in this study.

The sub-category of technology within which recombinant DNA techniques are historically placed has two main characteristics. Firstly, there is the potential for considerable benefits in terms of increases in the efficiency of undertaking tasks, or introducing new products, seen as desirable in a liberal economic sense.[23] Secondly, there is the hypothetical possibility of catastrophic disaster, but at very low levels of subjective probability. However, at higher levels of subjective probability there may be the possibility of less harmful effects that may also manifest themselves through the application of the technology by society.[24] Nuclear energy, the chemical industry, and more recently the microbiological advances in recombinant DNA, all, to varying degrees, fit, or were perceived to fit, these characteristics.

Recombinant DNA techniques are very new, dating from 1973, and have not been discussed in the International Relations literature like the other two examples. Indeed, within social science in general, there has been relatively little coverage outside the areas of the philosophy, history, and sociology of science.[25] The very newness of the technology and some unique characteristics make it of special interest. Unlike nuclear energy and the chemical industry, there was less chance of developing precisely calculated technical solutions to problems of risk because,

among other reasons, the techniques under discussion involve living organisms which have fundamental properties of replication. Further, the calls for caution came prior to accumulation of empirical evidence, on the basis of conceptual assessment of risk. The focus is, therefore, towards the characteristics of early response under uncertainty, in contemporary times. Control measures within the nuclear and chemical industries are well established,[26] and levels of uncertainty today are more amenable to estimation, unlike recombinant DNA.

Such was the impact of the new methods of manipulating DNA that they have often been hailed as a major turning point of great magnitude catapulting forward the 'state of the art' unlike any other development since the microchip. Two of the leading individuals central to the events which unfolded have in retrospect observed:

> "But with the new recombinant DNA tricks the genetic engineering of microorganisms, and later of higher plants and animals, would help to shape the world of the future. Without doubt molecular geneticists now had the power to alter life on a scale never before thought possible by serious scientists." 27

Undeniable benefits seemed apparent since the very beginning, not least in enhancing knowledge itself. But the way that associated, if conjectured, risks were to attain publicity was simultaneous to the conceptions of benefits. Eleven of the leading knowledgeable scientists published an open letter calling for a worldwide halt in the work until more was known. The means of revelation of their concern was both dramatic and authoritative. The very act of seeking worldwide publicity, plus the extensive worldwide response, over the conjectured hazards made the case of interest to International Relations. Such revelation, however, does not imply that similar future perceived risks in other technological or scientific field would have equal attention focused

upon them.

The nature of revelation and its profound impact could be taken as a yardstick by which other technologies might in future be compared. If there are faults in the 'control' procedures developed after such an authoritative announcement of concern, then how adequate would the development of responses be in similar cases if little or no attention was publicly sought? In sum, recombinant DNA techniques and their potential impact deserve study, and in Chapter One the relationship with approaches to the study of International Relations will be more thoroughly developed. It has been stated that the characteristics of low probability high consequence disaster could be attributed to the early conjectures surrounding recombinant DNA techniques. It is important in this introduction to clarify this fundamental conception, which greatly influenced the politicisation of the issues, setting the extreme of potential risk considered.

1. LOW PROBABILITY, HIGH CONSEQUENCE DISASTER.

Throughout the period of international activity directed towards allowing recombinant DNA work to proceed under appropriate controls or safeguards, emphasis was on attempting to attribute categories of risk to different types of experiments. In the extreme, catastrophes could be envisaged by some scientists and were feared by many others involved. It is critical to note that all such perceptions of risk allowed for the use of facilities for containment. After a widely reported international conference held in 1975 to address issues of risk and containment, the summary statement of the conference noted:

"The new techniques, which permit combination of genetic information

from very different organisms, place us in an area of biology with many unknowns. Even in the present, more limited conduct of this research in this field, the evaluation of potential biohazards has proved to be extremely difficult. It is this ignorance that has compelled us to conclude that it would be wise to exercise considerable caution in performing this research... Furthermore, it was agreed that there are certain experiments in which the potential risks are of such a serious nature that they ought not to be done with presently available containment facilities." 28

Risk assessment is a theme returned to throughout this thesis. As emphasised in the above statement, uncertainty was a key factor which required caution and the use of containment facilities in carrying out the work. Recombinant DNA techniques engendered a perceived need for caution, guidelines and the use of means of containment before any risk was ever realised. The failure of the prevention of any subsequent disaster given this prior caution would have represented the failure of safeguards and control.

Most studies of disaster both within and outside the field of International Relations have been concerned with the consequences of disaster.[29] It is important to distinguish between totally unforeseen 'acts of God' and cases where risk is recognised and can be influenced by precautionary practices. These precautions may apply at many social levels from the workshop, to the community, to the state, to the international. This differentiation between unforeseen and conjectured risk enables focus to shift towards the prevention of disaster. Yet almost without exception, according to B. Turner, studies of disaster in a social context have examined the impact of disaster and the problems of rescue relief and recovery.[30] Turner's work is of note in that he attempts to fill the gap by focusing on the preconditions of disaster where disaster is defined as:

"... an event, concentrated in time and space, which threatens a

> society or a relatively self-sufficient subdivision of a society with major unwanted consequences as a result of the collapse of precautions which had hitherto been culturally accepted as adequate." 31

Thus a disaster in this sense is the failure of precautions previously thought adequate and where casualties or damage to property might actually be minimised through chance factors. In these terms a train derailment or an aircraft near miss could be conceived of as a disaster, even if there were no casualties involved. The same safeguards to a degree would have failed if there had been deaths on the train or the aircraft collided. It could, however, be argued that some disasters might occur where it was not known that precautions were necessary, but had it been known it might have been prevented or minimised. This situation has much more in common with 'acts of God', except that in subsequent periods precautions might be introduced. The case of recombinant DNA fits readily into a conception of an activity requiring culturally acceptable precautions, certain failures of which would in the above terms represent disaster. Derived from this, two further points are of note. In the first instance it is necessary to acknowledge that the level of disaster can be gauged in terms of either the numbers killed, maimed, or property destroyed, or in terms of the degree of failure of the safeguards and the resulting cultural readjustment. In the second instance, this puts emphasis on the need to examine the development and operationalisation of control options.

This thesis therefore examines the development of socially and politically accepted controls and precautions where a potential for catastrophe (or disaster explicitly involving great environmental damage, including many killed or incapacitated) was considered. However, even in the early days of expressed scientific concern, the likelihood of extreme consequences

was perceived at subjectively very low probability levels. Nevertheless uncertainty introduced the further complexity that this low level of probability, and higher probabilities for lesser conjectured risks, were all beyond rational calculation or estimation. Thus the question of socially or politically acceptable controls became less related to rational assessment, and more linked to issues such as legitimate participation in decision-making. It will be emphasied that these were transnational issues with international consequences.

It is an important aspect of the recombinant DNA case that both the risks involved and the benefits involved were of a highly conjectured nature based on theoretical considerations. In particular, the uncertainty enabled striking differences of opinion to emerge amongst the scientists involved, which provided fuel for a wider political debate over the assessment of risks, benefits and safeguards. Following Turner's view of the nature of disaster, attention is drawn to the international processes involved in the establishment and operation of controls in this rare case where uncertain risk was conjectured in advance of significant utilisation of research methods. Turner's work emphasised the incubation periods of actual disasters where culturally accepted controls fail. Emphasis here is on a case where some controls or safeguards were internationally seen as necessary, but where cultural formulation of those controls was transnationally politicised. Not least, a disaster involving casualties has not yet occurred.[32]

2. OUTLINE OF THE THESIS.

For clarity, the content of this study is divided into four sections. Section A, comprising two chapters, continues in substantial detail the conceptual introduction to the thesis as a whole. Chapter One considers

the most suited location of a case of this type in relation to the established literature in the field of International Relations. In particular, approaches which disaggregate the state and emphasise the roles of non-state actors are deemed most relevant. Broadly speaking, the examination of the operationalisation of control options for recombinant DNA techniques is facilitated by the application of systems concepts to decision-making and organisational activity in a transnational sense. Chapter Two presents the chosen framework in more depth, in order to develop a strategy for penetration of the issues relevant to the interests of International Relations. In effect, these two chapters provide the analytical base for the whole thesis and for convenience the first section is completed with a summary of the most important assumptions, hypotheses, research methods and sources, used in operationalising the study.

Of crucial importance to any overall assessment of recombinant DNA techniques is an understanding of the science involved and the precise origins of concern over risks as typified above. Section B elaborates on both of these, with Chapter Three summarising the methods of achieving in vitro recombinant DNA molecules, and Chapter Four tracing the emergence of concern over these methods, emphasising the internationally authoritative actions of a key group of scientists. The way in which sensible caution became internationalised is important in understanding the subsequent institutionalised decision-making.

Control options were developed in many states, although the early actions of two in particular influenced procedures adopted in others. Both the United States and the United Kingdom were quick to respond to the international scientific community's misgivings about risk. Within Section C Chapters Five and Six examine the institutional responses in each of these two states. However, responses occurred in a further thirty or so other

states, from the level of an initial examination of the issues to fully implementing safeguard policies. In addition, a number of international organisations held central roles in the international dissemination and interpretation of information and in attempts at guideline harmonisation. Chapter Seven, therefore, examines the remaining states and the international organisations involved.

Finally, Chapter Eight, which can be seen as the fourth section of the thesis, provides an analysis of the issues raised in the empirical narrative describing the origins of concern and the international responses. The estimation of risks and benefits under uncertainty is argued to be a politicised activity, especially when they are set against each other in risk-benefit assessment. Control options are then examined before formally identifying the transnational system within which the recombinant DNA debate proceeded. In general, Chapter Eight attempts to return to the conceptual insights developed in Section A and includes a return to the general hypotheses underlying the thesis.

As the research activity was carried out over some years, there was an inevitable historical dimension to much of the study by the time of final writing up. Nevertheless, the thesis, from the very beginning, focused on what can be described as the early institutional responses when uncertainty was greatest. In this context, the bulk of the analysis refers to events of the 1970s, accepting that in the 1980s perceptions of risk and operational procedures have in many instances changed.

SECTION A

RECOMBINANT DNA AND INTERNATIONAL RELATIONS

Chapter One: Locating the Issue in International Relations

Chapter Two: A Strategy to Penetrate the Issues

Summary and Operationalisation

CHAPTER ONE

LOCATING THE ISSUE IN INTERNATIONAL RELATIONS

1. Methodology

2. Approaches to International Relations and Recombinant DNA

3. Summary

LOCATING THE ISSUE IN INTERNATIONAL RELATIONS.

In discussing the relationship between the case study of genetic manipulation and International Relations, a number of important considerations must be embraced, in order to clarify the perspective adopted here. It is necessary to examine the approaches to International Relations with a view to identifying areas of conceptualisation which might provide valuable insights of assistance to this study. However, this exercise requires a brief summary of the general methodological issues involved in relating any empirical case study to theoretical literature. Thus, the first consideration of this chapter will be the problems relating to methodology. Following that, the case will need to be located within the field of International Relations, as the study does not readily fit into the dominant analytical approaches. Broad categories of approach can then be considered in relation to possible positive contributions to the penetration of the international issues surrounding recombinant DNA.

1. METHODOLOGY.

There is no clear consensus on the correct relationship between bodies of theoretical literature in social science and empirical evidence. A central two-way problem is involved: a question exists as to whether a theoretical framework justifies the choice, and therefore relevance, of the case study, or whether the case study, intuitively suggested as relevant to the field of International Relations, partially determines the type of theoretical approach. Further, International Relations in particular has had a chequered history of competing approaches, partly a manifestation of its eclectic nature. Thus, the question of appropriate approach and methodological relationship with the case in hand

is of importance.

Issues of scope of inquiry and relationships of International Relations theory to empirical evidence are well documented.[1] In a wider context they relate to issues of epistemology and philosophy of social science, not least including differences between induction and deduction, and their interrelationship.[2] Following both Reynolds and Waltz,[3] the argument adopted here is that practical research should involve elements of both. Pure induction is in effect impossible in that if particular facts are selected as part of a quest for a theoretical explanation, then some criterion, whether explicit or implicit, determines relevancy. Deduction can also be seen to have limits, as that which is deduced "is already present in either theoretical major premises or in empirical minor premises dealing with matters previously observed".[4] It seems, therefore, that some element of theoretical formulation aids the process of induction, but induction aids the development of theory. Waltz, acknowledging the limits of either on its own, suggests that they are both necessary in the construction of theory, but that they need to be used 'creatively'.

Reality is observed through conceptual filters and cannot be separated from the models and paradigms we use to codify and order our perceptions. In addition, we can only ever hope to understand a part of that reality, thus selecting on the basis of the perceived importance of its components. However, it can be suggested that utility provides some measure of the success of the selection. This point can be developed more formally by considering the main functions of bodies of theory, which can be taken to be description, explanation and prediction. These can be achieved at different levels of rigour and objectivity, and in different degrees in relation to each other. The problem becomes one of establishing the

appropriate strategy involved in gaining knowledge that has utility.

All three functions of theory are desirable, although rarely achieved together in any comprehensive fashion. They are further qualified by the meaning of theory that is taken. In surveying the meanings often attributed to theory, Rapoport has suggested four distinct classifications: the rigorous and specialist meaning of theory as used in the natural sciences; for the social sciences there is the more modest meaning covering activity that "aims only at subjective understanding" involving an "intuitive organisation of perception"; also within social science there is the possibility of marshalling factual material in such a way that a reader viewing the evidence through the metaphors, concepts and definitions involved will experience 'understanding'; and lastly, theory can be used in the normative sense of what 'ought' to be.[5] The aim here is to achieve subjective understanding, but in a rigorous fashion, at least in part borrowing from the methods of natural science. Although in terms of the associated functions of theory, depths of description, explanation and prediction must be more modest than in the natural sciences.

Rigorous method aimed at subjective understanding is a desirable legacy of the so-called behavioural revolution of the 1960s which challenged the traditionalists' dependence on wisdom and intuition applied to the 'substance' of international relations.[6] The behaviouralists, however, applying scientific procedures, took mathematical methods of logic and empirical analysis to extremes born of the computer revolution. Arguably, the field today has benefitted from that debate in identifying the limits to each methodology.

From an initial survey of the recombinant DNA case, and with some

reference to nuclear energy, a series of hypotheses was developed which it is proposed to test using a conceptual framework to assist in operationalising the case. If induction and deduction are to be seen as interrelated, in something of a chicken and egg fashion, then the starting point of this study requires some justification and clarification.

Firstly, this thesis is not primarily an exercise in the development of new theory, but rather an elucidation of a case study, argued to be of interest to the field. For this purpose there is a role for theory, and varying perspectives, in order to develop a strategy by which to penetrate the complex issues inherent in the case under study, insofar as they relate to the wider field of International Relations. It therefore seems appropriate to begin with an analysis of possible conceptual frameworks derived from the field, and to make a choice of relevant contributions. This again is obviously influenced by the initial inductive review of the case and its potential interest within International Relations.

Secondly, the style of presentation will be partially determined by the nature of the original source material, which, although abundant, is largely of a subjective documentary form.[7] Thus, although some analytical rigour is applied in selecting operational concepts and applying hypotheses, this is for the purpose of marshalling the documentary evidence rather than as part of a process of theory formulation in the grand sense.

2. APPROACHES TO INTERNATIONAL RELATIONS AND RECOMBINANT DNA.

Preliminary examination of the case study indicated a number of factors that would have to be allowed for in considering the potential application of analytical approaches within the field of International Relations.

The literature available is both diverse and eclectic, with differences in terms of basic assumptions, the relevant focus of study and methodology. Any approaches examining the international elements of the issues surrounding recombinant DNA need to be suitably flexible so as to allow for the following features:

i) The inclusion of actors at many levels of analysis including transnational and sub-state actors.

ii) The analysis of decisions in such organisations, under uncertainty and in interaction with each other.

iii) Analysis of the implementation of decisions and the incorporation of consequences in future decisions.

iv) The perceptions, values and norms of the different actors, whether individuals, groups or institutions.

v) An indication of the wider processes, of which the case study is perhaps a singular example.

In examining the operationalisation of control options it was necessary to identify the relevant actors, and in this instance it was quite apparent that many types of actor were involved, from government representatives to individuals, both within and outside science. Some actors were, however, organisations, or were at least organised groups which became important decision-makers in both the establishment and implementation of guidelines. In addition they reflected certain values, which were often contradictory. Although the case in question was in many ways novel, it would be sensible to consider wider processes which it reflects, for example institutional decision-making procedures in general, and difficulties associated with risk-benefit assessment. A series of approaches is presented below, with a view to the identification of useful insights for these expressed purposes.

The aim here is to focus upon relevant categories of approach, which in Chapter Two will be developed as operational concepts for the analysis of the case study. This, however, involves dismissing some traditional perspectives within the field of International Relations as not relevant. Thus the following will be considered:

a) The 'traditional' approach will be considered briefly because of its pervasiveness, but will be dismissed quickly as irrelevant to this particular study.

b) Systems theory will be considered because of the attempt it makes to transcend compartments of knowledge, both outside and within the field of International Relations. It will, however, be necessary to distinguish between some quite different applications of systems concepts to international behaviour.

c) Decision-making analysis, partly derived from systems theory, is discussed, in that it breaks down states as actors, and also because of its relevance in terms of analysing the behaviour of organisations in general, a number of which were involved in this case. A further reason, however, explicitly concerns its utility in discussion and criticism of the concept of rationality, a central consideration in this study. For this reason game theory, as a component of decision-making analysis, is also of note.

d) Transnationalism and approaches referring to interdependence, much in vogue in the 1970s, will be discussed because of their break with confining actors to states and their utility in providing a framework which incorporates a wider range of interactions between many units of analysis. It will be argued that a useful overlap, for the purpose of this thesis, exists between such approaches and certain frameworks of analysis based on systems terminology.

e) Within International Relations, international organisation theory covers a variety of different perspectives, of which functionalism,

and concepts relating to the process of organisation, might provide useful insights to assist in the penetration of the international aspects of the recombinant DNA issue area. In particular, processes of organisation at the international level can be focused on a range of actors and types of international institutions.

This list is not exhaustive, and to an extent the categories are arbitrary although at least commonly acknowledged. However, they provide a guide to the exercise of examining the relevance of existing approaches and their associated concepts to the issues in hand. The reciprocal of this is the location of the recombinant DNA case within existing interest areas in the field as a whole. It is the argument here that issues such as those discussed in this thesis should be of note in International Relations, and by implication can be taken to support certain approaches to the study of international phenomena, rather than others.

a) The Traditional Approach to International Relations.

Despite the eclectic nature of International Relations and lack of consensus on delimiting the field, there does exist a recognisably traditional approach. As a starting point it needs some acknowledgement. However, it is not the intention to enter, at this stage, the wider debate of the fundamental relevance of this approach to the field. Although it is widely questioned, it is dismissed here as an inappropriate approach for this study. The line of argument adopted is that different approaches have different utilities related to different issues under consideration. This is in keeping with a number of respected authors.[8]

The main reason for dismissing the approach in this instance is its emphasis on states as relatively cohesive and dominant actors. In effect there are two assumptions involved. States are unitary actors, which can

therefore be attributed with some characteristics of purposiveness and choice, similar to those of individuals, and states are the most important, if not the only important, actors to consider.[9] Although there are variations between the proponents of the traditional approach, it can be suggested that their interpretation of international relations derives essentially from this double assumption. Their focus is on the anarchic nature of the international state system,[10] drawing upon past writings in political philosophy, often emphasising the darker side of man's behaviour, for example the work of Hobbes and Machiavelli.[11]

As a consequence, authors have concerned themselves with questions of security or 'high' politics of the state, and the applications of military force and state power in general. To the traditionalist, states are the most important form of political organisation and their aims can be identified in terms of 'national interest'. No authority is seen as superior to that of the state, and the system is thus characterised as anarchic. Within this framework, patterns of interaction between states have been examined, often centred on the relative power of states, or on norms of behaviour between states, sometimes likened to the behaviour of individuals in societies.[12] It is further of note that in the methodological debate between traditionalists and those advocating scientific methods, often utilised in quantitative fashion, the assumptions of the latter were not much different.[13] Operational methods rather than perspectives on the nature of the international system were really at issue. Quantitative analysts were in fact testing many of the state-centric assumptions of the traditionalists, thus reinforcing their pervasiveness.

Such concentration on the state, with the restrictive assumption of its unity in international affairs, belies sufficient exposition of the many

other actors and associated issues. Economic, social and political issues involving non-state actors are considered as mere background or environmental factors for inter-state activity.[14] It is clear that the recombinant DNA issue area involved a variety of non-state actors such as international non-governmental organisations (INGOs), domestic pressure groups, government departments, industrial concerns, and so on. Nor could states be conceived of as unitary actors for this issue area. It is argued here, in keeping with other approaches, that a wider interpretation of international relations is desirable, involving many types of actors, issues, and processes of interaction. As far as a single case study can, the recombinant DNA issue at least lends support to the critics of the narrowness of the traditional focus. The case is important, but the traditional approach cannot give useful insights.

b) Systems Theory.

A second major approach in International Relations can now be examined. Of considerable influence in the field has been the notion of systems theory. However, from the outset it must be made clear that there are essentially two categories of systems theory to be distinguished. The first can be described broadly as systemic systems theory, which takes units of interaction to be states. The second category operates at levels of analysis other than the inter-state system perspective, associated with disaggregation and penetration of the state's boundaries. In keeping with the above discussion of the traditional emphasis on state centricity and states as unitary actors, the first category will be dismissed largely, although it is by far the most extensive in terms of contributors.[15] In many ways the forerunners of systemic approaches are traditionalists such as Hans J. Morgenthau who, like the systems theorists, took an holistic view of the interactions of states. They share, therefore, a conception of analysis necessitating an understanding

of the dynamics of the international system of states at a macro level.[16] Yet systems theorists offer a qualitative difference in terms of the form of their analysis, which is shared by both categories of approach, and which is of utility in this study.

The form of analysis makes the systems approach amenable to studies in all disciplines, as systems theorists would have it. Indeed, early theorists were attempting to apply General Systems Theory (GST) and hoped to break down the traditional compartmentalisation of the overall search for knowledge. GST was based on the notion of a series of abstract systems to which all knowledge could in principle be reduced. Concepts such as isomorphism, homeostasis and entropy were deemed to apply generally in the quest for knowledge, in both natural and social science.[17] Systems theory could therefore be applied to different areas of knowledge through identifying the relevant system in relation to the units in interaction. Thus the main difference in the two categories of the approach within International Relations was the identification of the units in interaction. As with the traditional approach, systems analysis taking the states as the units in interaction is rejected for this study, but as Little suggests:

> "There is, however, another strain to the systems approach in International Relations which has, at the very least, attempted to broaden the horizons of International Relations, some would say to a point where any idea of a boundary to the discipline has been lost altogether." 18

Further consideration will be given to the form of systems analysis, but in terms of approaches taking units of analysis more appropriate to this case study. Indeed this thesis as a whole will draw heavily on the frameworks suggested by systems theory, but also recognising important and sometimes similar contributions from the remaining approaches dis-

cussed below. The main theme is dissatisfaction with state-centric orientations in understanding many types of issue deemed to be relevant in the modern world. By implication, focus will be on approaches which suggest that conceptions of rigidly impermeable boundaries between states are at odds with the real world.

Penetration of boundaries can be attributed to many factors such as the capabilities of nuclear weapons, economic interdependence, communication of ideas, transnational political and social affiliations, and more, all of which have received attention from systems analysts. It could be argued that truly holistic viewpoints must acknowledge such penetration and the associated processes and issues. Domestic and international politics therefore become linked and a much wider set of issues can be focused upon.[19] Economic management, welfare, resource development and management, terrorism, multinational corporations, dependency and demands for a new international economic order are all issues which have gained prominence in the various approaches which eschew state-centricism. It is argued here that technology in general is a relevant issue and that recombinant DNA in particular displays characteristics more appropriately analysed by such perspectives.[20]

The upshot of these observations is that it is possible to suggest a move towards a different level of analysis, or collection of levels, from the inter-state. If the essence of a system is taken to mean a set of elements, components or units which interact in some way that forms a whole,[21] then state-centricity can be avoided by emphasising different units. John Burton has suggested that the individual should be the central unit. As he neatly puts it:

"A system exists when there are relationships or transactions

> between units of the same set. There is a system of states, and then there are also transactions between businessmen, traders, research workers, television stations, drug peddlers, students and others... It is the total of these which we need to see as a behavioural map of the world." 22

Collectively, Burton is interested in what he terms 'world society' rather than any one system, or indeed any one issue. Human values and human needs are taken to be of central concern, with individuals or units playing 'roles' within different systems. There is no doubt that elements of Burton's insights are relevant to this study and the whole area of taking units of analysis other than states will be considered in greater detail. Systems concepts such as the above are therefore noted, but they will be linked to another important usage of systems terminology that has occurred in examining decision-making processes. It has already been indicated that in addition to a variety of actors the study is concerned with decision processes within these actors and between them.

c) Decision-Making Analysis.

Decision-making analysis has long been associated with systems terminology, and like the systems approach in general has roots in the behavioural 'revolution' in International Relations.[23] Whereas most systems theorists (excepting Burton and some others) were to take the state system as their focus of attention, the decision-making analysts tended to examine the decision systems within states, but still seeing the state as the primary actor. They were in effect challenging the assumption that states are unitary actors, rather than the assumption that states are the dominant actors.[24] Although such a restriction cannot apply to this case study, this is not sufficient reason to dismiss decision-making analysis completely.

The systems approach to the analysis of decision-making is not restricted to International Relations and its traditionally dominant actor, the state. It is an approach that applies to the study in general of how organisations achieve purposive outputs. Chris Hill and Margot Light emphasised this point in surveying the literature on foreign policy analysis. They argued that foreign policy analysis is essentially the study of decision-making in foreign policy, and "cannot therefore be the child of International Relations alone". Attention was then drawn to "pure decision theory" seen as the "intrinsic logic of choice making", whatever the situation.[25] Thus in terms of analysing decision-making within and between organised groups concerned in one way or another with the recombinant DNA issue area, not only must there be a break with the usual use of decision-making analysis in the field, but also something of a return to basic sources actually adapted for the purposes of foreign policy analysis. Two aspects are of particular importance for this study: firstly, the limitations of rational choice-making need consideration; and secondly, systems concepts as used in organisational theory in general need assessment in terms of operationalising the case. In Chapter Two organisational theory will be developed further within the framework identified for the study. Systems concepts will in particular be used to elucidate both organisational behaviour and interorganisational relations, which are central themes in examining the development and operationalisation of control options for recombinant DNA research.

Decision-making as seen from the systems literature tends to be of the input-output variety,[26] utilising concepts along the lines of those following: an 'input' is the injection into the decision-system of information or a resource; information is stored and recalled through a 'memory'; a 'decision' is some action vis-a-vis the environment taken after an analysis of available information and capabilities; an 'output'

is the systems action; a 'goal' is whatever result is sought by the output; 'feedback' is new information about the results of the action, which becomes a component of further 'inputs' starting the cycle again.[27] This describes in general terms the decision-system, but it leaves unexplained the key section concerning the actual analysis of available information and capabilities. In particular, this provides reason to consider the concept of 'rationality', an area of some difficulty.

Much of the decision-making literature is a response to dissatisfaction with approaches which emphasise the rational nature of units under examination. Not all studies of decision-making are systems orientated, for example other perspectives include game theory, social psychology, simulation and documentary analysis, but most are behavioural and most need to come to terms with questions of rationality as it relates to human activity. The problem concerns both the assumptions made about how individuals or groups (including organisations) actually make decisions, and how the analyst examines decision processes. These are obviously related, but nevertheless each reflect particular dimensions to the overall problem. Perhaps the two-sided element can be summarised best by making the point that when decision processes are analysed it is easy to argue that if rationality is assumed, then analysis of procedures used becomes more straightforward. Further emphasis arises from the more subtle rider that even if real life decision examples do not reflect 'rational' activity, then they ought to. The normative side is often used, however, with an inadequate appraisal of what rational decision-making implies in operational terms. Indeed, it will be argued in this case study that conceptions of rationality were a vital component of the assessment of the risk involved in using recombinant DNA techniques. In particular, it will be argued that part of the politicised debate centred on whether or not more rational assessments should or could provide a

base for decisions concerning the development and application of appropriate controls. Many scientists called for 'rationality' and 'rational assessment' on the grounds that this was the 'scientific' way to proceed. Part of the reason for this was apprehension about unsubstantiated fears of risk, general politicisation of the issues, and even threatened legislation. The difficulties lay in that truly rational decision-making in any meaningful way is extremely difficult in some choice situations, and that imperfections in part of the procedures used can undermine the whole effort. Thus, because of the importance of the concept to decision-making analysis in general, and the stated desirability for rationality to apply within the context of this case study, it must be addressed further here.[28]

Graham Allison in his seminal work applying three decision-making 'models' to the Cuban missile crisis, defined rationality as follows:

> "Rationality refers to consistent, value maximising choice within specified constraints." 29

Drawing heavily on conceptions of 'rational man' which underlie study areas such as economics and game theory, Allison provides a very useful summary of the characteristics of rational choice in terms of four sets of concepts. Firstly, there are 'goals and objectives', or utility in economists' terms, which prior to taking the decision can be seen in the form of a "payoff function which ranks all possible sets of consequences in terms of ... values and objectives". Secondly, 'alternatives' exist of which a choice is made, and can be presented as a decision tree where alternative courses of action may include more than a single act, although a course must at least be sufficiently different from other courses. Thirdly, 'consequences' are important and vary according to the decision

made, and "variations are generated at this point by making different assumptions about the accuracy of the consequences that follow from the choice of each alternative". Fourthly, 'rational choice' consists simply of selecting that alternative whose consequences rank highest in the decision-maker's payoff function.[30]

Such concepts apply readily to microeconomic theory, where the realms of choice are carefully limited by narrowly defining them in terms of an economic definition of the choice situation.[31] Complex and rigorous models of choice can be developed, but, as Allison observes, at the price of too heroic assumptions. Fundamental to such optimal choice models is the idea of comprehensive, or even perfect, information about the choice maker's preferences, the range of possible alternatives (fixed in analytical terms) and all the consequences of the choice options.[32] Such information can be in absolute or probability terms.

In defending such positions, analysts have acknowledged that comprehensive rationality might be applicable to certain types of choice situation where rigour can have an heuristic value indicating complex potential relationships in an ideal world. Economists strongly defend the whole framework of welfare economics based on these and other assumptions. Alternatively, the analyst could make an assumption of 'limited rationality' and make limited subsequent claims concerning analysis of optimal choice. Traditional decision-making analysis in International Relations could be categorised more readily thus. Nevertheless, some writers have observed that there has been a degree of envy about the apparent success of economics within the field.[33] It should be remembered, however, that economists in general are trying to minimise value judgements by the use of rational analysis. In effect, some important political elements are either excluded from their model or 'internalised' by attributing nominal

values to them. For example, in welfare economics if one person is made better off, this is assumed to be an overall welfare improvement, no matter who the individual is or what his previous level of welfare was relative to others. Distribution issues of this sort are inadequately covered, because in effect they involve wider social and political questions considered to be outside the realm of economics. Sometimes externalities related to social costs and benefits might be 'internalised' in cost-benefit analysis by allocating economic values. Lives saved in building new roads might therefore be given nominal monetary values.[34]

Models based on rational assessment are seductive because large numbers of empirical facts can be interpreted by the application of a few simple assumptions about the goals that decision-makers are trying to achieve. Lacking precise information of the actual diary of events and considerations of decision participants, the analyst, by assuming goals and rational action, can infer retrospectively the alternatives considered and attempt to explain rationally the course chosen. A rational choice by a group of many individuals, or a single individual, would be precisely the same given that they have the same goals. Personification of organisations or states is therefore acceptable if decision-making is seen as comprehensively rational, or as near that as practicable. As Allison has demonstrated, however, models which introduce interpersonal differences in values and perceptions, or consider organisational processes of operation can provide different interpretations of decision-making in real cases.[35]

Regarding the recombinant DNA case study, it is the contention here that decisions were not taken in rational terms as outlined above. Yet many, scientists in particular, argued that such procedures should be adopted. The problem is that rational decision-making involves either some

certainty of information or reliable probability estimates, and clear goals shared by all participants. These were not the case. Problems of legitimacy also arise if goals differ, or if those with different goals are excluded from decision processes. Finally, perception and cognition affect individual decision-makers in different ways,[36] making organisational personification of some limitation.

However, even if rational choice analysis was deemed most appropriate, there are further difficulties, perhaps best shown by the theory of games. Designed to examine rational choice and strategy in a variety of contexts, game theory is particularly useful in examining situations where decision consequences are partially determined by the actions of at least one other decision-maker.[37] As a 'generator of ideas'[38] game theory provides a set of mathematical models to suggest the optimal rational choices from the point of view of each player. Logical deductions are made from the assumptions underlying each game in order to illuminate consequences. Games like 'the prisoners' dilemma' and 'chicken', both well known, serve to illustrate how individual choices seen as rational need not necessarily lead to the most desirable outcomes when the outcomes are also contingent on the actions of others, and when decisions are taken in isolation. Often overall outcomes are of the sort where the 'best of the worst' alternatives results. Rationality should not be overemphasised as leading to the best consequences in decision-making, at least in the sense defined above.

Schelling exemplified some further game theory insights related to 'tacit bargaining'.[39] If game theory tends to examine situations where participants do not directly communicate, it can be shown that in certain circumstances tacit communication based on background knowledge or threshold situations might arise. For example, individuals told, in the

absence of communication, that they could share $100 if they agreed on the split, tended to choose (36 out of 40) $50 each. Many similar, and sometimes less obvious, examples emerged. Alternatively, in the East-West political division, a common perception of a threshold between conventional and nuclear weapons is prominent as a qualitative phenomenon, while differences in the latter are perceived as of degree. In the recombinant DNA debate, tacit bargaining was likely between scientists with similar backgrounds and values who made isolated choices within and across states. An obvious example was that almost all scientists felt that the work should continue. A threshold was perhaps also noted in the difference between legislated controls and voluntary controls,[40] the former being seen as the final straw for many.

With many actors involved, to different degrees, in the many interrelated examples of decision-making, such observations as these about rationality indicate that it has limits in explaining the actual outcomes in the recombinant DNA case. Activities in different states and in different international organisations were linked, but these decision-systems could not be expected to agree on a single set of rational decisions. Compounded by the very uncertainty surrounding the case, value differences and differences in decision procedures led to a lack of harmony in international choices. Conflicts of values between various actors were reflected in different goals, making rational choices and consequences also appear different.

Rationality may be a problematic concept, but it is not completely irrelevant to the consideration of decision-making in the present case study. It has been said that much of the literature on decision-making has been in response to the limitations of the concept and its implied over simplification of actual decision processes. If its limits are

recognised, it still provides a useful component when the wider elements of decision-systems are addressed. Taking systems analysis of processes of decision-making, it is possible to examine choice making in relation to limitations or incompleteness of inputs, uncertainty of choice alternatives, uncertainty regarding consequences, and less than optimal outputs.

Allison characterised a body of literature applied to foreign policy decision-making in terms of what he called the 'organisational process' model.[41] It is in effect an acknowledged summary of literature from other fields, and notably organisational theories of the firm developed by economists. Although many authors have produced critiques of Allison's work,[42] they centre, as far as this second model is concerned, on the relevance of using behavioural models of economic firms when examining foreign policy making. It is argued that this is less of a problem for this study as interest is not with the aggregate output of government bureaucracies as extensive and varied as those concerned with foreign policy. Rather, the concern is with many individual organisations, and a number in interaction, where their decisions can be seen in terms not dissimilar to firms. Further, organisational theories of firms were a response to the perceived limits of rationality. With the clear limits of rationality in conditions of uncertainty, as in this case study, but with organised activity well evident, consideration can be given to organisational theory. Not least, systems concepts appear to apply and these are, as argued, useful in transcending academic fields. In effect, from an International Relations viewpoint, this thesis attempts to go back to the type of sources Allison used, but to apply them to different types of issues from those of foreign policy analysis, where decision-making has had its greatest impact in this field.

Central to this approach therefore is the identification of the relevant decision-systems, which necessitates establishing the appropriate units, or actors, which comprise the system. In general, systems concepts can be applied at many levels enabling systems to be disaggregated further into sub-systems. At one level, for example, a system may involve a number of actors in interaction, while at another level any individual actor itself might be seen as a sub-system. Comparing such ideas to more traditional International Relations conceptions of the state, John Burton noted:

> "... the state is a complex of sub-systems of which many are parts of transnational systems, operating freely across national boundaries, sometimes despite state authorities." 43

Overlapping systems thus exist, some of which themselves can be seen as units in other larger ones. For this study, organisations and groups attributed with purposeful behaviour are the units of a number of trans-national or national decision-systems, while each itself can also be seen in organisational systems terms. Of most interest here is the way actors have interacted in regularised fashions to develop constraints on the use of recombinant DNA techniques. Systems concepts are therefore applied in terms of examining decisions at these levels rather than examining activity within every individual organisation. The point is that in the recombinant DNA case we are dealing with a wide variety of types of organisation that would normally pursue differing goals,[44] often spread across state boundaries, and which have found their goals, or underlying values, in various degrees of conflict.

Yet decisions of central importance are identifiable in explicit terms, not least because they became formalised as guidelines which had to be administered, with both the decisions themselves and their operationali-

sation involving some complexity. Certain central features of organisational theory will be discussed in depth in the next chapter, including for example communications, systems interactions and boundaries, the nature of complex decision problems and organisational learning and feedback. In addition to this, some consideration will be given to cases where the output of one decision-system or organisation might provide an important input into another, in terms of interorganisational relations.

It seems, therefore, that systems terminology in general enables the necessary range of actors, and communications patterns between them, to be addressed. Specifically, systems concepts can be used to examine decisions made by organisations and, as developed in the next chapter, between organisations. Given the limits of rational assessment that were possible by actors addressing the issues surrounding recombinant DNA, it will be necessary to develop insights into decision-making in conditions of extreme uncertainty as outlined in the introduction to this thesis. There is, however, a literature based on incremental decisions aiming for satisfactory rather than optimal outcomes which readily fits into the strategy outlined here to examine the case.[45]

Thus far, little has been said of the political dimension to the decision-making evident in the recombinant DNA debate. Allison produced a third model linked to a degree with the organisational process model. His third model examined the political risks and relationships between the individuals, as heads of key organisations, privy to central decision-making within the state (in an example of crisis).[46] Again returning to the original tradition of thought Allison used to develop his third model, it will be necessary to consider the overtly political aspects of decision-making which are not the concern of the approaches derived from the

economics theory of choice, discussed above. Decision-making, it has already been said, involves goals, which might differ between actors in reflection of different perceptions and values. From this it is logical to extend the analysis of decision-making to include questions of who participates, and the corollary, who is excluded. Borrowing from political science traditions, participation, conflict of values and legitimacy are central to the framework outlined in Chapter Two. The case study is a political study and decision-making within it has to be examined both in terms of decision structures and decision content. So far, emphasis has been on systems of decision-making without considering content. Operationalising these systems concepts will involve identifying participants and their respective political stances. However, some clarification of types of actors can be made based on the following International Relations perspective.

d) Transnational Relations.

Not a new term, 'transnational relations' nevertheless became fashionable as a focus of study after the publication of a volume edited by Robert Keohane and Joseph Nye in 1971.[47] Such a focus can supplement the disaggregated systems approach being developed here by facilitating the classification of actors that comprise the systems which are identified. Transnational relations are defined as:

> "... the movement of tangible or intangible items across state boundaries when at least one actor is not an agent of a government or an intergovernmental organisation." 48

Transnationalism as a phenomenon can be traced back through the influences of colonialism, the growth of commerce, trade, science and technology, migration, peace movements, skill transfer, multinational corporations and the like.[49] Increased international communications, assisted by

technological progress, have greatly facilitated the transfer of ideas and commodities, between all levels of the societies that comprise states. It is the widening of the range of actors that makes trans-national relations of interest, and it reflects again the limitations of state-centric approaches. It enables the inclusion of issues associated with many levels of analysis, including the inter-state level. Keohane and Nye provided a simple diagram to indicate the differences in terms of actors and interaction patterns between inter-state politics and transnational relations:[50]

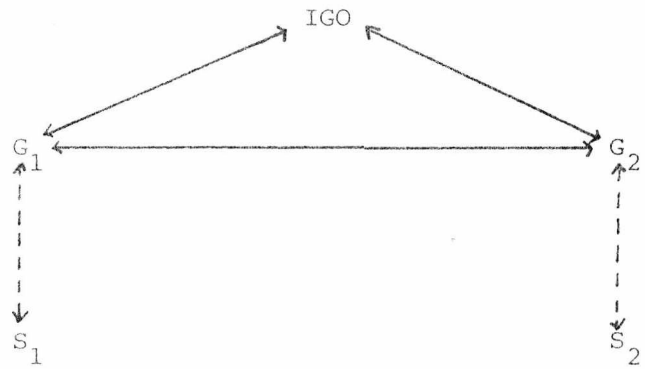


DIAGRAM 1. A State-Centric Interaction Pattern.

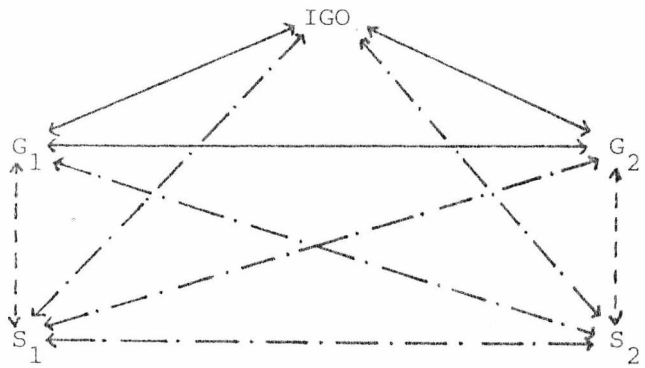


DIAGRAM 2. Transnational Interactions and Inter-State Politics.

KEY: ——— Classic inter-state politics
- - - - - Domestic politics
—·—·— Transnational interactions

G = Government; S = Society; IGO = Intergovernmental organisation.

In general terms a number of observations associated with analysis in this vein are of note. In particular, the concept of interdependence deserves some attention. As the states of the world have modernized, the structure of the international system can be seen to have changed. Oran Young defined interdependence as:

> "... the extent to which events occurring in any given part or within any given unit of a world system affect (either physically or perceptually) events taking place in each of the other parts or component units of the system." 51

Often considered in terms of economic activity being interdependent, this concept has been used as an alternative to the supposed independence of the sovereign state. By widening the range of issues to be considered as important, emphasis can be taken away from the dominance of the state or government in high politics. Issues traditionally seen as 'low' are only understandable by examining many actors and rejecting state independence. However, interdependence involves many political factors, in terms of its consequences, and it cannot be taken as intrinsically desirable. It is a structural phenomenon and its desirablity depends on circumstance and whether or not the associated links between actors are stabilising or destabilising.[52]

Technology has long been seen as internationally interdependent, from research and development to the marketing of resultant commodities. Multinational corporations and international non-governmental organisations as transnational actors are in effect part of the mechanisms of interdependence, along with trade and financial structures. It is interdependence in this context that is of interest here. For example, the failure of safeguards regarding recombinant DNA in one state could have transnational repercussions, in terms of readjustment of procedures, and

perhaps even direct environmental effects, depending on the type of failure.

Further, interdependence and transnationalism suggest the limits of governmental autonomy. Modernization has put constraints on the limits of government choice affecting both domestic and foreign policies. In the North-South context, in economic and technological terms, it is fair to talk of relationships of asymmetric interdependence or dependence.[53] The transnational issues involved in the recombinant DNA issue area were not the central concern of governments in any traditional foreign policy context. Parameters of choice were largely set in terms of interdependence but they affected a wide range of actors, including government agencies. Indeed, a supplement to the concept of transnationalism of note is the concept of transgovernmentalism.

R. Harrison Wagner provided a review of both Allison's work above and that of Keohane and Nye on transnationalism. Arguing that the former challenged the idea of the state as a unitary, monolithic actor and the latter largely challenged the state-centric assumption, he suggested the interesting possibility of simultaneously challenging both.[54] Influenced by Allison and those writing about bureaucratic politics in the context of foreign policy decision-making, Keohane and Nye have referred to transgovernmental relations or relationships of bureaucratic bargaining across national boundaries. Although emphasis was on bargaining and political conflict, the term can also be taken to refer to any communications and interactions where the bureaucracy or governmental organisation acts with relative independence. It is argued in this thesis, and developed in the next chapter, that communications patterns, or actual linkages, are important as well as communications content. Transnational interactions, for example sharing information, between like-

minded organisations might influence wider political outcomes. The concept of transgovernmentalism explicitly challenges the concept of a monolithic government and when combined with the generic concept of transnationalism, the two foundation concepts of the traditional approach are challenged.[55]

In terms of the recombinant DNA issue area, if it is clear that governments were not representatives of monolithic entities, it is not clear how the governmental role should be identified. Government departments in many states were actively involved in developing policy, but so too were other actors, both within and across state boundaries. Included were a number of quasi-autonomous non-governmental organisations (QUANGOs) many with important transnational links through representation on specialist international organisations. To an extent, therefore, hard and fast distinctions between transnational and transgovernmental relationships are not possible. Direct communication between government departments within and between states is of obvious importance, but so too are indirect links where a government department might ask a 'quango' to represent its view at international levels. An example involving these varying levels of communication can be seen in the case of a proposed EEC directive on guideline harmonisation discussed in this thesis. Technical and policy issues were involved and a variety of organisations at different levels of government department influence provided input and channelled information. Of importance, therefore, in challenging the joint assumptions underlying the traditional approach in this fashion is that:

> "... it becomes possible for individuals and groups to participate directly in the decision-making processes of more than one state, rather than simply to bargain with them or otherwise influence the consequences of governmental actions. Moreover, other sorts of transnational influences on national decision-making, such as

information flows and socialization processes, become subjects for investigation as well." 56

It is apparent that the recombinant DNA case study involves some consideration of decision-making and operationalisation of options in transnational terms.[57] This involves examining decision and communication processes as they affect a number of transnational actors, including international and domestic groups. It is argued that decsion-making analysis and systems concepts can assist in this task. However, they are not enough. There is a need to examine the overtly political aspects of decision-making in such contexts, and for this reason reference will be made to some traditional political science deliberations on the conflict of values and participation.

Keohane and Nye, introducing their above edited volume, drew attention to some further observations. Transnational relations, they noted, would affect attitude changes due to face-to-face contact between societies, and could in turn influence the opinions and perceptions of elites. It is necessary to examine here the transnational attitudes within the relevant field of science. International pluralism, they suggest, might arise from the linking of interest groups in transnational structures, usually involving organisations for co-ordination.[58] In effect this would represent an internationalisation of domestic politics. Pluralism, as it relates to perspectives on decision-making, is given treatment in Chapter Two, but with explicit recognition of the important transnational elements associated with the case of recombinant DNA, and the general phenomenon of transnational relations. Decisions in the case arose from a politicised process involving in part the roles of international organisations and the development of internationally linked political strategies on the part of some actors. Associated with these

above effects is the emergence of non-governmental international actors,[59] with their own independent policies. Such organisations are not new and have long been featured in some International Relations literature,[60] but arguably can be seen to be on the increase in reflection of the general increase in transnational contact.

All in all, the framework of transnational relations outlined above, and including transgovernmentalism, helps to classify the type of actors involved in the case of recombinant DNA, and the type of interactions. The approach gives further support for developing analysis of issues not readily covered by traditional conceptions.[61] Concern here centres on inter-state, transgovernmental and transnational actors, with patterns of interaction linking the three types. The precise nature of those interactions will be analysed, drawing on other insights outlined above, with the next chapter outlining the formal framework. Some precedence, however, exists for applying transnational relations in the context of basic science. D. Crane has observed:

> "In the area of basic science governments and IGOs have been steadily expanding their control over important decisions. In turn, however, scientists as transnational actors have been attempting to increase their influence on these actors by developing new types of non-governmental organisations and associations and by strengthening their informal communities or invisible colleges through exchanges and increased mobility of personnel." 62

In consequence, within the 'transnational social system of science', she identifies three types of 'actors' and four types of organisations. The actors are scientists, administrators and politicians, and the organisations are informal communications networks, non-governmental organisations, international governmental organisations and national governments. Such categories are relevant to this study, but it should be noted that Crane's interests were more modest than here. She was interested in

scientists and science organisations attempting to further their interests in the context of furthering science in general, and in competition from time to time with the political goals of states. As they stand these factors are of interest here, but are additionally complicated when constraints on furthering the science incorporate assessments of associated risk, perceptions of which differ between the various groups involved. The case is therefore more explicitly politicised and in transnational terms. Finally, any investigation involving the roles of international organisations needs to take note of that area of academic research utilising theories of international organisation. However, for the reasons outlined above, particular focus will centre on their inclusion of transnational organisations.

e) International Organisation Theory.

Within the field of International Relations, and indeed prior to its existence, processes of international organisation can be seen as an important focus of analysis.[63] Theorists of international organisation have, however, noted a distinction between the general process itself and individual institutions. Both factors are relevant here, and a conceptual linking clarifying the distinction has been usefully provided by A.J.R. Groom. Patterned interaction between actors, he suggests, is likely to give rise to forms of organisation, and these can act as an indicator of a system of 'transactions'. The organisational form can also be more than this, and can be seen as a nodal point or decision-making forum within the system. Studies of decision-making and analysis of the systems involved can be seen as crucial, with institutional studies comprising a part of this. Groom clarifies the distinction thus:

> "While organisation refers to the fact that there is a system, that behaviour is not random and that it has an element of repetition which creates additional systemic inputs, institutions refer to the

structures within, by and through which the systemic functions are performed." 64

In the case study here, it is necessary to consider the systems of decision-making, their identification and the mode of interactions involved. Further, in terms of interactions between actors in the systems, and within organisations themselves as sub-systems, the contents of messages, signals and transactions are important. Thus the framework applied to the case will examine the transnational network linking important actors at different systems levels, but will also consider the general content of exchanges. Yet all this must be undertaken with an awareness of the nature of wider processes involved, as suggested by approaches to international organisation in the field. A number of such approaches comprise the study of international organisation, differing for example in their emphasis on state-centricity and the processes of integration involved.[65]

International organisation theory or integration theory tends to fall into four main categories, which have had influence on both academics and political leaders.[66] The oldest and best known is federalism, which suggests a vision of a supranational state possessing sufficient political power and authority to satisfy member states' needs for internal security, defence and the like. This approach draws on schools of thought which consider institutional designs for pacifying the relationships between states on the one hand, and the actual practice of federal government on the other. However, explanations as to how such institutions could come about rely very much on the political elements of power and bargaining between leadership elites.

At an inter-state level, pluralism or confederalism can be identified as

the second approach, again with a considerable tradition. No supra-national authority would govern from this viewpoint, but rather high levels of amity would suggest that war could be seen as inconceivable amongst member states of the 'community'. However, as with federalist perspectives, the pluralist sees the explanation of any such integration lying with the attitudes and behaviour of the elites. Thus patterns of communication and the predispositions of political elites in a system of sovereign states are the central focus.

Whatever their merits, these two categories of theory have little relevance to the transnational character of the present case study. Recombinant DNA as an issue was never likely to encourage political elites to propose integrative moves. At best it could be suggested that had a federal structure of confederal community existed, then it might have facilitated international harmonisation of responses. Both approaches are too state-centric in describing the process of integration and need not be considered further.

A third approach, functionalism, has been summarised by Pentland thus:

> "The whole point of functionalism, it is argued, is in the flexible creation and adaptation of institutions to social and economic needs as these arise, change and die out." 67

Of note in this approach is that desirable future end points are not specified in the way of federalist-based writings. A network of organisations develops, each of which meets specific social, economic or technical requirements. Functionalists such as the 'father' of the approach, Mitrany, hope that these organisations will lead to a 'working peace system'.[68] From this perspective it is important that integration may be initiated at the intergovernmental level or the transnational levels.

Indeed, as Groom suggests, "the functionalist argument starts from the basic notion that form should follow function".[69] Thus, functional needs lead to, although this is not always the case, a variety of institutions and could perhaps lead to final situations compatible with those of federalists and pluralists. Overall, the approach is largely inexplicit, and is not scientific in any testable way, nor does it claim to be. It is, however, prescriptive, suggesting a means by which a variety of actors might gain access to political processes related to their concerns. In particular it suggests the transcending of state boundaries as often a more effective way of providing for functional needs.

Of question here is the compatibility with this study. There are no reasons to dismiss the characteristics of the recombinant DNA case and the 'innovations' involved in terms of relevance to functionalist thought. On the other hand, a single case study is not sufficient to provide support for the approach. All that can be said is that functionalism is consistent in many ways with that already considered, and with the transnational framework developed in Chapter Two. It could be suggested in normative prescriptive terms that transnational interactions, manifest in cases like the recombinant DNA issue, are desirable. Insofar as it represents a technical problem requiring organisational choices to implement actions for the common good (the development of safeguards) then functional benefit accrues from transnational co-operation and communications. However, as Groom has noted, even functional organisations might display power-ridden and non-participatory characteristics. Uncertainty in the issues requiring choice, with risk attached, it is suggested here, will make purely technical co-operation difficult as a consequence of the very limits of achieving any technical or rational solution. Participation, not least, becomes a politicised issue. A

further question relating to functional imperatives requires consideration of the extent of institutional innovation involved, whether new organisations are created or whether existing ones are adapted. Central to functionalist conceptions, and shared here, is the importance of learning processes. New institutions (or operational systems) might reflect learning processes with future consequences for recombinant DNA and other techniques.

Functionalists importantly utilise the concept of 'spillover', whereby transnational groups organising themselves across state boundaries in order to influence policy decisions may lead to group pressures spilling over into the federal sphere. In particular, economic, welfare and technical co-operation and integration might influence the process of political integration. If recombinant DNA research, development, financing and control display transnational characteristics, then at best, in terms of functionalism, the case study could be used alongside other studies to illustrate the processes in general terms. In its own right it could not provide sufficient evidence to support the 'spillover' concept.

The final main category of international organisation theory combines elements of functionalism and the federalist approaches. Neofunctionalists have assumed as an end product a form of supranationalism, based on studies of the EEC, reflecting collective decision-making among a group of states having in turn developed from functionalist style integration. 'Spillover' is seen as essential, leading to an integrated economy across states governed by a single authority.[70] Important supplements to the process, however, suggest 'spillover' as only one possibility dependent on other factors such as the issue at hand, the degree of elite consensus and supranational authority. As far as this study is concerned, it is

not likely to contribute to debate in this area as it is too far removed from the regional conception underlying neofunctionalism. Granted the European Community had a role in the issue, but it was not central, nor was the issue of great importance relative to the other work of the Community.[71]

It could be expected that theories of international organisation might benefit from organisational theory in general. Decision-making approaches in International Relations, it has been argued, owe much to the studies of organisation in general, and that in a sense the study here, manifestly transnational, returns to the more general conception of organisation, in conjunction with a disaggregated systems approach. However, there has been limited work in the field on the possibility of applying organisational theory to international organisations. Gordenker and Saunders consider the possibility,[72] but emphasising intergovernmental organisations as the focus of study, in keeping with much of the international organisation literature.[73] These limitations are of less concern here, where emphasis is on a much wider set of transnational organisations. Of more importance is their observation that there is little work specifically examining interorganisational relations, a pattern of interaction well within the scope of transnational relations, and this study.

Taking both of these shortcomings in the literature, Gordenker and Saunders make some observations of note here. They suggest that there would be difficulty in applying organisational theory to two types of international organisation. Decomposition[74] would be too difficult where international organisations have a membership comprising other organisations or where 'patchwork' or para-organisations are the case. However, it is argued here that at least when dealing with primarily non-govern-

mental organisations, or with specialist governmental organisations or departments in transnational terms, then systems analysis of organisations can be applied. If organisations are themselves seen as decision-systems then these can be conceived of as sub-systems of a larger whole, defined in turn by the system of their interactions. It would be quite appropriate to examine decision-systems where participants are other organisations, although some elements of 'black boxing' might be necessary to transcend levels of analysis. In addition, the institutional identity of the organisation can be assessed partially in terms of the degree of openness of the system, to an extent overcoming conceptual problems of loosely consolidated organisations. More important here are communications patterns and content because the key role of many of the organisations involved, identified by themselves, was as information co-ordinators. In this context many institutional differences could be overlooked. It is the function that is of importance, rather than the precise method of fulfilment, and organisational roles can be analysed at many systems and sub-systems levels.

In reference to studies of interorganisational relations, Gordenker and Saunders indicate potential problems arising out of the sociological conceptions of organisational structure and function that dominate over more political concepts such as power and authority. The view here is that to overemphasise either approach would be misleading. Indeed, this case study raises an interesting point already touched upon. As John Burton has suggested,[75] functionalism is decision-making "within a specialist area by persons skilled in that area", a very 'technical' orientation. Of interest here are institutions specifically established to look at clearly delimited non-controversial 'technical' questions. Insofar as this goes then sociological or functional perspectives are very relevant. Over time organisational procedures develop and standardise

around the usual functions. A striking feature of the recombinant DNA issue area was the surprise of scientists and scientific organisations at the way the issue rapidly left the narrow technical sphere of rational assessment using applied expertise, and became politicised. Thus the case study must address transnational institutions established to operate in relatively non-political issue areas, finding themselves dealing with a politicised issue. Political insights are therefore equally relevant.[76] From this, however, an important question arises: to what extent do technically orientated groups, faced with a politically controversial issue and uncertain information, try to make the issue 'fit' a technical assessment? This question is returned to in this study.

The point to note is that while Gordenker and Saunders correctly indicate the limited application of organisational theory to international organisations and interorganisational relations in International Relations, their criticisms are limited by their focus on international governmental organisations.[77] In the transnational framework to be adopted here, the organisations often act both domestically and internationally, and distinctions are not perhaps appropriate. It is thus worth pursuing further the possibilities of using organisational theory in an interorganisational context, where organisations are seen as decision-systems. As Gordenker and Saunders suggest, this is best presented by the work of W. Evans.[78]

Evans bases his model on systems concepts applying at different levels of analysis, such as organisational sub-systems, the organisation in its entirety, and the suprasystem. As he observes:

> "The suprasystem level of analysis of an organisation necessitates at the very least an inquiry into the network of interactions or linkages of a given organisation with various organisations in its environment." 79

In examining the recombinant DNA issue area more will be said of the model that Evans develops, and in Chapter Two its concepts will be fleshed out somewhat. The intention, however, will be to complement the political concepts applied to the same actors.

3. SUMMARY.

In order to locate the recombinant DNA issue in International Relations, this chapter has attempted to survey the likely approaches to which the case study might be related. Much of the literature shares the common features of challenging the state-centric and state as unitary actor assumptions of traditional viewpoints. As a substantial element of the debate surrounding recombinant DNA reflected the decisions and decision processes of institutional groups, it seems important to consider decision-making approaches as central to this study. However, from the start actors were identified as interacting in a transnational fashion, which made the approaches incorporating concepts associated with trans-national and international organisation of special interest. In order to link the many levels of decision-making, a systems-based analysis appears most appropriate.

Such issues as recombinant DNA techniques and their control are clearly of relevance to particular orientations to the field of International Relations. It could be argued that since the recombinant DNA debate had little to do with state power, national interest and security, it is not of importance to the subject. But it should be said that there is room for a division of labour within the field. International Relations has much to benefit from approaches that widen the range of issues and actors examined. It is also argued that the interdisciplinary nature of such approaches often provides a different perspective to issues all too often

examined without explicit acknowledgement of international factors. International interactions must be seen as important at many levels of analysis in order to give a more complete picture of our contemporary world.

CHAPTER TWO

A STRATEGY TO PENETRATE THE ISSUES

1. Communication
2. Communications Content
3. Systems Interaction and Boundaries
4. Complex Decision Problems
5. Uncertainty Avoidance
6. Organisational Search
7. Organisational Learning and Feedback
8. Cognition and Perception
9. Values
10. Conflict
11. Participation, Decisions and Non-Decisions
12. Summary

A STRATEGY TO PENETRATE THE ISSUES.

Having established that the main features of the topic of recombinant DNA are in keeping with a number of respectable approaches in the field of International Relations, it is now necessary to develop an appropriate conceptual strategy to penetrate the issues involved.

In outline, this chapter will examine in turn a number of analytical concepts which can be operationalised within the context of the interactions of units in a system. It is argued that within a transnational political perspective these concepts are applicable across levels of analysis and in relation to the different categories of actor and decision-systems defined in Chapter One. In support of the approach, the limited work on interorganisational relations is acknowledged. The following concepts will therefore be taken in turn, encapsulating some variations of approach in the literature:

Communication

Communications content

Systems interactions and boundaries

Complex decision problems

Uncertainty avoidance

Organisational search

Organisational learning and feedback

Cognition and perception, in and between organisations

Values

Conflict

Participation, decisions and non-decisions.

1. COMMUNICATION.

Within the literature on organisational theory, considerable emphasis has been laid on the roles and patterns of communication. Much of this is due to the influence of cybernetics analysis in examining organisational activity. In particular, cybernetics can be applied, according to Karl Deutsch, to organisations of all kinds because:

> "... the viewpoint of cybernetics suggests that all organisations are alike in certain fundamental characteristics and that every organisation is held together by communication." 1

However in this study it is argued that important decision-making involved interactions between many organisations and therefore communications may be seen as of interest both within and between decsion-systems. In addition, Turner, in his work on the causes of disaster, suggested that:

> "It may be concluded ... that the nature of communication patterns and the barriers to communication which prevail during an incubation period are likely to be of particular interest to those concerned to study the origins of disaster." 2

By inference, any study of the development of acceptable safeguards would also need to address communications, both in terms of the networks or patterns displayed, and in terms of communication content. In more political terms the former helps to identify participants, while the latter gives substance to the conflict of values and perceptions involved. It has already been stated that this study involves an examination of both organisational elements of decision-making and political elements, and support for this approach can be gained from the work of Deutsch.

In his seminal work assessing communications factors in political

systems,[3] Deutsch draws parallels between technical systems of communication and political systems. His conceptions are therefore relevant in examining politicised features of decision-making, derived from the interactions of diverse organisations, and they are readily applied at transnational levels. Regarding transmitted information, Deutsch suggests that two classes of conditions influence effectiveness. Firstly, he suggests that the system in receipt of communication should have at least some parts in 'unstable equilibrium' so that receipt of signals might initiate otherwise disproportionate processes of change, or effects. This case study will involve an evaluation of the impact of the transnational communication of information between various governmental and non-governmental organisations. But the evaluation will have to relate to the responsiveness of the different organisations relative to each other, and including comparison between the rigidity of their standard operating procedures (see below). Deutsch's second class of conditions involves the 'selectivity' of the receiver, or the significance that is attached to incoming information in relation to information already stored. This involves the question of how specific the information must be to engender reaction.[4] Procedures for determining relevant information might thus be of importance, and could reflect differences between new and older decision-systems or organisations, where the older might have substantially more case experience. Areas of concern for the organisations involved vary in scope, and those with wider interests would perhaps respond to a greater range of information.

In sum, the basic features of communication, as seen by cybernetics analysts, are networks of information flow, the capacity of organisations to receive and combine new with stored information, the making of decisions, and the ability to change performance by taking into account the results of previous goal-seeking actions.[5] Information is the key

linking concept, which can be created, destroyed, quantified and, when measured, used to assess the efficiency of a communications channel. However, in this study anything more than tentative and subjective estimation of quantities is beyond scope, although it is argued that this is at least sufficient to identify important channels of communication. Indeed, the identification of such channels combined with an assessment of their relative importance was considered a prime function of this study as a first step in fleshing out an otherwise theoretical framework of analysis.[6]

Of perhaps more relevance in a single case study is the content of the communications. It has been suggested that:

> "In communication systems the goal is understanding - getting the sender and receiver 'tuned' together for a particular message." 7

When information is exchanged or distributed with regard to a politically contentious issue, then we must look beyond <u>who</u> is sending or receiving, the quantities of information passed, and consider <u>what</u> they are sending or receiving. It has been argued that genetic manipulation has been characterised, in its early years, by lack of information. Full participation in the surrounding political debate required not only access to available information, but also its comprehension or explanation. Any risk-benefit assessment requires the maximum use of available information, or legitimate conjecture, and organisational factors, actors' roles and political standpoints can all influence the filtering of information in terms of content.[8] Boundaries between technical communication linkages and politicised communication content are, therefore, somewhat blurred.

2. COMMUNICATIONS CONTENT.

In terms of the content of communication it is useful to distinguish between the transmission of intangible and tangible items. Intangible items include: messages carrying information; ideas, which might enhance viewpoints and approaches to issues between groups; values; credit; promises; instructions; and the like. On the other hand, tangible items are those which can be transferred physically, and can include the carriers of intangible items. Included are: goods in the economic sense; human beings; films; recorded radio and television programmes (rather than transmitted). These could carry intangible items, for example in the relationship of a letter, as an object, and its contents, or computer hardware in relation to software. Both types of communication are important, but their distinction in part underlies the difficulty of quantification.[9] For the most part it should be possible to take both types of communication together, for example as 'transaction flows' where information and physical items might be interchanged.[10]

Once attention is given to exchanges of items between actors, it is possible to introduce further politically relevant considerations. Exchange theorists for example have brought attention to associated concepts such as power, dominance and dependence in relationships. Deutsch himself, following Talcott Parsons, suggests that transactions operate through mechanisms of interchange or 'currency'. Examples might be power, with prestige as a form of credit, or force, which, in relation to power, could be seen in terms similar to gold in relation to paper money. Concerning the recombinant DNA case, it is possible to conceive of information as a currency of exchange. Information could be readily shared between groups holding common values or goals in a politicised debate, while denied or not interpreted to organisations or groups with

opposing outlooks. Marshalling of information to support viewpoints is at the heart of many political interactions, but this is especially so when the issues of debate have a technical or scientific base, where knowledge itself becomes a basis of power. Sources of information (perhaps experimental data) and information interpretation are both relevant in organisational terms and in political terms. A common ploy in debates on political issues is to state that the expert knows best and that opposition fears have no scientific basis. Of interest in the recombinant DNA debate were the processes of information acquisition, interpretation and dissemination, following the great uncertainty when hazards were first conjectured. It is necessary to examine communications patterns and content in this light. The corollary is to examine barriers to communication, both intentional and as a result of organisational limitations.

3. SYSTEMS INTERACTIONS AND BOUNDARIES.

A problem with any analysis involving systems terminology is that of defining systems boundaries. If we take the global state system level of analysis, the problem is essentially solved.[11] However, analysis of sub-state decision-making or webs of overlapping transnational systems and sub-systems, as envisaged by Burton, involve boundary problems. In general, systems analysts have advocated the idea of seeking explanations at the level of the 'whole', but as Burton suggests:

> "... systems and sub-systems are wholes in themselves, acting within their environments of other systems and sub-systems." 12

From this, and in keeping with organisational theory, it can be suggested that individual organisations can be seen as decision-systems, which in some way are related to larger systems comprising their environment.

Burton has suggested a means of identifying appropriate systems which can overlap through different levels, by defining each system in relation to the roles fulfilled by the component units. Systems comprise, therefore, units of the same 'set',[13] where sets can be identified by collective roles. The individuals or groups can be members of different sets, and hence systems, depending on the role they play in each. Scientists, for example, are members of the international science community which could be described in systems terms, but some might be involved in science policy decisions within governments, and nearly all could be located in terms of membership of specialist groups reflecting their field of interest or specialisation. In this sense, systems are open and receive inputs and produce outputs in relation to their surrounding environment, or other systems. For conceptual purposes there are boundaries, although permeable, and these in some instances might reflect institutional identities or organisations with regularised linkages.

If system delineation can be attributed to roles played by members, then communications between different decision-systems or organisations are likely to be facilitated by individuals or groups who are members of more than one system on the basis of playing a number of roles. Indeed, communications patterns and roles played by members of systems can both represent operational indicators of system boundaries. However, a framework of analysis identifying many overlapping webs of systems does not solve the level of analysis problem conceptually. It suggests that different levels can be linked, but other than giving the general advice of trying to see things from the point of view of an appropriate 'whole', the approach does not determine which is the 'best' system level for any set of issues. This study will attempt to identify suitable systems, assuming that the appropriate levels of analysis are less than the inter-

state level and are in some way transnational.

Initial categorisation of relevant systems involved the identification of the patterns of interactions within the United States and the United Kingdom. Each of these states responded to the early expressions of concern by establishing investigative committees charged with collating information and opinions with regard to risk, containment, suitable guidelines and procedures of implementation. Systems existed in terms of the interactions which produced final decision outputs in terms of guidelines and operational procedures. Implementation also reflected organisational activity assumed to be amenable to systems analysis, on the basis of the shared characteristics of organisations outlined above. Regularised interactions were quite apparent within these and other societies. However, the speed and influence of the results of these two cases make them of special interest. Transnational characteristics were much in evidence, in terms of information exchange and recommendations from outside these states being acknowledged, throughout the development of their procedures. Similarly the outputs of the decision-making processes were noted, and often directly copied or modified, within other states. International organisations assisted the channelling of information and the generation of new data.[14] Science is usually seen as international, especially at the research level,[15] and in an example such as recombinant DNA, perceptions of rigid national boundaries would not apply. Indeed, the transnational dimension became even more apparent as knowledge of the techniques progressed and guidelines operated, and pressures eventually developed for guideline relaxation.

For the purposes of this thesis, boundaries to many decision-systems are recognised, either at national levels or at institutional levels including both domestic and international organisations. Roles can be

seen to relate to the remits or constitutions of organisations, the goals required of them (either internally or externally determined) or viewpoints they represent, perhaps in political terms. However, as stressed, uncertainty was also a characteristic, which in part meant there was a process of the identification and development of roles for various actors, as the overall issue area transformed with time. Organisational learning and feedback were of relevance in this, and are discussed below.

Thus, emphasis on decision-making and operationalising these decisions necessitates analysis of the roles and actions of organisations. This also implies the analysis of organisations themselves in interaction. It is worth, therefore, considering further the notion of interorganisational relations, particularly as Evans, the main exponent, uses systems terminology.[16] Evans has developed what he terms 'an organisation-set model', assuming organisations are open systems which interact with their environments, with at least three levels of analysis involved: organisational sub-systems; the organisation in its entirety; and the supra-system. The latter is of particular note here, as in the suprasystem other organisations are part of the environment. For analytical reasons Evans suggests that reference organisations or classes of organisations should be seen as 'focal organisations' which interact with a complement of organisations in their environments or, as he refers to them, the focal organisation's organisation-set. Inputs and outputs are categorised by sets. Thus a complement of organisations providing resources to a focal organisation he terms an 'input organisation-set', and those that receive goods or services from it can be seen as an 'output organisation-set'. Feedback (see below) can therefore be included from the output set to the input set either directly or via the focal organisation. Organisations in the input and output sets can be seen to vary in size,

homogeneity, functions and so forth within their set. Finally, Evans suggests, the formal interaction networks for both input and output sets can be seen in the following terms: a dyad in which the focal organisation interacts with one other; a wheel network in which the focal organisation interacts with more than one organisation, but where there are no mutual interactions between those in the organisational set; an all-channel network, in which all the members of the set interact; and a chain network in which the members are linked in series with the focal organisation.[17] Apart from emphasising one organisation as the analytical focal point and describing four possible patterns of interaction, the approach is very much as that utilised here and is therefore relevant. However, Evans produces further insights which might enhance the developing strategy of penetration of the issues.

'Boundary personnel', Evans argues, should be investigated with regard to the focal organisation, in terms of numbers, their background and expertise, their position in the organisational hierarchy and their normative orientation towards the norms of their own and other organisations. This reinforces the need to consider key individuals at boundaries between decision-systems and, as outlined above, who might play roles in more than one. Assuming actors or groups considered in the case study display at least minimum characteristics of organisation, then models such as that produced by Evans, below, are applicable:[18]

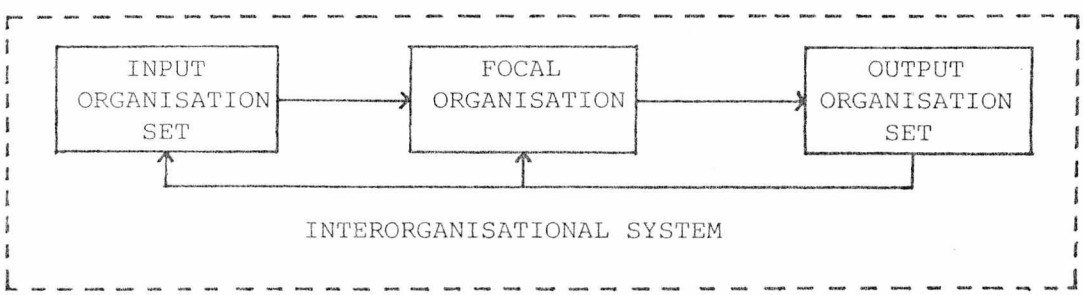


DIAGRAM 1

It might, on this basis, be necessary to examine the politics involved in establishing the boundaries of the organisation-sets. If key organisations are identified in the transnational interactions concerned with recombinant DNA developments, then taking them as focal organisations, their impact on other organisations or actors should be assessed. It may also be that political factors influence the determination of membership of the input organisation-set and subsequent inputs into the focal organisation. Such boundary and communications elements will therefore be considered and will involve an amount of mapping activity in order to highlight key organisations and decision-systems at various levels of analysis.

4. COMPLEX DECISION PROBLEMS.

Organisations and decision-systems are concerned with making choices. Many decision choices made by organisations are quite routine and not of great analytical concern, unless they represent decisions perceived to be routine and later shown as inadequate. Cognitive factors are discussed further below. On the whole, this thesis is addressed to a rather different category of choice making, described by Steinbruner as the 'complex decision problem', and which he characterises as involving the following features:

> "1 (a) Two or more values are affected by the decision.
> (b) There is a trade-off relationship between the values, such that a greater return to one can be obtained only at a loss to the other.
>
> "2 There is uncertainty (i.e. imperfect correspondence between information and the environment) ...
>
> "3 The power to make the decision is dispersed over a number of individual actors and/or organizational units." 19

Taking these characteristics in turn, it could be said that the first

feature applies to any political situation by definition, in that differing values are at the heart of all politics. The qualification that a trade-off relationship exists between values is less straightforward. In making decisions or choices there is always the opportunity cost factor if resources are required to make and implement them. In these terms there is an obvious trade-off. That complex decisions involve trade-offs in values affected is less clear, especially in such zero-sum terms as a gain to one is at the cost of a loss to another. In many instances this may be the case, but in others the conflict of values itself may be as a result of misperception. The fear that a certain action might affect an individual's or group's values or goals could initiate an aggressive response, even if the choice to be made in reality would not affect them. Access to information, and knowledge of values held by each group involved, could help reduce such consequences of misperception. Suspicion and mistrust might promote value conflict, while wider participation and input into decisions might help reassess apparent zero-sum choices as positive sum, where all sides could benefit. Legitimacy is central to this. Decisions are more likely to be accepted if the process of choice making is seen, by all affected by it, as legitimate.[20] In the case of the choices surrounding recombinant DNA techniques, it was clear that some influential decision-makers wished to treat the problem in a way amenable to rational assessment. On the whole, such attempts (despite problems of uncertainty) framed the problem as one of risks in relation to 'containment' or safeguard precautions. Questioning of the benefits of the research was much less, and seldom set directly against the risks by any one decision-making group. In general, the questioning of benefits by many groups was limited. Rather, great benefits were both conjectured and assumed, the only real question being one of time or complexity in their achievement. This was compounded by many stressing the tenets of academic

freedom in investigation, to support continuation of research, whatever the direct benefits. Trade-offs did characterise the case of recombinant DNA in the above sense. Work could go ahead but with restrictions on the type of laboratory, others questioned the benefits from the periphery of decision-making and academic freedom was questioned regarding the applications of the knowledge.[21] Perceptions, however, also changed, although not necessarily reducing conflicts but often transforming the issues at their centre. Scientists advocating great caution changed their views, while others, after voluntary guidelines emerged, called for legislation. More recently, on the basis of increased knowledge, risks have been shown to be less than first thought.

It is worth repeating that rational assessment does not avoid conflict of values, but rather it needs a basis to internalise values held by groups into the assessments. If choices affect differing groups' values, then rational assessment necessitates a means to compare those values in an optimising fashion. Even positive sum outcomes are not, however, without difficulty, as shown in Chapter One. In any case, Steinbruner's second feature of complex decision problems makes the likelihood of such rigorous rational choice very low.

Uncertainty was central to the recombinant DNA case, which led to its very emergence as an issue. Although often formalised in decision studies by the allocation of probabilities, risk assessment exercises in the case of recombinant DNA suffered from a lack of the information or knowledge with which to assign probabilities. Probability assessments also tend to reflect fairly rigidly structured problems, not characteristic here, with diverse views held by the many actors. Indeed, much of the decision-making of interest was centred on the first steps of how best to proceed, and how best to establish decision-making frameworks to cope with further

issues as they arose. Thus, uncertainty was of a wider nature than simple probability conceptions, taking the decision-making outside rational choice making and into areas of value judgement, differing priorities, and goals, despite some efforts to the contrary. Much, in this thesis, will therefore be made of the results of the uncertainty involved and in particular its consequences in terms of questions of legitimacy in the making of influential decisions.

The third feature of complex decision problems certainly applies in this case. Choices were not made, in terms of safeguards and their implementation, by single organisations (although some were obviously of relatively greater importance). If uncertainty and conflictual values were evident, then these were reinforced by not just the range of actors which were directly involved, but also by the number of actors which saw one of the central values at stake as being the very right to participate in decision taking and implementation. Section Eleven below will return to the question of participation in more detail. For the purposes of presenting an analysis of organisational elements of the recombinant DNA case from the transnational level, suffice it to say that the issues reflect complex choices, conflicting values and a situation fundamentally characterised by uncertainty.

5. UNCERTAINTY AVOIDANCE.

A characteristic of organisational behaviour in general terms is that organisations seek to minimise uncertainty. At least two authors, Allison and Steinbruner, on the basis of surveys of organisational theory, suggest methods by which organisations handle uncertainty. In essence, both suggest that organisations seek to avoid uncertainty. Allison, for example, notes that:

> "The first rule is: solve pressing problems rather than developing long-run strategies. The requirement that events in the distant future be anticipated is avoided by using decision rules that emphasise short-run feedback. The second rule is: negotiate with the environment. The requirement that future reactions of other parts of the environment be anticipated is avoided by imposing plans, standard operating procedures, industry traditions and uncertainty-absorbing contracts." 22

Steinbruner observes that uncertainty control can lead to concentration on a few incoming variables while eliminating entirely any serious calculation of probable outcomes.[23] Prior experience influences the process, suggesting given 'values' for the types of variable involved. Both authors indicate the likely use of standard operating procedures, and these can, in particular, be emphasised in relation to interactions with other organisations and the environment in general. The net effect of such procedures is the overall simplification of the decision-making process, with the least impact on organisational routines. Thus, an analysis of decision parameters on the part of relevant actors might provide useful insights into the extent of effort to reduce uncertainty by avoiding or bypassing it. If it is shown that such procedures were applied with regard to decisions relating to new conjectured risks and the allocation of controls, then there could be cause for concern.

6. ORGANISATIONAL SEARCH.

In their influential challenge to traditional economics theory of the firm founded on assumptions of rationality, Cyert and March refer to organisations undertaking 'search' activities stimulated by specific problems.[24] Relatively simple rules can be seen to apply generally, where problem symptoms are identified and compared with currently identified alternatives. It has even been suggested that:

"Organisations may engage in elaborate processes to justify a decision that has already been made." 25

Alternatives might be identified by organisations themselves, or they might originate as suggestions from outside. Either way, increased complexity arises from the possibility of individual biases affecting selection. Such factors can create sources of potential dis-information, or veils, through which the analyst must attempt to locate the source of decisions. For example, a charge was made against the US National Institutes of Health (NIH) that in assessing the impact of its measures for control, and possible alternative courses of action, it never seriously considered a long-term ban on the research. In effect, the charge was that the NIH was working to a prior assumption that the work would continue, the question merely being how. Further, it seems that it took threats of legal action to get the NIH to fulfil its statutory obligations to produce an Environmental Impact Statement, which involved an analysis of alternatives, and even then only after it had issued guidelines.[26] The difficulty, however, lies in identifying where biases affected the decisions, where limited search procedures operated and where suggestions of alternatives came from. This is especially so in a transnational study.

As far as this case study is concerned, a number of consequences are of note, especially where suggestions for choice are from outside the organisation. In the science community, interactions between groups and agencies are at a high level, but arguably often from a similar 'science' viewpoint. Thus, alternatives suggested by like-minded organisations may not be 'real' alternatives, but suggestions around a preconceived set of ideas, which in fact reinforce those ideas. Although these observations apply to behavioural characteristics of organisations in

general, they are also of particular note where political activity is involved. For example, the communications patterns identified might suggest which agencies make such suggestions to each other, and whether or not there is significant input from agencies representing different sets of beliefs, values and norms. Again this reinforces the need to assess whether political factors influence the membership of input organisation-sets, in Evans' terms.

With conditions of uncertainty well in evidence, for example in establishing guidelines in different states, there may be high correlations between the approaches adopted, as a result of transnational inputs from other systems. Of particular importance in the recombinant DNA case was that early decision outputs of the UK and US decision-makers influenced those that followed. In itself, this is not a criticism of 'borrowing', if the extent of borrowing is reasonably acknowledged, as questioning of decision processes can more narrowly be directed at the original source. The issue would assume greater importance if a particular decision inquiry professed to be independent of alternatives suggested by other agencies, but in the event was significantly influenced by them. This would include negative influences. If one organisation investigating an issue deliberately ignored a possible alternative, it might be that future inquiries elsewhere would ignore that same alternative on the basis of precedent, while actually going on to choose a quite different approach from the first organisation anyway.

Thus the nature of the search for alternatives is both relevant to this case study, and in keeping with the literature on organisational decision-making. Emphasis must, however, be placed on biases revealed in the choice making, which are related to values and norms, and which comprise political activity. It will be important, for example, to try to

identify how comprehensive were organisations in attempting to assess overall risks and benefits, both in relation to each other and in relation to containment requirements. If a comprehensive assessment of alternatives is not identified for any organisation, it will be necessary to consider the degree of 'satisficing' activity involved, where organisations search in sequence for a sufficient option.[27]

7. ORGANISATIONAL LEARNING AND FEEDBACK.

A key concept in cybernetics is that of 'feedback', which applies to all "self-modifying communications networks whether they are electronic control devices, nerve systems, or social organisations". Deutsch defines feedback as meaning:

> "... a communications network that produces action in response to an input of information, and includes the results of its own action in the new information by which it modifies its subsequent behaviour." 28

Further, it is possible to distinguish between positive and negative feedback, where the former refers to the amplification or reinforcement of existing behaviour, while the latter refers to margins of error relating to actions taken towards a specific goal. Consequently, when applying feedback as a concept to the behaviour of organisations or systems, it facilitates the analysis of organisational learning or adaptation. Emphasising negative feedback in his definition above, Deutsch considers four factors relating to the efficiency of feedback processes. Loads refer to the amount and rate of change of inputs into the decision-system, or the amount of information that the system must process. Lags refer to the time gaps between reception of information concerning the goal aimed for and the implementation of actions in

response. The third factor, gain, refers to the extent of corrective action taken, with a view to redirecting action towards a goal. However, there is always a possibility of overcorrection, leading to inaccuracy, or undercorrection, falling short of the necessary direction of action. Finally, lead refers to the distance between the accurately predicted position of a 'moving target' or changing goal and the actual position from which the most recent signals were received. The amount of lead depends on the efficiency of predictive processes available to the decision-system, hence its degree of preparation time. These factors taken together can be used to assess efficiency in terms of the adaptability, learning or steering actions of organisations or decision-systems in pursuing goals. As Allison notes:

> "Organizations are ... dynamic institutions. They change adaptively as the result of experience. Over time, organizational learning produces changes in goals, attention rules, and search procedures." [29]

With regard to organisational responses to the recombinant DNA debate and the subsequent recognition of the lack of empirical knowledge, it would be expected that some characteristics of organisational learning and adaptation through feedback would be evident. However, it will be necessary to identify the goals involved, whether or not they change, and the effects of organisational outputs as a consequence of the impact of previous action.

Controls, if decided as necessary, need to be monitored in a variety of ways with regard to assessing their continued relevancy in relation to the state of the art, levels of knowledge, and in terms of appropriate modification.[30] This is arguably essential within the context of this case study, and observations concerning the nature of feedback, and factors relating to its efficiency, are likely to be important. To

qualify this, it needs to be said that feedback and interactions with the environment need to be considered in relation to cognitive factors and the value judgements of individuals involved. In particular, there is a possibility of the overemphasis of supportive positive feedback, where the monitoring of previous action is biased towards information which legitimises that action. Unless organisations or decision-making groups look for falsifying information, there is a risk of the selection of information which justifies their original decisions. Perception and values, therefore, require discussion.

8. COGNITION AND PERCEPTION.

Complex decision problems, seen to involve trade-offs between values, also reflect differing perceptions held by individuals involved. Situations of conflict are directly linked to participants' perceptions of the underlying problem. Decision-making analysis has a tradition of considering the psychological dimensions involved, usually in the social psychological setting of small decision groups or the individual's cognitive factors.[31] Although of relevance, this area of research is comprehensive and could no doubt be applied in detail to the many individual decision groups involved internationally in the recombinant DNA issue area. This would quite simply be beyond the scope of this study and not wholly relevant where the emphasis is on values and decision principles as revealed by the actors involved, largely drawing on their communications. The formulation of the values and principles is of less interest here than the way they gave rise to political conflict in an historical case study. Yet awareness of cognitive factors is useful, in that certain perceptual difficulties of importance were quite evident. Of note were decisions related to conjectural risks and benefits, and misperceptions on the part of scientists concerning the consequences

of publicising their fears.

Decision-making analysis is centrally important to this study, but in the context of varying systems levels. With cognitive factors tending to be located at the micro end of the scale, where individuals or small groups are of note, application at other levels requires a personification of the actors, organisations or systems. Alternatively, in the literature on organisations, structural parallels are made with individuals. Thus, organisational learning, memory, information gathering and so on, are likened to similar functions evident within human beings, for example 'eyes and ears', human memory and the human brain.[32] Many of the concepts applied in this chapter are to an extent the organisational equivalents of those for individuals; for example, uncertainty avoidance, search, feedback and learning. Nevertheless, of particular usefulness for this thesis are the contributions of psychological and cognitive analysis applied to the concept of rationality and rational choice.

If pure rational choice necessitates a perception of all alternatives and an assessment of all related consequences, then the obvious limitations on perception in the real world have implications for rational choice. Where organisations are concerned, it is perhaps more realistic to conceive of rationality as being limited, or, as Herbert Simon termed it, 'bounded rationality'. He states that:

> "... the capacity of the human mind for formulating and solving complex problems is very small compared with the size of those problems whose solution is required for objectively rational behavior in the real world ... or even for a reasonable approximation to such rationality." 33

Bounded rationality refers to conditions where the decision-maker lacks complete knowledge of the situation. He, therefore, operates in an

incremental fashion, aiming for 'satisficing' outcomes. Taking organisations we can go a little further and consider different sets of assumptions and perceptions evident within different organisational subsections. We can also consider agreed bounds to rationality where decision problems and organisational functions are compartmentalised. Compartmentalisation of problems may also occur between a variety of organisations in interaction. Thus, to greater or lesser extents there may have been shared assumptions and perceptions involved at varying systems levels, within and between the organised groups which were involved in the recombinant DNA decision process. Public interest or trades union representatives on Britain's Genetic Manipulation Advisory Group, for example, might have wished to frame decisions within different parameters from those of scientific representatives. Alternatively, complex problems might have involved fragmentation, for functional reasons, along specialist lines. This would be more likely to occur at the operationalising stage where more routine activity of monitoring and day to day decision-making was involved. All such consideration must apply in transnational terms, examining a variety of agencies within states, and a variety of international organisations. In particular, shared assumptions or biases will be searched for.

Returning to cybernetic analysis, it is worth noting Steinbruner's contribution which, in recognising the compartmentalising involved, suggests that there may be more to consider in addition to cybernetic processes. As he observes:

> "Organizational arrangements are susceptible to human manipulation, and the problem is readily removed to the question of how organizational structure becomes established". 34

He proceeds to introduce elements of cognitive analysis into the study

of cybernetic processes. In particular, Steinbruner seeks to show how decision structures, or the hierarchical compartmentalisation of complex problems, can result other than from environmental imposition. He investigates the means by which important constraints on cybernetic processes can arise from sources of individual beliefs rather than objective reality. Complex problems are structured partly on the basis of the perceptions underlying beliefs, which among other things help resolve elements of uncertainty.

When the operational environment strongly influences the decision structure, then, he argues, more purely cybernetic processes may operate. But in the recombinant DNA debate, levels of uncertainty, the sophisticated nature of relevant information, the shortage of precedents, and the vocal rendering of different opinions combined to suggest that cognitive factors were relevant to the fragmentation of the complex problems involved. More emphasis, though, will be put on the fact that differences of belief were in evidence, rather than on detailed assessment of how patterns of perception and cognition influenced these beliefs. Yet the recognition of all those influences helps reinforce the view that political elements are important in decision processes.

9. VALUES.

Values, or sets of beliefs, both influence and are influenced by perception. Sometimes individuals may face difficulties in reconciling what they believe with what they perceive, and in extremes cognitive dissonance may occur, with either perception or beliefs having to alter. Of importance is that political relationships involve actors with different values, and it is the contention here that the debate surrounding recombinant DNA was politicised. Decision-making was in a political context

with conflicts of values in evidence. However, although the essence of politics is the conflict of values, the concept itself is not easy to define or operationalise. All that is hoped for here is that some insights regarding values may be applied in terms of organisations and decision-systems. Standpoints of actors will be assessed as they are revealed, with emphasis on resulting conflict and actor participation.

Although the social sciences have tackled the concept of values from different perspectives,[35] a fairly modest definition will be used here. 'Values' are seen to be qualitative and abstract, including such notions as freedom, order, equality, justice, mercy and the like. As Vickers points out, however, they are both explicit and general.[36] Further, he links the concept to that of 'norms' where the latter refers to commonly accepted standards, that may even become 'rules' and 'regulations'. Of particular importance is the observation:

> "That values affect norms is the faith behind all attempts at mutual persuasion and the experience which sustains them." 37

Norms can therefore change. Alterations in values have enabled norms such as slavery or male-only franchise to be replaced in many societies. Values as they apply in this sense are central to this thesis, especially as the study focuses on an issue area where decision processes were attempting to establish suitable norms in terms of rules and guidelines. Conditions of great empirical uncertainty facilitated a greater resort to values. Further, norms in this sense are compatible with Turner's notion of precautions which are "culturally accepted as adequate", as described in the introduction.

Values and perceptions held by actors involved are likely to influence

the political structuring of any decision-system, especially when one group is facing the regulation of its activity. The taking of 'sides' in the uncertainties surrounding the recombinant DNA 'debate' needs assessment, in association with questions of participation. Implicit, however, is that the issue area under examination involved elements of conflict, between actors, within decision-systems and between value sets.

10. CONFLICT.

In retrospect this study will attempt to identify the main issues of conflict regarding recombinant DNA. It will also consider the degree to which conflicts between the various viewpoints held by the actors were resolved at the various stages of organisational decision-making. Overall, however, the recombinant DNA debate was dynamic, with issues becoming modified over time. Because the norms of the situation were only developing, it was not possible to identify definite sides on all of the issues. Viewpoints changed as further knowledge was gained. An example of the problems involved can be seen in the way the improvements of knowledge led to perceptions of rapid increases in the future manipulation of life. Although the increased knowledge showed physical risks to be less than first feared, the very rapidity of the growth of knowledge led some individuals to develop doubts about its future indiscriminate application, for example in treating human genetic diseases, or in genetic interference with evolution. Uncertainty giving way to increased knowledge for some people, therefore, simply raised new issues about the applications of that knowledge. Within all this, the conflicts of values and the actions of actors holding different viewpoints need to be located.

Conflict is not necessarily a bad thing as at a minimum it represents the

interaction of ideas. It can be seen as a component of processes of change and development. To the economist, for example, competition as a form of conflict can lead to efficiency. Of note was the lack of physical violence in the case studied here, although speculation on deliberate misuse, or military use, of recombinant DNA techniques is noted. These various aspects of conflict are all considered as they revealed themselves, and in the degree of resolution of associated problems. They are also examined in terms of how values were fed into the decision-making systems. Associated with values in conflict is the participation in decision taking, or at least the legitimising of decisions if actors are not directly involved.

In structural terms it will be necessary to examine the various levels of interaction within which conflict occurs. Institutional, domestic, transnational and international levels must all be assessed. Thus issues relating to participation within and between organisations are as relevant to this study as issues of competition between national research efforts and industrial development. Because of these rather broad aims, conflict is taken in definitional terms in a fairly loose sense.[38]

11. PARTICIPATION, DECISIONS AND NON-DECISIONS.

The approach applied in this study suggests that decision and organisational systems can be defined by reference to characteristic 'sets' and the roles played by participants. Participation need not imply the direct involvement of all individuals who display concern, but can mean the representation of their views in the decision process. Traditionally, participation in decision-making involving contentious issues has been related to the concept of 'power', and traditionally disagreement over the precise nature of power has been endemic.[39] In the context of

decisions involving areas of conflicting values, power and participation are related to the political achievement of the goals of actors. Participants wish to see their values as predominant in the outcomes.

In many ways the political issues within this study can be reduced to questions of participation, the associated power which results, and legitimacy. To be accepted, both decisions and the processes by which they are made need to be seen as legitimate by all who have a perceived interest. This does not mean that every detail of a decision output should be acceptable to all concerned, but rather that any compromises or trade-offs of values are acceptable on the basis of general recognition of the validity of how they came about.

A number of analytical insights, however, can be applied in attempting to assess issues of participation and legitimacy. These insights are acknowledged to come from a consideration of sociological and political traditions, although they are applied here with regard to actors operating in a transnational context.[40] Firstly, it may be necessary to assess whether any actors applied power or influence in order to restrict the scope of decision-making to relatively 'safe' issues, in their view. Secondly, it may be expected that both organisational and political activity can be examined in order to determine just how issues entered the agenda of decision-making, and the overall politicised debate. These are important points to be borne in mind when considering the recombinant DNA issue area, not least because of the relatively technical nature of information relating to both perceptions of risk and benefit. Participation and legitimacy both involved the need to have technical and scientific information explained sufficiently well for non-scientist participants. Expertise in these areas could potentially give power to those in its possession, or could raise distrust if observers of the

decision-making activity questioned its legitimacy. As an example, at least one important issue, on the face of it, was downplayed in most decision forums; namely the possible application of the techniques in developing bacteriological weapons. A third insight suggests that:

> "All forms of political organizations have a bias in favour of the exploitation of some kinds of conflict and the suppression of others because organization is the mobilization of bias." 41

Although many of the organisations involved in the recombinant DNA issue area were primarily concerned with aspects of scientific research, they found themselves involved in a politicised debate. Insofar as they directly made decisions, or supplied inputs into decision-systems, then organisational bias, reflecting the shared perceptions of the membership, might have been in evidence. It is therefore crucial to consider where decisions were taken and by whom. Fourthly, and implied in the above, is that the concept of non-decision-making could be important.[42] That is, primary methods of sustaining a given mobilisation of bias are through the exercise of coercion or power, the blocking of challenges to the prevailing bias, the definition of certain issues as outside the scope of inquiry and taking active measures to reinforce dominant values. Although difficult to operationalise the concept, there may be indicators, for example, in degrees of grievance held by those who were disfavoured as a result of non-decisions or excluded from participation. The sort of difficulties involved can be compared to those related to pollution, which reflects non-decision: pollution is everywhere opposed, but we find pollution everywhere.

The point of raising the above insights is to suggest that although organisational analysis of decision-systems sets a useful framework for this transnational study, we must not forget that political activity is

also an important focus of this thesis. These insights are particularly important in that they derive from studies of organisational activity, and therefore provide a complement to systems analysis. Finally, it is worth saying a little more on the importance of legitimacy.

For authorities to be accepted, they must be legitimate, which implies that authority derives from those to which it is addressed. Reciprocal relationships are therefore involved, which, in the systems concepts applied here, suggests that loyalties are directed to the roles (representing values) played by participants. That is to say, participants involved in the various decision forums represent sets of values to which those not directly involved can at least focus loyalty. Problems arise when participants play roles which are not legitimised in this fashion. If participants face a failure of legitimacy, there is the possibility that what Burton calls 'role defence' may arise.[43] Participants might try to remain in authoritative positions through, it is suggested here, activity similar to that above, where bias is mobilised or decision frameworks narrowed.

In operationalising this study, it will therefore be important to consider where sources of authority lie, and where legitimacy exists, or is lacking. Because of the importance of information under conditions of uncertainty, the authoritative standing of the source of information is very important. It was after all the authoritative statement of a number of scientists expressing their concerns over conjectured risks that represents the start of this case study. It is also clear that as the debate unfolded, a number of non-scientist actors began to question the legitimacy of leaving decision-making to scientists, including those who initiated the concern. Such shifts in the perception of legitimate authority require explanation. It also requires a degree of comparative

analysis between the different international decision-systems involved, relating these in turn to the overall transnational system.

12. SUMMARY.

This chapter has outlined the conceptual foundation of the study, in relation to the relevant location of the issue area within the International Relations literature as outlined in Chapter One. The concepts apply at the various levels of analysis and to all of the systems of actor participation involved. Nevertheless they only provide insights to assist the investigation, and are not to be seen collectively as a theory to be tested. A variety of literature has been considered in these two chapters, but it is all applicable to the international characteristics of the recombinant DNA debate. Some of the insights are, however, likely to be of more utility than others. To complete Section A of this thesis, the operating assumptions and hypotheses will now be presented.

SUMMARY AND OPERATIONALISATION

1. Assumptions and Hypotheses

2. Research Method and Sources

3. Operationalisation

SUMMARY AND OPERATIONALISATION.

1. ASSUMPTIONS AND HYPOTHESES.

Many of the operating assumptions relevant to this study have already been stated implicitly or explicitly in addressing the International Relations and interdisciplinary literature. However, the most important assumptions are collected here, in order to clarify the position.

A. Assumptions as Related to International Relations as a Field.

i) The levels of analysis involved are multi-layered and conveniently categorised as transnational systems and sub-systems. The state-centric and state-as-unitary-actor assumptions of traditional analysis are deemed as not relevant to this study.

ii) It is assumed that mapping the patterns of interactions between the actors involved is a productive exercise and is related to the operational delineation of system boundaries.

iii) A number of analytical approaches are assumed to provide insights useful for the purposes of developing a strategy to penetrate the issue area. In particular, systems concepts, decision-making analysis, organisation theory and transnational concepts are of considerable use in a behavioural orientation.

iv) The case study has relevance to the study of international behaviour on the basis of:

a) There were perceived fears of low probability disasters knowing no international borders. The risk itself was 'transnational'.

b) The subsequent controversy was international in scope and the

issue influenced events in over twenty states, with the involvement of a number of important international organisations.

c) Operational controls and their development were transnational phenomena.

d) The case of recombinant DNA involves a dramatically new technology with unprecedented characteristics. International Relations has a tradition of considering technological impact.

e) Some observers have alluded to possible deliberately harmful applications of the techniques in the context of biological weapons. Although not the immediate concern of this thesis, it is of note as part of the wider controversy. Public information on this subject is not in abundance.

B. General Assumptions.

i) Technological progress is desirable, subject to general controls and sometimes more specific risk-orientated controls.

ii) It is assumed that laboratory and industrial utilisation of recombinant DNA techniques can be analysed on the basis of the risks that were once perceived in an historical sense, whatever the perception today. Responses and interactions were well established, if not also partially responsible, when the perceptions began to modify in terms of the conjectured risks involved.

iii) Although there are general difficulties in achieving internationally agreed and compatible controls, reflected here, there are also specific problems related to this case. The innovative nature of the scientific techniques involved, their biological nature and the involvement of industrial concerns at the initial laboratory stages are of note. This is of particular importance given the perceived

location of risk as involving laboratory research itself.

iv) A disaster, should it have occurred or if it does occur, is unlikely to be a consequence of the failure of isolated controls and safeguards of a specifically technical nature. Turner has adequately demonstrated the importance of organisational, sociological and other factors. The whole issue is controversial in a politicised sense.

v) If risk assessment is a technical attempt to estimate levels of risk involving acquired data and conjectural scenarios, then the difficulties are compounded if the exercise is taken to involve a balancing of risks against benefits. Risk-benefit assessment is a term applicable to the overall social and political scrutiny of the case. However, it is assumed that further difficulties relate to risk assessment and risk-benefit assessment when the risks and benefits involved are highly conjectural. A political dimension is assumed.

vi) Rational assessment (in the economics derived, optimising objectives sense) is of very limited usefulness when risks and benefits are both conjectural and uncertain. Such assessment is normally taken to mean the identification and ranking of all alternatives on the basis of maximising desirable outcomes and minimising 'costs'. In the absence of sufficient empirical knowledge, such an approach is of questionable utility. This problem is further complicated when some 'values' which it might be desirable to impute are highly subjective. However, if 'true' rational assessment were possible, then this would be desirable. Of question would be attempts claiming rationality on dubious empirical evidence or incomplete evidence.

vii) It is assumed that the innovative nature of the developments in recombinant DNA, in conjunction with the novel characteristics of risks and benefits, heralds implications for future developments in technology and science. These may be at the level of insights applicable to future biological research with similar characteristics; or they may be implications concerning social and political responses to risks arising from any new science, any 'high-intensity' science, or simply at the level of cultural adjustments to conjectured risk in general.

viii) Multiple channels of communication are assumed to exist, but in particular communications content is deemed very important.

ix) Finally, it is assumed that the politicised nature of the issue, involving values in conflict, may lead to instances of 'mobilisation of bias' or 'non-decision' on the part of major actors. Even if this cannot be proved either way in testing hypotheses and examining the case, conclusions must take account of such a possibility. This qualification is made in the light of the expected difficulties involved in identifying reasons for non-occurrences, or the absence of decisions and alternatives which may be politically evaded.

C. Hypotheses.

It has already been stated that this thesis is not primarily concerned with developing or testing any particular theory. At best, existing approaches within International Relations are being used to generate insights with which to investigate a case, argued to be of relevance to the field. Concepts are borrowed in order to generate questions which can be operationalised (see below). However, from the very start of this project a number of guiding hypotheses have been used to provide some

structure to the investigation. They are the products of an initial purview of both the recombinant DNA issue area and the nuclear energy issue, a topic which was of initial background interest.

These hypotheses are to be tested in a subjective sense, as discussed below, but with an awareness of a probable need for revision of one or more in the light of their operationalisation. Research is an ongoing process and this thesis, although a substantial first phase, will be likely to raise new questions suggesting modified hypotheses and further empirical investigation. Yet there is a substantial need for guiding questions and therefore these preliminary hypotheses were devised early [illegible].

i) Certain technologies have the potential for international catastrophe: such outcomes would partially be a direct or indirect consequence of political constraints and failings in the procedures used to operationalise control options.

Political constraints on operationalising control are at more than one level of analysis.

In addition to political constraints, the operationalisation of control options is subject to fault.

ii) In theory, control options exist that are feasible (within the context of the case in question) but were not considered, or were subject to political or economic constraint and thus not applied.

iii) Controls are looked for within existing systems based on an assumption that the systems themselves should not have to accept more than

minimal change. This hypothesis is related to the above discussion of the need to define systems.

iv) Lessons from the control of different technological phenomena displaying characteristics of risk are not adequately considered in terms of general procedures.

The tendency is to see the problem of control in isolation, thus resulting in a minimum of information crossing technologies.

v) Communication difficulties and information processing procedures within and between involved organisations are likely to affect significantly the possibility of disaster. These problems are international, transgovernmental, transnational and domestic.[1]

These guiding hypotheses underlay the operationalising of this thesis, the methods used now needing further elaboration. Empirical research took place over a period of two and a half years in the attempt to operationalise the above assumptions and hypotheses. The methods as discussed below were used.

2. RESEARCH METHOD AND SOURCES.

The aim of this thesis has been to penetrate the issue area with an essentially subjective analysis of the empirical evidence. However, although there are problems with relying on subjective assessment of relevant evidence, it is often the only way to investigate a particular case. The difficulties of subjective investigation of historical events are well documented by E.H. Carr, who identifies the nub of the problem when he suggests:

> "It is the historian who has decided for his own reasons that Caesar's crossing of that petty stream, the Rubicon, is a fact of history, whereas the crossing of the Rubicon by millions of other people before or since interests nobody at all." 2

It is for this reason that the assumptions used here are made clear. They provide a key to the thought processes which have influenced the interpretation of the empirical evidence. In a sense subjectivity cannot be avoided as if nothing else the decision to be objective in the first place is itself subjective. However, commonly accepted assumptions can be the reason why subjective observations might remain unrejected for long periods of normality within a field.[3] Explicit stating of assumptions gives others a reference point to locate a contribution within or outside a paradigm.

It has been argued that rigour in the use of subjective methods is both possible and desirable, although the form of the interpretation of empirical evidence is partially related to the source material. Not all types of data are amenable to the sophisticated techniques of manipulation provided by statistical and mathematical analysis. This proves to be the case in a study utilising the following sources.

Sources used for this study take the following forms. Firstly, the scientific press[4] provided many news reports, conference summaries, critiques of issues and were publishers of articles commenting on events and issues. Secondly, some journalistic style book length accounts provided useful preliminary information,[5] which assisted the initial entry into the issue area. Thirdly, the many government reports[6] provided vast reservoirs of potentially useful analysis, and in many cases supporting documentation or minutes of evidence. Fourthly, a number of the involved organisations have published annual reports or documents speci-

fically relating to particular issues.[7] In some instances they included both analysis and research details such as questionnaire responses. Fifthly, a number of organisations kindly made available minutes of meetings, sometimes not for general publication. Other informal and formal documentation of this nature has been acquired from the very substantial recombinant DNA archive at the Massachusetts Institute of Technology.[8] In addition, the archive provided a large number of interview transcripts and letters between many individuals and institutions. Weiner, or his co-researchers, visited many people involved and photocopied contents of their personal or institutional files. Sixthly, a number of interviews were conducted personally in the United Kingdom, on an informal basis.

The source material is preponderantly of document form, necessitating careful reading, analysis and co-ordination on a subjective basis, but guided by the above assumptions and hypotheses. However, the strategy of penetrating these sources and their content needs further clarification in the context of its relationship to the literature contributions discussed in this chapter.

3. OPERATIONALISATION.

A number of key elements structure the task of applying the framework, developed in Section A of the overall thesis, to the case under investigation. These can be summarised as follows:

A. System Identification.

In a transnational context, it is necessary to make some preliminary identification of the boundaries of the systems involved. Two national decision and implementation systems were examined in some depth, in terms

of the interactions of actors and important sub-systems. The decision and implementation systems of the US and the UK were important in being quick to respond to the voiced concerns, and were of influence in the subsequent development of controls in other states. Much of the total laboratory work was carried out in the UK and, especially, the US.

Important organisations at domestic and international levels were identified and their interactions were identified as comprising transnational systems. The aim was to develop an overall map of the transnational and international activities. Appendix One illustrates an early operational conceptualisation to which study was directed in order to add weightings to the lines of potential interaction. A further assessment is made in Chapter Eight.

B. Systems Interactions.

Throughout the study, concern has been to try to identify interactions between these systems, which in essence are defined by function. Thus the US, the UK, Western Europe, national institutions, governments, and international organisations will all be considered in terms of system-to-system linkages, at all levels of analysis. The identification of key communications channels should facilitate this, in conjunction with communications content which may influence each system. Elements of identification of inputs and outputs are therefore relevant.

C. Communications Content.

Communications content means the important information which is transmitted from actor to actor within a system or between systems. Political issues comprise information exchange and value judgements related to differing perceptions of how activities under discussion should be interpreted. It is therefore necessary to link cybernetic analysis of

communication with political conflicts. Information content and dissemination provide a link.

D. Activity.

The techniques of recombinant DNA need to be presented in order to give context to the investigation and to give substance to the issues. In addition to this, the actions of individuals or groups involved need to be identified where there is a political relevance. Thus publishing controversial claims, holding conferences, calling a moratorium on the work, imposing guidelines and such actions need to be identified where relevant to the issues of concern.

E. Participation.

Participation in decision-systems needs to be considered in positive (who participates) and negative (who is excluded or deliberately stays out) terms. Use of the mobilisation of bias to contain decision-making within certain parameters or within restricted groups may be of concern.

F. Decisions and Non-Decisions.

Where important decisions are made they need to be examined in a content sense and also in terms of their impact, within the system, between systems and in feedback terms. Non-decisions, if they are relevant, need consideration. These may reveal themselves through the activity and communications of relatively excluded groups. Relative importance can be assessed in terms of the extent to which the response is vociferous.

G. 'Rational' Reductions.

In view of the assumptions concerning rationality this thesis must examine the extent to which either, decision parameters are defined to facilitate rational assessment (especially if value-laden factors are omitted) or,

normative considerations are interpreted or altered 'to fit' rational assessment procedures. Where rational assessment appears legitimate, this too must be said.

H. Issues.

Where substantive questions of issue are raised by relevant actors, these must also be indicated, later collated (in the final chapter) and assessed, in relation to issues postulated here.

I. Comparisons.

Elements (C) to (H) must be considered intuitively in terms of each of the identified systems, and at different levels of analysis. Comparison may then be made between systems. This is particularly relevant in the US and UK guidelines' development cases. Factors such as participation, nature of decisions, degree of open scrutiny, parameters of investigation and enforcement may differ in quality.

J. Assessments and Conclusions.

The final chapter will return to a consideration of the assumptions and hypotheses in relation to the substance of the study, and the conceptual framework. The hypotheses operate at differing levels of analysis and in different operational contexts. (For example failure to consult the lessons of other technologies may be a consequence of elements of: system formation and interaction; participation; decision-making; issue identification.) The hypotheses are broad guidelines to which the above operational factors must finally be related.

SECTION B

RECOMBINANT DNA TECHNIQUES AND THE ORIGIN OF CONCERN

Chapter Three: The Techniques and Applications of Genetic Manipulation

Chapter Four: The Origins of Concern

CHAPTER THREE

THE TECHNIQUES AND APPLICATIONS OF GENETIC MANIPULATION

1. The Unravelling of DNA

2. The Techniques of Recombinant DNA

3. A Problem of Definition

4. Areas of Application of Recombinant DNA Techniques

THE TECHNIQUES AND APPLICATIONS OF GENETIC MANIPULATION.

This chapter is intended to provide a conceptual background to the development of technical scientific methods of producing what have become known as recombinant DNA molecules. No attempt will be made to cover exhaustively all the technical problems and underlying science, a project both difficult, given the author's academic background, and unnecessary, with regard to the issues towards which this thesis is directed. However, a summary of the nature of the recombinant DNA methodology and its potential applications is desirable, in order to put the subsequent chapters into perspective.

An important point to bear in mind is that these techniques are presented with the benefit of hindsight concerning their development. The next chapter will indicate the origins of concern in an historical context and show how fears developed before some of the methods presented here were achieved. Indeed the general decline of expressed fears, which became evident in the latter part of the 1970s, was related in part to some limitations of the techniques themselves, further influenced by attention being drawn to natural processes of recombination.

Although it is customary to present alternative definitions relating to matters under discussion as early as possible, this approach must be deferred in this instance. The term 'recombinant DNA' is not completely standardised within the scientific community, and even more importantly there are different usages among the non-scientist actors involved in this case study. Two aspects of the different opinions require mention: firstly, the nature of the phenomenon to be categorised, which is the descriptive purpose of this chapter; and secondly, the label to be applied to this phenomenon, an often controversial exercise, once it is

categorised.[1] While discussion of definitions is necessary, this is best accomplished in relation to the science and methods involved. It is, therefore, proposed to return to the questions of categorisation and labelling later in this chapter.

After a reference to the sequence of developments in knowledge, the three main methods of achieving recombinant DNA molecules, relevant to the concerns discussed in this thesis, will be described. The general requirements of such techniques can then be summarised. Recognition will be given to 'recombination' which occurs in nature, before presenting some definitions of what recombinant DNA can be taken to mean and a brief analysis of some areas of potential application of the techniques.

1. THE UNRAVELLING OF DNA.

Charles Darwin's theory concerning the evolution of species through the natural selection of desirable characteristics was formulated without knowledge of mechanisms of inheritance. Yet it is the modern understanding of genetic structure which underlies an explanation of the process of evolution which he advanced. Genes have become identified as the determinants of hereditary characteristics of all living organisms and are associated with a particular kind of molecule known as deoxyribonucleic acid, or DNA for short.

Because of the fundamental importance of this chemical molecule for both microbiology, in general, and recombinant DNA techniques, in particular, a background to its structural characteristics is necessary. Its importance is emphasised in that the principal 'dogma' held by biologists today is that DNA makes RNA (ribonucleic acid, discussed below), RNA

makes proteins, and proteins make everything else.

In 1869 Fredrich Miescher, a Swiss biochemist, isolated a substance given the name 'nuclein'. He later showed that sperm nuclei consisted of approximately 60% nucleic acid and 35% protein-like compounds.[2] However, until the 1920s the prevalent view was that biological specificity resided in proteins and not nucleic acid, the proteins being made up from chains of amino acids. The latter half of the 1940s produced the first conclusive evidence that it was DNA which was responsible for transmitting genetic information. It was shown that further purification of DNA improved the efficiency of transferring traits, and later in 1952 that when a virus infected a cell, only DNA entered.[3] Thus DNA became identified as the main determinant of genetic information.[4]

Identification of DNA as the main genetic determinant was not the same as understanding its chemical structure and the means by which it functioned in this role. The most important insight into the processes of heredity, and indeed evolution, was to come from the work of James Watson and Francis Crick, published in 1953.[5] In effect they deduced the precise three-dimensional structure from the available data, which they then used to propose a completely new suggestion as to how genes could replicate (and how mutations could arise).[6]

Part of the existing evidence that Watson and Crick were able to use was that experimental tests showed that four of the known components of DNA, termed bases, appeared in quantities suggesting some form of pairing. Work by Chargaff et al. and Wyatt, suggested that two of the bases, adenine (A) and thymine (T), occurred in approximately equal amounts, as did the other two, guanine (G) and cytosine (C). Further,

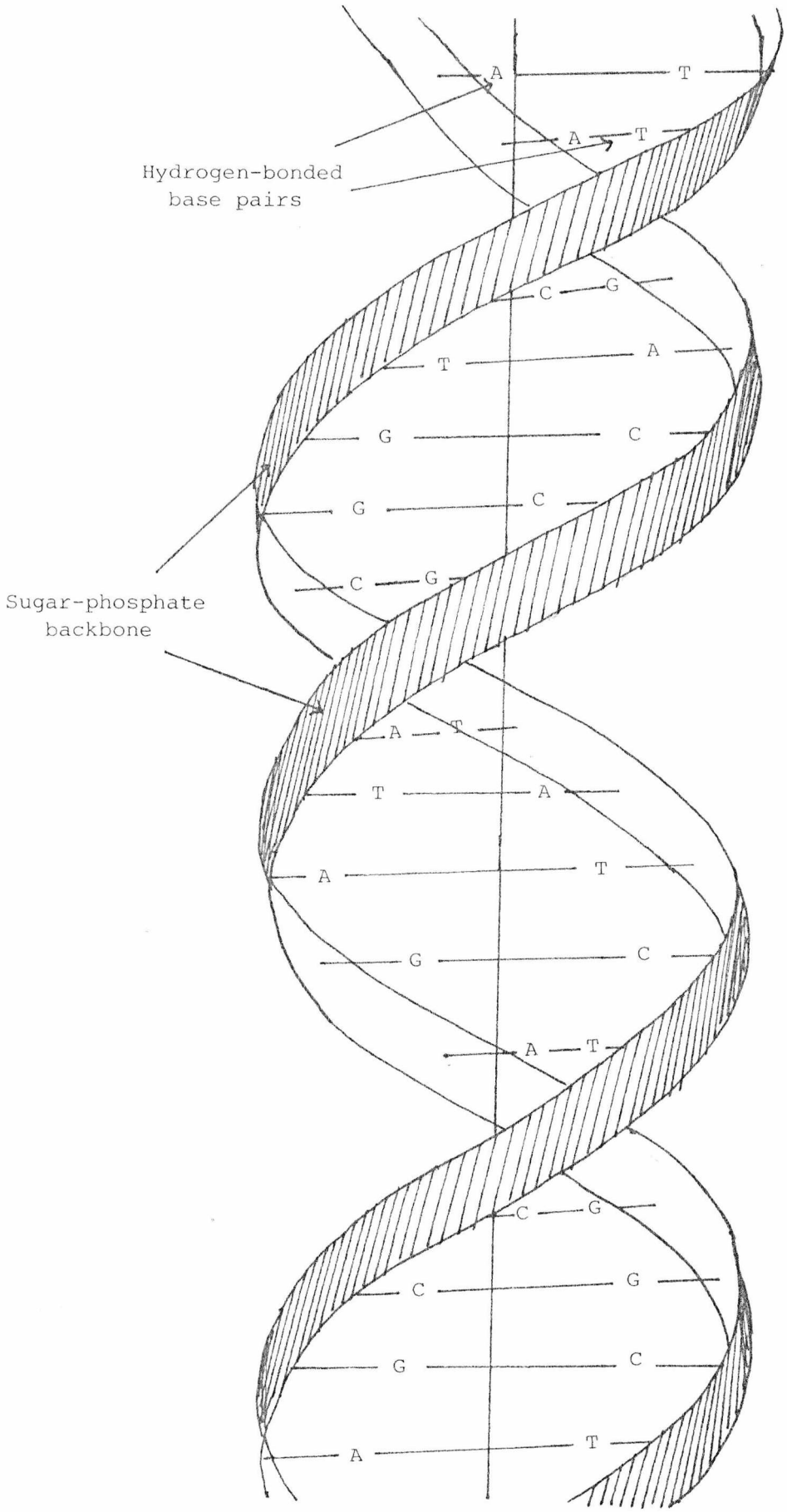


DIAGRAM 1. The Double Helix.

adenine and guanine were of one type of molecular base known as a purine, while thymine and cytosine were of another type known as a pyrimidine. The pairings therefore included one purine with one pyrimidine, but always the same ones.[7] It was also important that the paired bases could differ quantitatively in samples, a factor which assisted the identification of the pairing above, while the total quantities of purines and pyrimidines were apparently equal. The different quantities involved between the two paired sets reinforced the potential for astronomically large DNA sequence differences.

With the aid of further information gained from X-ray photographs of crystalline DNA, they pieced together a model of DNA that has subsequently enjoyed universal acceptance.[8] With A always paired with T and C always paired with G, the DNA molecule was found to comprise two helices which rotated around the same axis and were of the same size. Finally, the chemistry of DNA, which was partly known, involved a phosphate group and a sugar, which in the Crick and Watson model formed a 'backbone' to each helix, between which the paired bases were arranged. These 'backbones' were also noted to run structurally in opposite directions in the way that their components were linked.

It was the pattern of pairing in the bases that turned out to be the key to both the transmission of genetic information and the process of duplication. Each of the individual bases would be linked to one of the two backbones. The base, the sugar and the phosphate group at that point was termed a nucleotide and it was sequences of such nucleotides that according to Crick in 1958 provided the code which could lead to the production of at least twenty amino acids. In diagrammatic form nucleotides were made up as follows:

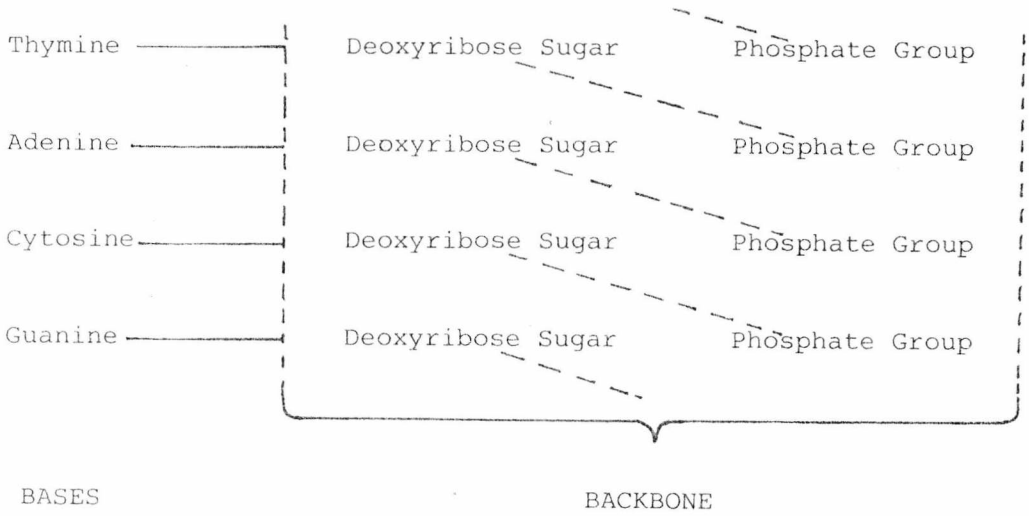


DIAGRAM 2

Diagram 2 shows four nucleotides in sequence indicating the links between the base, a phosphate and a deoxyribose sugar, and in turn the links between each nucleotide, which comprise the completed backbone.

Protein molecules are made up of combinations drawn from twenty different amino acids with properties stemming from the sequence of acids in the protein chain. Such is the complexity of possible combinations that, as mentioned above, early researchers thought protein might be the hereditary material. Crick's revelation focused attention on nucleotide sequences determining the position of amino acids and hence the protein molecule. In essence it is the four bases (and the letters A, T, C, G) which provide a genetic code or alphabet from which genetic specificity derives.

However, the coding process must be completed by introducing the role of RNA. Chromosomes which carry genes are found within the nucleus of

cells, while protein synthesis occurs in the surrounding cytoplasm. RNA was identified as the means by which genetic information was transferred out of the nucleus where it can sequentially order the amino acids.[9] A primary product of a vast number of genes is ribonucleic acid, which is a single strand of bases complementary to one strand of the original double helix and almost an exact copy of the other strand.[10] It is almost an exact copy in that in RNA the base thymine is replaced by a structurally similar base called uracil (U). An enzyme catalyst termed transcriptase is involved in the process by which RNA forms off one original DNA strand. Thus from a double DNA stranded gene, a single strand of messenger RNA forms, which in turn controls the order of amino acids on a protein chain. Each amino acid is positioned from the 'message' carried by a sequence of three nucleotides or bases, as in the diagram below, and known as codons.

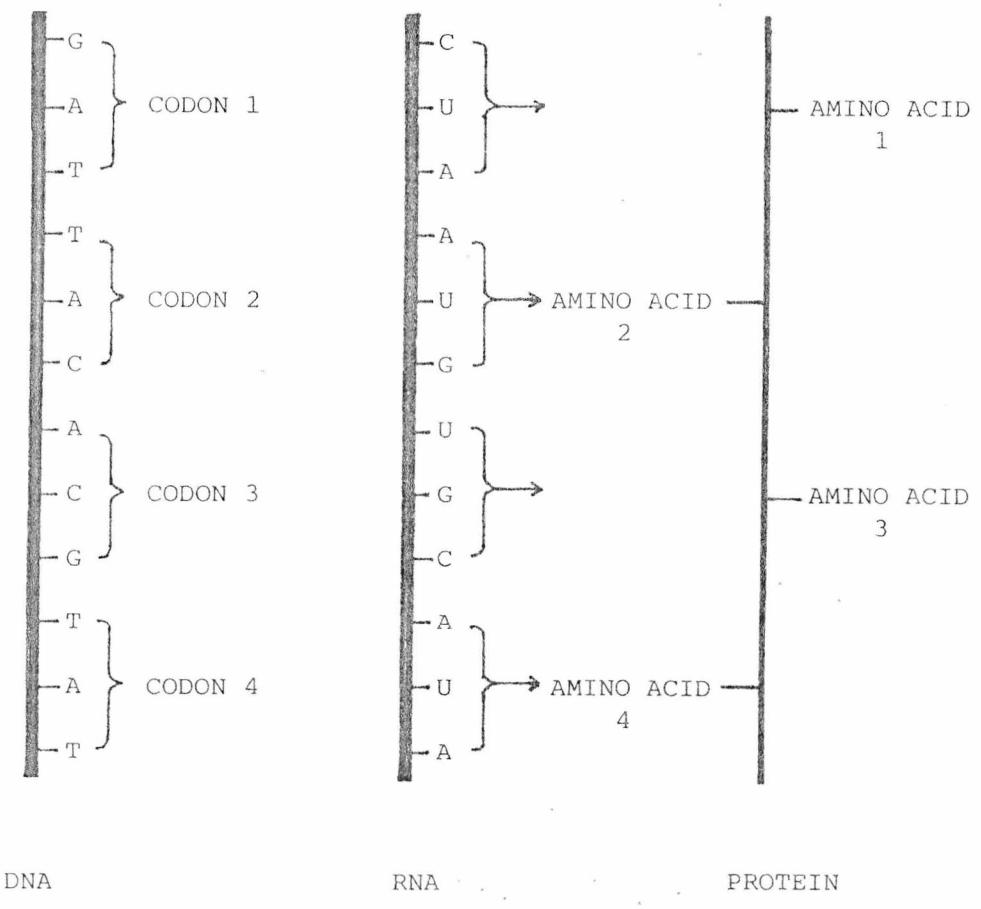


DIAGRAM 3

Thus it can be seen that the original sequence of bases on the DNA strand determines the final characteristics of the protein. The term translation is given to the process of an RNA 'template' ordering protein chains.[11]

A typical gene is about 1,500 base pairs long and simple organisms such as single-celled bacteria have enough DNA for about 3,000 to 4,000 genes. However, each human cell contains about a thousand times as much DNA as a bacterial cell, or enough DNA for three to four million genes,[12] suggesting the enormous complexity of the code arising from only four bases.

However, the DNA code is not only responsible for the transmission of information within an organism. It is also responsible for the passing on of genetic information to subsequent generations. Under appropriate chemical conditions the hydrogen bonds of the paired bases weaken and the two helices unwind and separate. In the presence of suitable enzymes and available nucleotides of the four kinds, a new strand will form by complementary bonding to the exposed nucleotides of each of the older, but now separating, strands. Two exact duplicates of the original double helix then form. Each separated base pair of the original double strand finds a replacement complementary partner from the 'pool' of nucleotides, as in Diagram 4. All the genetic information of the original DNA double helix is incorporated in each of the subsequent copies. At cell division the appropriate conditions for this to occur exist, its importance summarised by Grobstein:

> "At the level of molecules, like begets like through DNA replication. This phenomenon occurs in the reproduction of every organism on earth and it has been happening, so far as we know, ever since the first time life emerged eons ago. As a chemical process, the doubling of DNA is undoubtably the most prolific and portentous of

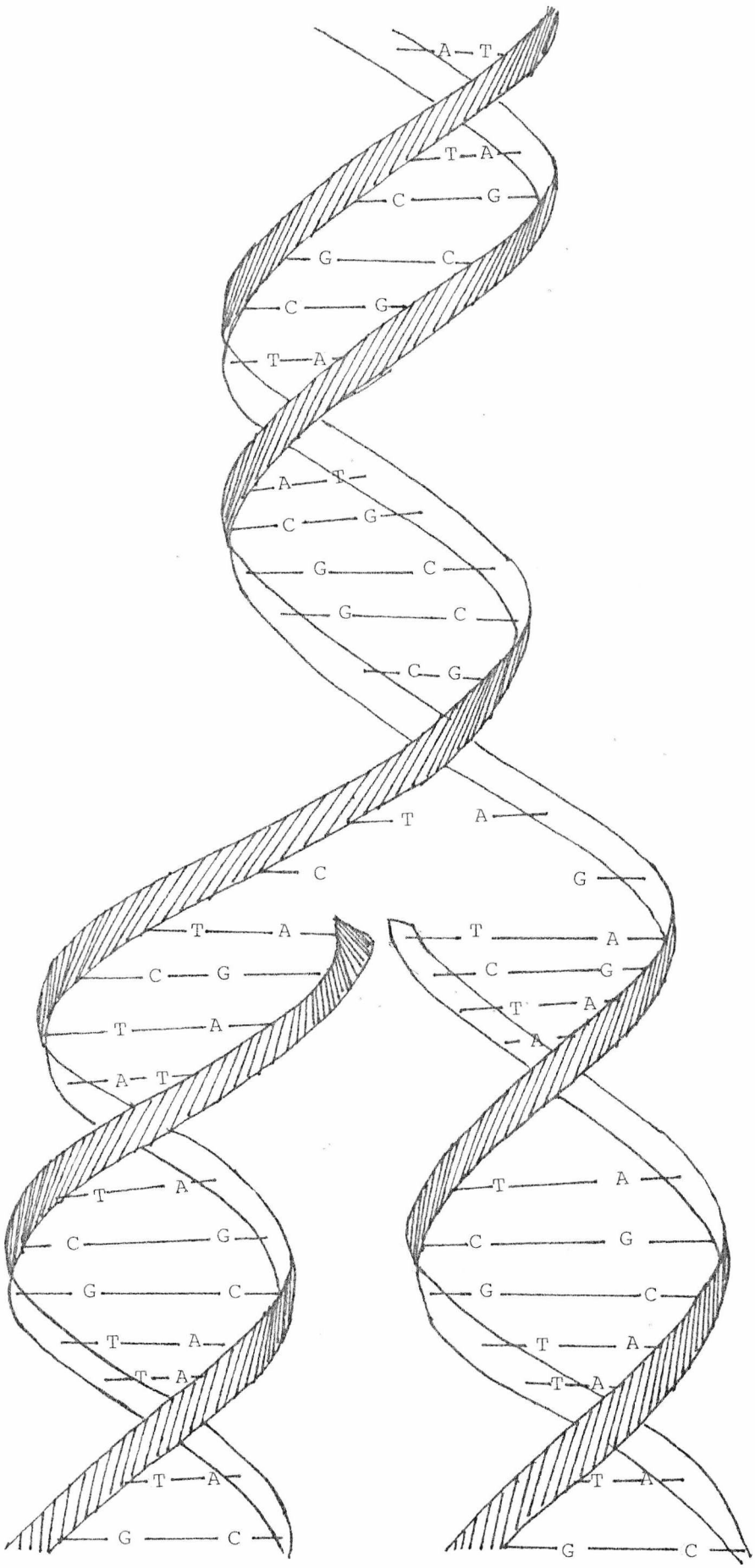


DIAGRAM 4. The Replication of DNA.

nature's entire bag of tricks." (13)

Not all replication is perfect, however, and variation enters the endless production of copies, through mutation, which can be defined thus:

> "A mutation occurs when the sequence or the number of nucleotides in a nucleic acid is altered and the new sequence or number is passed from parent to offspring." (14)

Mutations can therefore arise from changes in the pattern of the bases, such as the substitution of a base pair, the addition of a base pair, the deletion of a base pair, or in some instances the mispairing of two bases, producing either a T + C or a G + A. Subsequent generations would then be affected, although some correction would occur in the case of a mismatched pair on DNA replication, where the correct base in the pair would acquire the correct complementary base. The other base would, however, acquire its complementary base and all future replications in its line would carry a base pair now fully substituted for the original pair at that point in the gene. A new base pair would alter the RNA message and the codon at that point of change could lead to a different amino acid entering the protein chain.[15]

Many such errors must accumulate in serendipitous combinations to produce a species change, although mismatched pairs are less likely, due to distortions they cause in the structure of DNA.[16] Further, the whole phenomenon of mutation is much more complex than outlined above, not least because there are even mechanisms involved which correct mutations when they occur, and are themselves in turn capable of failure.[17]

To a large extent the unravelling of DNA and its biochemical functioning,

with all the attendant mechanisms, has given a model which can accommodate Darwin's much earlier theory of natural selection. However, the 1970s were to see major breakthroughs in the ability of man to manipulate DNA and increase his understanding of its functioning, through the application of a number of biochemical laboratory techniques.

2. THE TECHNIQUES OF RECOMBINANT DNA.

For centuries man has used selective breeding techniques to develop 'errors' that have occurred in breeding populations, through mutation, when the resulting characteristics were seen as desirable. Thus agricultural and pet animal selection has taken place. Natural selection in the Darwinian sense also makes use of these mutations, but the success of both forms of selection is dependent on the random occurrence of desirable mutations. The importance of recombinant DNA techniques is that for the first time genetic change can itself be directed.[18] As Grobstein indicates:

> "The new techniques enable one to deliberately introduce known and successful nucleotide sequences from one strain or species into another, thereby conferring a desired property." (19)

Because DNA from all living organisms is made up of the same four bases, interest grew in the possibility of mixing DNA from different organisms and species. The tools of chemistry and physics had from the 1950s become more relevant to the study of life, and a number of developments in the 1960s were to set the scene for the use of recombinant DNA techniques in the 1970s.

By 1961 DNA from bacterial and other sources could be purified and isolated. DNA because of its 'rod-like' structure had been prone to

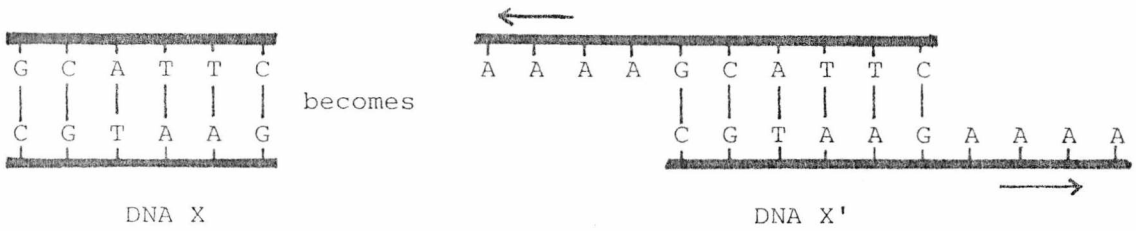
breakage when passed through small apertures, for example during pipetting, and the problem had been how to obtain segments long enough to carry genetic 'information'.[20] Work on the coding determined by sequences of nucleotides led to research aimed at specifying sequences precisely and if possible isolating, purifying, and duplicating the key ones. As has been shown, the nucleotide sequences, in groups of three, code for amino acids and hence proteins. But in the course of research on the sequencing, it was discovered that not only are proteins a product of this process, but that certain proteins are also essential to DNA replication itself.[21] A major function of proteins is to act as catalysts, or enzymes as they are known, in the linking of DNA during replication. However it was in 1965 that a particular example called terminal transferase was accidentally discovered while trying to isolate a different enzyme. It was important because it was found to have the ability to add either As or Ts to the end of DNA, one nucleotide at a time.[22] This provided the first method of joining molecules of DNA.

Method 1

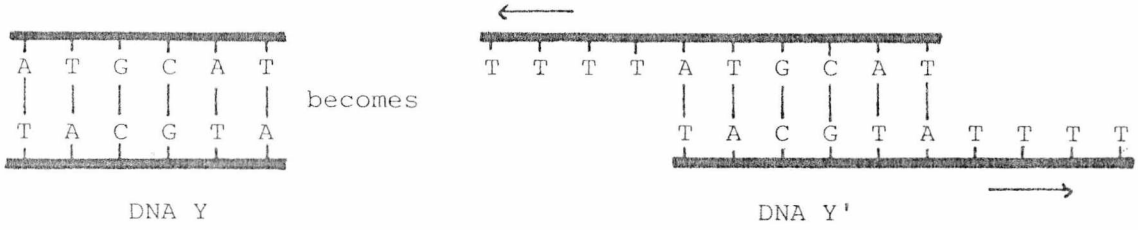
It has already been described how complementary strands of paired bases form in an environment including free bases of the four kinds. Terminal transferase could specifically add As to one end of a DNA segment, on one of the two helices, and As to the other end, but on the second strand. This ability is related to the opposite directions of 'polarity' of the two helices. By taking DNA from one source and adding As to one end (a poly-A tail) and DNA from a different source but adding Ts (a poly-T tail), the use of the enzyme ensures the appropriate strand is selected in each case such that the extensions on the two pieces of DNA are complementary. Diagram 5 illustrates the sequences involved in joining DNA in this fashion. However, as can be seen in this diagram,

1. Two DNA molecules to be joined:

2. DNA X is treated with terminal transferase to add Poly-A tails:



3. DNA Y is treated with terminal transferase to add Poly-T tails:



4. Because A and T are complementary bases, DNA X' and DNA Y' will join:

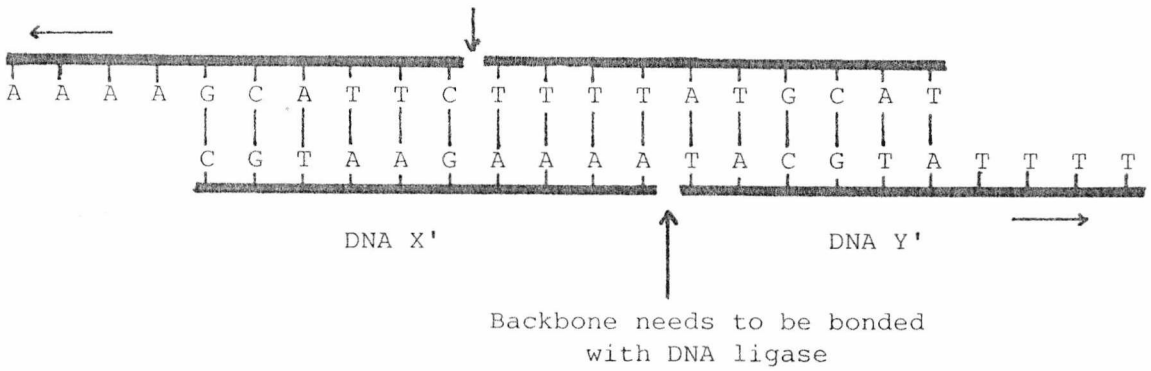


DIAGRAM 5. The Joining of Two Molecules of DNA Through the Use of Terminal Transferase.

the backbone of each strand is not joined, and the two DNA molecules are only held together by the relatively weak hydrogen bonding of the base pairs.

In 1967, a number of laboratories had independently discovered a class of enzymes, which could here be applied to bond the backbone, given the name polynucleotide ligase.[23] This type of enzyme could catalyse the reaction necessary and after its application the joined DNA molecules are as complete as any single one. Although the steps toward joining DNA as outlined here are conceptually simple, the biochemical practices involved are complex, involving the use of highly purified enzymes and a considerable degree of technical expertise. A major advance simplified the whole procedure.

Method 2

The 1960s saw more and more work concentrating on lower forms of life such as bacteria and viruses, rather than higher organisms. These simpler organisms differ in that their cells do not have a nucleus, and are called prokaryotes (pre-nuclear) to distinguish them from higher organisms whose cells do contain a nucleus, given the name eukaryotes ('true', 'nucleus'). This shift in emphasis enabled the experimenters to deal with generations measured in minutes rather than weeks or years, thus making genetic errors more identifiable and manipulable.[24] The simplicity of such organisms is easier to understand than the complexity of multiple chromosome higher organisms, making them attractive to study.

In 1962 it was demonstrated that certain bacterial viruses, known as bacteriophages (or phages) that grew on one strain of the bacteria Escherichia coli, E. coli K-12, grew poorly on a different strain, E. coli B.[25] However, those few particles that survived were perfectly

capable of infecting E. coli B, but not E. coli K-12. It seemed that E. coli had a mechanism by which it could protect itself from foreign DNA. It was found that a particular enzyme, called restriction endonuclease, introduced a number of breaks in the backbone of the infecting viral DNA. Moreover, the restriction endonuclease does not attack its own cell because of protection provided by a set of modification enzymes. In general, an endonuclease attacks the backbone of DNA, while a restriction endonuclease only attacks the backbone at points identified by specific sequences of nucleotides.[26] Each strain of bacteria, it seems, has its own modifications carried out to protect it from its own restriction enzymes. On the other hand, invading DNA is cut before the modification enzymes of the cell being attacked can modify the foreign DNA. The utility to recombinant DNA techniques was that certain restriction enzymes could cut any DNA where a particular sequence of nucleotides occurred, but in a staggered fashion, as described below.

It was found, in 1972, that a restriction enzyme from E. coli known as endonuclease Eco RI could generate staggered cleavages by cutting the parallel backbones in such a way as to leave overlapping ends which could reassociate through pairing of the bases. This particular restriction enzyme, for example, recognises the following symmetrical sequence:

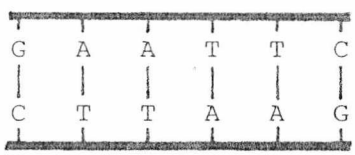


DIAGRAM 6

The enzyme then makes a staggered cut between the adjacent A and G on each backbone, which as discussed above have opposite polarities:

DIAGRAM 7

Complementary single strand tails, four bases long, result, whatever the source of DNA,[27] thus enabling DNA, diverse in origin, to be joined. As with Method 1, however, the newly bonded DNA requires the use of ligase to join the backbones:

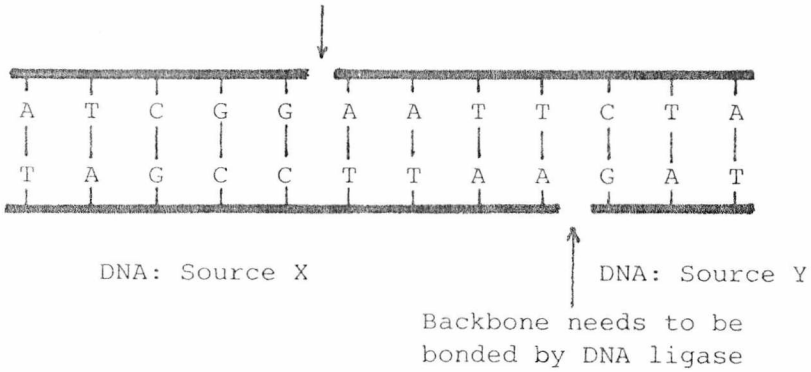


DIAGRAM 8

Weak hydrogen bonds hold the two sections of DNA together more effectively at low temperatures (below 16°C) until the DNA ligase is added. Overall, this second method of joining DNA is simpler than the first method and has the additional advantage of providing the means to segment the DNA prior to its rejoining in different arrangements, whatever the source of the DNA.

Cleaving and joining DNA is, however, only a part of the whole process involved in obtaining something <u>useful</u> from recombinant DNA techniques. Some complexities and further techniques must now be mentioned, before indicating Method 3, which bypasses a number of stages.

Some Modifications.

Eco RI, for example, cuts DNA on average every 4,000 base pairs. Jackson points out that if one attempted to join 'duck' and 'orange' DNA, the use of the restriction enzyme would produce some 250,000 fragments from each duck and orange cell. All of these 500,000 fragments will have Eco RI termini at each end, enabling a variety of possibilities to occur: each fragment could circularise as its own ends join; each fragment could interact with essentially equal probability with any of the other duck or orange fragments; it could join with another copy of itself; when two fragments have joined they in turn could react like a single piece, with the same possibilities. Thus the potential linkages are very complex.[28] Because of the crucial importance of the organisation of chromosomes in order for the regulation and functional expression of genes to occur, there is very little likelihood of anything viable as an organism resulting from this mixture.

Some technical modifications enable more useful outcomes. A major change is to ensure that the source of genes used is much simpler than ducks and oranges, thus reducing the complexity of the DNA mixture, which increases the relative proportion of the desired recombinant molecules. By using terminal transferase, it would be possible to have all the DNA from one organism to have A tails (poly-A tails) while DNA from the other organism could have T tails (poly-T tails) avoiding circularisation of any single fragment. It would also ensure the mixing of DNA sources.

An extremely powerful modification is to make sure that one of the sets of DNA to be combined has the power of self-replication. Replication of DNA, as discussed above, requires the DNA to be physically linked to special sets of DNA which code for replication functions.[29] These

particular genes are relatively rare, and bacteria which contain about 3,000 to 5,000 total genes only contain a single set of replication genes. Nevertheless, a particularly useful means of gaining access to replication functions was developed, through the use of plasmids. These are small circular pieces of DNA which are found in some prokaryotic cells, independent of the large circular chromosome, and are capable of self-replication.[30] Almost every known form of bacterial cell can house plasmids, although only a very few individual cells will actually contain them.

In 1973, Stanley Cohen and Herbert Boyer led an experiment using the plasmid pSC101 (plasmid Stanley Cohen 101), selected because of its property of having only one Eco RI cleavage recognition site. Thus when cut, the plasmid could link with foreign DNA also cut with the same restriction enzyme such that a new hybrid circular plasmid could form. Cohen and Boyer used 'foreign' DNA derived from another plasmid in this first experiment, but the way was opened for similar experiments using DNA from other sources.[31] Diagram 9 illustrates the method by which plasmids can be utilised for their replication functions to obtain large quantities of the inserted DNA. However, not all cells will contain the independently replicating plasmids, and some means of selecting which cells actually contain the plasmids becomes necessary.

Identification has been facilitated by the fact that many plasmids contain one or more genes which confer resistance on the cell to one or more antibodies that would normally kill it. Antibiotic resistance can thus occur from plasmids which specify enzymes that can break down drugs. By using the above techniques to insert modified plasmids into plasmid free cells, future generations of the cells containing plasmids can be identified by introducing the antibody to which the plasmid

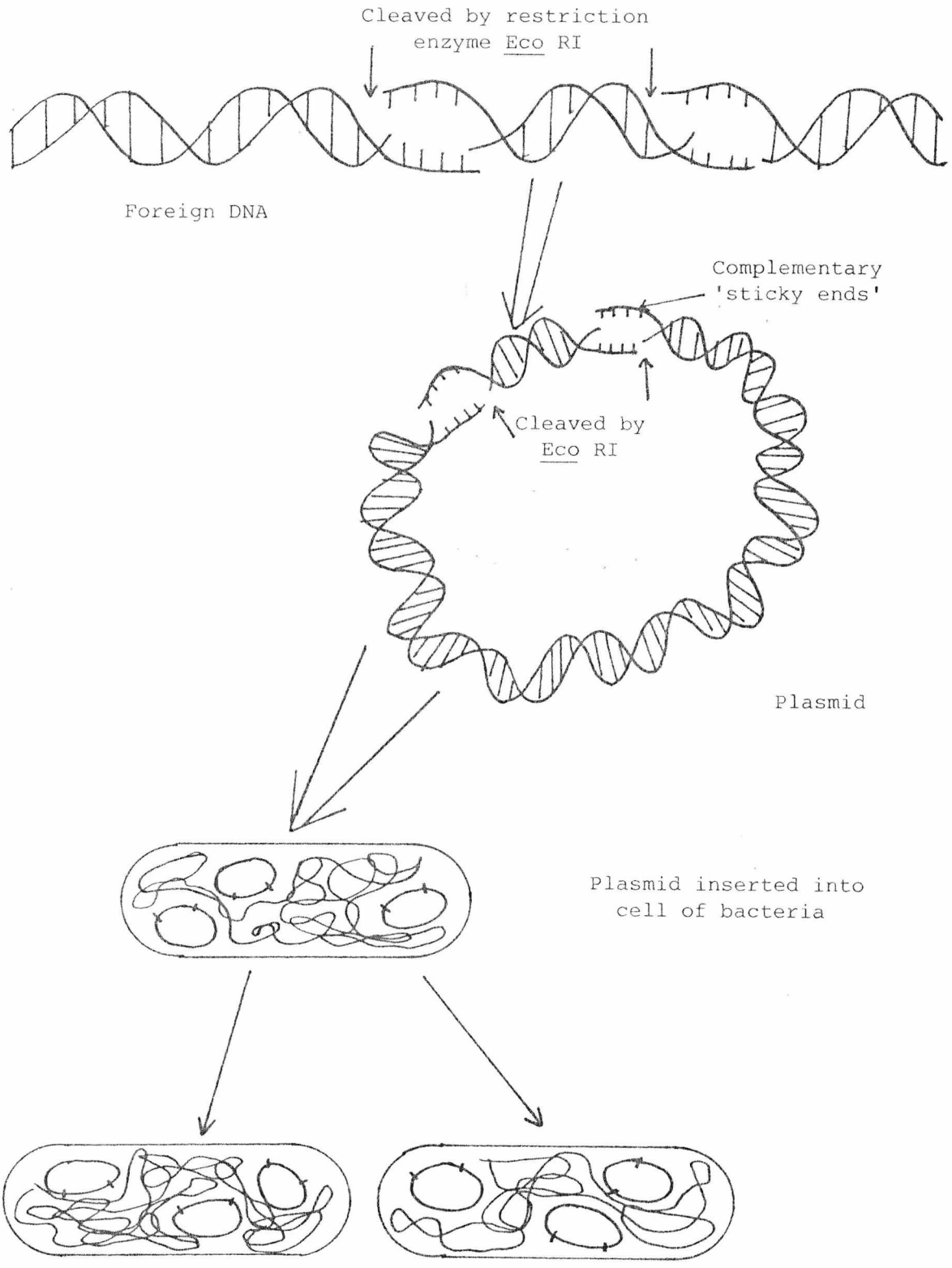

Cleaved by restriction enzyme Eco RI
Foreign DNA
Complementary 'sticky ends'
Cleaved by Eco RI
Plasmid
Plasmid inserted into cell of bacteria
Cell propagation

DIAGRAM 9

provides resistance. Flexibility exists in the approach in that different plasmids can be used which respond to different antibodies, in relation to experimental requirements. This, however, is only part of the identification problem. It is also necessary to be able to tell which plasmids initially acquired the additional DNA after cleavage and which did not. In order to do this, use can be made of plasmids that contain genes which code for resistance to more than one antibody. The plasmid must then be cleaved by a restriction enzyme that recognises a nucleotide sequence that occurs within one of the gene sections coding, for example, for one of two resistances. Insertion of foreign DNA at such a point inactivates that resistance by altering the sequence of nucleotides. Resulting cells displaying resistance to only one of the two antibodies most likely contain foreign DNA.[32]

A more direct method of screening is to look for abilities of the recombinant plasmid that the cell otherwise would not have. For example, the bacterial cell may not be able to grow in the absence of a certain amino acid. But if the inserted fragment contains the information necessary for synthesis of this compound, then the cell could grow in its absence. Although a very powerful selection method, it depends on the information contained in the inserted DNA being functionally expressed.[33]

Finally, the complementary structure of DNA provides a further basis for identification and selection. Hybridisation involves the ability of DNA strands to reassociate with DNA from the organism from which it was derived, but not with the DNA of the cell into which it is inserted. Foreign DNA should be detectable in this fashion.[34] A refinement of this procedure involves the use of 'nucleic acid probes'. Radioactively labelled messenger RNA which derives from a known gene in the donor

organism is first isolated in as pure a form as possible. Although difficult to achieve sufficiently pure mRNA, it is possible. Using hybridisation screening procedures these RNA probes can be used to identify the bacteria which have had this gene inserted.[35]

A second means of gaining access to replication functions was based on the use of a class of viruses known as temperate bacteriophages, which grow on bacterial cells. The DNA molecules of the phages have long been known to be capable of acquiring genes by recombination[36] from the chromosomes of the cell they infect. However, in bacteria they can also be incorporated into the chromosomal DNA itself. A phage often used is lambda phage, which even with sections deleted can still replicate. It was also found that DNA inserted into the phage would have to be of a certain size in order to maintain its viability. In 1974, researchers took advantage of the above to generate special forms of lambda phage into which foreign DNA could be inserted, but which contained only a limited number of restriction enzyme cleavage sites and a large DNA deletion. In addition, the phage would not propagate in E. coli without the foreign DNA inserts. Diagram 10 shows the locations within the cell of both plasmids and phages.[37]

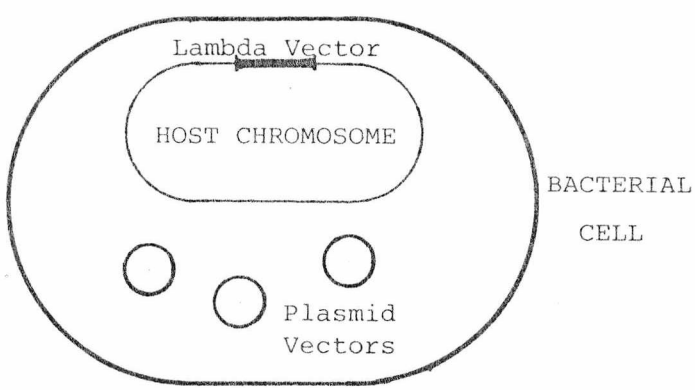


DIAGRAM 10

By way of terminology the plasmids and phages used in replicating inserted DNA are collectively known as vectors. In effect they allow the magnification of quantities of DNA, once the foreign DNA is inserted. However, the foreign DNA-vector combination requires the services of a bacterial cell in which the replication process proceeds. This is termed the host. It is common to talk of the host and vector taken together as a host-vector system, in the context of the manipulation of DNA. They are standard microbiological terms. Nevertheless, one important area of difficulty, already mentioned in passing, needs further elaboration.

Inserting foreign DNA into a host-vector system can obtain large quantities of the DNA molecule in question. This is not the same as obtaining the final product for which a particular gene may code. That is, the DNA may not be functionally expressed in the sense of directing the final ordering of amino acids to produce specific proteins.[38] Two aspects to this problem became apparent as work proceeded in the 1970s: firstly, there was the expression of genes from one prokaryote inserted into the cell of another; and secondly, attention focused on the expression of higher eukaryotic genes when inserted into prokaryotic hosts. Early success in obtaining the expression of foreign prokaryotic genes in a prokaryotic host, led researchers to believe in general that this would be the result when prokaryotes and lower eukaryotes were the source of the donor DNA. On the other hand, the expression of DNA from higher eukaryotes when inserted into bacterial hosts proved to be a much more complex problem. The difficulties involved are usefully summarised by Ehrlich and Goze, who indicate the requirements of expression:

"Expression of genetic information involves: (a) transcription of

DNA; (b) processing of RNA; (c) translation of RNA; (d) processing of proteins. The correct execution of each of these steps depends on the correct interpretation by the host cell of the different signals carried by implicated macromolecules. Consequently, the barriers to heterospecific gene expression can be related to divergence of such signals between organisms." (39)

The 'signals' referred to by Ehrlich and Goze are sequences of nucleotides on the DNA strand, and their relation to other features of DNA already discussed is illustrated in Diagram 11. Incorporated into the sequence of nucleotides comprising DNA are 'start' and 'stop' signals which control the process of transcription where messenger RNA forms from a DNA 'template', as outlined above.

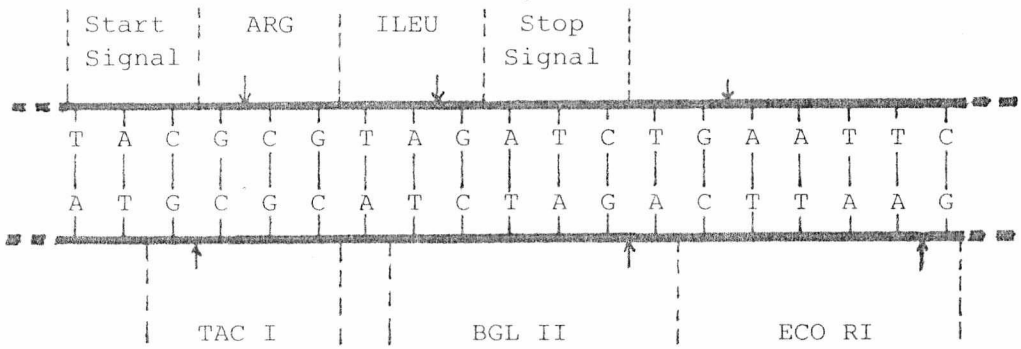


DIAGRAM 11

"Structural Features of a DNA Molecule. ... Groups of three nucleotides provide the basis of the genetic code as indicated in the upper strand. TAC represents a start signal which tells the protein synthesizing machinery of the cell where to start reading the code. ATC indicates when to stop. Shown on the lower strand are recognition sequences for three restriction enzymes. The arrows indicate where the phosphodiester backbone is cleaved by these enzymes." (40)

E. coli has proved particularly powerful as a host in that it can 'read' the start and stop signals of foreign genes from other prokaryotes, although the reverse may not always be the case if different transcription initiation signals are present in other organisms.[41] Further to

this, expression requires that the code held in the mRNA be translated (see above) such that amino acids are correctly ordered to produce proteins.[42]

However, RNA in eukaryotic systems differs in complexity from that of prokaryotes, involving a degree of 'processing', or the removal of sections which are not necessary in the coding for the gene product. In effect, it was found that in nearly all mammalian and vertebrate genes, and in the genes of eukaryotic micro-organisms such as yeast (although less frequently) there were interspersed inserts of non-coding DNA, termed introns. Simplified, it has been shown that the DNA template initially allows a primary RNA transcript to form which subsequently has the intron sections 'spliced' out. In this fashion what is known as mature messenger RNA results which forms in turn the code for amino acid ordering.[43] It is probably the lack of appropriate 'splicing' machanisms in prokaryotes that represents the most important barrier to the expression of foreign genes taken from eukaryotes. Finally, a problem to expression of foreign DNA may relate to the fashion by which E. coli 'degrades' short protein chains deriving from mutations. Foreign proteins may perhaps also be degraded if they are 'unprotected'.[44]

To some extent, however, these and other barriers to expression may be overcome, although there is no generally applicable strategy. Ehrlich and Goze nevertheless suggest some useful rules. Degradation has been overcome in the laboratory by attaching the foreign gene to a particular host gene. To overcome difficulties in the 'reading' of signals, adequate transcription and translation signals have been added to the foreign gene prior to its insertion in the vector used. In essence the foreign DNA is first adapted to the requirement of the gene-to-gene product converting machinery of the new host.

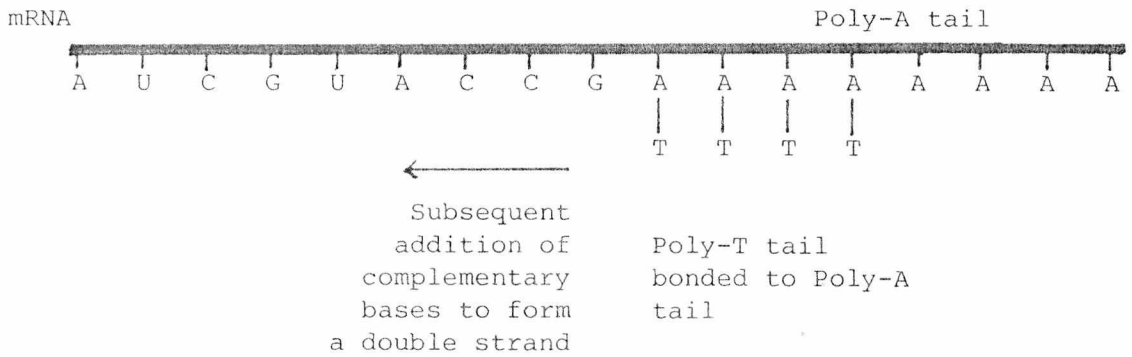
A further means to overcome the barrier problem, as suggested by Ehrlich and Goze, might better be taken as a third method of importance for the creation of recombinant DNA molecules.

Method 3

A major problem with the first two methods of obtaining recombinant molecules, as described above, is that the segments of foreign DNA to be incorporated into a host-vector system will include more than the DNA of one gene. If an average gene contains some 1,500 base pairs, and the commonly used restriction enzyme Eco RI cuts DNA approximately every 4,000 base pairs, it can be seen that the resulting fragments will contain some partially included genes. This underlies some of the problems of barriers to expression, and may not be the appropriate approach if one gene in particular, or more exactly the gene product, is of prime interest to the researcher. If the DNA inserted into the host-vector system could be limited to that of the particular gene then many difficulties might be bypassed. The technical difficulty is in obtaining the desired gene in isolation.

As already described, DNA provides a template for the production of mRNA, but with thymine (T) replaced by uracil (U), with the help of an enzyme known as transcriptase. It is, however, also possible for DNA to be produced from mRNA using an enzyme appropriately termed reverse transcriptase. If a 'tail' of Ts (a poly-T tail) is hybridised to the end of an mRNA molecule most of which have a natural poly-A tail at one end, then reverse transcriptase can use this to commence the production of a DNA strand complementary to the mRNA strand. The poly-T tail is complementarily bonded to the poly-A tail on the otherwise single stranded RNA. Using the mRNA as a template, the complementary sequence of Ts is continued with the appropriate complementary bases for the rest

of the mRNA strand, as in Diagram 12.



Thus:

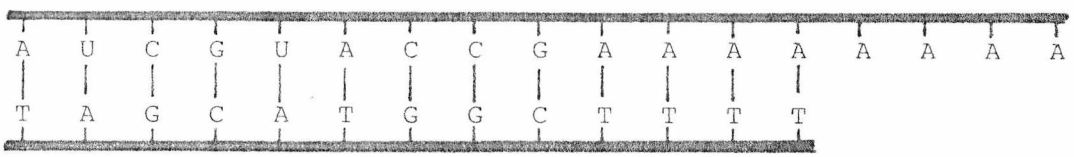


DIAGRAM 12

The subsequent hybrid mRNA-DNA molecule can then be separated and the DNA strand can again, using reverse transcriptase, synthesize the the complementary DNA strand. The result is a DNA molecule complementary to the mRNA, carrying the genetic information specified in the RNA.[45] This approach is very useful because in certain highly differentiated cells in higher organisms, for example those making haemoglobin, antibodies, or muscle protein, the mRNA for those proteins constitutes ten to thirty per cent of the total mRNA in the cell, even though the gene they are synthesized from is only one part in one million of the total DNA.[46] With such high proportions, conventional biochemistry techniques can be used to purify and isolate this mRNA. The above method can then be used to synthesize the best part of the original gene. It can then be inserted into a suitable host-vector system as in Methods 1 and 2

in order to utilise replication functions. It is worth noting that specific cells in an organism which contain larger quantities of otherwise relatively rare mRNA molecules can be used to begin with. In some cases, cells might be induced to produce larger amounts of protein, and thus the necessary mRNA.[47]

A more intriguing adaptation of the third method is actually to synthesize the gene itself from scratch, so to speak. This can be achieved by working backwards from a known sequence of amino acids comprising a protein molecule. New methods in chemical synthesis coupled with enzymatic ligation enable the construction of any given nucleotide sequence. For smaller proteins where the sequence of amino acids, and thus codons of three nucleotides for each acid, is perhaps known, such synthesis might be practical.

Some of the expression problems can be overcome by synthesizing DNA from mRNA which already contains the correctly processed genetic information, at least in its natural host. Alternatively, DNA synthesis might eventually be used to provide the necessary promotor or start signals, and other necessary genetic information to enhance the techniques of the first two methods of producing recombinant DNA molecules, outlined above. Cleaved segments might be attached to the necessary sequences.[48]

Much work has been carried out concerning the sequencing of genes from a variety of organisms, partly through the use of recombinant DNA techniques themselves. Indeed, it has been advocated that an international 'bank' using computer facilities be set up for depositing completely sequenced genes.[49] Such knowledge, if readily available, would provide supporting information to aid the application of recombinant DNA techniques.

Finally, it should be stressed that the divisions above are somewhat arbitrary, as there is some degree of overlap, and many experiments have involved combinations of methods. Overall the requirements of recombinant DNA techniques can be summarised as involving:

i) A means of isolating and purifying DNA.

ii) The production of fragments of DNA that can be joined with other fragments, whatever their source.

iii) The 'sealing' of backbones of the joined strands, or ligation.

iv) A host into which the recombinant DNA molecules can be inserted which has a means of replication in order to produce greater quantities of the molecules.

v) A means of identifying the hosts which contain recombinant DNA molecules.

vi) Expression of the gene of interest may be a requirement of some work. However, many experiments might only require the acquisition of quantities of the DNA of interest, as in (v) above.

The technical details of the methods used in this work have been greatly simplified. Individual experiments are likely to involve many refinements quite beyond the scope of this chapter, and indeed beyond the scope of most of the references used. However, the conceptual description of the methods has been the main intent, to provide background for subsequent discussion.

It is important to reiterate that these techniques have been described with the aid of some years' hindsight, whereas the controversial debate surrounding their use began almost as soon as the first breakthroughs were being achieved. The origins of concern about these developments is considered in the next chapter. As discussion of the issues progressed, reference was often made to the ability of recombination to

occur in nature, and some reference to this is therefore in order.

Recombination in Nature.

In nature, recombination is a second more moderate way of producing genetic variation after mutation,[50] and for a long time has been known to occur within cells of a given species, of both single-celled organisms and more complex animals and plants. DNA can be exchanged between chromosomes and between different regions of the same chromosome. Exchanges may involve the DNA of the single organism or the DNA of viruses and plasmids found only in that species. In this fashion, antibiotic resistance can be transferred within a species. In a limited number of cases, inter-species recombination has been described.[51]

On the basis of laboratory work, A. Campbell suggests four possible ways in which gene transfer might occur in nature, through transformation, transduction, conjugation, or cell fusion. Transformation would involve DNA liberated from a donor (under appropriate chemical conditions) becoming free in a solution and subsequently entering another cell and recombining with the host DNA. This has been observed with a small number of species of bacteria. In transduction, fragments of donor DNA may be packaged within the protein coats of bacteriophages and later may be transferred to a host via the mechanism that the phage uses in infecting other cells. Such viral transfers may occur without cell contact. Conjugation involves a sideline to plasmid transfer, where donor DNA may transfer carried by the plasmid or, indeed, instead of it. However, direct cell contact is necessary. Finally, cell fusion involves the chemical modification of their surfaces, so as to promote fusion of the outer membranes, thus generating a single cell from two parental cells. This naturally occurs between the gametes of eukaryotes and sometimes between other eukaryotic cells. Evidence does exist, according to

Campbell, to suggest that such fusion may occur between bacterial cells.[52]

Campbell argues that it might be expected that transduction and conjugation would occur in nature because they constitute side reactions to the transfer of natural agents, while the expectation of transformation is less obvious because of the two conditions that need to be met. Firstly intact DNA must be liberated from the cell and secondly taken up by a host. The uncertain element concerning cell fusion is with regard to bacterial cells or prokaryotes.

Overall genetic exchange between closely related organisms is more common than between distantly related. Further, any exchange of DNA would face barriers to expression similar to those discussed above. For example, in closely related organisms, properties of the cell surface, restriction enzymes, incompatibility between entering and resident plasmids, and lack of corresponding base pairs might all affect the success of exchange. The first two are barriers to transfer, while the latter two are barriers to establishment.[53] That is, many possible exchanges might be genetically disadvantageous to the recipient as reflected in evolutionary selection.

It can be seen, therefore, that although microbiologists had in the 1970s developed some extremely powerful tools in the techniques of obtaining recombinant DNA molecules, there is evidence to suggest that natural biological processes may include similar methods. A further possibility to note is that experimenters could potentially utilise the natural phenomena to their ends in the laboratory. Thus, more traditional selective breeding techniques could be applied to isolate the products of natural recombination. Laboratory work has enabled researchers to induce natural recombination, not least in the efforts

to understand the phenomena involved. A summary of such *in vivo* genetic manipulations was produced by G. Bertoni for the 1979 Wye Conference, discussed elsewhere in this thesis.[54] He concludes his review by observing that:

> "In general, geneticists have tended to work with isogenic material, i.e. to avoid hybridization between less closely related strains, in order to secure firmer interpretations from their experiments. It is likely, however, that as interest in genetic interactions between distant organisms increases, rational methods will be found for overcoming in the laboratory some of the isolating barriers found in Nature, even without using *in vitro* recombination techniques." 55

The use of natural or *in vivo* processes to achieve recombinant results in contrast with *in vitro* recombination methods leads suitably to a discussion of the difficulties involved in defining recombinant DNA techniques, not least for considering the issues surrounding regulation of the activity.

3. A PROBLEM OF DEFINITION.

There are two aspects to the definition of recombinant DNA techniques. Firstly, there is the question of appropriate label, and secondly, there is the need for precision in identifying exactly which techniques should be included. Labelling has been quite diverse since the techniques were developed. The technical term 'recombination' provides a basis for the first relevant label: *recombinant DNA*, or such variations as *recombinant DNA techniques*, *in vitro recombination* and *recombinant DNA molecules*. This label derives from the technical description of new combinations of genes, or any rearrangement of genetic material, as used by micro-biologists and geneticists.[56] It is also the term used by the United States National Institutes of Health and other official bodies. A second label, *genetic manipulation*, is self-explanatory in general terms

and has been adopted by the United Kingdom Genetic Manipulation Advisory Group and the EEC. Similar, but here taken to be a third label, is the term genetic engineering, used for example by the UK House of Lords Select Committee on the European Communities.[57] These three labels have all had common usage in the press. Nicholas Wade, a leading writer for Science on this topic, uses the term gene splicing in most of his articles and his book on the subject,[58] while Stanley Cohen, an important figure in the relevant scientific community, has suggested gene cloning as more appropriate.[59]

The above terms are perhaps the main labels applied, although more recently there has been a tendency to combine the techniques considered here with other microbiological and biochemical techniques and applications (industrial on the whole) under more general headings. In particular, biotechnology and biomolecular engineering are of note,[60] and are taken to subsume recombinant DNA techniques. Again these terms, notably biotechnology, have been widely used in the science press. Thus, a variety of descriptive terms exist, none of which can be taken as singularly dominant. This thesis will restrict itself to the two used by the official bodies of the United States and the United Kingdom, namely recombinant DNA techniques and genetic manipulation. As genetic manipulation produces recombinant DNA as a product, the two labels are quite complementary.

A more important aspect of definition is, however, the identification of the precise phenomena to be labelled in the first instance. Most of the definitions formally recognised by official bodies in different states for regulation purposes were essentially concerned with the use of Methods 1 and 2 above, or Method 3 which is really a refinement of these. They do not cover means of arriving at the same result through in vivo

processes, even when laboratory selection procedures are involved.[61]

The 1980 US National Institutes of Health Guidelines stated as follows:

> "In the context of these Guidelines, recombinant DNA molecules are defined as either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules that result from the replication of those described as in (i) above." 62

A similar definition had been adopted by the United Kingdom's Genetic Manipulation Advisory Group (GMAG):

> "For the purpose of these regulations, genetic manipulation shall be defined as the formation of new combinations of heritable material by the insertion of nucleic acid molecules produced, by whatever means, outside the cell, into any virus, bacterial plasmid or other vector system so as to allow their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation." 63

The UK definition was explicitly intended to cover the new techniques of genetic manipulation and not the end results or products, which it was acknowledged might also be achieved by conventional techniques, of which some had by then been in use for many years.

These definitions have been reproduced to show the emphasis on the new techniques of producing recombinant DNA molecules, but also because the United States and the United Kingdom have led the field internationally in the development of guidelines, many elements of which have been borrowed in other states. Both definitions explicitly refer to the recombinant molecule being formed outside the cell. It is interesting that the European Molecular Biology Organisation (EMBO) as early as 1976 proposed that a wide and a narrow definition could be delineated. The former referred to recombinant DNA research as "combining DNA molecules of different biological origin by any methods that overcome natural

barriers". The latter specifically referred to a limited definition of *in vitro* recombinant DNA research, the emphasis here being on techniques applied outside the cell, *in vitro*. As EMBO reasoned:

> "The production of recombinant DNA molecules in cell-free systems has become known as recombinant DNA research. This term is, perhaps, unfortunate because it does not take into account the fact that there are many natural and experimental ways of obtaining recombinant DNA. The usage of the term recombinant DNA research, meaning *in vitro* recombinant DNA research, has found widespread acceptance." 64

It can be seen therefore that both labelling and definition were both open to differences. The labels adopted here will refer to the narrower *in vitro* recombinant DNA techniques, in keeping with the predominant custom, and referring to the three methods outlined in this chapter. However, this is done with the explicit awareness of the wider context of all processes of recombination.[65]

As with the discussion on the actual techniques of genetic manipulation, consideration of the appropriate definition also involves elements of historical development and subsequent hindsight. For example, the original 1976 US guidelines did not explicitly include the use of synthetic DNA.[66] It is also of note that developments in the field brought a further definitional issue to the fore, concerning so-called 'self-cloning experiments'. In such experiments, DNA may be removed from an organism or cell by genetic manipulation techniques and, possibly after enzymatic steps, reinserted into the same species of organism or type of cell from which it originated.[67] The 1980 US guidelines exempted this type of experiment, while GMAG recognised that although strictly speaking self-cloning might be within its definition, certain such experiments (which they listed) should be exempted from their requirements of notification.[68]

This chapter has presented a brief summary of the more important technical developments and science which underlie the substantive issues of this thesis. In the course of the remaining chapters a number of these points will be located in the context of their wider political, social and economic implications. For example, the development of guidelines and later revisions were directly influenced by the increasing knowledge of these methods, and by some of the difficulties touched on here concerning precise definition of the relevant scientific techniques. To conclude this chapter, there follows a brief indication of the areas of application of *in vitro* recombinant DNA techniques.

4. AREAS OF APPLICATION OF RECOMBINANT DNA TECHNIQUES.

It is not proposed to give an exhaustive rendition of all the potential and realised applications of genetic manipulation, but rather a number of general areas of utility will be indicated. Firstly, the techniques provide a highly useful research tool for the microbiologist, aiding him in the task of increasing knowledge of the functioning of life at the molecular level. There are perhaps two reasons for this. The more obvious is that all the information for growth, development, organisation and reproduction of an organism is encoded in the genetic material, that for the first time can be manipulated in a controlled way. Indeed, any technique aiding the investigation of this material would have wide applicability. The less obvious advantage is that for the first time the new techniques provide the researcher with a reductionist approach to the analysis of the genomes of higher organisms. Higher organisms have genomes of incredible complexity which prior to *in vitro* recombinant DNA techniques were impossible to study in terms of each individual gene. The developments described in this chapter enabled the smaller, more manageable, sections of DNA to be selected and with the aid of host-

vector systems magnified in quantity for analysis.[69] A great deal of new information has thus been acquired since the advent of these techniques.

Secondly, the techniques are likely to be of great importance in the manufacture of drugs, chemicals and fuels, and in particular hormones, vaccines, enzymes and fermentation products. Proteins such as interferon,[70] antibodies, blood-clotting factors, insulin, growth hormone, and many other pharmaceutically important compounds might be produced in this way. Traditional techniques of producing these products (for example by extraction from animal cells) can only provide limited quantities. Bulk products, however, such as methane and ethanol, involve problems in designing industrial-scale processes. The difficulties in getting eukaryotic DNA to express in prokaryotic hosts represents a problem to overcome.[71]

A third area for applying genetic manipulation is in crop improvement, both in improving the breed of a given crop plant, and perhaps in bypassing the need for fertilisers. The latter might be achieved by providing the means for plants to extract nitrogen from the atmosphere, either directly or indirectly through modification of bacteria which inhabit the plants. Certain plants can extract nitrogen and it may prove possible to transfer productively the genes coding for this function into other plants. Some plants on the other hand, obtain nitrogen from bacteria which inhabit their roots, and the appropriate bacterial genes may be transferred to the natural bacterial inhabitants of different plants. Again difficulties have proved evident.[72] Another area of crop research, for example, concerns the way genes are controlled in the defence mechanisms of plants against diseases.

Fourthly, genetic disease may in future be treated by manipulating DNA. The external production of enzymes that a patient, through genetic disorder, cannot produce, might enable these enzymes to be introduced into the person in question. In general, medical practice might be improved through the more efficient production of drugs and other chemicals, as mentioned above. Or, more specifically, internal modifications to undesirable mutant genes, such as those causing sickle cell anaemia, might offer new types of cures. For example, extensive bone marrow transplanting could provide the means to introduce the modified cells.[73] Such applications of genetic manipulation still need considerable development, and are likely to involve considerable ethical discussion.

Fifthly, applications may accrue in conjunction with older techniques such as enzyme technology and fermentation. Such linkage and the potential developments discussed above have become labelled as biotechnology.[74] Biotechnology has in general led to a large number of commercial firms emerging to develop recombinant DNA techniques for industrial research and development, in some states forging new links between large corporations, specialist research firms and universities.[75]

Finally, it is worth noting here, although more will be said in later chapters, that one more, but sinister, application of the new techniques could be in the biological or chemical weapons areas. New weapons of various degrees of debilitation might accrue, or alternatively existing toxins might be more efficiently produced.[76]

A technical background has thus been provided to elucidate the general concepts involved concerning the techniques of achieving recombinant DNA molecules. This provides a reference point from which the other chapters

can be put in perspective, particularly with regard to the origin of perceived risks, the politicisation of the issues, and the politics of risk-benefit assessment, that have accompanied their development. Much of necessity has been simplified, but the technical level adopted is sufficient for the purposes of this thesis. Again, however, it must be stressed that the techniques and definitions of genetic manipulation have been presented with the benefits of hindsight. It is now necessary to provide an historical overview concerning the associated growth of fears of potential risk.

CHAPTER FOUR

THE ORIGINS OF CONCERN

1. The Berg Experiment

2. Two Influential Letters

3. The Asilomar Conference, February 1975

4. Deliberate Misuse of Genetic Manipulation

5. Summary

THE ORIGINS OF CONCERN.

With a lack of quantifiable information indicating reasons to consider recombinant DNA techniques as hazardous, the approach adopted here will be to demonstrate that although concern rested on conjecture, it came from authoritative sources. In order to do this, a descriptive and historical summary is presented, indicating the fashion by which attention became drawn to potential hazards. In particular, the events behind the publishing of two influential letters and the holding of a now famous international conference in California deserve special attention. Together these were responsible for initiating institutional responses in many states.

1. THE BERG EXPERIMENT.

An experiment which Professor Paul Berg of Stanford University proposed to do in 1971 has been commonly suggested as the first step in a chain of activity leading to the international discussion of potential hazards and the development of experimental guidelines.[1] He had intended to implant the DNA from Simian Virus 40 (SV40) into the bacterium *E. coli*, a normal inhabitant of the human digestive tract. Attention became drawn to this when a graduate student from Berg's laboratory, Janet Mertz, attended a course at Cold Spring Harbor Laboratory, New York. There, Robert Pollack gave a lecture which included discussion on matters such as safety and ethics in work with mammalian cell cultures. In particular, Pollack was concerned with experiments to study viruses, cancer and the like. Not least, he referred to some of the less well known hazards involved in indiscriminately mixing cells of different species under artificial conditions.[2]

Mertz described Berg's proposed experiment. SV40 was a virus known to cause tumours if injected into new-born hamsters, although was thought to be safe in humans.[3] In general, viruses associated with causing tumours were of particular interest to those who hoped to find a viral component of human cancer. Pollack began to wonder about the risks in introducing SV40 into E. coli, which could then perhaps produce the virus in large quantities. Although apparently safe in humans, SV40 might find itself transmitted more readily in E. coli, and if introduced into humans the E. coli, reproducing and carrying the virus, might have long-term effects.

Berg has acknowledged in interview that he took some convincing from Pollack and Mertz that his experiment would be risky.[4] Consulting many other scientists, Berg found a number were very critical, including Maxine Singer and David Baltimore, who were later to become important in publishing concerns. Still uneasy, Berg sought advice in the summer of 1972 in a lecture at the European Molecular Biology Organisation (EMBO). After a lengthy session, it seemed that no one was sufficiently confident or knowledgeable to give him his answers.[5] In subsequently abandoning the experiment, although partly because Berg saw inherent difficulties in it (the virus might not be expressed in the E. coli), Pollack felt that Berg's action would deter others from similar experiments, much to his relief.

From this modest beginning, discussion of potential hazards in biological research gained momentum. A series of conferences and meetings gave vent to the issues. Andrew Lewis, of the US National Institute of Allergy and Infectious Disease (NIAID) presenting a paper on SV40 hybrids (at a symposium at Cold Spring Harbor, immediately following the workshop in which Pollack and Mertz had been involved) again raised the question of

risk.[6] A yearly NATO meeting convening in 1972 in Sicily, following a lecture by Berg, gave over an evening to discussing the political and social consequences of genetic engineering.[7] Later in the year, an EMBO workshop held in Basle on DNA restriction and modification gave another evening over to issues surrounding the creation of genetic hybrids.

November 1972 saw the establishment by the US National Institutes of Health (NIH) of a Biohazards Committee, and Andrew Lewis initiated action on the part of NIAID to control the supply and use of possibly hazardous hybrid viruses. Lewis was responding to hazards he saw in his own work, but it became NIAID policy that those wanting virus samples must sign a memorandum of understanding in which they agreed to take certain safety measures. If they passed the virus to anyone else, they should be required to promise likewise.[8] In general, these moves were paralleling the development of the methods of cutting and joining DNA through the use of restriction enzymes.[9]

By now, Berg had become convinced that there was a question of biohazards to face up to, and in conjunction with others was to take events further. A series of special conferences was proposed, the first to be a fact-gathering exercise on tumour viruses and at least one other to address types of experiments being proposed and the associated hazards. Berg asked two colleagues, A. Hellman and M.N. Oxman, to assist him in organising the first conference specifically on biohazards. Sponsored by the US National Science Foundation, the National Cancer Institute and the American Cancer Society, it was held between 22nd and 24th January 1973, at the Asilomar Conference Center, Pacific Grove, California. This was to be the same venue as a later and much more important international conference. (For convenience they can be termed Asilomar I and Asilomar II.)[10] Essentially the discussion at Asilomar I was on biohazards in

general rather than on recombinant DNA.[11] Later more specific concerns would develop. One issue of note was to remain important, as far as this case study is concerned. It was noted that the background training of those dealing with virology was all too often in biochemistry, and a tendency existed for viruses to be seen as yet another chemical reagent.[12] Other issues examined included: laboratory infections from animals; evaluation of experimental results; tumour viruses; hazards; modifications to viruses; common sense in the laboratory; and the control of hazards in cancer research. It was noticeable that no hard evidence was presented to prove conclusively specific hazards, yet an awareness of overall hazard was fostered. Equally of note was that ethical and moral questions were not raised, as they had been at the NATO meeting. Nevertheless, the potential hazards to health were taken seriously as James Watson, co-discoverer of the structure of DNA observed at the meeting:

> "Of course everyone working with a given virus hopes very much that his particular virus is indeed safe. But I think we must now help create the situation where the real reason for a decision [for biohazard prevention] is the awfulness of the alternative possibility - which I suspect is how the AEC calculates the low probability of a catastrophic accident to a nuclear power plant." 13

In sum, the development of discussion on biohazards, following Pollack's worries over the experiment which Berg proposed, provided a background to which specific concern over recombinant DNA techniques was later voiced. The next significant development was the publication of two letters.

2. TWO INFLUENTIAL LETTERS.

By the spring of 1973, Stanley Cohen, Herbert Boyer and some colleagues had succeeded in inserting DNA from one plasmid into another using the

restriction enzyme Eco RI. Their main contribution was finding a plasmid which maintained its replication functions even with the DNA inserts.[14] Their work was published in November 1973,[15] and it attracted much interest. The technique spread quickly as Cohen made the plasmid which had been so useful available to other researchers. Recognising the question of hazards, he requested that they made assurances that tumour viruses would not be inserted into it, or any other DNA which might make the E. coli carrier of the plasmid more resistant to antibiotics. He requested that they did not pass the plasmid to anyone else without similar assurances. However, this self-regulated control broke down as other useful plasmids were discovered elsewhere.

In the same year a conference was held, this time explicitly addressing, in a special session, the newly developed techniques. More importantly, the participants voted for a letter to be sent to the National Academy of Sciences (NAS) and the journal Science. The conference was the annual Gordon Conference on Nucleic Acids, and the vote followed a special session called for by participants after they had heard Boyer talk about the new techniques. Maxine Singer opened the session from the chair, noting the potential for the techniques and that moral and ethical issues were involved. The scientists were then told of their responsibility to co-workers, laboratory personnel and the safety of the public.[16] Following the discussion, a vote was taken in which seventy-eight of some ninety participants voted in favour of the two chairpersons sending a letter to the NAS. A significantly narrower vote of forty-eight to forty-two decided in favour of giving the letter wider circulation through publication.[17] As it has come to be known, the Singer-Söll letter addressed a matter of 'great concern', the joining of DNA from diverse sources. Briefly describing the new techniques,[18] they noted that hazards, although not established, could be potentially involved. Referring to

the fact that the letter was voted upon, Singer and Dieter Söll said that the conference was calling upon the NAS to establish a study committee to recommend "specific action or guidelines, should that seem appropriate".

The response was very prompt and in October 1973, Singer was invited to a meeting of the Executive Committee of the Division of Life Sciences at the NAS,[19] where it was decided to proceed with NAS involvement. On Singer's suggestion, Berg was asked to advise them on the basis of his earlier actions. A study committee resulted.

After consulting Watson and J. Edsall, an "elder statesman of biochemistry" as he described him, Berg decided to call a meeting of those in the field.[20] Eight scientists subsequently attended a meeting at the Massachusetts Institute of Technology (MIT) in April 1974, although Singer, unavoidably detained at the last minute, played no part in drafting the more important letter which eventually resulted from this group.[21] Berg revived his earlier idea of a large conference,[22] although the meeting was not sure whether or not to go ahead with this. Nevertheless, Berg booked the Asilomar centre in case it was needed, for February 1975, a time when it was free. To Berg some experiment proposals he was hearing of were "very worrying".

Agreement from Berg's colleagues was forthcoming and planning for the meeting began. In the meantime, Norton Zinder made a suggestion that if they "had any guts at all" they would request researchers to halt their experiments. Watson has attributed part of this concern to the 'mysticism' surrounding the way tumours could result from certain viruses and the discovery of human viruses similar to SV40.[23] It was decided to draft a letter, although a number of arguments were put regarding how forceful their request to halt the work should be. Of importance is the order of

the two decisions made that day. The decision to hold a conference was agreed upon before the idea of a letter, which was to be seen as a stopgap measure.[24] Both must be taken together. The conference when held was not a consequence of the letter as is often implied,[25] although the meeting undoubtedly received stimulus from it.

Often criticised in retrospect by some members of the scientific community as a hasty document, the 'Berg letter', as it came to be known, was on the contrary not so. It went through a series of drafts over a period of two and a half months, and it was widely discussed in the US and abroad. Despite its name, the first draft was produced two days after the MIT meeting by Richard Roblin, and sent to Watson and Baltimore for comment, before Roblin redrafted it. On 20th May, Roblin produced what was hoped to be the final version, which was a composite of the second draft and versions produced by Nathans and Berg. It was sent to all who had been at MIT plus the NAS (who had financed their meeting), Stanley Cohen, Herbert Boyer, David Hogness and Ronald Davis. Philip Handler, the NAS president, was, however, unhappy as it did not make clear the NAS role. Thus the president of a prestigious institution rewrote it! Nevertheless, Berg et al. disagreed with the latest version, arguing that it made their requests appear to be an edict from the NAS.[26] Berg, himself, had felt that to have impact the letter should appear as a personal appeal from the scientists. After an abortive attempt by Roblin to include Handler's suggestions, they met the latter for discussion. It seemed that Handler had the impression that Berg's group was an NAS committee, a view they disputed, arguing that none of them saw themselves as a committee, and in any case had expressly been told not to consider themselves as such. Finally, Berg and Handler produced the version actually published, which included a paragraph saying that the NAS had invited the group to meet.

During the months of drafting, opportunity for wider discussion of the letter had existed, including a meeting of EMBO at Ghent, Belgium, convened in May 1974 to discuss restriction enzymes and nucleotide sequencing. At this, Nathans and Zinder presented the idea of the statement, to which there was general agreement. In the United States, Baltimore read the tentative draft to a symposium on tumour viruses at Cold Spring Harbor, in June. Thus, as Weiner observed, "the relevant scientific community knew what was up".[27] Indeed, following its presentation at New York, twelve European scientists wrote to John Kendrew, the Secretary General of EMBO, requesting urgent consideration of the matter, and in particular the provision of a special risk laboratory.[28] Therefore, by the time of its publication in July 1974, the letter had been well considered, internationally.[29]

In brief, the Berg letter requested the deferment of two types of experiment until the hazards could be evaluated: firstly the construction of new autonomously replicating bacterial plasmids that might introduce antibiotic resistances to plasmids which do not have them, or introduce novel combinations of resistances; secondly, the linkage of DNA from oncogenic or other animal viruses to autonomously replicating DNA elements such as plasmids or other viral DNAs. It was also advised that great care be taken in linking any animal DNA to plasmid or bacteriophage DNA, because of the uncertainty involved in creating any new recombinant DNA molecules whose properties would be difficult to predict. To the director of the NIH they requested the establishment of an advisory committee charged with: overseeing an experimental programme to estimate hazards; developing procedures to minimise the spread of such molecules in human and animal populations; devising guidelines for investigators to use. Finally they requested that an <u>international</u>[30] meeting of involved scientists be held early in the new year (the venue already having been

booked).

Nothing like the publication of such a set of requests had occurred in the history of biological science.[31] Other technologies or scientific developments may have displayed risks sufficient to suggest caution, but none in recent years have had debate, subsequently politicised, begun in such dramatic form. All of this had occurred in the case of recombinant DNA, before any hazards were even proved. Because risk could be conjectured, however, authoritative scientists requested important measures.

The period following the Berg letter has become known as the 'moratorium', a term Berg believed arose from the press. In conjunction with their letter, Berg's MIT group had decided that it would hold a press conference on 18th July to stress their requests. Between fifty and sixty reporters attended. Although Berg himself was critical of the strict interpretation of the letter as a call for a moratorium,[32] this does not in any way detract from the fact that, as Watson reflected in 1979, the letter was indeed very strong.[33] Such a letter could not help but be newsworthy, and even if the authors did not anticipate the response that over the years would develop, this in no way reduces their authority. With responses to the letter so widespread internationally, and the NIH responding to the requests made of it, it would not be surprising if the press had found their own story. Press sensationalism, however, is a charge that had more bearing in the United States, while the responses to the letter were international. For example, in the United Kingdom, also a very important respondent in an international sense, the popular press never took much active interest in the ensuing issues. The politics of congressional lobbying in the United States may explain partly press interest and the higher profile of public debate on that side of the Atlantic.

On the basis of the actions so far described, a worldwide voluntary deferral of certain experiments, no matter how unlikely this might appear to sceptics, did in fact occur. In retrospect, the NIH has argued that evidence for this success comes from both informal communications in the field, and from the inspection of publications in scientific journals.[34] Some scientists even suggested the deferral of those experiments involving animal DNA over which Berg's group had advocated caution.[35] A Japanese scientist, Kohji Hasunuma, for example, who wrote to Berg fully agreeing with the letter was one. Roy Curtiss, an American, took it upon himself to raise the standard of caution even further. Drafting a sixteen page single-spaced memorandum, he sent it to about a thousand scientists around the world. Again agreeing to the principles of the Berg letter, he made technical suggestions to widen the categories to four types of experiment to be deferred.[36] Indeed, in the United Kingdom, the Medical Research Council (MRC) did put into operation a complete ban on the third type of experiment, in addition to those recommended in the letter, for all the work which they sponsored.

In general, the point to note is that caution became endemic amongst those scientists who might plan to use the new recombinant DNA techniques, a credit to the standing of those who signed the Berg letter.
But deferring work was only one of the requests that had been made. It was always intended that the work should continue as soon as possible, under appropriate precautions. Risk assessment was asked for, as was an NIH committee to oversee progress from that point on, at least as far as the US was concerned.

Even before publication of the letter, the Director of the NIH, R.S. Stone, indicated to Handler at the NAS that a committee would be formed, and that the NIH would support the international meeting.[37] In the US, the

NIH is the main federal government agency for the conducting and funding of biomedical research, of which microbiology is a part. On 7th October 1974, the promised committee was established, with the ungainly title of the Recombinant DNA Molecule Program Advisory Committee. In later years it became more commonly known as the Recombinant Advisory Committee (RAC) and, for simplicity, this latter address will be used here.[38] The committee was to advise the Secretary, Health, Education and Welfare (HEW), the assistant secretary for health, and the Director, NIH, on three defined functions: "the evaluation of potential biological and ecological hazards of DNA recombinant of various types"; minimising the spread of such molecules; and devising guidelines to be followed by investigators "working with potentially hazardous recombinants".[39] Of note is its Charter, describing the RAC as a "technical committee", which reinforced the early dominance of the health hazard issue, within institutional responses, rather than wider issues. To support this, the membership of twelve was to be drawn from the fields of molecular biology, virology, genetics and microbiology. It would be some years before non-scientist representation would appear on this committee. Chapter Five will consider the role of the RAC and criticisms against it in more detail. However, it is worth stating at this point that it was to become very influential both within the US and, in giving advice or as a precedent to follow, abroad.

In addition to the MRC-imposed deferments on experiments, the UK was quick to respond to the Berg letter by establishing a working party under the auspices of the Advisory Board for the Research Councils (ABRC). Again this was announced, a week after the letter appeared in Nature, and on the day of its US publication. From the Ashby working party, the UK response would begin proper. Thus, on the day of US publication of the fundamentally important Berg letter, key chains of activity began on

both sides of the Atlantic. Subsequently, the procedures adopted in both the US and the UK would act as models to influence other states.

It is abundantly clear, however, that Paul Berg and his co-signatories had no conception of the sheer extent of the eventual consequences of their action. From the origins of concern within a relatively small scientific community, the subsequent debate over recombinant DNA would go through various stages domestically and internationally. More scientists would become involved, public interest would grow, controls would develop, legislation would loom and increasingly the original small band of scientists with their honourable sense of duty would begin to wish they had acted differently. In short, their actions had both scientific and political consequences. As Stanley Cohen was to say in 1979:

> "... in retrospect, it seems to me that while the letter was perceived as responsible, it was not really responsible at all. The most incriminating thing that any of us could have said at the time about recombinant DNA research was not that there was any indication of hazard, not that there was even any valid scientific basis for anticipating a hazard, but simply that we could not say with certainty that there was not a hazard. The same thing could have been said about virtually any other kind of experimental endeavour." 40

The extent of consultation and thought underlying the Berg letter has already been indicated. Cohen's comment, typifying similar views held by other scientists by 1979, needs response on the basis of its logic. Firstly, Cohen underestimates the extent of deductive reasoning that was applied to the empirical knowledge of the day. The Berg letter was a reasoned appeal. Secondly, and perhaps more subtly, he is in effect saying that the hypothesis that there might be risk, at the time, could not be falsified. There are philosophical arguments to suggest that the latter is preferable as a statement to a continued collection of inductive evidence supporting an hypothesis. Even by 1979 the hypothesis of hazard

was not resolved, although there was powerful motivation indeed to try to falsify it. Finally, the Berg letter itself was actually calling for research to obtain the necessary information to determine the extent of risk. It is not the intent here to enter into discourse on the relative merits of differing methods of scientific investigation. The point is that comments like Cohen's in general were much influenced by the failure of risk to manifest itself, and the acquisition over the years of new knowledge.[41] Cohen's observation is too simple. Something cannot be irresponsible simply because in retrospect the conjectured reasons for caution have proved less evident. Any action must be related to perception of the time. As Cohen says, at the time, the action was perceived as responsible. Perceptions can change, but later additions to knowledge, which modify perceptions, are not sufficient reason to challenge the responsibility of actions under earlier perceptions. Cohen must have perceived his signing of the letter at the time as responsible.

Given the authority attributed to the letter at the time, the next major event was responsible for extending the number of scientists involved, and the extent of internationalisation of the issues. The international conference proposed by the Berg group was in this sense a landmark. With internationalisation and even greater publicity, the politics proper began. Despite other options, all the proposals in the letter were followed.

3. THE ASILOMAR CONFERENCE, FEBRUARY 1975.

In late February 1975, 150 participants attended the international Asilomar II conference. Organisation, however, had begun on 10th September 1974 at a meeting, held at MIT.[42] Some initial decisions on participation were of note: two Europeans were to be invited to join the

organising committee;[43] individuals were to be invited on their own merits rather than as representatives of any body, as it was hoped to avoid the meeting appearing political; the meeting was to concentrate on the science and technology in relation to health, and the participants would reflect that in being nearly all active scientists, from a variety of backgrounds;[44] experts in infectious disease, immunology and gastro-enterology were to be present; to provide a wider input, a number of lawyers were to be invited, including Maxine Singer's husband; the press were to be invited, but with the novel provisos that they registered as attendees and that they agreed only to report after completion of the conference agenda, to avoid hasty reporting.[45] Thus, in terms of participation, the emphasis was on scientists, with only four lawyers and the press to complement this.

Some technical decisions were also made on the same day, which provided the structure for the conference agenda. Three working groups were proposed, which would meet prior to the conference and finally submit a report to the attendees. A Bacterial and Plasmid working group would look at the biology of these in terms of the introduction and transmission of drug resistances, general epidemiology and similar questions. A Viruses and Viral DNA group was to examine animal viral DNAs, virus fragmentation, SV40 hybrids, relationships with tumours and immunology aspects. The third group was to examine Eukaryotic DNA and consider animal gene transfer and amplification, summarise pertinent work, assess risks and consider the advantages of actually doing hazardous experiments. It was hoped that with these groups, most concerns of the day would be covered.[46] That is, most technical issues of risk.

It is worth at this point saying something of the activity that occurred between September and February, when the conference met, which furthered

interest in the biohazards that might be involved in genetic manipulation. In the same month as the meeting of organisers, an international organisation of note expressed positive interest by holding a meeting in Tokyo to discuss biohazards. The International Association of Microbiological Societies (IAMS) established an ad hoc committee which began with groups in different states.[47] Contact was established with members of Berg's group and the Ashby working party. It was important as the first international organisation to establish procedures to monitor and assess issues surrounding recombinant DNA, and reflects growing international awareness.

Less technical, and more ethical, issues were addressed in one particular meeting, despite the trend to narrow the focus towards the science in most discussion forums, including Asilomar II. In October 1974, in Davos, Switzerland, an international meeting was called explicitly to look at wider concerns associated with recombinant DNA work.[48] Although the meeting lacked coherent direction and the structure of discussion degenerated somewhat,[49] at least it established wider interests. Directly a result of the Berg letter, the Davos meeting never really found its target in terms of establishing a conference view on the issues. Paul Berg, in attendance, made it clear he was not interested in ethical issues, but only public health, while other participants either wanted to curb generally unbridled scientific research or wanted to remove all controls. Whatever its failings, it made some impact, if not directly, then through its published proceedings. Its chairman, H. Wheeler, writing after the event, criticised both the Berg conference and the Ashby working party for having insufficient non-scientist representation. He observed that the problems were social as well as scientific, and that a lost opportunity had presented itself at Davos where both biologists and social scientists had met. In some ways it was unfortunate that the

scientists, about to embark on self-regulation at Asilomar, had not widened their horizons, as they might have realised the full extent of what they were unleashing.[50] Issues discussed at Davos would be raised time and time again as participation in the debate widened to include non-scientists.

A final development of note which was timed deliberately to occur prior to the forthcoming Asilomar II meeting was the publication of the Ashby report in the UK. Published a month beforehand, it was planned to be available to represent something of a British input to the forthcoming discussions.[51] Ashby hoped that the report would act as a consultative document in the UK, and it was acknowledged as a first attempt to respond to the issues raised by Berg's group. Of note is that the report recommended that means be devised to enable the work to continue as soon as possible, in that great benefits could result.

Eventually, the Asilomar II meeting convened between the 23rd and the 27th February in the very pleasant setting of Pacific Grove, California.[52] Four main issues can be identified as having dominated the proceedings.[53] Firstly, the meeting had to come to terms with what it was trying to achieve. Secondly, a major theme was the desirability and content of guidelines for use by investigators. Thirdly, debate arose over whether or not some experiments should be deemed too dangerous to undertake under any circumstances. Fourthly, there was a proposal that enfeeblement of biological hosts might overcome many problems of containing risk. These can be taken in turn.

Establishing the aims of the conference was partly determined by the prior decisions calculated to restrict discussion essentially to technical questions. Indeed, it has been said that the conference perpetuated the

assumption that the analysis of risk was 'narrowly technical in nature'. Broad public and scientific input was not considered.[54] It was, however, hoped that a 'consensus' of those at the meeting would be forthcoming, assisted by the choice of invitees. David Baltimore, opening the conference, stressed the importance of avoiding splits which would infer that they had failed in their duty. Uncertainty is nevertheless revealed in his comment that:

> "The procedures by which the consensus will be determined will be largely determined by the extent of the consensus." 55

It was clear that it was hoped that any consensus would include some form of self-imposed guidelines under which the seven month moratorium could end. This in itself would be something of a landmark in the history of science. Particularly influential at the meeting, Sydney Brenner, the British member of the organising committee, pressed for guidelines so tight that no one could accuse them of being self-serving. A good guideline would be one in future revised downwards.[56]

Two voices were notable, though, in their arguments against any regulation, and both were Nobel laureates. Joshua Lederberg and, perhaps surprisingly, James Watson, argued respectively that delays to research would delay benefits accruing and that academic freedom was at stake. Watson went so far as to recommend the use of common sense and "live with the fact that someone may sue you for $1 million if you are careless".[57] Their fears were shared by others in that their drafting of regulations could subsequently lead to legislation.

Guidelines were produced out of Asilomar II, although discussion of their content was long and revolved around the reports submitted by the three

working groups. From the Bacterial and Plasmid group came the suggestion of six classifications of experiment to which physical containment recommendations were attached. It was during this debate that Brenner made his defence of guidelines and Watson and Lederberg raised their views. The Viruses and Viral DNA group produced the controversial suggestion that existing National Cancer Institute guidelines for handling oncogenic viruses would be quite sufficient. Andrew Lewis of NIAID fuelled the debate by recounting his experiences with trying to get people to impose self-regulation when he supplied SV40. Some passed on the virus without obtaining guarantees on its use. Such criticism of self-regulation was not popular, given the evolving aims of Asilomar II. Yet more controversy followed the report of the Eukaryotic group. Suggesting that research with eukaryotic DNA might be the most fruitful of all, they proceeded to outline their fears of the 'shotgun experiment'.

Viewed as potentially quite frightening, the 'shotgun experiment' involved using a restriction enzyme to fragment a strand of DNA, the fragments to be then cloned in a host-vector system. Each fragment might contain two or three genes, each coding for the production of particular enzymes or proteins. This sort of experiment it was thought would be popular as the isolation and categorisation of mammalian genes was likely to be of high priority in future microbiology. Uncertainty about the risks arose from the observation that certain segments of mammalian DNA appeared to be very similar to the structure of known tumour viruses. It was postulated that these segments were perhaps kept in check by their location relative to other genes in the strand. Isolated and placed in a bacterium they might be expressed. A further possibility was thought to be the introduction of an unknown foreign gene that happened by chance to code for toxin production, or fundamentally altered the bacterium itself.[58] The Eukaryotic group had put the 'shotgun experiment' on top of a hazard list

within some guidelines, which led to wide discussion, but with problems as Wade noted:

> "The central dilemma the experimenters faced was that, despite the various attempts to rank the experiments in order of risk, no one had any real idea of what the risk might be or how to assess it." 59

A question also arose at Asilomar II regarding whether or not certain experiments should be totally avoided. After much discussion, it was decided that there were some, although not defined at that time.[60] The last major issue was related to all assessments of hazard in that it concerned the use of E. coli, which had been at the heart of perceptions of risk for some time. At Asilomar II, the British scientist E.S. Anderson suggested that the laboratory strain of E. coli did not in fact survive long in the human gut. A productive session followed, where it was proposed that strains of E. coli could be bred such that they could not survive at all outside their culture medium. This would reduce reliance on physical safeguards which could always fail. It began to appear that guidelines involving biological as well as physical containment would be more attractive.[61]

Each of these were important technical issues, but two final sessions were important to the overall influence of the meeting. On the evening of the third day the lawyers spoke, with forceful impact. A number of issues were raised regarding risk assessment and participation. Singer and Capron attacked the idea of academic freedom if it could lead to harm to others, and they challenged the competence of the scientists to assign overall risk. Capron argued that the public had a right to act through the legislature and even to make 'erroneous decisions'.[62] However, the talk which had the scientists most worried was delivered by R. Dworkin. He raised the issue of legal liability, suggesting, for

example, that the US Occupational Safety and Health Act might be applied to protect laboratory workers and the financial liability of institutions. By the end of the session the scientists were being advised to examine the possibilities of extended liability insurance!

Some scientists lost sleep that night for quite different reasons! The organising committee in search of a positive result from the meeting worked through the last night drafting a conference document. Synthesising earlier suggestions, they reduced the six categories of the plasmid group to four - minimal risk, low risk, moderate risk and high risk. Playing on their minds in addition to this was that the conference all along lacked means of registering opinions of the group at large. Voting was not in effect organised, and Berg in particular was reluctant to call a vote on their draft document. Berg hoped that a consensus would simply appear and be obvious.

On the last day, however, a principle which they had drafted was put to the vote. It read:

> "The new techniques combining genetic information from very different organisms place us in an area of biology with many unknowns. It is this ignorance that has compelled us to conclude that it would be wise to exercise the utmost caution. Nevertheless the work should proceed with appropriate safeguards." 63

When taken, the vote unanimously endorsed this principle as a first paragraph in a statement. During the morning, modifications and suggestions were made and voted upon, and discussion progressed to consider the body of the conference statement. Despite vocal objections during the past few days, it appeared that the silent majority approved of the actions of the organising committee. The committee began to think that the whole statement would be acceptable. A revealing note was

passed from Maxine Singer to Berg. It read:

> "Paul. If you sense, as Dick and I do, that all the votes will go in favor of the statement, or, indeed a somewhat stronger statement, then there may be a lot to be gained by taking a vote.
>
> "We are already over the main hurdle, since we have overwhelming votes in favor of the principle." 64

When moved the vote was overwhelmingly in favour of the draft prepared that morning, although by then it had many qualifying statements along the lines of how 'provisional' it was, and that it was a 'first assessment'. It also suggested that investigators had a responsibility to increase containment if they felt that their experiment required it.[65]

A number of drafts were made after the meeting before publication of the final form in June 1975, in the US and the UK. An erratic and narrowly focused conference in the end produced an output of considerable influence, not least in enabling some research work to begin again. The statement produced guidelines relating hazard to type of biological 'material' used: prokaryotes, plasmids and bacteriophages at the low end of the scale, through animal viruses in the middle, to the use of eukaryotic DNA at the more hazardous end. Such self-regulation was unique on this scale. If this thesis rests on the authoritative announcement of conjectured hazard, then the Asilomar statement, resulting from a conference of some 150 relevant scientists, simply completes a repeated announcement of perceived potential hazards and uncertainty. In conjunction with the Singer-Söll and Berg letters, it provides conclusively a base upon which to examine the organisational responses to the expressions of concern made very early indeed in the development of this important technology. Creditable caution was the norm.

Perhaps justifying the strictures on when the press could report, their articles, produced on completion of the meeting's business, were on the whole sober and cogent descriptions and analyses. Weiner, commenting on their behaviour, observed:

> "At Asilomar, the press representatives were not allowed to write about the meeting until it was over. Instead, the scientists were the ones rushing to the telephones to tell their colleagues back at their own laboratories what was going on and to suggest ways to get involved in the new technique." 66

As the debate developed and international response grew, participation would widen to include an increasing proportion of non-scientists, subsequently challenging the scientists' control of the events. Their responsibility displayed so openly led inexorably to perceptions in some quarters that because scientists had acted thus, then there must be an underlying hazard. One group, the Boston Area Science for the People had actually sent an open letter to the Asilomar meeting. They suggested that scientists alone could not make the decisions on the future direction of the research and that those at risk through working in the scientists' laboratories, plus the wider public, should have a say. They expressed worry at the research going ahead before all the requests of the Berg letter were met, in particular, and they had a good point here, the risk assessment called for. Also of interest, they requested wider participation in the RAC, which by then had been announced and met for the first time the day after the Asilomar conference.[67] Such issues will be returned to in later chapters.

A summary of the conjectured hazards is presented as Appendix Four. However, to complete this chapter, some mention should be made of growing perceptions of a particular hazard, namely the use of recombinant DNA techniques in biological weapons production.

4. DELIBERATE MISUSE OF GENETIC MANIPULATION.

Scientists themselves, as with the origins of overall concern, began the speculation about the utility of recombinant DNA techniques in assisting the production of biological weapons. Between 28th August and 2nd September 1974, Pugwash held its annual conference in Baden, Austria. Under 'other business', and as a result of the Berg letter, Martin Kaplan, also involved in the World Health Organisation, presented a short paper informing those attending of the developments which had occurred in genetic manipulation.[68] In discussion following the paper, he and Ole Maaløe, from Denmark, presented the hypothesis that if a gene for a toxin could be isolated, it might be possible to use the E. coli host-vector system to produce large amounts of the toxin (assuming its successful expression) more efficiently than with fermentation methods.

Some forty to fifty scientists and social scientists were present and their collective feeling was for the moratorium to be endorsed, for legitimate public interest to be represented and for their concerns about the use of genetic manipulation for biological weapons to be made known. In particular, they wanted these views brought to the attention of the Pugwash Continuing Committee, the NAS in the United States and the scientific community in general. The latter would involve use of scientific journals and "the usual channels used by Pugwash".[69] It is important to note that Pugwash, and in particular Kaplan and Maaløe, had long been interested in the question of biological warfare. At the 1976 Pugwash annual conference the issues were again raised with a similar conclusion, perhaps if anything more strongly worded.[70]

If the Berg letter was important in raising general concerns about the hazards of recombinant DNA research, we can only speculate as to what its

impact would have been if the following paragraph, included in two of the drafts, had been published:

> "Finally, since it is evident that these new technological capabilities could potentially be used to create new sophisticated weapons of biological warfare, we urge citizens, scientists and government officials to take appropriate steps to prevent such applications." 71

Somewhat sceptical about biological warfare, having worked at Fort Detrick, Watson commented on the omission of this paragraph:

> "... this phrase was removed at a later draft because it would raise an issue which would involve unavailable classified data. Moreover, no one believed that if the CIA or the army wanted to do such work that our moratorium would stop them." 72

The availability of classified data is an irrelevant excuse, as concern in 1974 was with conjectured uses, for which no data could exist. A more understandable explanation for the omission of the statement was the Berg group's wish to avoid sensationalism.

Some concern was therefore evident regarding the use of the new techniques in biological weapons production. That it was played down by the scientists who raised the whole question of conjectured hazard is not surprising, as it would almost certainly have precipitated the involvement of many interest groups. It might also have brought uncomfortable comparisons with that earlier technology - nuclear energy.

5. SUMMARY.

This chapter has traced the historical origin and development of concerns over the possible hazards associated with the microbiological techniques

outlined in Chapter Three. Of note is that the actions which were taken in an authoritative fashion were not hasty. If Asilomar II marked the high point, then two and a half years of increasingly international discussion had led to that point. The responses of institutions in the US and the UK will now be treated in some detail, followed by a summary of over thirty other states and the important international organisations.

SECTION C

INSTITUTIONAL RESPONSES

Chapter Five: The Institutional Response in the United States

Chapter Six: The Institutional Response in the United Kingdom

Chapter Seven: Other States and International Organisations

CHAPTER FIVE

THE INSTITUTIONAL RESPONSE IN THE UNITED STATES

1. The Development of Guidelines

2. The First US Guidelines for Research Involving Recombinant DNA Molecules

3. Operationalisation of the NIH Guidelines

4. The NIH Environmental Impact Statement

5. Hypotheses

6. Summary

THE INSTITUTIONAL RESPONSE IN THE UNITED STATES.

Events in the United States (US) must be considered to be of particular importance, not least because of the extent to which guidelines produced by the National Institutes of Health (NIH) were to influence those of other states. A report published in 1980, having surveyed membership of the International Council of Scientific Unions (ICSU), records twenty-eight states with guidelines in operation, fifteen of which had modified those of the US.[1] Because of the extent of adaptation of their guidelines, it is necessary to examine in some detail the processes by which the US guidelines were developed and how they were operationalised. For this purpose an historical review of the decision-systems will be followed by a summary of the system involved in their implementation. Events in the US were by no means closed to the influence of foreign actors, but for analytical purposes the activity can be seen to be within a distinct system. The historical overview will provide a description of the functioning and adaptation of the decision-systems involved. Chapter Six will make some comparisons when the institutional response in the United Kingdom is outlined.

Although some important issues will surface during the course of the narrative, it is intended to defer much of their analysis until Section D of the thesis, when a more transnational perspective will be apparent. This chapter will, therefore, set out the US institutional responses to the events and actions described in Chapter Four, before relating these, in summary, to the hypotheses.

1. THE DEVELOPMENT OF GUIDELINES.

On 23rd June 1976, the NIH issued guidelines to be used in all cases of

recombinant DNA research funded in part or whole by the NIH.[2] The body responsible for drafting them, the Recombinant DNA Molecule Program Advisory Committee (RAC) had spent many months since Asilomar II in producing a set of guidelines upon which they finally agreed and could recommend for acceptance by the Director NIH. In the interim period the Asilomar Summary Statement provided the only guidelines under which limited work continued.

After the momentum of the early expressions of concern culminating at Asilomar in early 1975, a wave of debate, which included many non-scientists, spread across the US. From this it had become evident that scientists within the field were not in agreement to anything like the extent that appeared to exist at Asilomar II, and in particular at the session devoted to the drafting of a statement. Debate became vociferous at many levels including: the university campus; the city council; the state; the national level; and, as discussed elsewhere, the transnational level. Within the US, however, national publicity made the deliberations at all levels of note, including the campus.

For example, many issues were aired in depth and given considerable press coverage in a debate which raged for a year at the University of Michigan. Three separate committees were eventually to examine different aspects of recombinant DNA techniques, their implications, and guidelines, with a view to developing policy for the university.[3] Questions were raised about what the scientists were trying to achieve, the potential risks, the appropriate guidelines and their implementation, and the role of the university in all of this. During the discussion, significant in that much of the input came from non-scientific sources, the NIH guidelines became available in draft form. The result of the extensive deliberations was a proposal to the Regents that the NIH guidelines be followed, subject

to two reservations. No work should be undertaken in the riskier categories, without the Regents' approval, and biologically enfeebled strains of bacteria should be used more frequently than required in the guidelines. In accepting the proposal, the University of Michigan demonstrated a problem for the US scientists to be repeated again in other universities, cities and states. It became apparent that the requirements facing scientists in the US might not be uniform across the land, and that local level debates, well publicised, could provide many forums in future for opposition viewpoints.

Reinforcement of these observations occurred in an even more documented and significant politicised discussion, which took place in Cambridge, Massachusetts. This internationally reported, and heated, discourse arose out of a proposal by Harvard University to construct a laboratory of moderate containment.[4] Some university biologists opposed the move to allow research at that level of containment. A campus forum considered the problem which engendered interest from the Mayor of Cambridge, Alfred Vellucci. Subsequently, the City Council held public hearings and on 7th July Mayor Vellucci announced a three-month moratorium on all recombinant DNA work involving high risk.[5] The City Council then established its own committee, the Cambridge Experimentation Review Board (CERB) to investigate what safety implementation measures would be required. It was of note that Cambridge was both a centre of interest in using the new techniques, but also an area of vocal opposition from within the science community itself.[6] During the autumn of 1976, the CERB heard testimony from many scientists on both sides of the controversy before publishing, after four months, its report. In addition, many non-scientists had added pressure to curtail the work, including Friends of the Earth.[7]

As a result of their deliberations, the CERB produced recommendations that

the NIH guidelines be used for all work, but with a number of extra conditions to be met. Institutions proposing to use the techniques should prepare a procedural manual, their biohazard committee should be approved by the City Council, the purity of hosts providing DNA should be adequately screened, and health monitoring should be applied more stringently.[8] In all, the work could proceed under wider controls more rigorous than those required by the NIH.[9]

Both the Michigan and Cambridge examples serve to show the widening interest within the US regarding the expressed concerns about recombinant DNA, and the fact that the NIH had produced guidelines. By February 1977, however, a number of localised debates of various levels had begun in addition to these two. At the state level, New York State, California and New Jersey had all begun to consider legislation or regulation, while the cities of San Diego, Madison and Bloomington scrutinised some university proposals.[10] Later in this thesis, the question of legislation will be addressed, but it should perhaps be said that when Federal legislation was eventually proposed, the issue arose as to whether individual states should have the right to 'pre-empt' it by imposing tougher legislation. Thus, the production of guidelines in the US from the beginning would face questions of the uniformity of their application. These local debates were important elements in the wider questioning of how recombinant DNA techniques could best be controlled. Emphasis here will be on the institutional activity which attempted a centralised response, but acknowledging the local pre-emption issue.

Although established before the Asilomar II international meeting, the RAC had been a response to the Berg letter. Having already outlined the function required of the committee, it remains to trace its subsequent development and its efforts at drafting and later implementing guidelines.

Its first meeting, on the day after the Asilomar conference adjourned, was mainly devoted to procedural business. Even so, ten members of the press joined the all-scientist group which adopted the Asilomar conference recommendations as an interim measure. Of note, the meeting also considered some early steps in the procurement of research into the potential hazards,[11] and whether there was a need for a local review function within the implementation of guidelines. However, by the time of the second meeting there had been some further developments in the US as a whole. It was during this period that the University of Michigan debate began, and in April the Senate Subcommittee on Health and Scientific Research, of the Senate Committee on Human Resources, held its first hearing on genetic engineering, under Senator Edward Kennedy.[12] In May 1975, the final draft of the Asilomar statement was submitted for approval by the NAS. The American Society for Microbiology (ASM) held a session in New York on genetic manipulation and hazards, and Harvard made its proposal for a moderate containment laboratory, again both in May.

Despite these events, which reflected a widening of the overall discussion, and the consideration, by some at least, of the risks and benefits together, the RAC would not officially follow suit. Instead conjectured and often intuitional assessments of risk would only be set against containment requirements. At its second meeting on 12th May, the main decision of the RAC was to establish a subcommittee under D.S. Hogness, charged with beginning to draft guidelines for recommendation to the RAC. Two other decisions should also be recorded. It was proposed that a programme to develop safer hosts and vectors be set up as soon as possible, and it was suggested that a newsletter be established.[13] The newsletter would be run under the auspices of the National Institute of Allergy and Infectious Disease (NIAID) and was given the unwieldy name 'Nucleic Acid Recombinant Scientific Memorandum' (NARSM). Intended to be informal

scientific communications, it was of note as an attempt to provide a link for the involved scientists, although some sections would be distributed wider. At this meeting it was also disclosed that the European Science Foundation at the time was requesting letters of understanding from those investigators it sponsored, stating that they were aware of the Asilomar principles.

After a rather pedestrian start for the RAC, it was their third meeting which introduced outright controversy into their deliberations. Often called the 'Woods Hole' meeting, it was responsible in July 1975 for both examining and watering down the draft guidelines which were presented by the Hogness subcommittee. Confusion seems to exist, however, over the extent of agreement on this action. Only eight out of the twelve members of the RAC were present, for example. By this time, the Asilomar statement, acting as interim guidelines, was well publicised and known, but it seemed that the Hogness draft, as modified, was considerably less stringent. It did, nevertheless, give a greater description of the concept of biological containment involving enfeebled hosts and vectors, and went into more detail on the allocation of physical containment. Despite this, many critical letters were received in response to these guidelines.[14] At first the criticism came informally from those shown the guidelines, but such was the response that the RAC chairman, D. Stetten, decided to circulate them more fully amongst the scientific community. A letter from Stetten to one of the minority, who actually saw the Woods Hole draft as <u>too strict</u>, is revealing. Stetten observed that:

> "At the conclusion of the meeting in Woods Hole, it was my impression that the membership of the Committee had indeed reached a consensus. I have since learned otherwise. I have received a flood of letters both from members of the Committee and from interested professionals like yourself. Most of these letters have argued for greater stringency." 15

Of particular note was a letter, organised at a meeting at Cold Spring Harbor, which attracted some fifty signatures, and which expressed concern over the lowering of safety standards. It called for work with all mammalian DNA (not just animal viral DNA) to be categorised as requiring the second highest level of physical containment (P3) and the widening of representation on the RAC. They suggested that more members expert in plant pathology and genetics, and epidemiology should be appointed. Their view was that the RAC should include more scientists not directly involved in carrying out recombinant DNA work themselves.[16] Other voices of dissent were those of Paul Berg, Roy Curtiss and Stanley Falkow. Berg was willing to accept the original Hogness draft as it was before the revisions of the RAC, while Falkow's objections arose out of his being one of the members of the RAC who missed the meeting. Curtiss, however, wrote at length criticising the likely success of biological containment, with supporting evidence from work in his own laboratory, which had been trying to produce modified E. coli through mutation selections. He also questioned the idea of enabling trade-offs between relaxing physical containment in exchange for higher biological containment. In sum, he saw the Woods Hole guidelines as "contrary to the spirit of the Asilomar meeting".[17]

A member of the Boston Area Science for the People group, Jonathan King, a biologist at MIT, was particularly critical of the fact that four members of the Hogness subcommittee were involved in developing recombinant DNA techniques. King added to calls for wider representation on the RAC, suggesting that it should include someone from the Environmental Protection Agency (EPA) or the Occupational Safety and Health Administration (OHSA). A detailed and technical critique of the guidelines was produced by King's group and sent to the NIH, but "was never published since no avenue of publication was available for such a document".[18] Indeed, the

future activities of the RAC, even beyond the completion of the guidelines, would be influenced and monitored by a rising tide of interested bodies. In essence, the disagreements reflect the political nature of the decision-making exercise. Critics of the process had then already raised the important issue of participation. King, however, felt the pressures of counteraction against this. As he claimed:

> "The critics were continuously referred to pejoratively by the proponents as 'kooks', 'Those who have inflamed the public ...' 'incompetents', 'those who want to destroy science'. Life became quite unpleasant for those of us who were trying to bring the issue out into the open." 19

Hogness defended the actions of his subcommittee and the RAC as a whole on the production of guidelines. His view was that the critics were not weighing the benefits of research, in their widest sense, against the conceivable risks.[20] It could be said of this, however, that scientists always assumed benefits, even though they would occur well in the future. The controversy that arose as far as the guidelines were involved was not over the definition of the containment levels, but over the allocation of types of experiments to those categories. Subsequent meetings of the RAC would return to this central problem time and time again. An example of the debate concerned the containment requirements for 'shotgun experiments' using genetic components of animals closest to man, such as other primates. Under the Woods Hole proposals the highest containment level was not prescribed.

As a result of the criticisms of the Woods Hole draft, the RAC chairman appointed a second subcommittee to produce a tighter set of guidelines. Elizabeth Kutter, a supposed 'lay' member of the RAC, appointed at its request, was to chair the subcommittee. As a biophysicist (although she worked with phages) accusations of self-serving might be avoided. The

NIH view had, therefore, responded, if only to a limited extent, to questions about the legitimacy of the RAC structure.

Prior to the fourth RAC meeting, a workshop was held, sponsored by NIAID, on the "design and testing of safer prokaryotic vehicles and bacterial hosts for research on recombinant DNA molecules". Some sixty scientists attended the meeting organised by, among others, Curtiss and Falkow. A critical requirement, it had been recognised at Asilomar II, was the development of appropriate enfeebled bacteria. The excessive optimism that a suitable strain would be developed in weeks had been somewhat modified by the time of this workshop. As a measure of the problem, it was the lack of such an organism that led to some experiments having been under a moratorium for some eighteen months.[21] The Woods Hole meeting had been handicapped by the absence of these enfeebled strains, in turn reinforcing the RAC objective of developing safer hosts and vectors.

Between 4th and 5th December, the RAC held its fourth meeting, starting the day after the NIAID workshop and in the same town. A summary of the workshop was presented by Dr. Helsinki. He reported the good news that suitable plasmids, and lambda phage vectors and hosts had now been developed, and were awaiting testing. Ironically, despite his earlier misgivings, the breakthrough had occurred in Curtiss' laboratory.[22] Applicable to all three drafts so far produced, the Hogness, Woods Hole and Kutter versions, the use of enfeebled organisms could now be written in with some confidence. Thus the fourth meeting held at La Jolla, California, set about reconsidering, in effect, the business of the previous meeting. In addition to the now fifteen members of the RAC present, there were forty-two others. Eight were classed as '<u>ad hoc</u> consultants to the committee', three were 'liaison representatives from other organisations' (including the NAS and NSF), eight were NIH staff,

five were members of the press and three were from Europe including S. Brenner of the UK Medical Research Council and J. Tooze of EMBO. Most of those remaining were scientists from various laboratories.

There was a general feeling that this particular meeting must produce draft regulations or "the dam would be likely to break".[23] Unconfirmed rumours were circulating concerning experiments being carried out clandestinely as patience began to wane. The relevant US scientific community was directing pressure for the RAC to produce something, while at the same time the eyes of other states were following developments closely. Some were delaying the production of their own controls as they awaited the US outcome. In the event, guidelines more strict than those of the third meeting were forthcoming, perhaps as a result of two main factors: firstly, there was the relatively imminent provision of suitable enfeebled host-vector systems (of EK2 level, see below); secondly, three of the most influential organisers of Asilomar II were present, Berg, Singer and Brenner. The existence of the potential for biological containment bypassed pressure for relaxing that provision, as had occurred at Woods Hole, and the Asilomar organisers added their influence in support. Thus the 'weaker than Asilomar' proposals of the previous meeting gave way to a 'stricter than Asilomar' new set.[24] A background threat, perceived by those involved, assisted their motivation. If they failed to act, then others might take over, and in particular that might mean Congress. It would be interesting to speculate as to what the outcome might have been had the enfeebled organisms not come along at that time. Adoption of weaker guidelines might have precipitated the very consequences the scientists feared - greater public controversy and legislation.

As an individual, Sydney Brenner has been recognised by commentators of

the time as influential in the maintenance of caution. Repeating the performance of Asilomar II, he applied his powers of reasoning and his oratorical skills to instil a sobering influence. Caution was implemented in a novel fashion. By the time of the fourth meeting, there were three drafts to consider, those of Hogness, Woods Hole and Kutter. Ground rules were established to enable a paragraph by paragraph comparison. No more than ten minutes would be allocated to each paragraph in the first instance, and where no discussion developed then the chairman would simply choose a version. Difficult points, needing more than the allotted time, would be returned to, and although only the committee could vote, the chair would recognise all in attendance if they wished to speak. Many paragraphs were passed over without discussion, while some required a simple vote on which of three versions would be chosen. Only with paragraphs or sections which needed complete or partial redrafting was there any difficulty.

An example of the debate can be drawn from the consideration of the 'shotgun experiment'. Hogness argued that particular experiments (such as any using DNA from cold-blooded vertebrates) should have the risk explained in detail. Brenner, however, responded by suggesting that the class of source DNA was not so relevant, in the case of shotgun experiments, as the type of experiment per se. The risk lay with fragmenting such large samples of the genome, whatever its source. Brenner also warned the RAC of outsiders viewing their actions in terms of trade-offs and bargains over the assignment of particular categories to DNA of various classes of source.[25] Indeed, future criticisms of final guidelines in both the US and the UK would in part be directed against the rationale of assigning risk in relation to the biological distance of the donor organism from man.

Finally, a draft was completed and presented to the Director NIH for his approval. However, before this was forthcoming, the Director would hold further discussions, including a public debate. Meanwhile, at La Jolla, the RAC considered further business. It was hoped to receive all contract proposals for the construction and testing of safer hosts by January 1976, and to offer contracts by March. It was decided that the RAC, for the time being, would certify proposed host-vector systems, and would give advice regarding the usage of clones constructed under the interim Asilomar recommendations. Of note, though, was that the chairman was asked if the NIH would explore what impact the RAC would have on industrial applications of recombinant DNA technology. Brenner suggested that an experiment be carried out to test whether biological mechanisms existed to transfer DNA from a lower organism to a higher organism. Under maximum containment, a polyoma virus would be inserted into a plasmid, in turn put in a bacterial host and placed in new-born mice. The mice would then be monitored for infection by the virus. Unanimously, the committee decided to request NIH assistance in developing such an experiment. Lastly, the RAC set up a subcommittee to design further experiments aimed at assessing biohazards.

Undeniably, the RAC was a central actor in the US institutional decision-system and had great influence with the Director NIH, D.S. Fredrickson. It was not, however, his only source of advice. Early in February 1976, he called a special meeting of his 'Advisory Committee to the Director' to review the proposed guidelines. This committee was charged with advising the Director on matters relating to the broad setting within which the biomedical sciences developed, including scientific, technological and socioeconomic factors. Membership included individuals knowledgeable in the fields of basic science, clinical biomedical sciences, physical sciences, social science, research, education and

communications.[26] For this particular meeting, additional participants were invited, for example past members and other scientific and public representatives. Seven people made presentations, including Fredrickson, Stetten, Singer, Hogness, Berg and Curtiss. Thirteen members of the public made statements, and a further nineteen individuals attended. A wide range of views were presented, a credit to Fredrickson's notification of the meeting to a large number of public interest groups.[27] Such was the range of backgrounds at the meeting that Michael Rogers has commented:

> "Compared to the nearly exclusive academic background of the guidelines committee this was really almost the public." 28

There was much more public interest than expected and more press in attendance than for any previous meeting. Singer and Berg outlined the guidelines, but as Rogers observed, the real contribution of the meeting was that it provided a forum for the critics to express their views. Most critics were young and had little scientific background, yet were critical of the motives and possible gains of the original guideline writers. Rogers agreed, however, that at least some bias was evident in the selection of magazine articles given to the Advisory Committee to read, as they tended to defend the guidelines. They were not representative of the range published in journals such as Science.

Overall in the recombinant DNA debate, and particularly around this time, two critics were of note: Robert Sinsheimer, a member of the Advisory Committee who participated in the February meeting, and Erwin Chargaff. Sinsheimer, Chairman of the Division of Biology at the California Institute of Biology, had, for example, sent a letter to Fredrickson prior to the meeting,[29] which raised four key points. Firstly, he saw the failure of physical containment as inevitable in the long run, given

the likely number of laboratories which would move into the field.[30] That is, physical containment was limited and dependent on human efficiency. Secondly, Sinsheimer questioned the effectiveness of biological containment in that genetic information might be passed from enfeebled strains of organisms used in the work to other organisms through natural recombination. Man himself contained many organisms capable of initiating and carrying out such recombination with E. coli. Thirdly, Sinsheimer raised the possibility of 'breaking' the genetic species 'barrier' between prokaryotes and eukaryotes through the transferring of DNA segments with their promotor or terminator sequences, thought to differ on each side of the 'barrier'.[31] Thus he warned of upsetting "an extremely intricate ecological interaction which we understand only dimly". Finally, Sinsheimer introduced a point he felt was underestimated, namely that they were dealing with self-replicating organisms potentially making any hazard, should it appear, irreversible. This situation he inferred was unlike any other physical or chemical hazard.

As a consequence of the points he raised, Sinsheimer recommended to Fredrickson that all recombinant DNA work should only proceed under the highest possible precautions and at one national site. This most eminent biologist went as far as to say that he would only allow this much because of the extraordinary benefits that could accrue. He concluded:

> "I will say, though, that in my judgement, if the guidelines are adopted and nothing untoward happens, we will owe this success far more to good fortune than to human wisdom." 32

After the meeting of the Advisory Committee, Sinsheimer repeated his concerns in another letter to Fredrickson.[33] In this he challenged some explicit defences addressed to the critics, which had been made at the

meeting. It had been argued, for example, that a justification for proceeding with the research was the fact that recombination occurred in nature. Sinsheimer, however, argued that this occurred at some unknown frequency which man would be increasing by "many orders of magnitude". He still feared irreversible consequences, whatever the probability. In addition to his earlier comments, Sinsheimer suggested a way to proceed with the work which in general would be unusual in basic biological research outside industry. He suggested that the starting point of research should be the objective. If synthesis of a particular protein could be deemed desirable, then safe procedures could be tailored for that objective, rather than trying a multifunctional approach. Further, he repeated worries about using E. coli by arguing that a suitable animal virus should be found, to which we have known defences, rather than using "free-living ubiquitous bacteria".

Yet, despite his views, Sinsheimer agreed with that part of the mood of the Advisory Committee meeting that seemed to fear future legislation and, in particular, prior approval of experiments, which, he thought, might impede science. It is worth noting, however, that this need not have been too problematic as prior approval was precisely the approach used in the UK to commendable effect, even if criticised from some quarters (outlined in the next chapter).

Erwin Chargaff, Professor Emeritus of Biochemistry at Columbia University, was the second of the two influential critics who produced forceful and somewhat authoritative arguments. Their standing makes them of note, whatever the judgement that can be applied to their arguments in retrospect. Not in attendance at the Advisory Committee meeting, Chargaff did, however, write to Fredrickson on the day before.[34] He called for a two year 'cooling off' period, involving prohibition of the work, accompanied

by "discussion and reflection". He stated that:

> "... I can only express my strong dismay about the whole program, as it has been formulated, restricted, expanded, and drowned in a verbiage of silly claims and counterclaims." 35

Soon afterwards he wrote to Science[36] commenting, like Sinsheimer, although rather sarcastically, on the undesirability of using E. coli and the potentially irreversible ecological significances. However, of particular note was that he broached the ethical question in claiming that the issue was not one of public health, but was more related to their right to put "an additional fearful load on generations that are not yet born". The NIH, he suggested, was not the appropriate institution to address such problems.

These arguments of Sinsheimer and Chargaff have been presented at some length, partly because of the importance of the points made, given the knowledge of the time, and partly because opposition groups rallied to them. Non-scientists, in particular, tended to identify with scientists reflecting their views in order to enhance the legitimacy of their own arguments. The two critics in short were preaching caution and social responsibility.

It should be stated, nevertheless, that the arguments concerning the crossing of the 'barrier' between eukaryotes and prokaryotes was not acceptable to many scientists. One group had, for example, argued that any such barrier might have no purpose and simply reflect different evolutionary paths. A second group had argued that it did not exist at all and that they were merely ignorant of the flow of genes between species. A third group suggested that evolution had already tested all genetic combinations and dismissed those not useful. Sinsheimer attri-

buted many such arguments to those who emphasised the benefits to be gained from the research. For example, he pointed to a flaw in the third group's argument. If nature had tested all gene combinations, then their own proposed genetic manipulations could not be novel, and by implication beneficial.[37] To an extent it was the existence of this division of views between respected scientists that is of interest here, as it reflects the latitudes involved as a result of uncertainty.

Numerous others also wrote to Fredrickson, including Berg, Singer, Handler and Goldstein.[38] Berg and Singer expressed general satisfaction, although Singer did suggest greater stringency in dealing with SV40.[39] Goldstein urged a meeting of both sides to avoid:

> "... opting only for development, rather than development, leadership and control of a new technology." 40

A wide variety of issues were therefore aired after the drafting of guidelines at La Jolla. One more RAC meeting would occur before final publication, and for this Fredrickson recommended discussion of a document which he distributed. It was a summary of the responses which he had received after the February meeting of his Advisory Committee.[41] The document listed a number of headings: Methods of Containment; Prohibited Experiments; Biological Containment Criteria...; Classification of Experiments ... [using the new enfeebled E. coli]; Experiments with Eukaryotic Host-Vectors; Implementation. Under these headings, Fredrickson provided a summary of comments which he had recieved, whether technical or more general. It was, however, noticeable that Fredrickson tended to favour certain views which were for the most part those less critical of the draft guidelines. For example, despite comments from some scientists going so far as to suggest a complete ban on SV40, he made it quite clear

that he favoured its use, and under the provisions of the planned guidelines. The difficulty with the course of action chosen by Fredrickson is that it can be criticised on the basis that it was the role of the RAC to present him with advice and not the other way around.

At the RAC meeting held in early April 1976, most of the suggested amendments were rejected,[42] and in reflection of the tone of Fredrickson's document broader issues, as raised by Sinsheimer and Chargaff, were not discussed. N. Wade reported the outcome as:

> "... a clear victory in sight for those who wish research to go ahead under stiff but not grossly inconvenient safety conditions." 43

If the suggestions of Fredrickson guided the RAC meeting, then it should be noted that Fredrickson himself faced constraints. Wade identified these as: firstly, an effective veto held by the European Molecular Biology Organisation (EMBO) which had made it clear that it would only go along with the NIH guidelines if they became no stricter; secondly, Wade suggested that there was a fear that if the guidelines were unacceptably rigorous, then the scientists would ignore them. An assiduous follower of the events as they unfolded, Wade identified two members of the RAC as dominant, David Hogness and Charles Thomas, of Stanford and Harvard, respectively. Both were forcefully against stricter guidelines and both were personally involved with recombinant DNA work. Whether or not they genuinely reflected a majority view of the scientists at large, they were open to the charge of conflicts of interest.

In the interim period between the fifth RAC meeting and publication of the guidelines in June, the Director, NIH received further correspondence. Berg, for example, expressed dissatisfaction with biological containment

preferring emphasis on physical containment as the "only tried, tested and acceptable means available for containing dangerous pathogens". He also noted that in the UK it was physical containment on its own which was being relied upon.[44] A non-scientist, J.F. Kelly, requested that a broad policy statement be attached to the guidelines. He argued that as it was, they were in effect a set of implementation procedures, the underlying policy of which had to be inferred.[45] Others raised questions of the appropriate actions if environmental contamination were to occur, and the assumptions in general upon which the NIH and RAC were operating. In technological fields, preventive measures are often taken, but without contingency plans for failures, perhaps because the latter could imply a weakness in the safeguards. The Federation of American Scientists despatched to the NIH the results of a poll of their members. Their results showed only a small percentage of biologists (9.3%) and non-biologists (5.7%) who thought the guidelines were too restrictive. Overall, more than 80% of both biologists and non-biologists who responded thought the guidelines either about right or "probably insufficiently cautious". In all, some 56.2% thought the guidelines "about right".[46]

An even more systematic poll was later organised by a science correspondent for the Boston Globe. Robert Cooke, between February and March 1977, mailed questionnaires to some 1,250 senior biologists working in universities, industry and government. Of the 490 respondents, 39% believed the guidelines should be more strict, while 44% thought them strong enough.[47] Both of these polls reflect the degree to which caution was seen as desirable by many interested scientists and non-scientists. It is of note that the RAC itself was unanimous in its recommendation to Fredrickson to go ahead and publish. Yet as late as a few days before publication, a petition carrying some thirty signatures called for a postponement on the release of guidelines.[48]

Having considered the many comments received over the months, Fredrickson, on 23rd June 1976, released the official NIH guidelines, some two years after the publication of the Berg letter. They were accompanied by a document drafted by Fredrickson which summarised the history of the debate, thus far, and indicated his own attitudes.[49] To be fair, he provided a useful synopsis of the views discussed above and in the many representations he received. Aside from making some general comments regarding the speculative nature of hazards and the by then more certain promise of benefits, Fredrickson failed to detail the assumptions and policy choices to which he was working. At one point, for example, he summarised the two arguments concerning the 'barriers' between eukaryotes and prokaryotes. On the one hand, recombination in nature was argued to have been occurring for so long that man's efforts would merely utilise specific combinations of genes. On the other hand, man could cross the barrier in the laboratory and if the donor DNA was expressed in the host, it might alter the host in "unpredictable and undesirable ways". Fredrickson concluded:

> "The fact is that we do not know which of the above-stated propositions is correct." 50

Nowhere does Fredrickson give any indication of the strength of feeling that was, for example, expressed by Sinsheimer and Chargaff over potential environmental damage and the evolutionary effects. A further example of his style of argument which is of some concern can be seen in his resolution of the fears expressed over the use of E. coli, which in one of its natural forms inhabits the human gut. Fredrickson countered this by arguing that because the bacterium was also the most understood (the laboratory strain which would be used) it should therefore be "safer than other candidate micro-organisms". Any underlying method of balancing

such arguments is not revealed, and in effect the guidelines are much as recommended by the RAC.

Perhaps to avoid charges of self-serving, as after all the NIH had a responsibility to promote research, assumptions were not made too explicit. In organisational terms this could relate to bias and non-decision. After a summary of the guidelines and the procedures of implementation, some further questions will be raised.

2. THE FIRST US GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES.

Four principles were stated as underlying the published guidelines:

i) There were certain experiments for which the assessed hazard was so serious that they were not to be attempted at that time.

ii) The remainder could be undertaken with appropriate safeguards of a physical and biological kind.

iii) The level of containment should match the estimated potential hazard of the different classes of recombinants.

iv) The guidelines themselves would be subject to periodic review (at least annually).

Four levels of physical containment were incorporated in the guidelines, ranging from P1 to P4 as the physical design of the laboratory, the equipment and procedures used increased in complexity. P1 would be in essence an ordinary microbiological laboratory where work could be

carried out on open bench tops. At the other extreme, P4 containment would involve a whole host of measures to limit the potential for environmental contamination. The laboratory at this level should be effectively isolated, maintained at negative air temperature, be completely sealed as a monolithic unit except for stringently controlled access, and exhausted air should be decontaminated. Sophisticated double-door autoclaves would be used for sterilisation and work would be carried out in safety cabinets. With these and other features the laboratory would be a maximum security unit of the likes of Fort Detrick in the US and Porton Down in the UK. In summary, the physical containment was to cover minimal (P1), low (P2), moderate (P3) and high (P4) risk levels.

However, the guidelines also designated three categories of biological containment, EK1, EK2 and EK3. EK1 containment referred to the use of the basic laboratory strain, E. coli K-12 with existing plasmid and bacteriophage vectors. Apparently a harmless micro-organism, it does not usually establish itself in the bowel, but if ingested it stays alive in passing through. It was necessary, however, to consider the possibility of genetic exchange between E. coli K-12 and other residents of the gut. Consequently, this organism was thought to offer only moderate containment. EK2 containment would utilise genetically constructed host-vector systems demonstrated to provide a high level of biological containment through data from suitable laboratory tests. Modifications to the E. coli K-12 host or the plasmid or phage vectors were to be such that a genetic marker, carried on the vector, should not show up in other than specially designed and carefully regulated laboratory environments at a frequency greater than 10^{-8} (or one in 100 million). EK3 containment was designated as the same as EK2, but with the specified level of containment shown to exist through appropriate tests in animals, including humans and primates, and other relevant environments. This additional validatory data would

set EK3 apart from EK2 as a category, by increasing certainty.

A number of experiments were banned, including any involving the use of DNA from dangerous pathogens,[51] or oncogenic viruses, or DNA from cells infected with such agents. Also banned was the use of DNA containing the genes coding for the biosynthesis of potent toxins such as botulinus and diphtheria, or the venom from snakes. The use of plant pathogens was similarly excluded. In addition, certain other activities, of less direct hazard, were to be avoided at that time, including the transference of a drug resistance trait to an organism not known to acquire it naturally, the release of any recombinant DNA molecule into the environment, and finally, the exceeding of the maximum of ten litres of culture to be used in recombinant DNA work.[52]

All the remaining experiments were identified in categories related to the biological distance from man of the DNA used. Each category was then assigned physical and biological containment requirements, and in some instances alternative combinations of levels were permitted. For example, P3 and EK1 was considered comparable with P2 and EK2, while P4 and EK2 could substitute for P3 and EK3. Well summarised by a number of commentators,[53] some examples of the containment classifications are as follows:

DNA from non-pathogenic prokaryotes that naturally exchange genes with E. coli	P1 and EK1
DNA from embryonic or germ-line cells of cold-blooded vertebrates	P2 and EK1
DNA from non-embryonic cold-blooded vertebrates	P2 and EK2
DNA from non-pathogenic prokaryotes that do not naturally exchange genes with E. coli	P3 and EK1
DNA from embryonic primate-tissue or germ-line cells	P3 and EK2

DNA from non-embryonic primate-tissue	P3 and EK3 or P4 and EK2

In addition to biological distance from man, containment was also applied on the principle that containment should never be less than that already required of the most hazardous component of the experiment in existing guidelines or regulations. However, the guidelines suggested that a further precaution be reflected in the undertaking of work involving recombinant DNA techniques. It was emphasised that there was a need to ensure thorough training in microbiological practice, including aseptic techniques and instruction in the biology of the organisms used in experiments so that potential biohazards could be understood and appreciated. Laboratories were required to prepare emergency contingency plans and to make it known to workers where experiments involved "known or potential biohazards".[54]

One of the main features of the NIH guidelines was their comprehensiveness. This arose out of the policy adopted in the US to issue guidelines from a central source, but leave the identification of containment categories regarding individual experiments with the laboratory and institution concerned. The UK system will later be contrasted in that allocation of containment levels for all proposed experiments was centrally determined. A large proportion of the NIH guidelines was therefore given over to their implementation. The operationalisation of the guidelines is of great relevance to this thesis.

3. OPERATIONALISATION OF THE NIH GUIDELINES.

At this stage, discussion of the implementation of the NIH guidelines will refer exclusively to their use in the US. It is, however, noted

that their influence was international, and Chapter Seven will outline the activities in many other states. As a prelude to the discussion of their international impact, it is worth noting that in June 1976, the State Department despatched a telegram to forty-four of its embassies and missions in countries believed to support considerable biomedical research. It requested that appropriate officials of host government agencies be informed of the impending release of guidelines and the address of the Director, NIH. The telegram, not least, acknowledged the need for "world publicity and co-operation on the problem".[55] It was the comprehensive categorisation of types of experiments in relation to containment which made the NIH document an attractive 'off the shelf' option for other states. Yet its implementation within the US itself was not without difficulty.

An issue of particular importance was the enforcement of the guidelines. The NIH had opted to avoid elevating the guidelines to Federal regulations. Acknowledging that many commentators would prefer this course, Fredrickson stated that the scientific community in general urged against it. He added his support to these scientists, suggesting that there would be more flexibility and administrative efficiency if Federal regulation was avoided, although he acknowledged that the whole matter needed further attention. The question of ensuring compliance with the guidelines had, however, a further weakness. As they stood, the guidelines only applied to NIH-funded research, of which the control of grants could be called upon to give them credibility. Yet research was likely to be done by many who were not funded, even in part, from the NIH.

At the time of the release of the guidelines, first moves were in hand to have inter-Federal agency discussions to assess the possibility of widening their application. This activity reflected one strand of the problem, a

potential solution being other agencies requesting compliance as a condition of funding. A more disturbing problem to many at the time was the question of ensuring compliance from wholly industrial sponsored research. For his part, Fredrickson, prior to the release of the guidelines, had held a meeting with industrial representatives, under the auspices of the Pharmaceutical Manufacturers' Association (PMA). Fredrickson had been hoping for the acceptance of the guidelines throughout the US, and, at least similar guidelines, internationally.[56] Although Fredrickson's statement accompanying the guidelines is not very revealing regarding the attitudes of industry at that time, some letters which he subsequently received do throw some more light on their views.

W.N. Hubbard of the Upjohn Company gave two reasons why industry felt concerned: firstly, he expressed a fear, often to be repeated on both sides of the Atlantic, that industrial confidentiality could be compromised if research results were disclosed prior to patenting; secondly, Hubbard stressed a worry about industry becoming involved with self-serving regulations. He concluded that:

> "It is my impression then that industry will avoid committing itself in very formal ways to policy statements out of a reasonable and deep-seated fear that this is just the first step of another wave of bureaucratic intervention into individual endeavor." 57

C.W. Pettinga of Eli Lilly and Company indicated that his company would "adhere to the intent and spirit of the NIH guidelines" and had taken "several steps towards this end". A safety committee had been set up and a P3 laboratory established. However, Pettinga suggested that industry had more experience than anyone else in working with large-scale contained studies, and that if they were convinced of the safety, they would have no hesitation in exceeding the ten litres maximum level. Further, the

intent to follow the spirit of the guidelines was qualified by saying:

> "There are specific instances where we might not be in strict compliance. In these specific instances we feel either that the wording of the guidelines is too non-specific or we are capable of guaranteeing the safety of the exercise in question." 58

Interestingly, Pettinga also suggested that the RAC membership should include a well-informed representative of industry.

Thus on release of the guidelines, there was general uncertainty over how closely industry would comply with them. Two pressures were being experienced at the time. On the one hand, industry wanted to wait and see what the guidelines would be like and the extent of their enforcement before becoming too public in their opinions. On the other hand, however, they faced competitive pressures to actually get ahead and utilise the new research tools. Conflicting pressures of this sort would not be conducive to effective operational control of a voluntary nature. A telling summary of the meeting in June, which thirty industrial representatives attended, observed that:

> "In general, the industries seemed to be somewhat hesitant to commit themselves with regard to the guidelines since it was believed that the guidelines might eventually assume the status of regulatory law and this would place an entirely different perspective on their views about the details of the guidelines." 59

This summary went on to suggest that although the President of the PMA had implied during Congressional hearings that the guidelines were endorsed by the drug industry, this spirit was general through all industries. Thus, the NIH guidelines from their inception were faced with a problem of ensuring compliance in their implementation and the treatment of industry in particular was to remain a somewhat controversial

issue. Nevertheless, the guidelines did describe roles and responsibilities for persons and organisations concerned with recombinant DNA activity. From this an outline of the operational control framework can be drawn.

a) Principal Investigator.

The Principal Investigator would have primary responsibility at the laboratory level for a whole range of functions including: estimating the hazards involved; determining the appropriate containment; selecting methods for handling recombinant DNA materials; preparing procedures to handle any spillages; determining the applicability of various precautionary medical practices; securing approval for proposed work; submitting information on purported EK2 and EK3 systems to the RAC and making strains available to others; reporting to the Institutional Biohazards Committee (IBC) and the NIH Office of Recombinant DNA Activities (ORDA) any new information bearing on the guidelines; applying to the RAC for approval for any experiments involving more than ten litres of culture; applying to the RAC for approval to lower containment levels after rigorously characterising any recombinants deriving from shotgun experiments.

Before commencing work, the Principal Investigator was required to advise the other staff in his programme of the nature and assessment of hazards, and ensure that they were suitably trained. Any illness or other problems were to be reported to ORDA and his institution's IBC. Thus, a great deal of the responsibility for the implementation of the US guidelines fell to the individuals undertaking the work itself.

b) Institutions.

The institution in which the work was undertaken would have to bear all

the responsibilities of the Principal Investigator, in addition to setting up an Institutional Biohazards Committee charged with: advising the institutions on policies; creating a central reference of relevant information; developing a safety and operations manual for any P4 facilities; certifying to the NIH on applications for research support that all the conditions were met.

The IBC was to comprise individuals of "a diversity of disciplines relevant to recombinant DNA technology, biological safety, and engineering". In addition, the IBC was to possess, or have available to it, the competence to determine how its findings related to applicable laws, regulations, standards of practice, community attitudes and environmental considerations. Indeed, the last point would help to enhance the legitimacy of the committee within its local area, and as an overall component of the operationalisation of the guidelines. To supplement this, minutes of the meetings were to be made public.

c) NIH Initial Review Groups.

These groups were to review the scientific merit of each grant application and make an independent assessment of the hazards which might be involved. They would then determine the adequacy of the proposed containment safeguards, referring any difficulties encountered in risk assessment to the RAC or ORDA.

d) NIH Recombinant DNA Molecule Program Advisory Committee (RAC).

In addition to the requirements of its Charter,[60] the RAC would have responsibility for: revising and updating the guidelines; evaluating and certifying proposed EK2 and EK3 systems; resolving questions concerning potential biohazards and containment if requested by the NIH staff or review groups; reviewing and approving experiments exceeding ten litres of culture.

e) NIH Staff.

Staff at the NIH were required to: restrict grant awards for recombinant DNA research, unless use of the guidelines was confirmed, the proposal was reviewed and a Memorandum of Understanding and Agreement (MUA) was properly executed; review and respond to questions or reports submitted by IBCs or Principal Investigators, disseminating any findings; receive and review applications for approval to lower containment categories on rigorously tested products of shotgun experiments; refer items from the above to the RAC as deemed necessary; perform site inspections of P4 facilities.[61]

f) Office of Recombinant DNA Activities (ORDA).

Although the guidelines document did not describe the role of ORDA in any detail, it did announce its existence. Its functions were, however, to become important and can be summarised as follows. It was to interact with the office of the Director, NIH, keeping the latter informed, and partaking in planning activity. An important function would be the dissemination of information to the many groups involved. ORDA would collate information from sources such as divisions of the NIH and would in turn provide summaries of NIH policy. Much of ORDA's activity was to involve the development of relationships with federal and non-federal agencies, the science press, professional societies, industry and international bodies. It was also to monitor IBC membership and problems which might occur in laboratories. Finally, ORDA would in effect service the RAC, providing management, staff and executive secretarial functions, assisting in general the publicity of RAC activity.[62]

g) Office of the Director, NIH.

The office of the Director, NIH, was to be responsible for the promulgation and enforcement of regulations or guidelines, and for accountability

to Congressional committees, the Department of Health, Education and Welfare and the public.[63] At the time of the release of the 1976 guidelines, an institutional framework had been established which would enable US research to proceed on a large scale. However, the assignment of roles and responsibilities had not been without criticism during the planning stages. Indeed, Fredrickson in his statement accompanying the guidelines recognised the conflict of opinions.

With regard to IBCs, one view had been that they should be required to determine containment conditions for given projects. (In the draft guidelines it had been stated explicitly that this function would not be carried out by IBCs.) The RAC opposed the suggestion, arguing, instead, that the most appropriate level for scrutiny of containment conditions was the national level, using NIH study sections. Fredrickson again applied his own judgement and chose to take a line whereby IBCs would not be required to undertake such a function, but could if their institutions so wished it.

The structure of the RAC had also involved some differences of viewpoint. For example, it had been suggested that the scientific advisors on the committee should include a number not involved in undertaking recombinant DNA research, and that in addition there should be a committee to offer more policy-oriented advice. Fredrickson opted to defend the inclusion of involved scientists in that they would have "the expertise to assure that the guidelines are of the highest scientific quality" and would in any case be complemented with scientists from other fields.[64] On the policy side, Fredrickson noted that the RAC itself requested the inclusion of a non-scientist, and that a Professor of Government and Public Affairs had duly been appointed. An ethicist had also been nominated. However, the main source of policy advice was to be the Advisory Committee to the

Director, considered above.

The two committee structure, commendable in that it provided a wide range of expertise and political advice, was weaker than necessary in that both committees independently advised the Director, NIH. There was little opportunity for cross-fertilisation of ideas between the committees themselves. In the United Kingdom, for example, a single central committee comprised many scientists and non-scientists and could address a wider range of issues than the RAC. Thus, in the last resort, the Director, NIH himself had considerable latitude in how he synthesised advice.

To complete the outline of the US institutional response and operational structure, the diagram below indicates the main patterns of interaction within the overall decision and implementation system. It can be seen that the RAC and ORDA represent focal points of information exchange, the content of which can be identified in relation to the above roles and responsibilities of the various groups involved. Likewise, the central position of the Director, NIH is evident. The events described in this chapter have shown how the system came into being, with particular emphasis on the use of an existing institution, the NIH, and the early creation of the RAC.

A number of criticisms have been presented in passing, and further analysis will be presented after the examination of activities in other states, notably the UK. However, within the US, the Director, NIH himself was legally required to make an analytical appraisal of his actors in establishing guidelines, in the context of an Environmental Impact Statement.

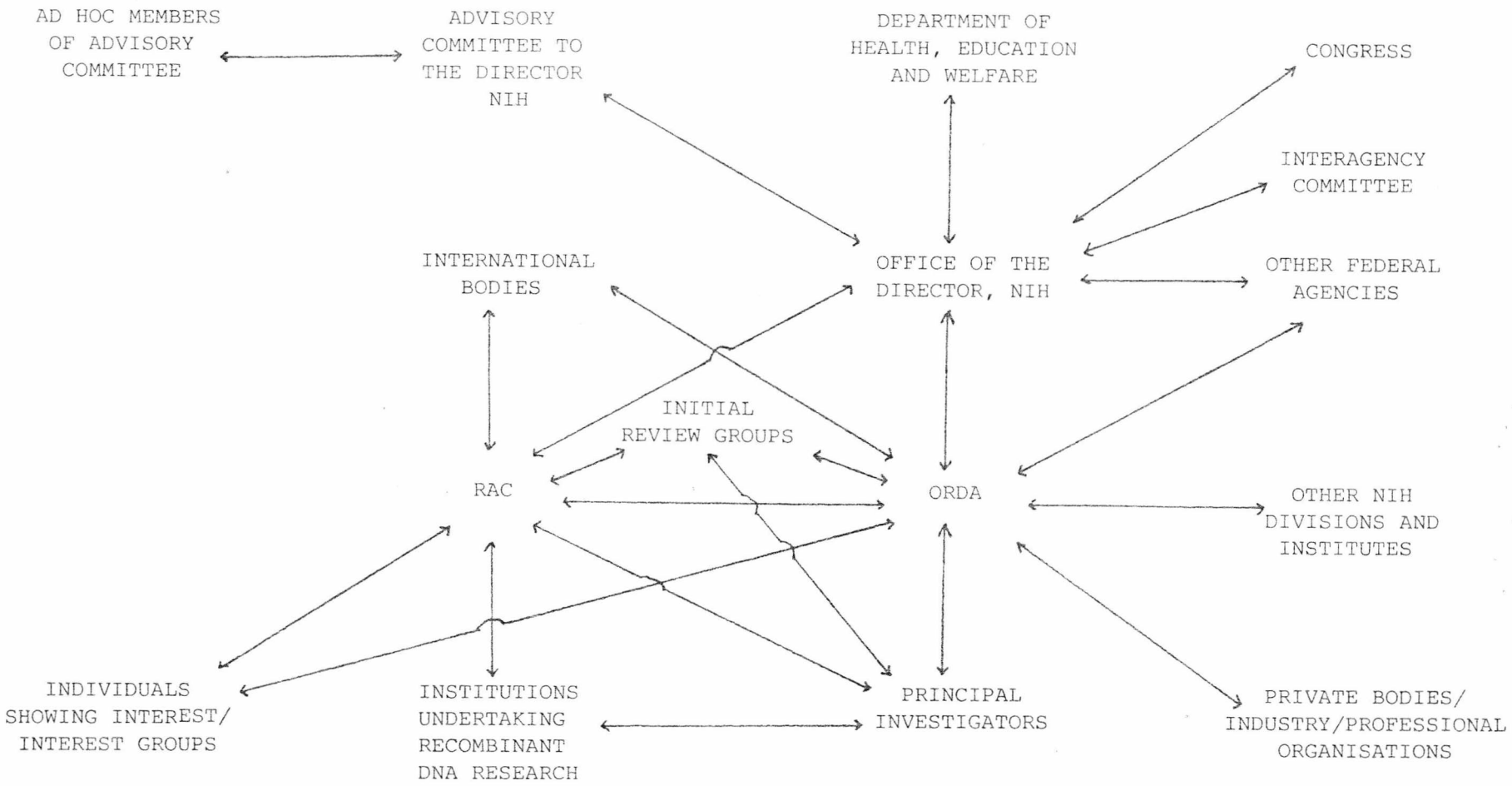


DIAGRAM 1 Diagrammatic Illustration of the Central Roles of the RAC and ORDA in the United States Response to the Recombinant DNA Debate.

4. THE NIH ENVIRONMENTAL IMPACT STATEMENT.

Early in 1976, the Director, NIH began to receive requests for him to publish an Environmental Impact Statement (EIS) on proposed actions relating to recombinant DNA. The National Environmental Policy Act (NEPA) of 1969 was cited as applying to all agencies of the Federal Government, covering "every recommendation or report on proposals for legislation and other Federal actions significantly affecting the quality of the human environment". Under this law, a detailed statement was required on: environmental impacts of the proposed action and environmental effects which could not be avoided; alternatives to the proposed action; long-term implications; and any irretrievable use of resources involved.[65]

In complying, Fredrickson opted to produce an EIS as soon as possible, but not at the expense of holding up publication of the guidelines. His view was that the whole process of developing guidelines was "in large part tantamount to conducting an environmental impact assessment".[66] It was clear, however, that many thought the analysis involved was narrowly based and inadequate.

Thus it was on 9th September 1976, some eleven weeks after the guidelines were released, that a draft EIS on their impact was published in the Federal Register.[67] The public were then invited to submit comments by 18th October 1976, and one year later the final version appeared which incorporated the comments received.[68] In a very descriptive fashion, the EIS summarised the main events, underlying principles and assumptions leading to the guidelines. As such it has provided source material for this chapter. Of particular importance was that it was required to address different possible courses of action with respect to the new

research techniques. Five options had therefore been identified in the draft EIS:

i) No action.

ii) NIH prohibition on the funding of all experiments with recombinant DNA.

iii) Development of different guidelines.

iv) No guidelines, but NIH consideration of each individual proposed project before funding.

v) General Federal regulation of all such research.

The 'no action' choice on the part of the NIH would have left researchers with only the Asilomar Statement to act as guidelines. Public concern would have been higher, while the costs to researchers in both time and resource terms would have been less. Aside from the public concern, such an option would, in effect, have meant ignoring the explicit call for NIH involvement expressed in the Berg letter.

A refusal by the NIH to fund any recombinant DNA research would not imply a complete US ban, as other public and private sources of funding existed. Not least, industry would have still shown interest. From the NIH point of view, two main arguments were used to dismiss the option. Firstly, an intuitive risk-benefit argument was used to emphasise that many benefits were to be gained from the research, and therefore it should continue. This does not overcome a possible criticism that a more thorough risk-benefit assessment should have been undertaken before allowing the research to proceed. The second argument was more worrying. It was illogical and irrelevant as far as any safety considerations were concerned. In essence, having acknowledged how US scientists had played a major part in drawing attention to the potential hazards, the draft EIS argued that the NIH guidelines were likely to be accepted as a model

internationally, and that "prohibition of the work would undermine American leadership in the establishment of worldwide standards for safety".[69] This can easily be countered by suggesting that US caution to the extent of extending the moratorium might also provide the international lead regarding safety. In terms of prestige, however, it could be suggested that the harsher the restrictions faced by US researchers in an internationally competitive field, the less likely it would be that other states would in fact follow suit. A more honest argument related to this, reproduced in the draft EIS, was that the banning of the work in the US could undermine its leadership in biological research, if the work continued elsewhere. The whole associated question of international harmonisation of guidelines will be returned to in Chapters Seven and Eight.

Discussion on 'different' guidelines was confined to giving examples of controversial differences of opinion over the containment requirements for specific experiments. It has already been shown how arguments differed in this respect. More fundamentally, the NIH can be criticised for not justifying more thoroughly the underlying principles and assumptions it operated upon. For example, it never really explained why immediate health concerns should dominate over ethical or long-term ecological considerations.

The possibility of the NIH assessing each individual proposed experiment, in relation to criteria applied by a panel or committee, was considered by way of an alternative to the existing guidelines. Whatever the value of making such a comparison after the guidelines option had been chosen, the draft EIS quickly dismissed the possibility. Its advantages were recognised as providing a system of greater flexibility in adapting to new knowledge. Disadvantages in a US context would, however, be notable,

even though this was essentially the approach adopted in the UK. Enormous time and resource costs would apply given the size of the US and the potential research interest. It was doubted whether sufficiently knowledgeable individuals could be found for what were likely to be full-time jobs on the central committee. Besides, it was argued that IBCs would initially assess each proposal, which would then be re-evaluated by the NIH Study Section in reviewing the scientific merit of the proposal. At best, this would be seen as a compromise. More will be said of central experiment assessment when examining the UK institutional responses.

Perhaps the only option given serious consideration as an alternative to the NIH implemented guidelines was the possibility of Federal regulation of all recombinant DNA work. This option was, in particular, given substantial coverage in the final EIS as a consequence of a development between it and the earlier draft EIS. In October 1976, the Secretary of Health, Education and Welfare had established, with approval from the US President, an Interagency Committee on Recombinant DNA Research, chaired by the Director, NIH. This committee was important as Fredrickson had felt that the question of Federal regulation was beyond the purview of the NIH, a research agency.

It was intended that the Interagency Committee would determine the applicability of the NIH guidelines to industry, and to other Federal agencies. All Federal departments and agencies which might support or conduct relevant research, and all regulatory agencies which might have potential authority over it, were represented on the committee. If necessary, the committee was to recommend appropriate legislation or executive action. Nineteen different bodies were represented, including the Department of Defense, the Food and Drug Administration, the National Science Foundation and the Executive Office of the President.[70]

Appendixed to the final EIS was an interim report of the Interagency Committee, which presented the results of it having examined the applicability of existing legislation to recombinant DNA research.[71] A number of problems had been encountered. For example, under the Occupational Safety and Health Act, the term 'employer' did not cover US states and their political subdivisions, unless they volunteered to adopt this status. Only twenty-four had done so. Self-employed persons were also excluded. Under the Toxic Substances Control Act, although recombinant DNA materials could be covered, the act explicitly exempted the need to register small quantities used for the purposes of scientific experimentation or analysis. Indeed, similar problems arose with all of the existing legislation examined, such that the Interagency Committee concluded that although there was coverage within the legislation broad enough to include recombinant DNA, it "would probably be subject to legal challenge".[72]

From their survey, the Interagency Committee itself recommended elements to be incorporated in legislation. Both the production and use of recombinant DNA molecules, it felt, should be covered. They suggested that projects should be registered, facilities licensed, a single set of regulations should apply nationally which would pre-empt state legislation, and inspection and enforcement should be implemented. Only two abstentions (from the Council on Environmental Quality and the Justice Department) were recorded in a report which recommended legislation.

As a result of the report, the Secretary of Health, Education and Welfare, J. Califano, had legislation developed. The Administration Bill was then reviewed by all members of the Interagency Committee, and by all departments and agencies. Senator Edward Kennedy, Chairman of the Subcommittee on Health and Scientific Research of the Senate Committee on Human

Resources, and Representative Paul Rogers, Chairman of the Subcommittee on Health and the Environment of the Interstate and Foreign Commerce Committee, introduced the Bill in each House. Congressional hearings followed, and by the time of the final EIS, both House and Senate Bills were pending. Thus, of all the options outlined in the EIS, only Federal regulation was examined in depth. The actual failure of legislation to be completed is discussed in Chapter Eight.

A number of letters received in response to the draft EIS were very critical of the limitations and superficiality of the discussion of alternative options. It was, for example, suggested that true evaluation required much more than a cursory summary.[73] Yet despite many comments, the final EIS did not adequately respond to them. A chapter given over to the comments on the draft EIS followed the same format, using the same headings as in the draft. Each section was then taken individually and a response was made to any criticism which fitted that particular category. Thus, when the five alternative options were returned to, there was no slot for those comments which were critical of the limited range of options, or to the superficial level of the discussion.

An important criticism raised by a number of respondents concerned the failure of the draft EIS to address the long-term evolutionary factors. The final EIS made this excuse:

> "The omission of this matter from the Draft EIS was based on several considerations, including the almost total lack of relevant scientific facts, the highly controversial nature of modern evolutionary theory, the consequent inability to impose a theoretical framework on the issue, and difficulties in analysing the arguments of those who have expressed serious concern with this matter ..." 74

This is tantamount to arguing that because of uncertainty and extensive

disagreement, the issue can be omitted from an assessment of environmental impact. Controversy should, on the contrary, necessitate its inclusion. A very brief reference to the issue was included in the final draft.

Criticisms applied to the guidelines rather than the draft EIS were simply forwarded to the RAC, which at this time was beginning the process of guideline revision, discussed further in Chapter Eight. In sum, the legal requirement for a wide ranging assessment of environmental impacts of somewhat controversial actions by the NIH was finally fulfilled. Much of the criticism of the draft EIS would suggest that something of a minimalist approach was adopted. Much of the importance was omitted or glossed over.

5. HYPOTHESES.

At this stage some limited response to the hypotheses (outlined in Section A of the thesis) is possible.

a) Hypothesis One.

Although this chapter is primarily a descriptive account of the US institutional responses, some indication of the political constraints on operationalising control is possible. In terms of implementation, the views of scientists or administrators specialising in the promotion of science were dominant. The NIH was working within a constraint of not impeding the development of recombinant DNA work more than necessary. Many debates did, however, occur involving a wider set of participants, at various decision-making levels within the US, but it is suggested here that although the many viewpoints were acknowledged by the NIH at the Federal level, their influence was limited to being reflected in the general level of caution. Implementation procedures were not directly

affected to any significant extent, other than in more localised debates, such as Cambridge, Massachusetts.

Details of the operational methods have been described and criticism mentioned in passing. An overall assessment is better made on the basis of comparisons with other systems such as that of the UK.

b) Hypothesis Two.

Undoubtedly, control options were not analysed exhaustively by the US institutions. The discussion of the EIS illustrates this point, suggesting that the limited options examined were somewhat superficially addressed. Indeed, the NIH simply followed a course originally asked of it by the Berg letter. Guidelines to enable the work to continue were the order of the day all along.

c) Hypothesis Three.

It was not until the formation of the Interagency Committee some two years and three months after the Berg letter that any serious thought was given to going beyond the adaptation of existing frameworks in the implementation of controls. The guidelines did bring innovation in the context of regulating a new area of research, but the procedures used required minimal change to the body which promulgated them, the NIH. This need not be a criticism if the body which had effective authority was most suited anyway. It is argued here that it was assumed that the NIH was suited by the scientists involved. This was supplemented by a perceived fear from the scientist viewpoint of non-scientist dominance in the control if the NIH was not used. As will be shown, no major changes to the implementation procedures for controls were to be forthcoming as pressure group activity and changing circumstances were to ward off legislative developments.

d) Hypothesis Four.

Although a number of non-scientists were to make comparisons between recombinant DNA techniques and nuclear technology, no institutional efforts were made to make systematic applications of knowledge from other fields, regarding technological control in general.[75]

e) Hypothesis Five.

Communications patterns are probably best addressed at the transnational level. Nevertheless, some points are of note concerning the US. The central bodies of the RAC, ORDA and the Office of the Director, NIH, were very well linked, on technical and implementation criteria. Overall, the non-scientists had great access to information, through the open publication of much material and the public operations of groups like the RAC. Popular press activity was substantial in comparison with European states, and interest groups made active use of these sources. Input into the decision process was also substantial, although biases in the handling of the impact were evident. The question of communications patterns, content, and participation will be examined further.

6. SUMMARY.

This chapter has provided essential background to the institutional activities which led to the production of the NIH guidelines, their form of implementation and the assessment of their impact. The initial importance of the authoritative announcements of concern was undeniable in affecting subsequent US choices. Many critics were yet to challenge the legitimacy of the procedures adopted as guideline revision was undertaken, and legislation threatened. These issues are discussed further in Chapter Eight from a more international perspective, and in addition within the context of the whole issue of risk-benefit analysis.

CHAPTER SIX

THE INSTITUTIONAL RESPONSE IN THE UNITED KINGDOM

1. The Ashby Report

2. The Williams Report Proposals

3. Operationalising the Code of Practice

4. Further Forums of Discussion

5. The UK Institutional Regulatory System

6. Hypotheses

7. Summary

THE INSTITUTIONAL RESPONSE IN THE UNITED KINGDOM.

Some of the reasons given for examining institutional responses to the expressed concerns about recombinant DNA apply to both the United States and the United Kingdom. Both states witnessed urgent investigation of how to proceed safely with the research, and both states found their guidelines, and procedures for their implementation, borrowed or adapted by others. It is important, therefore, to consider the developments within the UK which paralleled first responses in the US. Although both the UK and US approaches influenced other states, they were in fact quite different from each other, reflecting differences in policy and national requirements. In particular, there were major differences in the way in which the overall control procedures were implemented, especially regarding the functions of central committees. The RAC was constituted and operated quite differently from the UK Genetic Manipulation Advisory Group (GMAG), so much so that the acronym GMAG ('Gee-Mag') became an international byword to describe a particular approach to the problem. A degree of comparison between the two approaches is therefore necessary.

Because of the speed with which both the US and the UK responded to the Singer-Söll and Berg letters, they established lead positions, with many states preferring to await the results of their assessments. Uncertainty has been identified as a key variable of interest to this thesis, and it was at its height when the first UK working party examined the issue. Even states that devised their own guidelines were on the whole more hesitant. However, the lead of the US and UK was not only confined to assessing the issues and producing operational control measures. These two states significantly led in terms of the actual utilisation of the recombinant DNA methods. By 1978, some fifty US and forty-five UK laboratories were exploiting the new techniques.[1]

The approach used in this chapter is essentially the same as that applied in considering the US. For analytical purposes, the UK operationalisation of control is seen to operate within a distinct system, although it is acknowledged that activities within other states, and notably the US, were of some influence. Again, an historical overview will provide a description of the development of guidelines and their implementation, deferring much of the analysis of consequences to Section D of the thesis.

In many ways, the task of describing how the UK as a whole responded is more straightforward than in the case of the US. Being a somewhat smaller state facilitated the development of a more centralised method of assessing the issues and implementing the control system. Regional difficulties did not arise like those resulting from the federal structure of the US. Indeed, it will be shown that the ease of central administration of control in the UK led to a particular mode of operation which in some ways was also seen as suited to other European states. Also, and in part attributable to the different internal setting of the UK, there was a relative lack of public and popular press discussion of the issues. The more open form of government in the US, coupled with traditions of interest groups lobbying Congress and decision-makers in general, fostered an environment more likely to promote wider public discussion. Added impetus to this derived from the fact that it was mainly US scientists who had taken the first actions in publicising the whole issue area.[2]

Overall, documentation on issues as they developed in the UK was considerably less than in the US. With a less obvious debate involved, there was correspondingly less need for quite the same volume of official material to be published. Communication was more obviously informal as the community of scientists and relevant administrators was less dispersed. However, the few official reports which were issued must be seen as of

great importance, both within the UK and within the wider international context. In effect, the participation leading to the development of a UK approach to control of the recombinant DNA techniques was narrower than in the US. This point must nevertheless be separated from the fact that, in implementing the resulting guidelines, participation was wider than in the US, both in terms of the number of agencies involved and in terms of the interests represented on GMAG.

In examining how the implementation system was arrived at, the official reports of UK working parties were important steps in that process (as well as important sources of material for this investigation). Publication of the Berg letter in Nature on 19th July 1974, one week before publication in the US, drew the rapid announcement on 26th July that a working party would examine the issues.[3] It was to be chaired by Lord Ashby, the Master of Clare College, Cambridge, under the auspices of the Advisory Board for the Research Councils (ABRC).

Part of the reason for the speed of response can be explained in the light of the consequences of a smallpox outbreak in London over a year beforehand. The outbreak was important in creating an awareness, or at least providing a recent reminder at that time, of the need to contain hazardous viruses. It also created an institutional response in its own right, that was in many ways to interact with subsequent responses to genetic manipulation. The details of the smallpox case are well documented as a consequence of a report published by a committee of inquiry.[4] Of interest here is that the origin of the outbreak was a failure in the containment procedures of a research laboratory, at the London School of Hygiene and Tropical Medicine. A technician from a different laboratory had, on 28th February 1973, witnessed an experiment involving the harvesting of smallpox virus. On 11th March the technician fell ill and she was transferred

to hospital by her doctor a few days later with suspected meningitis. Yet it was not until the 23rd March that smallpox was disclosed, and then only after a combination of factors.[5] Relevant information had been spread between a number of people, who were each in ignorance of the other. Further, the technician had been placed in a public ward prior to the correct diagnosis, and as a consequence two visitors to a neighbouring patient subsequently died, although the technician herself recovered.

A significant point was illustrated with the London smallpox outbreak, and a second outbreak in Birmingham some years later. Once a dangerous organism escapes from its confinement, the consequences might not immediately be apparent. If difficulties could occur with known pathogens, then this would beg the question of monitoring the impact of unknown pathogens, particularly if, in recombinant DNA work, there was a delay in the 'expression' of the cloned DNA in its host.[6] In the case of the 1973 outbreak, the smallpox virus was only recognised as a result of worry on the part of the technician's superior, who took a skin sample from her during hospital visiting hours! The identification of the two visitors who subsequently died as being infected was a result of some inspired deduction by a social worker who read about smallpox in the press.

At the time of publication of the Berg letter, the lessons of the smallpox case were being processed. As a result of the inquiry into the case, the Secretary of State for the Social Services set up a working party, under Sir George Godber, with the following brief:

> "To consider whether there are organisms capable of causing communicable diseases that require measures to be taken in laboratories or elsewhere additional to those now recommended in order to prevent infection in man or in animals and to make recommendations as to the measures required." 7

The UK was, therefore, institutionally discussing biological hazards when the specific issue of genetic manipulation emerged. Thus the Ashby working party moved quickly, in part as a result of this earlier experience and the existence of the working party examining dangerous pathogens. However, the rapid response was also due to the transnational discussions which occurred between members of the Berg letter group and others over the months prior to the publication of the letter. The Medical Research Council (MRC) in particular began to consider an official response before the letter,[8] and in July 1974 sent confidential letters to its laboratory directors effectively banning all the types of experiments questioned by the Berg group.[9] Thus a British ban was very quickly introduced pending the investigation of the problem by the Ashby working party.

1. THE ASHBY REPORT.

Two preliminary points should be noted regarding the Ashby Report. Firstly, the investigation of the issues was over a very short time period, at the request of the ABRC which hoped for an opinion before the autumn. It was left for the Ashby committee to decide whether or not it would be a final or interim report.[10] Produced after only five months, the report became designated by Ashby as a "consultative document", rather than in any way as a final report. He hoped that it would "stimulate discussion both in the scientific community and by the general public".[11] Secondly, the report was published before the Asilomar II meeting to enable something of the UK position to be determined and fed into this very important international meeting. Any criticism of the report must therefore take account of its expressed intention of fostering domestic and international discussion. A later report, examined below, would work on UK policy.

The Ashby working party operated within the following terms of reference:

> "To assess the potential benefits and potential hazards of techniques which allow the experimental manipulation of the genetic composition of micro-organisms; and to report to the Advisory Board for the Research Councils." 12

It would almost appear that the remit included an idea of risk-benefit assessment. However, in terms of what is meant in this thesis by risk-benefit assessment[13] the attempt was very limited. No clarification of the criteria by which risks and benefits could be compared and assessed was given in any rigorous fashion. In the context of a technology displaying features of low probability, high consequence risk, it is argued here that risk-benefit assessment would be inescapably politicised, in reflection of the different values and perceptions involved. The Ashby Report, although it acknowledged the wider non-scientific debate already in evidence, did not take up any of the issues explicitly. Essentially what the Ashby Report did was, in the first instance, to present a summary of the techniques to date and their conjectured potential benefits.[14] Hazards and potential methods of their reduction were then outlined, from which conclusions and recommendations were drawn.

Taking the report as a whole, the overall feel is one of subjectivity. In effect, hazards were listed, benefits were listed, and, based on evidence from scientists in related fields,[15] a subjective balancing exercise was conducted. The working party to its credit acknowledged its dependence on 'experts', but failed to justify its confidence in the type of expert called to give evidence. At the time only a handful of scientists worldwide were engaged in recombinant DNA work, although many anticipated using the techniques. The latter group more accurately describes the witnesses called. In general, the report did not sufficiently

stress the conjectured nature of both the risks and the benefits. Conjecture itself implies uncertainty, yet the report emphasised the 'informed' status of the witnesses.[16]

Many would probably argue that the fact that a working party of this sort was set up at all was a stimulus for discussion.[17] Nevertheless, this does not belie the importance of accuracy in such a report. Assumptions based on inaccuracy were apparent in at least one example. It was stated that:

> "... our general philosophy for defences against potential hazards is that they should not be employed when it is patently unreasonable to do so, as, for instance, in most experiments on plants." 18

This statement displayed ignorance of the need for safeguards at the plant level, for example to avoid potential crop infections. Indeed, a report following on from Ashby argued that "suitable measures of containment for ... plants will be needed".[19] As the second report was directly important in the establishment of UK containment procedures, plant experiments were incorporated in the UK guidelines, as with those of the US.

In addition to accuracy, a discussion document can have influence through what it declines to discuss. Besides avoiding ethical, political and social factors, often omitted in officially sponsored reports, the Ashby Report intriguingly raised a 'hazard' and then declined to discuss it:

> "We mention one other hazard, although only in passing because it is not within our remit. The question may be asked whether the techniques we are assessing could be used in bacteriological warfare. We have no special knowledge of this field; but we can conjecture possible malicious uses for these techniques." 20

It is curious that the report claimed that this hazard was not within their remit, when the terms of reference, above, merely suggested an examination of potential 'benefits' and 'hazards'. Definitions of benefits and hazards were their responsibility, and if they chose to term usage of the techniques for bacteriological warfare purposes as a hazard, then they would have every right, if not duty, to consider this. As with the US, the possibilities of recombinant DNA techniques for weapons development was never discussed in great detail within institutions charged with developing safeguards.[21]

Perhaps the dominant recommendation of the Ashby Report was that the moratorium on using recombinant DNA techniques should be "no more than a pause" and that work should continue. It should, however, be noted that, as in the US, initial response in assessing the issues raised by the scientists who voiced their concern was taken under the auspices of bodies concerned with the promotion of basic research, and not specifically with the control of risk. In the US this had been the National Institutes of Health, while in the UK the Medical and Agricultural Research Councils had called upon the ABRC to investigate, and hence the Ashby working party resulted. Subsequently, the Department of Education and Science would take up the issues, again a body charged with promoting science.

Given that the Ashby Report was an initial and speedily produced consultative document, with some inherent weaknesses, it is nevertheless important to assess briefly its impact. Many of its recommendations were to be adopted, for example, the establishment of a 'central advisory service' and the use of biological safety officers in research laboratories. These were made operational after the next working party took implementation considerations further. One science journal carried a leading comment summing up its reaction with the simple heading "Not Good Enough".[22]

The nub of its criticism was that work should continue with "not even a voluntary pause while ... safeguards are developed". In particular, the author, B. Dixon, saw this as disquieting on the eve of an international conference, Asilomar II, expressly called to consider the whole question. However, Ashby did propose that "rigorous safeguards" be applied, and as it happened Asilomar II was to recommend some interim measures regarding temporary guidelines. What was worrying was that the Ashby Report saw the use simply of containment practices which were applicable to any pathogen, in conjunction with good laboratory safety practice, as adequate. Asilomar II was more cautious and specific. Ashby talked of degrees of hazard applying to pathogens in general, but made no assessment of how to rank degrees of risk in relation to types of recombinant DNA experiments. Instead, the report implied that each individual biological safety officer should give guidance on the precautions necessary. The qualifications of such a person were not discussed, although as mentioned a central advisory service was recommended, and, in addition, it was suggested that somebody draw up a code of practice. An editorial in Nature summarised the problem thus:

> "The real question is whether it is possible to impose from scratch, on scientists and technicians who have not been used to them, the disciplines of institutions that deal on a day-to-day basis with pathogenic organisms ..." 23

It was not until the Williams Report that such issues were rigorously considered in the UK, and this was published nineteen months later. The Ashby Report was at least important in engendering discussion on the issues, for example by the above science journals and, in conjunction with the Asilomar II recommendations, it prompted the subsequent Williams working party to be set up. However, one final point regarding the Ashby Report has a direct bearing on the conception of disaster outlined in the

Introduction. Commenting on the then recent London smallpox outbreak, the Ashby Report said:

> "The dramatic response to any failure of containment illustrates how rare such failures are." 24

Apart from underestimating the luck that led to the identification of the virus itself as causing the technician's illness and the identification of visitors to the ward, infected later, the comment fails to appreciate the particular problem of perception involved in issues of low probability, high consequence risk. In general, the report seemed to rely too much on the idea of good but routine precautions, underestimating the uncertainties involved.

Thus a somewhat hastily produced document was the overall result, and these criticisms reflect that. Yet the report was of influence on both sides of the Atlantic in stimulating the impression that the moratorium should end quickly. One analyst, Edward Yoxen, has described the Ashby Report as having failed to encourage discussion on wider policy issues at "a pivotal moment in the emergent debate".[25] Not least this failure had a transnational dimension. The Ashby Report influenced Asilomar II, organised as a non-governmental conference in another state, which in turn influenced UK policy.

At this point, the scene was set in the UK for the second stage in the overall institutional response. This was to include, among other things, the development of guidelines, implementation procedures, and an increase in complexity at the institutional level. Additional complexity was to arise out of the involvement of a number of governmental departments. In turn, this was to cause interdepartmental rivalry, but more importantly

raise questions of efficiency and legitimacy.

Until the UK guidelines became operational, safeguard control had rested with the MRC, but, on 6th August 1975, the Department of Education and Science (DES) announced through a press notice the formation of a second working party.[26] Stating the conclusions of the Ashby Report, the Secretary of State, Mr. Fred Mulley, went on to give his reasons for establishing the working party. Acknowledging that scientific bodies had endorsed the Ashby Report, and that the Godber working party on dangerous pathogens had also considered it, Mr. Mulley outlined the government view. The government accepted that it had a responsibility to ensure the availability of authoritative advice and guidelines to enable work to continue in appropriate places and with stringent precautions. Mr. Mulley also noted:

> "At the same time we believe that the potential hazards associated with certain types of experiment are such that it would be appropriate further to examine the possibility of applying to them controls of the kind recommended in the Report of the Working Party on the Laboratory Use of Dangerous Pathogens." 27

Until advice from the new working party was available, Mr. Mulley asked that the various research councils and others concerned did not proceed with work "already identified as involving potentially serious hazard". Thus, as in the US, there was a relatively early decision taken in official circles to work towards the development of controls for genetic manipulation research.

2. THE WILLIAMS REPORT PROPOSALS.

The new working party was to be under the chairmanship of Professor Sir Robert Williams, Director of the Public Health Laboratory Service, London.

Williams was one of four members who had sat on the Godber working party which had examined dangerous pathogens and had himself also served on the Ashby group. There was, therefore, some significant linkage between the three working parties. Taking note of both the Ashby and Godber Reports, the Williams group was instructed:

> "(a) to draft a central code of practice and to make recommendations for the establishment of a central advisory service for laboratories using the techniques available for such genetic manipulation, and for the provision of necessary training facilities;
>
> (b) to consider the practical aspects of applying in appropriate cases the controls advocated by the Working Party on the Laboratory Use of Dangerous Pathogens." 28

Indeed the announcement in August 1975 of the new working party came fairly close on the heels of a meeting of some one hundred scientists, held in Oxford, over the weekend of 12th July 1975, at which, it appeared, patience regarding the moratorium was beginning to weaken. Several participants had indicated the intellectual pressure which was building up to get moving again in the field a year after the Berg letter. Although the press had been excluded, Nature carried an editorial which both criticised this fact and suggested that at the meeting it was conceded that some scientists had already begun work.[29] It appeared that some form of code of practice was urgently required.

It is interesting that the report which was finally produced emphasised the differences between handling known dangerous pathogens and the many types of recombinant DNA experiments. The former involved the application of well known precautions against a small number of easily identifiable and well characterised agents, while the latter would involve each experiment being assessed independently.[30] Ironically, some years later pressure developed to adapt the new genetic manipulation procedures of

control to dangerous pathogens as a consequence of a further smallpox outbreak.[31] In reaching its conclusions, the Williams working party had invited evidence from a much wider selection of interested parties than had Ashby. Of particular significance, it consulted representatives of trade unions, the Confederation of British Industry (CBI), government departments, the Committee of Directors of Polytechnics, as well as those with scientific interest or who intended to use or develop the techniques. Such wider consultation gave the report a sounder and more legitimate base.[32]

Perhaps the main results of the Williams Report were the production of a code of practice, or guidelines, and the designation of a central advisory body. These can be examined in turn.

a) A Code of Practice.

Important as the UK code of practice was, it did not differ greatly from the US guidelines. That is, they shared similar conceptions of physical containment categories, covering four in number. They were not, however, identical and a report of a meeting of the EMBO Standing Advisory Committee on Recombinant DNA includes a comparison.[33] In the UK guidelines no equivalent was specified for P1 in the US, Catogory I (UK) was more stringent than P2, Catgory II effectively equalled P3, Category III had no US equivalent, while Category IV was equivalent to P4. Differences were, therefore, sufficient for other states adopting either to have some choice (see Appendix Six).

Both sets of guidelines laid emphasis on the role of biological containment, but the Williams Report put far more emphasis on the role of physical containment. Regarding the possibility of enabling increased biological containment to offset physical containment requirements, the

Williams approach was to argue:

> "We assume that there are conditions of biological containment and nucleic acid purity that will allow an experiment to be moved from one category to another but these cannot be absolutely defined without reference to the individual experiment." 34

The report did not specifically categorise biological containment at all and, although physical containment was categorised, there was no comprehensive allocation of experiment types to the containment levels involved. Those few experiments which were collated with the four containment categories were not to be seen as anything more than a guide. The UK approach, it was intended, would utilise a central advisory service which, upon notification of proposed experiments, would allocate the containment category. It was hoped that in this fashion a body of 'case law' could be built up offering greater flexibility.[35]

Overall, these proposed UK guidelines, which were eventually implemented, stressed physical containment moreso than the US guidelines. They were, indeed, tougher than the latter, in terms of physical containment requirements, but unlike the US guidelines did not completely ban any experiments. An important shared element of the Williams Report and the NIH guidelines document was, however, the emphasis on the importance of appropriate training for workers who would use recombinant DNA techniques.[36] In particular, this recommendation was in recognition of the fact that many workers were likely to move into the field perhaps unaware of the routine techniques of medical microbiology.[37] It was argued that training would be one of the responsibilities of a Biological Safety Officer, one to be appointed to each laboratory concerned. His responsibility in general would be for precautionary measures and he in turn would require training. Indeed a number of training courses were subsequently run. Thus, the code

of practice was to include an important local element in the implementation of safeguard controls. It was not as extensive, however, as with US local Institutional Biohazard Committees.[38]

In essence, the main difference between the US and UK guidelines was that the former were designed in such a way that the leading researcher in any laboratory could consult them personally and determine the appropriate containment for his experiment. The US guidelines thus included a comprehensive listing of experiment typologies. The more flexible UK system enabled the central advisory committee to allocate containment on the basis of: the nature of the experiment; the laboratory's facilities; the experience, ability and training of the research workers, technicians and the Biological Safety Officer. Records of each laboratory would be kept, and annual reports were proposed.[39] Indeed, over time experience might alter perceptions of risk, or new developments in physical or biological containment might arise, with the built-in flexibility of the system enabling revisions of containment recommendations. In the US, such developments would necessitate guideline revision.

Central screening of all experiments, although occasionally suggested,[40] was not seen by the NIH as appropriate for the US. A problem of scale existed, both in terms of the likely future number of laboratories involved and the sheer size of the US. Local pressure was also evident in some US states and cities regarding the right to legislate for controls more rigorous than those advocated by the NIH and suggested in Federal legislative proposals. The dominant perception appeared to be that central vetting of all experiment proposals would be too cumbersome. This was not the case in the UK and an appropriate central committee resulted.

b) The Genetic Manipulation Advisory Group.

Recommended in both the Ashby and Williams Reports, a UK central advisory committee was established under the title of the Genetic Manipulation Advisory Group (GMAG). Eventually to be an important body in the UK control system, it was also a notable development in the whole concept of control of safety in scientific research. Its acronym, as mentioned earlier, was itself to became an international byword.[41] Although GMAG was outlined in the Williams Report as part of the overall package, the report itself faced a considerable delay in publication. The explanation for that delay is best made after GMAG and its relationship with another body, the Health and Safety Commission (HSC) is described. Essentially, the delay occurred to allow the HSC to produce a further document defining genetic manipulation.

In examining GMAG and its defined role, it is worth beginning with a comparison with the advisory group established in the UK as a result of the Godber Report, which was concerned with dangerous pathogens. GMAG was quite different from this group. It was planned from the beginning that GMAG, in order to "command the respect of the public as well as of the scientific community, including scientists in industry" should include a wide range of representation.[42] Involved scientists, industry, employees and the public interest were all to be represented. It can be argued that GMAG was a very innovative proposal, which implied that scientific work at the research level would be monitored, in terms of a code of safety practice by a group in which scientists as a whole were to be in a minority.[43] Other states were also to raise the question of non-scientist members on their advisory committees, including the US.

By the time the Williams Report was published, GMAG's cousin, the Dangerous Pathogens Advisory Group (DPAG) was already in operation.

Although the Williams working party considered that DPAG's functions might be extended to cover genetic manipulation, this was rejected on the basis of the different procedures involved between known pathogens and the uncertainties involved in recombinant DNA. DPAG when established as an advisory group saw these differences reflected in its structure. Whereas GMAG comprised participants from a variety of backgrounds, with non-scientists dominating in number, DPAG was more specifically based on experts in dangerous pathogens.

In composition, GMAG was to have nineteen members: four trade unionists were to represent employees working in laboratories carrying out genetic manipulation; four members were to represent the 'public interest'; two were to represent management; eight would represent scientific and medical experts; the first chairman was to be Sir Gordon Wolstenholme.[44] Of these, some controversy was to surround the appointment of the representatives of the public and employees. Public interest representatives were to be invited to join GMAG by the DES, but without any published criteria underlying their choice. The difficulty was highlighted at the end of GMAG's first two years when some replacements in the membership occurred. One of the public interest representatives, J.R. Ravetz, a Reader in the History and Philosophy of Science at Leeds University, did not want to leave GMAG, but was requested in writing to stand down. Ravetz was particularly active and not entirely uncritical of control policy in general.[45] The reason given was that new appointments were necessary to "ensure the balance and continuity" of the group. Yet two of the other public interest representatives were in fact keen to leave, which would leave only one of the original four. There would seem to be no reason why Ravetz could not have stayed on. If 'continuity' were to be stressed, then it should be said that it took some time to gain experience and understanding of the more technical and scientific issues involved in

GMAG's activity. Three replacements would represent a significant discontinuity.

Trade union representation from the beginning involved some active lobbying by at least one union, the Association of Scientific, Technical and Managerial Staffs (ASTMS). ASTMS had begun to show an interest in recombinant DNA issues prior to GMAG being set up, as a result of one of its members, Professor R. Williamson, a biochemist, having relevant contacts in the US. According to D. Haber,[46] the recombinant DNA case provided an opportunity for preventive action, rather than after the event court action, of which it was more familiar. Thus ASTMS lobbied the Williams party, both to establish a central advisory committee and to include trade union representation on it.

In practice, representatives of both trade unions and industry were to be recommended to the DES by the Trades Union Congress (TUC) and the industries concerned. At the time GMAG was set up in late 1976, the Secretary of State for Education and Science was Shirley Williams who in retrospect has stated that both she and her department consulted widely on all appointments. She did, however, qualify this:

> "... they were all consulted. That is not the same thing as accepting recommendations made by officers [of the various organisations involved] without further question." 47

Apart from Ravetz, others saw reason to question appointment policy. In particular, the Association of University Teachers (AUT) wanted a member on GMAG, but were unsuccessful in obtaining TUC backing.[48] A rather forceful letter to the Clerk of the Sub-Committee of the Select Committee on Science and Technology, which in 1978/79 examined recombinant DNA research, went further on the question of participation. Professor S.J.

Pirt of Queen Elizabeth College, the University of London, suggested the inclusion of representatives of the main scientific organisations in the field, including the Genetics Society, the Society for General Microbiology, the Biochemical Society and the Institute of Biology.[49] Pirt was somewhat critical of appointments being made by civil servants "trying to have their own way as usual".

GMAG, because of its innovative nature, had no real precedents from which to work in terms of the selection of representatives. Shirley Williams had been conscious of the difficulties in obtaining a suitable balance, and had been aware of the dangers of appointing too many scientists involved in the work, because being few in number they would effectively have regulated themselves.[50] Despite these problems, GMAG was a brave attempt to form an advisory group of some legitimacy. It was also quite successful.

In contrast, the underlying philosophy for the composition of DPAG was that it should be:

> "... a small independent body of experts consisting of individuals whose experience would command the confidence of those working in laboratories." 51

It was not until December 1978 that an offer was made to allow one trade union representative to sit on the group.[52] Yet, despite the differences with GMAG and the fact that it was administered by the Department of Health and Social Security (DHSS) rather than the DES, many of the issues which they faced were similar. For example, both groups were concerned with the safety of employees, the operational monitoring and implementation of a code of practice and the maintenance of public confidence. Confidence in DPAG was, however, to be shattered in a dramatic fashion in August 1978,

with the result that calls arose for it to be reformulated along the lines of GMAG.

The event of such significance was another smallpox outbreak, this time at Birmingham University, and after the laboratory involved had been vetted by DPAG. DPAG had sent an inspector to Professor Bedson's laboratory in February 1976 at a time when no work involving smallpox virus was under way. The subsequent report into the outbreak criticised the efficiency of that inspection in not examining adequately the details of the laboratory and the proposed techniques to be used in future experiments.[53] Details of this confidential report, however, first came to light only after ASTMS published their copy of it, which was then given further publicity in the science press.[54] One of the problems was that the inspector had decided to overlook a number of deficiencies in Bedson's laboratory, such as a lack of an airlock, a shower, a double autoclave and changing facilities, on the basis of accepting Bedson's reputation as an experienced and safety-conscious virologist.[55] A significant factor had been, therefore, the inspector's 'working colleague' relationship with the head of the laboratory. Indeed, most of the visit was spent discussing smallpox work in general.

Other factors were also involved in the smallpox outbreak, including the approach taken by the World Health Organisation (WHO) in corresponding with Bedson. Without the knowledge of the university the WHO had informed Bedson that it intended to cease supporting his work after the end of 1978. WHO recognition was vital for the continuation of the research, and the effect of the deadline was to make Bedson speed up his work. In addition the WHO sent three inspectors who were critical of the safety procedures, but in the event the WHO allowed his promising work to continue, subject to the laboratory ceasing such work when the deadline

expired. The tragedy of the whole situation was the subsequent infection and death of a photographer, who worked at the university, and the suicide of Bedson.

Calls for changes in the composition of DPAG soon appeared.[56] DPAG was eventually reformed with the addition of trade union representation. For a time, therefore, the UK had two contrasting examples of central advisory committees, one dealing with known biological hazards and one with new conjectured biological hazards of unknown risk. The latter, of more concern here, to an extent became a pattern for a reformed DPAG, a group that some, including the Godber working party, had originally thought could have extended its sphere of operations to include genetic manipulation.

Despite the importance of GMAG in implementing the UK code of practice, it was not the only organisation involved. It has already been said that there was some delay in publishing the Williams Report, due to the Health and Safety Commission. This body must now be considered.

3. OPERATIONALISING THE CODE OF PRACTICE.

a) Provisions of the Health and Safety at Work Act.

The Health and Safety Commission was established on 31st July 1974 under the Health and Safety at Work Act (HSWAct). It was to consist of between six and nine members appointed, by the Secretary of State for Employment, from the TUC, the CBI and local authority organisations.[57] Its function was to monitor safety and health provisions in general in the context of 'work'. In addition, it was to have an executive arm charged with implementing its policy and acting as an inspectorate, the Health and Safety Executive (HSE).

Although the Ashby Report had overlooked the provisions of the HSWAct, this was corrected by the Williams Report. Williams explicitly suggested that regulations be made under the Act to require laboratories to submit experimental protocols to GMAG.[58] Publication of the Williams Report itself was delayed three months to give the HSC an opportunity to produce a consultative document covering draft regulations.[59] Both were published on the same day, but were not equally received by the scientific community. The Williams Report was generally accepted, while the HSC consultative document was heavily criticised.[60]

Two major points of criticism stood out. The first concerned the attempt by the HSC to define genetic manipulation as follows:

> "No person shall carry out any activity intended to alter, or likely to alter, the genetic constitution of any organism unless he has given to the Health and Safety Executive notice ... of his intention to carry on that activity." 61

The problem was that the definition incorporated the traditional tools of genetics used for many years and could even be seen to cover activities such as spraying roses with pesticides, making yoghurt, and even human procreation!

Secondly, the HSC document appeared to many to reduce the importance of GMAG as recommended by the Williams Report, by breaking the 'close link' envisaged between laboratories and GMAG. The HSC argued that laboratories should statutorily report to the HSE, and that GMAG should become simply an advisory body to the HSE, although it would still assess proposals given the lack of HSE expertise. Roger Lewin of New Scientist suggested that part of the problem was emerging political manoeuvres between the different departments involved: the DES (GMAG); the Department of Employ-

ment (HSC); the DHSS (DPAG). More will be said on the roles of these departments below.

As a 'consultative document' the HSC had invited critical response.[62] This they got in abundance, although to be fair there was a degree of over-reaction on the part of scientists and scientific organisations. They feared, in particular, a legal bureaucracy developing. Whatever the merits of the HSC definition, it has already been shown in Chapter Three that genetic manipulation was a difficult concept to define. Even ASTMS subsequently tried and failed,[63] and it was not until GMAG was constituted that the HSE and HSC got their definition after seeking its advice.[64] Final regulations were not in fact introduced until 1st August 1978, some twenty months after GMAG first met.[65]

With this delay in introducing regulations requiring laboratories to submit proposed experiments to GMAG, the system in the mean time operated on a voluntary basis. By mid-February 1978, GMAG had received 102 proposals from twenty-seven centres, including industrial laboratories. Four proposals were for Category IV containment, twenty-seven for Category III, forty for Category II and thirty-one for the lowest category.[66]

Once the HSC regulations were in force, however, notification had to be made by law to both the HSE and GMAG, and the definition of 'work' under the HSWAct was extended to cover genetic manipulation by any person, self-employed or non-employed (for example a research student). This was an important difference between the UK and the US. The UK had a sufficiently flexible existing legal framework within which the Williams code of practice could be supported. Of further importance was that the legal provisions also applied to industry. From the beginning the UK approach was intended to encompass all users of recombinant DNA techniques. Thus, the

UK avoided the difficulties faced in the US regarding the limitation of the NIH guidelines to research wholly or in part sponsored by the NIH, or other government agencies with their agreement.

Because of the overall differences between the UK and US systems for operationalising control of safety, it is more appropriate to take each approach as a 'package', a conclusion that GMAG itself arrived at.[67] Implementation of the guidelines was much more centralised in the UK system, and this was reflected in the operations and the structure of GMAG. Because of this, GMAG needed an important legitimate basis in society, while in the US it was to an extent the Institutional Biohazards Committees which faced this requirement. This is not to negate, however, the particular issues surrounding the RAC in its role of developing and revising the guideline conditions for recommendation to the NIH. Their function overlapped in part the activities of the Williams working party which initially devised the UK code of practice. Of note, though, in terms of policy making, it can be seen that in the US the main source of policy was the NIH. In the UK, by contrast, there was an additional problem of competing departmental roles making the focus of policy making less clear.

The joint functions of GMAG and the HSE were at the heart of the UK package, although their overseeing departments differed. GMAG provided advice to both the laboratories and the HSE regarding containment, but it was the HSE which was to have the responsibility for inspection and, if necessary, legal enforcement. The function of inspection was a compulsory requirement before any Category III or IV work could be carried out. By January 1979, the HSE had three specialist inspectors in the field of genetic manipulation who in turn could call on the support of the HSE inspectorate's wider team, already functioning under the HSWAct in examining

laboratories in general. In addition, the HSE could bring in the resources of the Employment Medical Advisory Service and the Factories' Inspectorate to deal with enforcement matters arising out of inspections. In all, the HSE felt it had access to sufficient expertise.[68]

It was, however, recognised that some problems might arise if an experimenter, cleared to carry out work at one containment category, upgraded the experiment without notifying GMAG or the HSE. Categories I and II did not require prior inspection, and the possibility therefore existed for a Category II experiment to be revised such that it should really be carried out under Category III. In response to such a possibility, the HSE took the line that not to notify would involve an unlikely level of irresponsibility on the part of the experimenter and in any case he would run the risk of the HSE's unannounced visits which all laboratories could receive. Supporting this was the general need in science to publish results for peer review, which itself could bring attention to violations.

Nevertheless, resources at the disposal of the HSE were limited and there was no formal provision for regularised follow-up visits to laboratories. Against this, however, was the fact that initial visits were comprehensive to the extent of thorough interviews with local safety committees and employees' representatives, who would all be encouraged to maintain vigilance on laboratory work. It was thought that in the light of difficulties in prosecuting Birmingham University over the smallpox incident, legal sanctions might be difficult to apply.[69] Whatever the outcome of legal cases of this sort, the institution involved would invariably face much press publicity as in the case of Birmingham, itself a deterrent. Not least, a committee of inquiry could ensue. In all, the UK had available to it a much tighter system of ensuring compliance than in the US with its local level of enforcement supported by threats to funding where applicable.

In sum, the prior existence of legislation under which regulations could be drawn up was a great advantage, enabling a cautious approach of simply introducing requirements for notification. By redefining 'work' to cover the relevant research activity, the full force of the HSWAct could be applied. Yet in all this there were no regulations saying that advice had to be followed. Indeed, GMAG had been recommended to issue a disclaimer when giving advice, for fear that legal liability could go beyond them to the Secretary of State for Education and Science. The group itself, it should be said, had been willing to stand by its advice in law.[70] This was, however, a greater constraint in the US where the NIH did not give advice on individual experiments, in part because of the possibility of legal action against them if anything went wrong. In the UK, despite the disclaimer, it was felt that if GMAG advice was not followed and anything untoward occurred, then the courts would probably question the failure to take the advice, especially as the HSE had the power to implement legal action in the first place.[71]

One final aspect of the application of the regulations introduced was that they only referred to the experimental use of recombinant DNA techniques and not the use of the products. Although few regulations in any state covered usage, it was thought by GMAG that the HSWAct would put an obligation on any manufacturer, importer or supplier to ensure safety.[72] To include the use of recombinant DNA molecules in the definition of genetic manipulation could only be done after a further consultation exercise. Nevertheless GMAG expected that use of recombinant DNA molecules would be notified to them on the basis of it being expedient to use GMAG as a source of advice. GMAG would, in keeping with the NIH and recommendations of the ESF Liaison Committee on Recombinant DNA Research, also ask that anyone transferring products of genetic manipulation abroad, should request assurances that safeguards such as those of the NIH or UK be adopted.

b) Industrial Confidentiality.

The very nature of GMAG's broadly representative membership was to cause a number of difficulties concerning the examination of industrial proposals. Specifically the problem arose because industry feared that disclosure of information to GMAG, when notifying intent to carry out an experiment, would invalidate any future patents applications. In addition, industry feared the potential loss of industrial secrecy in that six members of GMAG were either management or employees' representatives who might have connections with rival firms. With increasing interest shown by firms in utilising recombinant DNA techniques, these fears became more urgent.

Although GMAG members all had to sign the Official Secrets Act, it was thought that this offered little or no protection in terms of industrial or academic confidentiality as the Act referred to government property. As a result, the chairman of GMAG established a subcommittee of fourteen members to examine the whole question of the confidentiality of proposals.[73]

To complicate matters further, the four trade union representatives, while respecting the need for confidentiality, refused to be bound by any secrecy agreement which could compromise their duty to their members. Nevertheless, pressure was on GMAG to do something in case industries with multinational connections took their research abroad.[74] After consultations with industry, GMAG, also allowing for trade union concerns, was able to introduce a formula for a trial period, initially of six months.

Firstly, any experimenter could ask that certain information be treated as 'sensitive', the chairman responding by deciding whether or not to accept the request and allow the proposal to proceed under the formula. Secondly, all members of GMAG were asked whether any other interests

they held would influence their judgement in sensitive cases. Thirdly, those members with conflicting interests would be required to withdraw from discussions on the proposal and would receive no relevant information. Finally, all members who would see the details of the proposed experiment would have signed a confidentiality declaration, to be broken only with the proposer's permission. To supplement this formula, GMAG obtained assurance that disclosure of proposals to GMAG would not in itself constitute prior disclosure within the terms of patent legislation.

Although recognising a diminishing of effectiveness in asking people to withdraw over some proposals, after a year of using the scheme GMAG was able to conclude:

> "This scheme is not ideal, but it has operated with reasonable goodwill on the part of industry (or others asking for commercial-in-confidence treatment); and GMAG has found it flexible to consider proposals in this way in spite of the diminished number of members present to assess them." 75

In its investigation of 1978/79, the Select Committee on Science and Technology was to express its unhappiness with the scheme, despite the fact that only a small number of proposals were affected. Taking evidence from members of GMAG (including Sir William Henderson, the second chairman) and Shirley Williams, the Secretary of State for Education and Science, they pressed the point on whether safety assessment would be compromised. Mrs. Williams defended the measures by saying:

> "I think our compromise is probably the furthest any country has gone in trying to regulate private-sector research in a very advanced field with very great commercial implications." 76

Acknowledging the arguments it heard in defence of the scheme, the Sub-committee on Genetic Engineering concluded by suggesting it was possibly

unsound that such an important advisory group as GMAG should have "apparently first and second class members".[77]

In view of the interest of this thesis, it must be said that Mrs. Williams' comments are more to the point. The UK was very successful relative to other states in providing coverage of industry. Most states operated on a voluntary basis in this respect. Confidentiality had been a recurrent phenomenon in many states, including the US, and whatever the faults of GMAG's compromise when the inspectorate role of the HSE was allowed for, then the UK system was comprehensive. Besides, those likely to be excluded, such as trade union members, were not likely to assess technical details anyhow. Whether they saw the proposal or not they could at least guarantee that it was assessed. By its very nature the problem was difficult and GMAG, itself representing a broad spectrum of interests, had put much effort into obtaining the compromise. In the US, for example, no single body existed with such a range of representation to address such problems. Thus the GMAG approach in this sense had some legitimacy.[78] Not least, GMAG had a good conception of the wider political dimensions to the discussion on confidentiality, and accepted the general understanding of the time that the UK should not have a regulatory framework which would put UK workers, including industry, at a competitive disadvantage.

In retrospect, the system appeared to work reasonably smoothly without any real national disadvantage. Nevertheless, some industrial spokesmen suggested reform. For example, the Association of the British Pharmaceutical Industry (ABPI), arguing that the UK was unique in its requirements of industry to disclose plans, suggested that this would indeed put British workers at a "grave disadvantage compared with their colleagues in other countries". From this the ABPI went on to argue that the tech-

nical roles of GMAG and DPAG should be taken over by a new Biohazard Advisory Group, run by the HSE. Policy would be developed by a Biohazard Advisory Committee, analogous to the Advisory Committees on Dangerous Substances and Toxic Substances, already established under the HSC. The chemical giant ICI similarly requested that GMAG be put under a professional group such as the HSE.[79]

Criticism of this sort can be seen to relect two things: firstly, there was a belief held at the HSE that industry preferred to work with it, partly because of a long association with the Factories Inspectorate; secondly, the ABPI did not allow sufficiently for the whole area of uncertainty and conjecture surrounding recombinant DNA which was quite different from 'dangerous' and 'toxic' substances.[80] It can be argued that there were at that time uncertainties regarding the future use of genetic manipulation techniques in large-scale industrial processes. Experience and a wide scope of input might be seen to facilitate such transitions to industrial-scale activity.[81] With uncertainty the experience of GMAG might have been invaluable, particularly with its flexibility. As it happened, by the time large-scale industrial involvement became significant, in terms of the imminence of developing products, the overall fears concerning recombinant DNA had declined.[82]

The HSE well understood the techniques of inspection of laboratories and industrial premises, but GMAG, being independent of them, could take a wider view of developments regarding conjectured risks and benefits. These functions were different and usefully separate. It is argued here that GMAG was suited to keeping a more general view of changes in the state of knowledge, and demonstrated this when it attempted a change in approach to the guidelines, as discussed below. Besides, whatever the complaints of industry, the inconvenience they suffered in complying with

GMAG was not great. Indeed, both the ABPI and ICI acknowledged the speed of GMAG's responses to their submissions.

If the tone of the comments also implied favour for the HSE, it should be pointed out that communications between GMAG and the HSE were very good indeed. HSE representatives attended GMAG meetings and often joint inspections of laboratories were undertaken, notably of Categories III and IV.[83] Communications were, for example, significantly better than between the RAC and the Advisory Committee to the Director, NIH.

c) GMAG and the RAC.

It was a credit to the success of GMAG that in the US the RAC was to become more similar in its composition. The requisites of legitimacy eventually made their mark and the RAC broadened its membership to include individuals with knowledge of law, public attitudes, public health, occupational health, professional conduct, or related fields, and who comprised at least one-fifth of all of the participants.[84]

It has been said elsewhere in this thesis that public debate was much greater in the US, and this was in part over the question of legislation. As the Federal Interagency Committee discovered, no existing statutes fitted the requirements of comprehensive application of the NIH guidelines to all researchers. In addition, local legislation became an issue. Public debate was facilitated by the relative openness of all the RAC meetings. By contrast, much of the UK machinery operated in secret, although GMAG was a little more open, given that some of the participants reported back to other bodies which they represented.[85] Susan Wright argued that the Official Secrets Act was such that "not even an illusion of openness characterized the proceedings of the various committees that examined the problem".[86]

However, the degree of openness was not the only factor affecting the levels of debate. Representation of different values was limited at the national level of decision-making in the US. From the beginning, by contrast, GMAG appeared more legitimate, was innovative and tended to engender more faith. On the contrary, the RAC with its domination by involved scientists appeared more self-serving. Yet most participants in the UK system would probably not have welcomed wider public involvement, as the inclusion of industry in the regulations did indeed make confidentiality a key issue. Trust in the representation, and notable support for GMAG from the trade union movement, negated more widespread concern.

Scientists similarly were not keen on publicity in the UK, perhaps fearing controversy as in the US and France (discussed in Chapter Seven). At two significant conferences, one in Oxford in July 1975, prior to the Williams Report, and an international one at Wye College, Kent, in 1979, there were intentions of excluding the press.[87] Legitimacy in the UK might have been enhanced further if more open discussion had been encouraged. Protecting the public from hazards always benefits when it is not just done, but seen to be done. Despite this, the UK 'package' and the US 'package' of control options became attractive options for other states to model their policies on.

d) New UK Guidelines.

To an extent, a degree of openness did enter the UK methods, when GMAG proposed to revise the UK guidelines. On 9th November 1978, it published in Nature[88] a radically different approach to allocating containment, and invited comments, rather like NIH practice. Discussed further in Chapter Eight, it was hoped in the new approach to assign where possible theoretically or empirically derived numerical values to the risks involved in each experiment before determining containment. The process was more

successful than the earlier consultation exercise involving the HSC document released with the Williams Report. Valuable responses were received and the new system was to become adopted.

4. FURTHER FORUMS OF DISCUSSION.

a) The Select Committee on Science and Technology.

Until late 1978, Parliament's role in the recombinant DNA debate had been limited to some questions tabled on 15th June 1978 by Leo Abse. Eleven questions in all were put to Shirley Williams on safeguard policies regarding genetic manipulation, and he called for "genuine control regulations". Abse recieved a general reassurance that things were under control, but had himself, according to New Scientist, initially failed to understand the subtle relationship between GMAG, the HSE and the HSWAct.[89]

Abse was not the only one who was unsure of that 'subtle relationship'. It was in December 1978 that the Genetic Engineering Sub-Committee of the Select Committee on Science and Technology began taking evidence, much of their investigation, indeed, examining that relationship. The subcommittee had been established in November 1977, but, under the chairmanship of Mr. Arthur Palmer, had decided that before commencing their inquiry in full they would hold a seminar on the science and technology involved. Thus on the day Abse tabled his questions, the subcommittee held their seminar at the University of Bristol. Their investigation proper was deferred until after the publication of the HSE notification regulations in August, which in effect meant the next session of Parliament.[90]

The subcommittee declared its interests to be in examining the public policy issues of laboratory and industrial use of genetic manipulation, including the distribution of manipulated organisms, domestically and

internationally.[91] During December 1978 and early 1979, the subcommittee undertook an extensive investigation interviewing representatives of the key organisations and departments involved, inviting submitted memoranda, and which included five members visiting the US for ten days.[92] The final document was, however, unusual in that the report only covered four pages, but with the minutes and appendices accounting for the remaining 263. The report was an interim measure because of an impending general election, after which the Conservatives replaced Labour in office, and subsequently disbanded the Select Committee on Science and Technology.

The value of the report itself was therefore somewhat limited, although the document as a whole provided a wealth of research material, liberally utilised in this thesis. Something of the Conservative attitude had emerged before the election when the then shadow minister for education and science, Mark Carlisle, expressed his faith in experts and concern that bodies such as GMAG and DPAG could have wider representation, including union representatives.[93] After the election, although no significant changes occurred in the composition of these bodies, or their operation, Mark Carlisle himself delegated the recombinant DNA issue to a junior minister, taking little personal interest, unlike Shirley Williams.

Despite its short length, three conclusions were apparent in the report. Firstly, recognising the difficulties of including industry in the safe-guard system, the subcommittee expressed dissatisfaction with the current arrangements. Secondly, they were critical of the DES being the 'lead' department, and would have preferred more involvement of the DHSS, which ran DPAG. Thirdly, they feared UK workers being at an international competitive disadvantage as a result of controls. In a sense, as Roger Lewin observed,[94] the subcommittee can be seen to have modified its concerns. Emphasis altered to a degree from concern over hazards to

concern over regulatory hindrance of the work. Perhaps influenced by the CBI, the ABPI, ICI and the AUT, who all wished for administrative changes, the efficiency of the current role of GMAG was questioned. Most witnesses, nevertheless, as late as 1979 did recommend caution and perhaps only a fuller report would have done justice to all of the issues. Some of these conclusions have been examined in discussing the UK procedures above.

During the period of the subcommittee investigation, a significant international meeting was held at Wye College, Kent.

b) The Wye Conference.

Organised in part by the Royal Society and a Committee of the International Council of Scientific Unions, the conference met between 1st-4th April 1979. The meeting itself is discussed in Chapter Seven given its international organisation and significance. Of note, however, is that the conference marked an attempt by many scientists to undo the consequences of their own earlier actions at Asilomar II. Perhaps of significance to the discussion of the UK responses was the choice of venue as "a small, quiet country where a display of emotion is, to say the least, embarrassing". These were the words of M.G.P. Stoker in his introduction and welcome to the conference.[95] The views of Roger Lewin, who was one of the journalists to attend after a last minute decision not to ban them, and Donna Haber of ASTMS will be presented in Chapter Seven. With the content and organisation of the meeting, it was not surprising that the organisers feared publicity. It was a very biased meeting of scientists, who on the whole held common views. Some significance must be placed on the absence of certain scientists.[96]

Insofar as the Royal Society was involved in the organisation, it can be said that they tended to see the issues essentially in the light of

challenges to the 'freedom of science'. Indeed the President saw one of the two reasons for the questioning of how recombinant DNA work was conducted as "essentially ideological and [including] quasi-religious objectives".

To conclude this chapter, a summary of the UK regulatory response can now be made, followed by a brief discussion of the hypotheses.

5. THE UK INSTITUTIONAL REGULATORY SYSTEM.

The diagram below illustrates the way that the main elements of a UK institutional response occurred, based on early expressions of concern. A three track development was evident based on three initiating factors, the Berg letter, the London smallpox outbreak and the HSWAct. Through a series of government reports and consultation exercises, a system of control developed, covering both known pathogens and conjectured hazards that might emerge from recombinant DNA experiments. Links existed, however, by which both GMAG and DPAG requirements could be applied, if, for example, a genetic manipulation experiment involved a known pathogen.

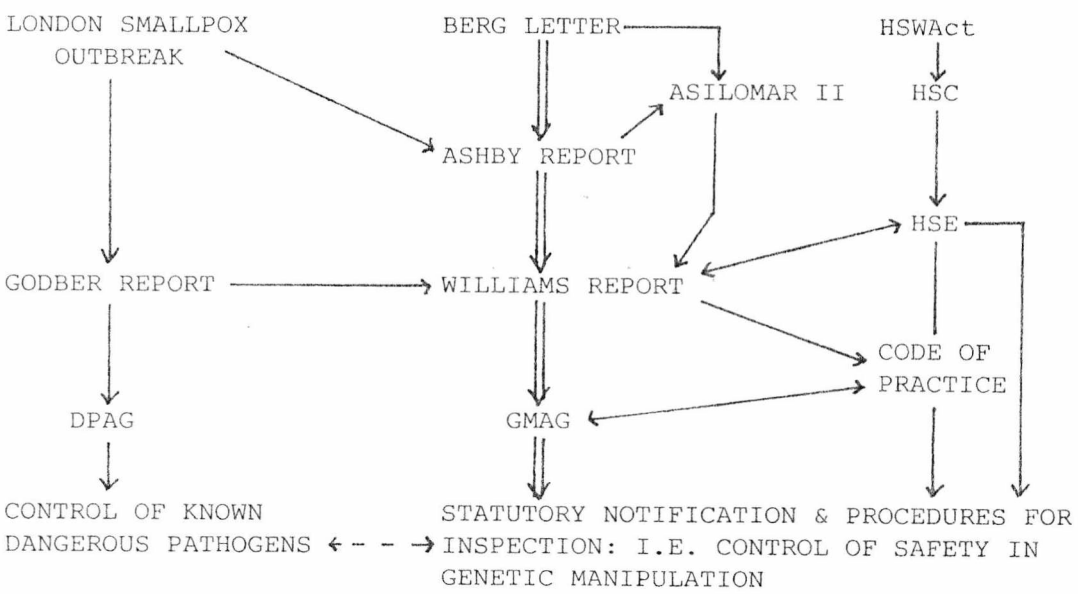
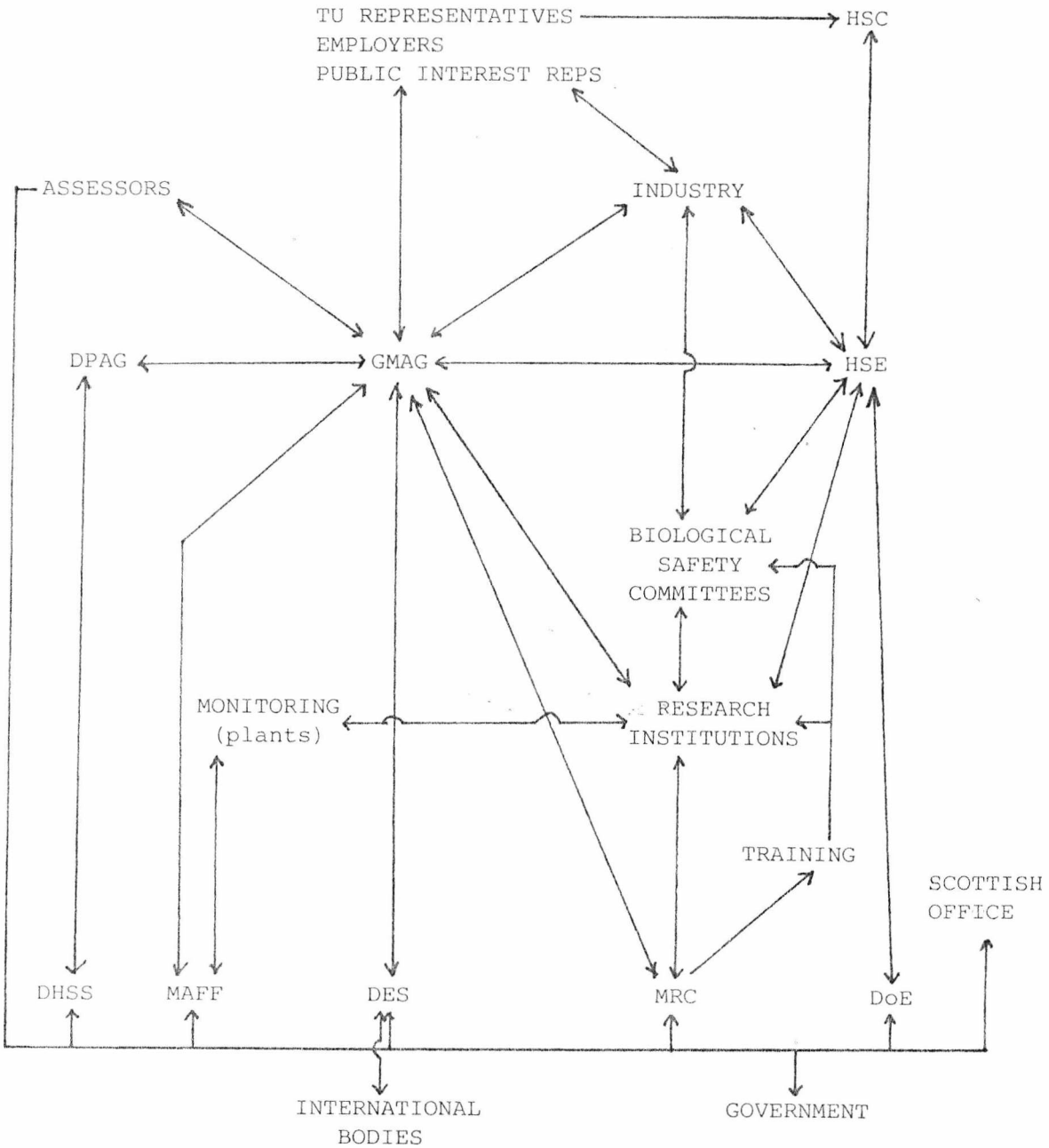


DIAGRAM 1

From this pattern of development, an operational system emerged involving interactions between a number of bodies, with GMAG and the HSE acting centrally. The main interactions are outlined in Diagram 2. Both industrial and non-industrial researchers would be monitored in terms of safety by GMAG and the HSE, the latter possessing statutory powers of inspection. At the governmental level, however, the UK situation was not so straightforward.

Within the UK, a total of four departments were involved significantly,[98] a situation which led the Sub-Committee on Genetic Engineering to question which should be the 'lead department'. Effectively the lead had been quickly taken by the DES in its capacity of responsibility for developing science and education. Its leadership covered both the UK domestically and in terms of UK interaction internationally. Criticism of this position of the DES centred on two points. Firstly, the question of conflict of interests arose, in that the DES was charged with promoting research.[99] This undoubtedly had influence in the early unquestioned assumption that the work should continue, the question merely being to determine under what conditions. With the composition of both the Ashby and Williams working parties, it was unlikely to be an assumption challenged by them either. Yet if the view is taken that whatever happened in the UK the work would continue, then the DES can largely defend itself against a bias to promote recombinant DNA work. The only regulation involved was to notify GMAG and the HSE of intended experiments in some detail. From then on both GMAG and the HSE took over, though not forgetting that the DES appointed membership of GMAG. Besides, the HSE was not charged with promoting work.

A second criticism, specifically brought up by the subcommittee report, was that perhaps the DHSS would serve better as the lead department given



KEY:

DPAG	Dangerous Pathogens Advisory Group
GMAG	Genetic Manipulation Advisory Group
HSE	Health and Safety Executive
HSC	Health and Safety Commission
DES	Department of Education and Science
DoE	Department of Employment
DHSS	Department of Health and Social Security
MRC	Medical Research Council
MAFF	Ministry of Agriculture, Fisheries and Food

DIAGRAM 2

its concern with issues of health and its control over DPAG. A defence of the existing system was in fact made by the Secretary of State for Social Services, who pointed out that the DHSS was more concerned with general health issues rather than research level issues, and that given an outbreak of any epidemic resulting from the work, then it would act. He went on to indicate that there would be difficulties enough in identifying any department that covered all the aspects involved. He thought, therefore, that the distribution of repsonsibility was about right.[100]

Given that there were diverse departmental interests - the DES with basic research, the DHSS with health, the DoE with safety and the Ministry of Agriculture, Fisheries and Food (MAFF) with plant work - then unless a new body was introduced to cover the issue, one factor would be very important. That factor would be the level and quality of interdepartmental communication. Traditionally, the 'Whitehall system' appointed a lead department in cases where there was not too much interdepartmental rivalry. In the case of genetic manipulation, all the departments were well briefed about any policy planning, and, apart from interdepartmental meetings, acknowledged to have occurred,[101] GMAG itself had assessors from each of the relevant departments in attendance at its meetings. As it happened, the extent of co-operation raised a worrying issue as far as the sub-committee hearings were concerned. A submitted memorandum from the DES referred to what was said in memoranda from other departments, leading the subcommittee to conclude that a degree of collusion had occurred regarding their evidence. N.T. Hardyman, Under Secretary at the DES, argued in response that rather than 'collusion' their communication was an attempt to give the subcommittee "the most helpful and most explicit description we were capable of giving".[102] The point, therefore, would seem proved, that communication was good between the departments, at least when it suited them. Insofar as the implementation of safeguard measures is concerned, such collusion is desirable when there are a number

of departments which must co-operate, whatever the ramifications are regarding the relationship between Parliament and the Civil Service. The lead department system again applied at the transnational level with the DES taking the prominent position.[103]

Some other points of interest concerning the UK institutional response will be addressed elsewhere, for example in considering interactions with other states and the European Community. Not least, the House of Lords held an investigation into the impact of a European Commission proposed directive on genetic manipulation.[104] However, to complete this chapter a brief reference will now be made to the hypotheses in the context of the UK.

6. HYPOTHESES.

a) Hypothesis One.

Political constraints were not great in the context of operationalising control over the safety of recombinant DNA research. The structure of GMAG was particularly innovative in that it included a wide range of participants representing most of the relevant interest groups. Limitations on participation were more noted in the early period of response when the working parties of Ashby and Williams had a narrow science membership. However, the Williams group did consult quite widely. To a large extent, the lack of public interest enabled political discourse to occur within the framework which resulted rather than from outside it. Nevertheless, as in the US, much of the discussion was about the structure and operation of the adopted framework itself.

Having a suitable professional inspection service effectively removed major criticism of enforcement of the guidelines, although dispute did

occur from time to time over which department should dominate the overall system of safeguards.

b) Hypothesis Two.

The early reports did not examine a range of control options. They accepted the need for a monitoring system, but advocated a flexible system involving continuous advice being researched and dispensed via a central committee. Thus a typically pragmatic British approach developed, based on the accumulation of case information. In many ways, this incremental implementation method outflanks all but one criticism regarding the search for alternative control options. With continuous discussion possible, the strictures and effectiveness of controls could be monitored and, if necessary, changes made. Indeed, GMAG regularly despatched Notes to all laboratories and bodies involved,[105] updating procedures and spreading information. The one criticism, however, was that the option of continuing the moratorium was never seriously considered. Nevertheless it could be said that one real alternative which was investigated was the possibility of applying the procedures for controlling the use of dangerous pathogens to the techniques of recombinant DNA.

c) Hypothesis Three.

The UK response was very much orientated to the existing HSE and HSWAct provisions, although with the parallel use of the new GMAG advice system. In this respect the UK fared better than the US in that it benefitted in having a more suitable existing framework, which itself was relatively new. It was only in 1974, the year of the Berg letter, that the HSWAct was passed, bringing the HSC into existence. Thus, general safety considerations were already being centralised, with a national inspection provision. Rather than genetic manipulation engendering a completely novel response, there was a significant element of letting the new HSC and

HSE framework show its usefulness in this, a new, area. Yet the overall pragmatism involved did provide for flexibility.

d) Hypothesis Four.

Comparisons were made with dangerous pathogens and the methods of ensuring public and laboratory workers' safety. This was, however, within the general field of microbiology, and no systematic comparisons were made with technologies which in general displayed similar risk profiles: low probability, high consequence risk. On the inspection side, the HSE did have general expertise regarding techniques of inspection per se, and some members of GMAG belonged to organisations with wider interests, such as trade unions or industrial firms. Indeed, some individuals themselves were appointed, for example as public interest representatives, because of their own general interests.[106] Despite such a lack of systematic comparison, there was at least a wide pool of experience between participants in the implementation framework.

e) Hypothesis Five.

As argued in the last chapter, communications patterns are best examined at the transnational level and with reference to all relevant groups. Yet with regard to the UK it can be said that given the small 'community' involved, including those who monitored and those who used genetic manipulation, communications were generally good. In international terms, it will be pointed out that official links with Western Europe on the control side were better than with the US, while press coverage made the US activity familiar to all concerned.

7. SUMMARY.

This chapter has outlined the distinct UK approach to the problems posed

at the institutional level following the growth of concern over recombinant DNA techniques. Some comparison has been made with the US as the two guideline 'packages' were of particular importance internationally. It can be said that the UK approach had a sounder legitimacy to it, despite the limitations of public involvement. The major issue in the US of the compliance of industry was greatly simplified in the UK to one of how best to use the regulations while maintaining confidentiality. However, the UK approach was designed to fit the UK situation, and some problems were to emerge in translating its methods into a form suitable abroad.

CHAPTER SEVEN

OTHER STATES AND INTERNATIONAL ORGANISATIONS

1. National Responses to Recombinant DNA Techniques

2. The Activities of International Organisations

OTHER STATES AND INTERNATIONAL ORGANISATIONS.

In this chapter, it is intended to provide a descriptive list of the institutional responses in states other than the US and the UK, and to identify the key international organisations which took part in the recombinant DNA debate.

1. NATIONAL RESPONSES TO RECOMBINANT DNA TECHNIQUES.

Although the US and UK developments of safeguard controls for genetic manipulation have been identified as being particularly important, there is a danger of neglecting the importance of activity in other states. In the first part of this chapter, it is intended to summarise the responses in those states identified as having interests in recombinant DNA techniques.[1] Many individual states will be discussed only briefly, because they were not of great importance on the basis of lack of recombinant DNA work carried out there, size of the state, or lack of impact in general on the transnational framework outlined in this thesis. However, a few do require more detail. Taken in alphabetical order, each of the states listed below had established their own guidelines or were using those of other states by July 1979.

STATE	NUMBER OF LABORATORIES
Australia	16
Austria	0
Belgium	6
Brazil	5
Bulgaria	At Least 1
Canada	10-15
Czechoslovakia	3
Denmark	Several
German Democratic Republic	5
Federal Republic of Germany	10-20
Finland	3
France	12
Hungary	1-2

STATE	NUMBER OF LABORATORIES (Cont.)
India	0 (2 in 1977)
Iran	0
Ireland	
Israel	1
Italy	
Japan	35
Mexico	
Netherlands	7
New Zealand	2
Norway	At Least 1
Poland	3
Sweden	2
South Africa	3
Switzerland	18
Taiwan	2
United Kingdom	45
United States	50
USSR	6
Yugoslavia	4

TABLE 1. Numbers of Laboratories Engaged in Recombinant DNA Research in the States Considered: 1980. 2

a) The States.

Australia.

This state was quick to respond to the 1974 Berg letter, led by the Australian Academy of Sciences (AAS) which established in the first instance an ad hoc committee to alert scientists to the issues and to ascertain the extent to which they might wish to carry out recombinant DNA work.[3] Following Asilomar II at which two members of the committee were present, a Standing Committee was established to devise guidelines, review research proposals, collect and disseminate information, and liaise at the international level. The Standing Committee comprised eight scientists, four of whom had particular expertise in the area. No other groups were represented.

The committee went on to produce a set of guidelines which was recognised as being a composite of those of the US and the UK. Physical containment

recommendations were derived from the UK approach, while biological containment recommendations were derived from the US.[4] A group of experiments which were thought to be too dangerous were also deferred. Guideline implementation was based on voluntary compliance, as it was argued that the numbers of scientists likely to be involved were very small and readily identifiable, enabling peer pressure to encourage their use. In addition grant agencies offered some support in requiring the use of the guidelines. Because of the small number of scientists involved, the committee was in a suitable position to receive experiment proposals in advance, much like GMAG.

In April 1979, it was reported that a committee established by the University Assembly of the University of Melbourne was highly critical after a two year investigation and called for a halt to recombinant DNA work. It wanted the wider ethical and social questions aired nationally. Further, it criticised the voluntary nature of the guidelines and the lack of legal regulation. Recombinant DNA researchers dismissed the report. Nevertheless, by 1980 the AAS hoped to hand over monitoring to the government, and relaxation of the guidelines in line with the US and the UK had occurred.[5]

Austria.

Although a report by COGENE summarising two questionnaires and the international responses[6] suggested that by 1978 no genetic manipulation work had been undertaken in Austria, it did have a group created by the Austrian Research Council to advise it on recombinant DNA matters.[7] If any work began, the approach to be taken was for the investigator and his institution to take most responsibility for safety.

Belgium.

The Belgian Committee on Medical Ethics established a subcommittee for recombinant DNA research with a view to establishing a voluntary, and later compulsory, register of all laboratories using the new techniques. A blend of US and UK guidelines was adopted.[8]

Brazil.

A group of Brazilian scientists studied the preparation of guidelines based upon US and European developments. A committee of the National Council for Research was then to decide policy, and the US guidelines were adopted.[9]

Bulgaria.

A national committee was established which monitored containment procedures which derived from a combination of the US and Soviet Union guidelines. No public interest representatives were on the national committee. Specific training was, however, required for workers and safety officers in using recombinant DNA techniques.[10]

Canada.

The Canadian Medical Research Council (CMRC) took responsibility after Asilomar II for creating an ad hoc committee to make recommendations on safety. Indeed, a draft report was produced and widely distributed before the NIH guidelines were finalised.[11] By February 1977, Canadian guidelines were produced which would apply to all research funded by the CMRC and, with their agreement, the National Research Council of Canada and the Council on Research and Health of Canada. The guidelines, however, differed from those of the US and the UK, in having six levels of physical containment and three biological.[12] Major responsibility for implementation would lie with the principal investigator, responsibility for moni-

toring with the research institution, through the establishment of a biohazards committee, while the CMRC would take responsibility in determining containment levels for proposed experiments (much like GMAG). Thus, the CMRC itself established a Biohazards Committee for the task of containment allocation for any necessary guideline revisions and for the certification of new host-vector systems.

In structure, the central committee had nine members: five laymen, including a lawyer, a businessman and three 'generalists'; and four scientists, only one of whom was using recombinant DNA techniques.[13] The Canadian approach, therefore, had strong elements of both the US and UK packages, with a GMAG style central committee. It is worth noting in addition that the CMRC saw itself as responsible for the provision of equipment needed to comply with the guidelines (many scientists in other states were to complain about the cost of implementing guidelines). Consideration was also given to the development of legislation comparable to the existing UK statutes, but was not adopted by 1979.

Czechoslovakia.

Czechoslovakia was to borrow elements of guidelines from the US, the Soviet Union and the Federal Republic of Germany. The guidelines (four physical and two biological containment levels) were to be monitored by a nationally directed mechanism, with enforcement in part based on the control of research funds by both the Academy of Sciences and the Ministry of Health. Violations were subject to fines, with industry also covered.

Czechoslovakia and Hungary were in fact the only two countries which gave authorisation to individual laboratories, rather than individual scientists, although the Soviet Union authorised institutions.[14]

Denmark.

Denmark adopted a system based on two central committees. The first, the Advisory Board for Recombinant DNA Research, was established by their research councils, was composed of experts in the field, and was charged with deciding upon the merits of establishing a genetic manipulation research programme. The second was initially an ad hoc committee which was to become the body to which research proposals, on a voluntary basis, would be referred. Early in 1980, responsibility for monitoring the work was being passed from the National Research Councils to the Danish National Health Service.

The guidelines in operation were those of the UK, and the central advisory committee comprised nine scientists or administrators. Control of research funds helped ensure compliance. In general, the UK and the European Science Foundation (ESF) influences were very strong, and laboratories were given approval by the Directorate of Labour Inspection.[15]

German Democratic Republic.

In East Germany, the monitoring of guidelines was to be carried out by local biosafety officers, although a nationally directed mechanism was also involved. Guidelines used were an amalgamation of those of the UK, the US and the approach of the Netherlands, and were compulsory to academic institutions and industry. The central committee had ten members, comprising eight scientists, a jurist and a representative of the trade union of the GDR. Violations, if serious enough, could lead to a loss of licence to carry out recombinant DNA work.[16]

Federal Republic of Germany.

In February 1978, West Germany finally adopted its own guidelines after what Chris Sherwell described as a "fretful search", which, by March 1977,

had produced four drafts.[17]

Following Asilomar II, the German Research Association (Deutsche Forschungsgemeinschaft) established a Senate Commission for Safety Questions posed by New Genetic Combinations. It was to advise on the construction of containment laboratories, the possible establishment of legal actions and international co-operation, as well as drafting guidelines. Initially the Asilomar interim guidelines were used and later those of the US, with their own guidelines, when produced, taking account of both the US and UK approaches.

From the start, the Senate Commission had non-scientist members, drawing on representatives of industry, trade unions and research-promoting organisations.[18] In applying for research grants, details of the experiments, laboratory facilities and training of the scientists and Biological Safety Officers would all be required, with the Commission supervising experiment classification, much like GMAG. West Germany also spent much time considering possible statutory reinforcement, and consulted the UK on that. Despite opposition to legislation from the scientific community and the Central Commission for the Biological Sciences, legislative drafts were produced. It proved to be, however, a very complicated task in the context of Federal and State constitutions. By the end of 1980 legislation was still being considered, but had not been introduced.[19]

In addition to a considerable national interest in using recombinant DNA techniques, West Germany hosted the international European Molecular Biology Laboratory, established under the auspices of the European Molecular Biology Organisation (EMBO) and discussed below.

Finland.

Finland is interesting in that, although only three laboratories were involved in recombinant DNA work by 1980, their central advisory committee had twenty-seven members, equalled only by Japan.[20] Yet despite the size of the committee, the report to COGENE by S.N. Cohen et al. implied that Finland's guidelines were entirely voluntary, without even control of funds acknowledged to ensure compliance.

France.

French response to the conjectured risks occurred very quickly following a grant request by Philippe Kourilsky made in June 1974, before the Berg letter was published. Kourilsky had proposed a two-part research programme, the second part involving recombinant DNA techniques. The request had been made to the National Centre for Scientific Research (CNRS) who gave their judgement, after the Berg letter, that the grant would be awarded but with an oral recommendation not to use it for genetic manipulation.[21]

In the light of the CNRS judgement, Kourilsky contacted the ten or so other scientists in France who were likely to be interested in undertaking such research in future. Collectively they wrote a letter to the chief of the Délégation Générale à la Recherche Scientifique et Technique (DGRST)[22] requesting that some sort of control be set up.[23] Combined with a request for control from French representatives on EMBO and statements on the usefulness of the new techniques, the call for control met with a quick response. About twenty or so individuals were asked to form a committee to discuss the issues and respond further. After the Berg letter, Kourilsky, who disliked the timing of the publicity surrounding it and the Asilomar II meeting, postponed his recombinant DNA work.

In general, press and public reaction in France to the whole issue was

relatively vocal and, in the view of Kourilsky, ill-informed. Kourilsky tried to reply to them by giving a lecture on Asilomar and the overall issues at the prestigious Pasteur Institute. An unexpected four hundred plus attended, with around one hundred from outside the Institute. Indeed, the Pasteur Institute itself became embroiled in internal controversy when a split emerged between the younger and older scientists over the desirability of doing the experiments at all. An unofficial vote of those in the Molecular Biology Department revealed that some 30% were against construction of a special room for such work. This issue, however, coincided with worries in general about finance for the Institute. A committee which ran the department decided in the event to proceed with the laboratory, even though by the time of that decision a wider sampling of opinion including technicians and junior scientists showed 80% against it.

Such controversial beginnings of the issue in France were followed by a 'convention' being signed between the DGRST and the major research institutions that all genetic manipulation experiments planned by their staff be submitted to a central committee.[24] According to Kourilsky, however, as the press became more aware of the technicalities of the issues, they played down the public concern. In June 1975 the French institutional response became more formalised with the establishment of a two-part central committee. The first committee was the Ethical Review Group, charged with investigating the philosophical, legal, moral and ethical issues related to recombinant DNA research.[25] This was a particularly novel provision compared with other states. Both the US and UK committees were more technical in outlook, although GMAG could, if it wished, raise wider issues over particular experiments proposed. The second French committee was the Control Commission, which met monthly to review recombinant DNA research proposals and to recommend appropriate

safety procedures, similar in effect to GMAG.

The ethics committee, although novel, was not involved that often in practice. Composed of noted individuals, or 'mandarins' as described by John Tooze of EMBO,[26] the committee only became involved if the technical committee felt the need to pass a case on. Thus it was the Control Commission which was the main central advisory group and was composed of fourteen members who were experts in the field, with four observers representing trade unions and technicians. In addition, local safety committees were to monitor compliance with procedures.[27] In the first two years of the formal system, some fifty proposals were considered.

Initially the Asilomar II guidelines were used, followed by those of the US, until the French developed their own, drawing on elements of those of the US and the UK. Draft guidelines were issued in June 1977, and were finally adopted in December of that year.[28] P. Kourilsky and G. Bernardi had been responsible for their drafting. Because the 'convention' in effect covered industry as well, legislation was not felt necessary.[29]

Hungary.

Legally enforceable guidelines (those of the US) were applied to individual laboratories in Hungary, with central monitoring carried out by the National Institutes of Public Health for any P3 and P4 laboratories. No high containment laboratories were, however, operating by 1980. Only scientists were on the national committee.[30]

India.

Although the COGENE report suggested that India may not have had any work under way as of 1979, an earlier report of the US Federal Interagency Committee pointed to work under way in 1977 in at least two universities,

with projects under discussion elsewhere. However, no national committee had been set up by 1977 and there was no acknowledged use of guidelines by 1979. By 1984, future research in India looked as though it would be much more extensive, with a research centre for Genetic Engineering and Biotechnology to be established under the auspices of the United Nations Industrial Development Organisation. It was to specialise in agriculture and human and animal health research.[31]

Iran.

A similar situation to that in India existed, where the US report suggested that some work was being done by 1977, prior to the revolution, at Tehran University. The COGENE report suggested that no guidelines were in use.

Ireland.

A national committee was set up by the Ministry of Health and was to be administered by the Medical Research Council. Research projects were registered on a voluntary basis, which the chairman of the committee claimed worked satisfactorily. As of May 1978, guidelines were in preparation, and, although tight laws existed which covered work with plant and animal pathogens, they did not cover pathogens dangerous to man. No new legislation was foreseen in January 1980.[32]

Israel.

A committee of the Academy of Science and Humanities was set up, composed of representatives from the government, universities, research centres and the National Council for Research and Development, which recommended the creation of a safety committee. Institutions would have their own special committees to recommend safety precautions, but with the National Committee having the final say. In general, the US guidelines were to be

followed, taking account of recommendations from the likes of EMBO.[33]

It is of note that it was in Israel that a US scientist carried out an experiment involving the treatment of a human being, in violation of the NIH guidelines which were intended also to apply abroad if any US institutions were involved.[34]

Italy.

In 1976, the Italian Society of Molecular Biology created a committee to prepare a report for the government. In April 1977, the Society requested the Minister of Health to create a central committee to register and manage the safety aspects of genetic manipulation, and a national committee was subsequently established. Later, in a public meeting, the Society was reported as encouraging recombinant DNA work but with appropriate safeguards and training. The central advisory committee was composed of twelve scientists and a civil servant, with Italy using its own guidelines.[35] Note, however, that the same US scientist who violated guidelines in Israel, did so likewise in Italy. A UNIDO facility was also planned for Trieste, in conjunction with the one in India.

Japan.

As of May 1980, Japan had the third highest number of laboratories involved in recombinant DNA research, after the US and UK. Its control procedures are therefore of some interest. It should also be said that as far as the industrial application of microbiology and related techniques, or 'biotechnology', is concerned, Japan undoubtedly leads the world. Increased use of recombinant DNA techniques would, therefore, seem likely.[36]

Japanese response to the issues raised by the Berg group was both quick

and widespread involving many newspapers and journals which carried articles by biologists and critics. In general, Y. Tazima reported[37] that there was an atmosphere of hostility to recombinant DNA work amongst non-professional readers. Professional scientists responded only a little slower. On 9th September 1974, the Genetics Society of Japan took up the issue at its annual meeting, and prior to Asilomar II it suggested that the Science Council of Japan (SCJ) should study the implications of the research. In January 1975 it was recommended to the President of the SCJ that an ad hoc committee be established. The Committee on Plasmid Research resulted.

Following Asilomar II, in a poll conducted by the Mitsubishi Life Science Institute, 80% of the respondents thought that the Berg group appeal was acceptable.[38] Tazima suggested that scientists were aware of the need to balance academic freedom against "potential risks to mankind". Discussion of the issues took place in symposia, with reports of Asilomar II presented under the auspices of the SCJ. Guidelines and the technicalities of host-vector systems were all considered.

The Committee on Plasmid Research made the following recommendations: a set of safety standards drawing on those of the US and UK be adopted; a Steering Committee be established; no government agency should fund research until the Steering Committee had ruled on safety; the government should subsidise the cost of safety equipment; training should be carried out at home or abroad; the government should construct a high containment facility; and a specific council should be set up to advise the Steering Committee, comprising experts and non-experts.[39]

In response the SCJ established a Special Committee on Science and Society to examine the broad impact of research activities on man and society.

It is both interesting and probably unique that the Japanese specifically attempted to put the recombinant DNA issue within such wider contexts. In most states it was usually only non-governmental interest groups which attempted this. Principles applied to nuclear energy by the SCJ, namely 'independence', 'democracy' and 'open to public scrutiny' were also applied to recombinant DNA research.[40] Indeed, a telegram despatched from the US Embassy in Japan describing the broad approach noted:

> "Move described above is typical of recent Japanese propensity to address scientific and technological problems from interdisciplinary viewpoint." 41

Not only was the Japanese approach interdisciplinary, it was also an interagency one. A study group representing eight government ministries was established, with an ultimate objective of producing guidelines, which would in particular emphasise the inclusion of industry. Overall the Japanese were very attentive regarding overseas developments and were active in sending large parties abroad for the purpose of examining controls in other states.[42]

Japan was subsequently to enter the ranks of states with their own guidelines and a nationally directed system supported by local safety officers. Its Steering Committee and Advisory Group, combined, included by 1980 seven recombinant DNA scientists, seven scientists from other fields, six specialists in medicine and biohazards, two lawyers, two specialists in physical containment and three public interest representatives.[43]

Mexico.

The Mexican Society of Biochemistry established a Committee on the Study of Recombinant Molecules. Many Mexican scientists were, however, trained in the US and the latter's guidelines were adopted.[44]

Netherlands.

After Asilomar II, the Dutch Royal Academy of Science established an ad hoc committee, which in August 1975 recommended to the Minister of Science that a permanent committee be established, with responsibility to the Ministry. As a result, the Commission in Charge of the Control over Genetic Engineering was established early in 1976, predominantly with scientific representatives. It was to survey all Dutch recombinant DNA work, advise laboratories on safety procedures and advise government on appropriate control measures.[45]

A report was produced by the Commission in March 1977 recommending that: the UK guidelines be adopted (in line with European Science Foundation policy) but with elements of the US guidelines; another committee be appointed to address ethical and social issues and to give consideration to the need for legislation; at least one Category III (UK guidelines) laboratory be established; a Supervisory Commission be introduced, composed of scientists, government officials and representatives of society, in order to register all experiments, issue certificates stating containment requirements, monitor compliance and impose any necessary sanctions on violators. For some time, however, the Dutch situation was very confusing with much media attention, debate and only a 'gentleman's agreement' underlying the framework in operation.[46] Not least, the Dutch government chose to ignore recommendations of the Supervisory Commission after lobbying by trade unions and left-wing political parties. An extremely cautious government allowed no clear policy to emerge such that nearly all recombinant DNA work was carried out either with recombinant DNA isolated and purified elsewhere, or by scientists using foreign laboratories. Confusion over the government's recommendations of "the greatest possible restraint" only eased after the government changed and relieved pressures at least on the lowest two levels of containment.

By 1980, seven laboratories were involved in recombinant DNA research and US guidelines had been introduced, enforceable through control of funding by the Netherlands Organisation for the Advancement of Pure Research. Specific training was also required. The central advisory committee contained fourteen scientists representing scientific, social and ethical aspects, although this was to be replaced by a further committee which included industrial and trade union representation.[47] Monitoring of the guidelines was to be carried out by a Site Inspection Commission. Yet as late as 1981 controversy was still very apparent with Dutch guidelines probably the toughest in the world, much to the chagrin of industry.[48]

New Zealand.

A national committee was established, comprising five scientists from different, but related, fields, to consider the issues raised by recombinant DNA techniques. Borrowed guidelines and the degree of compliance were to be monitored through local controlling committees and Biological Safety Officers.[49]

Norway.

A national committee was established by the Norwegian Research Council to supervise research which it funded and to examine the legal dimension of control. By 1979 the committee's responsibilities were broadened to cover all government funded projects. The committee, however, argued that no special legislation was required as existing law on the environment at work was sufficient. US guidelines were applied and industry voluntarily complied.

The central committee comprised six scientists, one lawyer and an 'artist'.[50] Physical containment was to be monitored by the Norwegian Institute of Public Health, and biological containment by the central

committee. Enforcement was to be through control of research funding as legislation was rejected.

Poland.

Poland was credited in 1980 with using borrowed US guidelines and with having three laboratories engaged in recombinant DNA research. Otherwise information is limited.[51]

South Africa.

Using the US guidelines, the South Africans established a central committee comprising scientists, government officials, university representatives, legal and public representatives. Training was required for workers and courses were introduced. Monitoring of work below the level of P3 containment was the responsibility of the central committee, while above P3 would involve a Biosafety Committee of the institute concerned. Violation could lead to revokation of licences.[52]

Sweden.

An ad hoc committee of the Royal Swedish Academy of Sciences was the first step, followed by an eleven member central committee charged with determining safety conditions and advising individuals and funding agencies. The central committee was run by the Natural Science Research Council and was composed of lay representatives (members of parliament), representatives of the research councils, the Board of Health and Welfare, the Academies of Science and Engineering, industry, and trade unions.[53] Thus the committee was in the mould of GMAG.

The central committee planned to use the UK guidelines, but banning those experiments deferred in the US. Under the Occupational Health and Safety Act and the law on the protection of the environment, Swedish scientists

were obliged to submit proposals for approval.[54] Local safety committees would be responsible for supervision. By 1980, US guidelines, then revised downwards and less stringent than those of the UK, were in use, although the administrative structure remained more in line with that of the UK.[55]

Switzerland.

In mid-1975, the Swiss Academy of Medical Sciences created a Commission on Experimental Genetics to study safety aspects of genetic manipulation, to recommend guidelines, establish channels of communication, and monitor domestic and international developments.[56] The Commission was at first composed entirely of experts from science, government and industry.

It was recommended that the US guidelines be applied and that a voluntary register of those doing recombinant DNA work be set up. A circular was then sent to all researchers with the Commission holding the view that the primary responsibility for safety should rest with the researchers themselves.[57]

In April 1977 at the Annual Conference of the Swiss Society for Cellular and Molecular Biology, the guidelines were discussed and overwhelmingly accepted. Some speakers, however, called for them to be legally binding, and for the public to be brought into the decision-making. It was felt that the legislative problems would have been difficult as the twenty-five cantons had responsibility for public health, which was not a federal concern. On the other hand it was suggested that the Swiss Epidemic Law would ensure general compliance, as it covered the general infection of laboratory staff, and it could easily be extended to cover the environment.[58]

Training courses were held and recommended and by 1980 the Commission had twelve members representing medicine, microbiology, molecular biology, antibiotics, industry, university management, and seven government department assessors.[59]

Taiwan.

In 1980, Taiwan was credited with having two laboratories involved in recombinant DNA work and a national advisory committee, and used a combination of US and UK guidelines.[60] Information is limited.

Union of Soviet Socialist Republics.

In 1980 the report by S.N. Cohen et al. to COGENE indicated that only six laboratories were involved in genetic manipulation, at relatively low containment levels. A committee had been established which drafted a set of guidelines taking into account those of the US and the UK. They were legally enforceable with provisions that:

> "Persons guilty of violating these guidelines shall be held legally responsible ... In a case of violation of these Guidelines (sic) the inspectorate has legal powers to stop the work." 61

The Soviet Union was thus one of the few states to use a legally based system of control, with a penalty specified as loss of licence to carry on the work. Under the guidelines, specific training was required for workers and safety officers, and the guidelines also applied to industry. The effectiveness of the guidelines was to be monitored by local biosafety commissions, State Sanitary Inspection and the control group of the Recombinant DNA Commission. The latter comprised simply eight scientists.

Yugoslavia.

In November 1976 a number of scientists formed a private group for the

discussion of recombinant DNA research in Yugoslavia. Subsequently a national committee was established. A registry of work was planned and it was intended to adapt existing law on the protection of the working environment. Helpful international discussions were undertaken with the French Committee and French scientists. The central committee was composed of three geneticists, the guideline advice of the ESF was said to have been followed, and training courses were run.[62]

b) Conclusions.

From the above review a number of points can be highlighted. To start with, it should be noted that the early expressions of concern such as the Berg letter and the Asilomar II international meeting had a very great impact worldwide, even in states which at the time had no laboratories actively considering recombinant DNA work. On the whole, the responses were creditably fast. All the states identified by either the report to COGENE or the US Federal Interagency Committee established at a minimum a central advisory committee. Functions ranged from giving technical advice, giving observations on social issues, examining individual experiment protocols, examining legislative possibilities and organising training to drafting guidelines. In part reflecting these functions, the composition of the central committees varied in the range of expertise and interests represented. The following types of response were all evident:

Adoption of the US package as a whole (local emphasis).

Adoption of the UK package as a whole (central emphasis).

Use of the US (detailed) guidelines with a GMAG type committee.[63]

Use of the US and UK guidelines in combination.

Development of an indigenous system (perhaps subsequent to one of the other alternatives).

Nevertheless, the international situation was by no means static. Many

of the states involved undertook processes of revision for both guidelines and implementation procedures. Not least the US and UK revised their guidelines. Although some states had guidelines more stringent than others, there was something of a tendency for the guidelines to even out. However, this was often only with downward revision of stringency.[64]

In most cases, enforcement of codes of practice was through central control of research funds, which often left industry only voluntarily controlled. Legislation to support control, even if only to ensure notification, was rare, although on occasion existing statutes had some utility. Many states did, however, consider the introduction of new legislation, but usually rejected the option or failed to achieve agreement between interested parties. The very uncertainty of the risks and the constant revision of perceptions made legislation often seem inflexible.

A common requirement of the bulk of the states, of some importance, was the recommendation of training in the use of microbiological techniques. This was, indeed, something felt to be necessary by many scientists.

In general, information regarding activity in other states was well disseminated between the many central advisory committees. Awareness of changes in perceptions of hazards, guidelines and the implementation procedures of leading states was particularly evident. Much of the responsibility for international communication of such information did, however, lie with the international organisations involved. In particular the international community followed very closely the early deliberations of US and UK institutions, and the accompanying documentation from the NIH and the UK working parties was well read internationally. Not surprisingly, an important perception that grew stronger was the need for some form of international harmonisation. In particular, this need was

recognised by the international organisations.

2. THE ACTIVITIES OF INTERNATIONAL ORGANISATIONS.

A number of international organisations were of great importance in the co-ordination of activities in different states, the dissemination of information, and the development of policy. The summary of the activity in the many states involved was undertaken with little reference to these organisations, yet it was apparent that the packages adopted in terms of operational procedures were not all that diverse between the states. Communication of the operational procedures of other states, and particularly those of the US and UK, was influential in making the responses so similar. With the internationalisation of science there are many specialist international organisations and those of relevance must be examined here, particularly as they fulfilled central roles in the system of communication. The following organisations will be taken in turn:

European Molecular Biology Organisation (EMBO)

European Science Foundation (ESF)

European Medical Research Councils (EMRC)

International Council of Scientific Unions (ICSU)

International Association of Microbial Societies (IAMS)

World Health Organisation (WHO)

United Nations Organisations

World Intellectual Property Organisation (WIPO)

North Atlantic Treaty Organisation (NATO)

Pugwash

European Community

a) The International Organisations.

European Molecular Biology Organisation.

EMBO is an international organisation of scientists from seventeen states. Although it is non-governmental in structure, it operates under the auspices and finance of the European Molecular Biology Conference (EMBC) which is an inter-governmental organisation.[65] The EMBC meets twice yearly to consider the budget for EMBO.

EMBO effectively became involved in the recombinant DNA debate when twelve Europeans attending a symposium at Cold Spring Harbor in the US on 7th June 1974 wrote to Sir John Kendrew, the Secretary General of both EMBO and the EMBC. They pointed to both the Berg letter of concern and the potential importance of the new techniques. They hoped that EMBO would urgently and carefully consider the problems and in particular provide an appropriate special risk laboratory for use with the new techniques.[66] At that time, Kendrew was deeply involved in the establishment of a European research laboratory at Heidelberg, Germany.[67] The proposal was therefore put for the new complex to incorporate a high containment laboratory for recombinant DNA work. Kendrew took the line that this could only be done if the member governments would provide the necessary finance. The UK, however, opposed the proposal, offering instead the use of the high containment facilities at Porton Down for European scientists. A counter argument was noted that a laboratory long associated with biological warfare would not be popular.[68] With subsequent international developments, pressures for the laboratory grew, leading eventually to a separate building of some seven hundred square feet at Heidelberg. Finance actually came from savings on the original estimate of cost for the whole complex. Thus a P4 (US category) laboratory was built for European use.

EMBO, again in response to the Cold Spring Harbor letter, financed five

scientists to attend Asilomar II with formal governmental approval at the level of the EMBC. Many other members attended of their own accord. The five were members of an ad hoc committee which had been established, to examine the issues, at the January 1975 meeting of the EMBC. Of note, at the same meeting Kendrew resigned as Secretary General of EMBO to run the European Molecular Biology Laboratory (EMBL).

On their return from Asilomar, the five members presented a report in which three recommendations were made. Firstly, they suggested that the Ashby Report and the Asilomar Conference Statement should serve in Europe as interim guidelines. Secondly, they suggested that EMBO appoint a Standing Advisory Committee on Recombinant DNA Molecules, as part of further elaboration and collaboration in Europe. Thirdly, they added to calls for the proposed EMBL to accommodate genetic manipulation.[69]

Established in January 1976, the Standing Advisory Committee, which consisted entirely of scientists interested in the new techniques, met for the first time in February 1976. Its functions were: to advise upon request governments, research councils, national committees, institutes and individual scientists on scientific and technical matters; to explore the possibility of instituting training programmes; and to maintain close liaison with the ESF and other governmental and non-governmental organisations concerned with recombinant DNA. Indeed, over the years this committee was to have considerable influence in Western Europe, directly through providing member scientists with up-to-date information, and indirectly through its advisory capacity in relation to the ESF. EMBO was in part a provider of technical support for a policy function carried out in the ESF (discussed below). A number of training courses were also run.

The provision of up-to-date information operated in two important ways.

Firstly, the EMBO committee was in a good position to compile information derived from observing international developments. This operated, for example , through members who attended the meetings of other bodies either as observers or participants. An individual of some importance in this respect, John Tooze, the Secretary of EMBO and a member of the Standing Advisory Committee, was also Secretary to the ICSU and a member of its genetic engineering committee (COGENE) and was on the Secretariat of the ESF and a member of its Liaison Committee for Recombinant DNA Research.[70] Tooze as an individual was, therefore, well placed to be of some influence within the transnational community addressing recombinant DNA issues. When contact was less personal, the EMBO committee was part of a network of formal and informal communication between individuals and various domestic and international, governmental and non-governmental bodies. Compilation of information was often taken further by providing analysis of various aspects of the issues.

In its second report, the Standing Advisory Committee produced, for example, a fairly comprehensive analysis of the similarities and differences between the US and UK guidelines. This included assessments of the relative importance in each approach of physical and biological containment, and of local and central implementation emphases.[71] A number of recommendations were included: that national advisory committees be set up taking into account both UK and US guidelines; that research protocols be submitted to the national committee; that the national committee should specify containment needs; that experiments in the lowest containment categories should be allowed to begin immediately; that national advisory groups should have the right to inspect laboratories; that the minimum level of physical containment should be the Category I level of the UK rather than the P1 or P2 levels of the US, which were both less stringent; that prohibited experiments under the US guidelines should not be undertaken anywhere at

that time. Recognising the differences in overall approach in the two sets of guidelines, it was recommended that combinations of procedures from each should not be used. Other recommendations covered training, the participation of staff in safety, the inclusion of containment details in published results, and that to facilitate international standardisation national advisory groups should keep close contact, for example through EMBO, the EMBC, the ESF and the ICSU.

Analysis of a broader focus was provided by John Tooze, who produced summaries of the development of control procedures in Europe for presentation to groups such as the RAC and the ICSU.[72] Thus the EMBO committee and Tooze took their roles very seriously both within the context of Europe and worldwide. Compilation, interpretation, analysis and dissemination were all involved.

However, there was a second important means of providing information. In line with recommendations made elsewhere, such as in the RAC and by the Ashby Report, the EMBO committee argued that "suitable experiments should be undertaken to assess conjectured risks associated with recombinant DNAs and to pave the way towards eventual adjustment of existing guidelines".[73] EMBO, therefore, supported some risk assessment experimental work.

In particular, an experiment was proposed by the committee's chairman, Charles Weissman, from Switzerland, which would involve co-operation with Ken Murray of the University of Edinburgh, to be performed in the UK and thus subject to GMAG oversight. It was intended to use a polyoma virus to which mice were known to be susceptible. The genome of the virus would be incorporated deliberately in a recombinant DNA molecule inserted into E. coli, which would then be introduced into the mice. GMAG approved the experiment, to be carried out under Category IV containment at Porton

Down. As many as one thousand mice were thought to be necessary for a study lasting some months. Originally proposed in 1977, the experiment was completed in 1980. The results of risk assessment are considered in Chapter Eight.

Further investigation of risks occurred in joint workshops organised with the NIH. One on the 'parameters of physical containment' took place in March 1977 in London, while one year later a second EMBO/NIH workshop was convened to assess the risks for recombinant DNA experiments involving the genomes of animal, plant and insect viruses.[74]

On the whole, communication between EMBO and other organisations was very good, and the advice given was valued by many bodies. Organisational biases will, however, be considered elsewhere.

European Science Foundation.

Although technically the ESF was established in 1974 as a non-governmental organisation, its membership is such that strong government influences prevail in it. Membership consists of representatives from forty-seven academies and research councils across eighteen member states.[76] Government influence affects the ESF inasmuch as they can influence the policy of their research councils. The organisation grew out of international discussions in the 1960s and 1970s regarding the development of European research. Improved co-operation and co-ordination on basic science was assumed to be desirable, and the ESF was charged with a number of objectives, including the promotion of mobility in research workers, assistance in the free flow of information and ideas, and facilitating the harmonisation of basic research activities supported by its membership. All member organisations were to contribute to its budget on a weighted scale, although the total was relatively small. It viewed science in the broadest

sense, and included social science representation.[77]

In April 1975, the ESF established an ad hoc Working Group on Genetic Manipulation, composed of twenty-one biologists, physicists and lawyers. Its functions were: to survey the recombinant DNA literature and European initiatives; to study the social, legal and philosophical implications of the research; to recommend action to be taken at the European level concerning the responsibilities of scientists and the regulations needed to minimise risk. At a meeting on 10th September 1976, the finalised NIH guidelines and the UK Williams Report were discussed, leading to a set of recommendations from the committee which were adopted by the ESF Assembly in October 1976.[78]

Taking the now familiar view that the US and UK systems should not be intermixed, in part because of the possibility of opting for the lowest common denominators in containment, the ESF recommended the UK approach for European states. It was argued that the UK code of practice covered all laboratories, required a slightly higher level of physical containment reflecting greater use of a more tried and trusted method compared with biological containment and was more flexible in that each experiment was individually assigned containment. It was also felt that the existing UK legal provisions would have their counterparts in other European states. The ESF committee hoped that states with less experience in genetic manipulation would consult the EMBO Standing Advisory Committee and they specifically requested that the EMBO comparison between the US and the UK guidelines be made.

Further recommendations included: research should continue; guidelines be rigorously followed; national advisory committees be established; national registers of all work in each state be compiled; states should ensure

compliance with guidelines; close contacts be maintained between all relevant European bodies; and that the ESF should establish a permanent committee drawing on the membership of national committees, the EMBO committee and the European Medical Research Councils (discussed below). Regular meetings of the new ESF committee, it was hoped, would emphasise the harmonisation of European policy. Thus, the ESF Liaison Committee for Recombinant DNA Research was established, and met for the first time in March 1977. As a policy forum, the new committee was to be influential as most national advisory committees were run by their respective research councils which were represented on the Liaison Committee.

In addition to the European members of the ESF, representatives from the US and Canada also attended meetings of the Liaison Committee, making significant contributions to its business. It was felt that the ESF committee was probably the best forum for first hand information on all recent developments and decisions.[79] The North American input was acknowledged to be highly valued.[80] If EMBO provided a general focus within Europe for the channelling of technical information, then the ESF committee provided a similar focus for policy information. The EMBO committee in effect provided an important back-up service. Guideline harmonisation, the relative stringency of guideline options and the need for legislation were all important policy questions to pass through the committee. Of particular importance was the role of the committee in establishing the views of affected states when the European Commission produced a Draft Directive on recombinant DNA research, outlined below.

From the point of view of the UK, as an example, the DES acted as the 'lead' department in international aspects, and therefore kept close contact with both GMAG and MRC involvement in the ESF. Indeed the DES considered that the ESF forum was more important than the European

Community in developing European responses, and the Liaison Committee itself felt that in 1980 similar safety precautions were in fact "effective or envisaged in all countries represented".[81] In the late 1970s, the European Commission had expressed great interest in international harmonisation and the ESF was arguing that in effect this had been sufficiently achieved, without the proposed Directive. This was qualified in that the ESF committee had come to the view that no one set of guidelines or procedures could fit the differing domestic political situations of the member states. Even though the ESF came to favour revised US guidelines it would, for this reason, not specifically recommend them.[82]

European Medical Research Councils.

The EMRC is an association of representatives of national medical research councils, or their equivalent, and was brought into being in May 1971 for the purpose of fostering collaboration in medical research. Regarding recombinant DNA research, the EMRC concluded in March 1977 in Berne that: uniformity of national guidelines was desirable and the EMRC should assist towards this; steps should be taken towards the registration of all European recombinant DNA activities; given the range of activities concerning recombinant DNA undertaken by other international organisations, the EMRC should limit its input to commenting on ESF proposals.

Three EMRC representatives were appointed to cover ESF activity, and to consider progress reports from national members. The EMRC was represented on the ESF Liaison Committee, although in general its concerns were technical.[83] It was not very important in terms of the more political aspects.

International Council of Scientific Unions.

Founded in 1919 as the International Research Council, the ICSU took its

present name in 1931, and in 1963 adopted new statutes. Its structure includes eighteen independent scientific unions with membership from more than sixty national bodies such as research councils or academies. It is thus non-governmental and not allied to any political movement. In general the ICSU tries to encourage scientific activity "for the benefit of mankind" and takes its members from both the East and the West. It has at times organised major co-operative ventures such as the International Geophysical Year and the International Biological Programme. The ICSU tries to act as a focus of communication of scientific information and the various councils organise international conferences, congresses, symposia and publish journals. Close co-operation and financial support come from international organisations such as the World Health Organisation and UNESCO.

When scientific activities of a wide ranging nature arise and the scope of the project is of clear interest to several unions, then the ICSU moves to bring these unions together to form a Scientific Committee. Many such committees have been formed, one of which was to look at the genetic manipulation issue. The ICSU was in fact quick to act on the developments in recombinant DNA techniques, in part due to the fact that Sir John Kendrew became Secretary General of the ICSU exactly at the time of the Berg letter. Combined with his role in EMBO and the development of the EMBL, he had an interest in getting the ICSU involved. In interview he said:

> "I really stimulated ICSU to set up a group on the world scale to consider these problems." 85

On 20th September 1975, an ad hoc committee was set up under the chairmanship of W.J. Whelan with essentially a watching brief. It was asked to

study and advise on the development of public opinion and government actions, give support to national and regional scientific groups, collect information and act as a central source, encourage the universal availability of strains of organisms suitable for safe use with recombinant DNA techniques and foster international exchange.[86] After an extensive meeting examining much of the international activity of the time, the ad hoc committee unanimously recommended that a Standing Committee on Recombinant DNA be established. This was duly enacted by the ICSU, with the support of seven of the unions. Established in October 1976, the new group was called the Committee on Genetic Experimentation (COGENE) and its references were widened from those above. COGENE increased in influence during the next few years.

It was to serve as a source of advice for governments, government agencies, scientific groups and individuals. Safeguards, containment facilities, training and scientific exchange were all to be monitored and encouraged by this new forum of discussion. It was also charged with taking note of the widespread concern over possible deliberate and inadvertant misuse of agents constructed by recombinant DNA techniques and, if necessary, promoting public discussion.[87] The chairman of COGENE was W.J. Whelan and the secretary J. Tooze, with a membership of seven appointed by the unions involved, and six others appointed by the ICSU Executive. Observers were to be sent by organisations including the WHO and UNESCO.

At its first meeting in May 1977, three working groups were set up to compare and analyse existing guidelines, to study the requirements for training, and to sponsor and gather information on risk assessment.[88]

COGENE's particular advantage over other bodies was its global scope and membership. However the investigations of its working parties made their

impact relatively late in the overall debate. At that first meeting, held in Paris, the future pattern of its activity was outlined and in subsequent years successfully developed. Underlying this activity there appeared to be a philosophy of conserving the interests of scientists, perhaps not surprising in the light of the general aims of the ICSU in promoting international science. Judgement on this element of the behaviour of COGENE is necessarily subjective but supported by a number of indicators, partly relating to the committee's past relationship with the press and its tendency to avoid publicity. Yoxen was to describe it thus:

> "COGENE became, in effect, a pressure group for minimal regulation of this research and its members exploited all their connections in governments around the world to get the message across." 89

More will be said of COGENE's relationship with the press, which in many ways reflected a certain political naivety rather than a deliberate 'cover up' of which some critics have complained. In the 1977 and 1978 meetings of COGENE, however, the activities of the working groups became clearer. The guidelines group, convened by Stanley Cohen, embarked on a questionnaire survey of all the ICSU member states producing a valuable report in 1980. The risk assessment group, convened by A.M. Skalka, using information from questionnaires and analyses of workshops held by other organisations, also produced a report, in 1978, in which it concluded:

> "... no risk unique to recombinant DNA research has been identified." 90

The risk assessment group, however, was still of the opinion that it was needed in 1979.[91] As far as training was concerned, the third working group, convened by K. Murray, concluded that this was already adequate in the area, and that COGENE could not make significant additional contri-

butions. Nevertheless, at the third COGENE meeting in March 1979, John Tooze suggested that COGENE assist in organising training in states or geographic regions where there was a defined need.[92] At the second meeting, a fourth working group had been established to examine the future benefits of genetic manipulation, and to share the promotion of training. In late 1979, a training course was run in Sao Paulo, although it was weakened by lack of participation. A further course was planned for India in 1981.

These working groups provided very useful technical services, and COGENE became an important support organisation at this level for the WHO, much like the relationship between EMBO and the ESF.[93] One particular action of COGENE was to be very important and it was regard to this that the difficulties with the press arose. By the second meeting in April 1978 a proposal had been made to organise an international meeting which was to bring together scientists, research directors, legislators, lawyers and public health experts. This meeting, held in April 1979 at Wye College, Kent, was both important and controversial. Ironically, the controversy grew out of an organisational decision to attempt to mute criticism and public discussion which in effect backfired.[94]

The organisers of the conference hoped that it could take place in "a cool, uncharged atmosphere, at least until the conference had assessed the situation and come to some conclusions".[95] The UK was selected on the basis of its quietness, and London was excluded in favour of a venue which would provide more opportunity for 'informal' contact.[96] A letter from the organising committee, dated 12th March 1978, to all participants had given the impression that no members of the press would be present and it requested attendees not to contribute to reviews for publication other than the official proceedings.[97] In response to a request from a writer

for New Scientist, the organising committee had agreed to invite three members of the Association of British Science Writers, provided that they agreed not to record or despatch reports directly from the meeting, in a fashion similar to Asilomar II requirements. A complete ban was only lifted on the day before (a Sunday) the meeting commenced.

Nature and The Guardian strongly criticised the treatment of the press. Nature, for example, prior to the meeting argued in an editorial:

> "... the committee has already set the tone - the discussions are too sensitive to be widely disseminated except in an official version. Others may conclude - perhaps quite wrongly - that there are other things to hide." 98

Criticism of the apparent wish for an off-the-record meeting was widespread, supplemented by comments made by Roger Lewin of New Scientist in a presentation at the conference itself.[99] He also suggested that the choice of venue was too remote, adding cause for suspicion, especially given the aims of the conference, which he argued included the presentation of views and evidence to show risks as much less than originally thought. Nature was, however, to record that change of heart as follows:

> "To the outside observer the views that risks are negligible went through on the nod." 100

To be fair to COGENE they always intended to publish the proceedings of the conference as quickly as possible, and to hold a press conference after the event. Yet the fact remains that of the 143 participants attending a very important international conference, only three were from the press, and only the UK press at that. It is generally acknowledged that the approach to press coverage was bungled. In hindsight, Whelan argued that the correct approach was taken when the organisers realised

that their call for an informal off-the-record meeting was being misunderstood.[101]

Perhaps a more subtle weakness in the conference was the absence of noted scientists who had been critical of the claims regarding the safety of the work. The criticism was left to a few individuals such as Donna Haber of the UK trade union ASTMS. She feared that hasty dismantling of the guidelines, and accused scientists as 'over-reacting' much as they had accused the public in its response to their early expressions of concern. She went on to point out that:

> "... the work really hasn't been stopped and it seems to me that it's gone on and gone on very well. I think that a meeting like this is not a way to reassure the public." 102

In summary, COGENE became an important actor regarding the issues surrounding recombinant DNA. Over time it was, however, to change its emphasis away from guidelines and risk assessment towards considering benefits and promoting training. Much of the information accumulated by the working groups was notable, even if COGENE impartiality became questioned over the Wye Conference.

International Association of Microbial Societies.

Originally founded in 1930 as the International Association of Microbiologists, the IAMS aimed to ensure that regular congresses and meetings were held. It is of note for its very early response to recombinant DNA issues rather than for its subsequent impact. The Executive Board of the IAMS decided at a meeting in Tokyo in September 1974 to establish a Genetics Commission under the title of the International Microbial Genetics Commission (IMGC). In the mean time, an ad hoc committee would suffice until the IAMS could make the necessary formal changes to its structure

to include the IMGC. The ad hoc committee paved the way by establishing contacts, for example with the Ashby working party and members of Berg's group. Indeed this committee was particularly active in pushing for the formal IMGC.

By early 1976, the ad hoc committee was supporting the Ashby Report and holding some reservations over Asilomar II statement. It recommended that national bodies implement the advice contained in these documents, while expressing fears in particular about the risks in future commercial development.[103] However, when the IMGC was announced in September 1976, with the planned intention of co-ordinating contact between laboratories, institutions and societies, it faced a limiting factor. Its predominant concern as part of the IAMS was with microbes and their genetic composition. Other organisations, such as COGENE or EMBO, were better suited forums for addressing recombinant DNA issues because they looked at many other organisms at different biological levels. Thus, for the purposes of this thesis the existence of the IAMS Commission is indicated, but because of its narrower interests is argued to be of little overall significance.

World Health Organisation.

The WHO entered the discussion on recombinant DNA taking a different perspective from most other organisations. With a long interest in pathogens in general, the WHO viewed the concerns regarding recombinant DNA in conjunction with other biological hazards.[104] Prior to the Asilomar II conference, Martin Kaplan tried unsuccessfully to secure an invitation from Berg to attend as a representative of the WHO. Berg was reluctant as he saw the WHO as too bureaucratic, preferring instead to consider the ICSU as an organisation with international interests. In June 1975, with the approval of the Director General, Kaplan introduced

the whole issue to a senior advisory group of which he was the secretary, the Advisory Committee on Medical Research (ACMR).

The ACMR responded by issuing a report in the same month arguing that recombinant DNA techniques should be scrutinised using the same methods of balancing hazards and benefits that would apply to microbiological research in general.[105] On the basis of applying rational assessments under uncertainty, it should have been expected that the conjectured hazards of recombinant DNA would require different treatment from those of known pathogens. This would not preclude general principles, not least of which was the very idea of even directly setting risks against benefits, a task universally avoided in scientific circles as far as recombinant DNA research was concerned. Overall, the WHO saw the issue as one of public health in relation to the general problem of communicable diseases, rather than in terms of guidelines per se. Indeed, recognising the limits of utilising existing methodologies, the ACMR suggested the need for further study to facilitate the "rational balancing of risks and benefits".

The ACMR saw the roles of the WHO as facilitating microbiological training in general, co-ordinating information, providing an inventory of national efforts in risk assessment, responding to requests for advice, registering accidents should they occur and undertaking specialist studies in relation to these roles. However, like many organisations involved, the WHO adopted a promotional view of recombinant DNA techniques, in parallel with their interests in public health. In particular, it was thought that the techniques might aid future medicine and health.

In 1976, the ACMR had a report prepared on the WHO Special Programme on Safety Measures in Microbiology.[106] It was planned to convene an inter-

national committee of experts to define WHO priorities and a joint WHO/ NIH consultation exercise was proposed which would also involve the International Air Transport Association (IATA) and the Universal Postal Union (UPU). The consultation exercise was to examine the facilitation and safety in the international transportation of research materials.[107] The report also addressed emerging international problems of the time, although acknowledging that essentially it was the scientific community which decided on risks and safety measures. The report argued that comprehensive recommendations covering all research projects could not be made at either national or international levels. Nevertheless, it was thought that individual states should provide the WHO with access to their particular areas of expertise in implementing safety considerations, in order to disseminate it. Advice might be centralised, it was suggested, through the ICSU or EMBO.

A particularly important observation in the report was that very few suggestions had been made regarding emergency services should a known pathogen or new recombinant DNA pathogen escape. Thus it was suggested that it would be desirable: to set up such services, including reagents and laboratories for diagnosis, and containment for patients and personnel; to maintain a register of experts, laboratories and isolation facilities; to assist states on request through an international advisory mechanism; to aim at international arrangements to facilitate rapid exchanges of experts, transport of patients and biological materials in case of emergency. This was all planned in the context of perceptions held in 1976.

By 1978 at a symposium held by the WHO in Milan, it was very evident that perceptions of genetic manipulation risks had changed amongst the scientific community.[108] Emphasis had shifted to stressing the safety

of the techniques while the consequences of the Berg letter were regretted. Yet in 1976 the WHO had proceeded to develop their programme on safety measures through the medium of four working groups.[109] The first group would list types of organisations needing physical containment for both natural pathogens or novel genetic combinations, summarise important physical containment requirements and make an inventory of relevant laboratories. The second working group would develop guidelines for the emergency treatment of contaminated individuals. The third group would examine laboratory safety elements covering a number of factors such as risk assessment, equipment design, laboratory practice, training, education and employee health, aiming in the long run to develop codes of practice. The fourth group was to consider further the international transportation of infectious materials.

However, the WHO was to be caught in the dilemma of combining two roles, the promotion of an activity and the monitoring of safety. In the case of smallpox, its programme on eradication was of such success that the WHO planned that the number of laboratories working on the virus should decrease. Thus in the UK the number of laboratories reduced from nineteen in 1973 to three in 1978. In 1977, Professor Bedson of Birmingham University was told that his laboratory was not to be granted the status of a 'collaborating centre' on smallpox research, which in effect would end this research there, on the basis of weak safety standards. But in 1977, the WHO also gave Bedson $7,500 to support his research. The decision not to allow Bedson's laboratory to continue came as Bedson was getting favourable research results and threatened to cut him off from the mainstream of world smallpox research. Originally, Bedson planned to complete his work in 1980, but compromised and said that he would instead complete by 1978. Part of the ineffectiveness of Bedson's safety precautions has been attributed to the enormous pressure he came under to

complete the work. The consequences have been discussed in Chapter Six.

As far as the WHO was concerned, because it was treating genetic manipulation within microbiology as a whole, then its credibility, which suffered somewhat as a result of the Birmingham smallpox outbreak, must also be raised here. For an organisation hoping to improve communications it did not set a good example in failing to inform either the DHSS or Birmingham University of its communications with Bedson. The WHO was both in favour of promoting and ensuring safety in genetic manipulation, but on the whole did not have great impact on the development of control measures. It did, nevertheless, provide for some useful peripheral discussions on fairly technical problems. Not least it held the Milan conference and sponsored the ICSU.

United Nations Organisations.

This group of organisations is mentioned essentially in a negative way. There was very little involvement, particularly in the early days of the recombinant DNA issue, by any of the UN agencies. UNESCO and UNEP[111] have given a little consideration to a limited set of issues. In September 1975 in Hungary the International Cell Research Organisation (under UNESCO) passed a resolution stressing the potential dangers and the potential beneficial applications of genetic manipulation. In essence the Executive Committee expressed a hope that regulations would not impede progress.[112] UNESCO also gave some thought to the ethical issues raised by the new techniques. In 1975 in Bulgaria a conference was held on "Science in the Contemporary World: The Human Implications of Scientific Advances" and a symposium on "Genetics and Ethics" was held in October 1977 in Madrid. Discussion at the latter, however, examined the implications of genetics research in its widest sense, although some support was given for training courses in cell biology.[113]

UNEP examined a particular question, namely the possibilities of engineering plants, such as wheat crops, such that they might extract nitrogen directly from the atmosphere rather than the soil. Some concern was evident over the release in this fashion of recombinant molecules into the atmosphere. In retrospect, this research area has not proved straightforward, even in the 1980s, and has not progressed as fast as was initially hoped.

Thus the UN and its agencies did not have significant impact on the issues of control of recombinant DNA techniques. Indeed, one DES official, in interview, has expressed relief that organisations such as UNESCO were not much involved, preferring to stress the suitability instead of organisations such as EMBO, the ESF and the ICSU for international co-ordination. The Whitehall view seems to favour organisations in which membership is not so universal that agreement is difficult to obtain.

In the 1980s, the United Nations Industrial Development Organisation has, however, shown interest in promoting the development of biotechnology with particular reference to the third world. It has recommended the establishment of two international centres for genetic engineering and biotechnology, one in India and one in Italy.

World Intellectual Property Organisation.

WIPO is an independent organisation whose board of directors is composed of members of various scientific societies, and is funded through grants and contracts (including those from the NIH). In April 1977 a meeting was convened in Budapest on an important issue, that of the international recognition of the deposit of micro-organisms for the purposes of obtaining patents. Patenting of the products, or even the techniques, of recombinant DNA has developed over the years as a controversial issue, particularly in

the US where legal proceedings have surrounded certain precedent-setting applications.[115] In other instances industry has feared disclosing information to advisory committees (for example to GMAG) which could compromise patent applications on the basis of prior disclosure.

The Budapest meeting was for the purpose of drawing up an international treaty to make the requirements of patent applications in more than one state simpler. This derived from a particular requirement of patent procedures involving micro-organisms. New 'inventions' for the purposes of patenting need only be described in detail and filed with the patenting agency in most states. However, for micro-organisms, the disclosure requirements in an increasing number of states appeared to necessitate a deposit of a sample of that organism in a special institution, costly to maintain, from which, subsequently, further samples might be withdrawn.

The treaty being proposed was to avoid the costly duplication of samples in each state, by establishing an agreement that a deposit in one state would suffice, covering future applications in several states. This would necessitate the recognition of 'international depository authorities' for storage and provision of samples internationally. The original proposal that WIPO should examine the problem came from the UK, and twenty-nine states attended the Budapest meeting. Ten non-governmental organisations, such as the European Federation of Agents of Industry in Industrial Property and the Committee of National Institutes of Patent Agents were invited as observers. The treaty came into force in the UK, for example, in December 1980.[116] This treaty is likely to increase in importance as biotechnology develops internationally.

North Atlantic Treaty Organisation.

NATO has a Committee on Science and Technology which set up a subcommittee

on genetic manipulation. The issues were examined from a similar perspective to most of the other organisations discussed here, taking consideration of the standard scientific viewpoint as well as the alternative viewpoint put forward by Robert Sinsheimer.[117] The NATO subcommittee favoured the inclusion of public interest representatives and concluded that the NIH system was more open than the 'behind closed doors' approach of GMAG. On the whole, the subcommittee merely summarised the international situation in a brief manner and from a non-military perspective.[118]

Pugwash.

As described in Chapter Four, Pugwash became involved in discussion on the potential deliberate misuse of recombinant DNA techniques. The organisation is simply noted in passing in this summary.

The European Community.

In January 1977, the Directorate General XII of the European Commission convened a meeting in Brussels of heads of all national advisory committees for informal discussions on recombinant DNA research. It became apparent that a Directive was being contemplated, as part of the Commission's role of putting forward proposals for legislation. Directives are binding on all member states, but allowing them to choose the means of execution.[119]

DG XII, the Research, Science and Education branch of the Commission, was headed by the Commission's representative on the ESF Executive Council and it was considering adopting a Directive whereby member states would have to harmonise their legislation, or in the case of recombinant DNA adopt the same precautions. At the January meeting there was not much objection to the idea of a Directive, provided it was not too specific or detailed. Much objection was to become evident, however, once the draft was produced. Sherwell suggested that most people at that time recognised

that the Commission possessed the authority both to hasten the harmonisation that was felt to be needed and to incorporate industrial private sector research within a common framework with all recombinant DNA research. Yet Sherwell also noted that some worry existed over the timing of the Commission's involvement - late in the 'debate' - which could lead to resentment amongst researchers, now that perceptions of the risk appeared to be ameliorating.[120]

In late February 1977, the outcome of the January meeting was discussed by the Medical Research Committee, a subcommittee of CREST, the Commission's Scientific and Technical Research Committee. No firm conclusions were reached at that time. In fact it was not until early 1979 that the Draft Directive was sent to member states for their consideration. This time-lag represented one of the major criticisms. Many groups were to argue that the European Community operated too slowly for the sort of exercise it was contemplating in this instance. A number of drafts were produced in extensive consultation with groups such as EMBO, the ESF and, within the Commission, the Medical Research Committee and various ad hoc groups of experts.[121] The following considerations underlay the Draft Directive submitted to the Council of Ministers on 5th December 1978 and published in the Official Journal of the European Communities on 15th December:[122]

i) It was hoped to avoid variations in the practices of different states through harmonisation. The Commission document argued that differing considerations of safety could arise out of some states having statutory provisions to cover recombinant DNA work, while others did not.

ii) The case of recombinant DNA, it was thought, provided an opportunity to test the possibilities of compatibility between legislation and

the development of modern technologies. This was seen as part of a process of protecting man against his own achievements, and particularly the long-term influences on society and the environment of the applications of modern biology.

iii) Taking the existence of expensive protection devices at the physical and biological levels as evidence of the seriousness of the conjectured hazards, the Commission document professed a wish to ensure that the measures were effective.

iv) It was argued that as more and more institutions were using the techniques, the risk, should it exist, was increasing with time in proportion with the number of new sites involved in the work.

v) Because biological material such as viruses and bacteria recognise no national borders, the issue was identified as 'transnational'. As a result, there would be a reduction to a certain extent of the liberty of states to define and follow independent policies. However, the Commission document argued that:

> "... agreements and ... guarantees can best be generated through legal dispositions, taken in each country, which are based upon a core of principles adopted in common." 123

This was controversial, as indeed was the whole question of legislative approaches to the issue of control.

vi) Because industry was not covered by measures such as the control of funding to ensure compliance with guidelines, the Commission feared different laboratories operating at the same levels of risk not observing the same rules.[124]

This analysis was used to support the following proposals embodied in the Directive: prior notification of all work would be required, including work involving recombinant DNA materials acquired from elsewhere; for all except low risk category work, prior authorisation would be required; member states would subdivide the various types of recombinant DNA work by their nature and the conjectured hazards involved explicitly allowing for the source and degree of purity of the DNA molecule, the host-vector system utilised and the manipulative procedures proposed; categories of containment would then be applied; sound laboratory practice and training would influence safety requirements and supervisory measures called for; all of the above would involve a 'national authority' and the exercise of notification would involve a detailed experimental protocol or description of materials if acquired elsewhere. The national authority would then have ninety days to give its decision. It could also revoke previous authorisation.

These proposals would have involved legislative changes, even in the UK, whose regulations did not cover the use of recombinant DNA molecules, did not require prior authorisation nor confer the powers of revokation. Further, even as the Draft Directive was being prepared, GMAG was on the point of changing to a quite different approach to risk assessment. Despite being almost already out of date in this respect, the Draft Directive included a provision for review of the Directive and revisions if necessary at least every two years.

Indeed, within the UK, the House of Lords Select Committee on the European Communities held hearings on the Commission's proposals, concluding them to be too restrictive and ill suited to the rapidly developing techniques. The Select Committee suggested that a Recommendation from the Council would be preferable to a Directive. It appears obvious that the UK system

provided the basis to a large degree for the Commission's proposals, and thus it is worth considering the attitudes of groups within the UK. While DG XII was examining the issues, the DES was the lead department for the UK and it argued for a Recommendation. However, when the Medical Research Committee became more involved, the DHSS took the UK initiative, although the Whitehall briefing system was utilised maintaining the above view.

Industry, as represented in the UK by the CBI, forcefully opposed the whole idea of a Directive, although they recognised the need for international harmonisation. The Directive, they thought, was out of date and only paid lip-service to the needs of flexible revision. In particular, they cited their relationship with Commission officials leading up to the draft as evidence of the latter's unwillingness to take sufficient account of scientific progress.[125] Further the CBI criticised the limits of having harmonisation across the membership of the European Community, if non-members were not brought into the agreement. The CBI felt that this could hinder European states, should inflexibility be evident given that perceptions of risk might continue to change in the direction of less risk.

On the other hand, the TUC welcomed the Draft Directive, although favouring further efforts to extend harmonisation beyond the Community. They even suggested a further proposal that all workers involved carried a card stating that they worked in a recombinant DNA laboratory, in the event of illness arising from a laboratory accident. GMAG, as far as the TUC was concerned, was a most suitable model for the proposals in the Draft Directive.[126]

In the event, the final result of two years of discussion on the document

was that it was withdrawn in favour of a Recommendation. It should be said, however, that the UK was not the only critic. France and Denmark were noticeable in their opposition. Nevertheless, even before a Recommendation resulted, there were further meetings including a public workshop, arranged by the Economic and Social Committee. By 1981, the main provision of the Recommendation was simply the registration of recombinant DNA work.[127] In August 1980 the option of a Recommendation had been submitted to the Council of Ministers, with a perception by then of an overall diminishment of the risks. Registration was still thought to be a prudent idea, and the Commission was mandated by member states to establish a committee of experts to examine at least annually the need for harmonisation of regulations and to keep abreast of new knowledge on hazards.[128] Thus, like most legislative attempts within states, the European Community's effort was unsuccessful, although the Community's interest in genetic manipulation did not end here. It also became an active promoter of genetic manipulation research.

The European Community first considered a programme of research and development which included genetic manipulation after a symposium in 1976, given further attention by the Commission in July 1977,[129] in a document submitted to CREST.[130] From basic principles, discussion moved towards a first description of possible Community action in the field of applied molecular biology, and in December 1977 CREST requested the Commission to intensify its studies relating to Molecular and Cellular Biology.

In response to this request, the Commission asked that two studies be executed. Contracts were put out to two national experts. One study[131] examined genetic manipulation while the other[132] was concerned with the more widely based enzyme technology, elements of which have long been known in fermentation industries. These two studies and an earlier

document provided a detailed appraisal of developments in biomolecular engineering and of the importance of such progress in agricultural and industrial developments. It was felt that there was a need to support research for the promotion of major breakthroughs.

In particular, study had shown that Europe was not as a whole co-operating to match the potential of Japan (particularly in enzyme technology) and the US. The criticism was made that in Europe scientists had better contact with US scientists than with other European scientists. A statistic of note was that Japan had four thousand PhD biotechnologists in comparison with about two hundred in France.[133] However, as already stated, the promotional activity of the European Community was only in part concerned with genetic manipulation, the subject of this thesis.

The promotion exercise was part of a move within the Commission to foster a wider approach to developing a "common policy in the field of science and technology", aimed at the long-term supply of natural resources, the promotion of internationally competitive economic developments, the improvement of living and working conditions and the protection of the environment.[134] The purposes of the particular research project being considered were to contribute to the improvement in the production of organisms with new genetic properties for 'bio-industries', to develop the utilisation of enzymes, to reduce a strong deficit in trade and patents in biotechnology on the part of European states, and to protect the environment through decreasing waste products or developing new detoxification procedures. This was all proposed with a healthy regard to hazards in both genetic manipulation and the industrial use of micro-organisms.[135]

It was suggested that 26 million European Units of Account (or approximately

£16 million) be divided between nine states over five years to finance six projects. Three of these projects were of direct relevance to genetic manipulation. However, although broadly backed by industry, the proposed projects met a number of setbacks after national consultation.

In particular, the French and the Germans raised objections, the former wanting more to be allocated for education (50%) while the latter wanted the projects to be reduced in number to two.[136] Part of the problem was a reluctance to duplicate potential national research. Eventually, a compromise was worked out by CREST whereby the number of projects was reduced to four, eliminating areas with likely immediate medical or industrial application, and the budget was trimmed to 15 million EUA. Twenty percent of this budget would go to education in response to the French. However, even this was not acceptable at the Council research committee level, nor was a further suggestion of allocating only 11.8 million EUA. Both the French and the Germans were insistent in their demands. Britain would accept the CREST compromise, and all other states would in fact accept the original proposal. It seemed that a key problem was that states with strong domestic research programmes and industrial interest were reluctant to share commercially sensitive information. France was, however, keen to include a training programme as it was having trouble recruiting for its new national genetic engineering company.[137] The final outcome was one of disappointment to many.

The European Community was therefore significant in its input into the transnational and international discussion of genetic manipulation. In particular, the issues surrounding the proposed Draft Directive were very important and were related to the general question of legislative options, returned to in Chapter Eight. Close communication existed with both states and other international bodies, even if there were notable differences of opinion involved.

b) Conclusions.

A review of the activity of international organisations has been presented to complement the review of individual states. Taken together, they should give an indication of the extent of international involvement and the speed with which it developed. However, as far as information exchange and co-ordination were concerned, the international organisations deserve particular emphasis. Much like the domestic activity in a number of states, a division of labour was evident amongst the more important organisations. Some specialised in the co-ordination and dissemination of technical information, such as EMBO and the ICSU, while others focused more upon the co-ordination or making of policy, such as the ESF, the WHO and the European Community. These divisions are somewhat arbitrary, given that some of the more technical organisations displayed policy biases. It could be said that globally a three-way relationship was apparent between the US, the UK and more collectively continental Western Europe. Many states awaited outcomes of deliberation and policy choice in the UK and the US, by which time harmonisation efforts were stronger. European organisations were conscious of this and were quite influential in the activities of European states. In general, communications between the three points of this 'triangle' were very good.

SECTION D

THE INTERNATIONAL POLITICS AND OPERATIONAL CONTROL OF POTENTIALLY DANGEROUS TECHNOLOGY: AN ASSESSMENT OF RECOMBINANT DNA

Chapter Eight

CHAPTER EIGHT

THE INTERNATIONAL POLITICS AND OPERATIONAL CONTROL OF POTENTIALLY DANGEROUS TECHNOLOGY: AN ASSESSMENT OF RECOMBINANT DNA

1. Risks and Benefits: Processes of Assessment

2. The Implementation of Safeguards

3. The Transnational Perspective

4. Decision-Making

5. Conclusions: A Return to the Hypotheses

THE INTERNATIONAL POLITICS AND OPERATIONAL CONTROL OF POTENTIALLY DANGEROUS TECHNOLOGY: AN ASSESSMENT OF RECOMBINANT DNA.

> "How the message of inheritance is passed from one generation to the next was discovered in 1953, and it is the adventure story of science in the twentieth century. I suppose the moment of drama is the autumn of 1951, when a young man in his twenties, James Watson, arrives in Cambridge and teams up with a man of thirty-five, Francis Crick, to decipher the structure of deoxyribonucleic acid, DNA for short." 1

This is how Bronowski, in his companion book to his monumental television series, "The Ascent of Man", described a key leap forward in human endeavour to understand the natural world in which we live. The developments described in Chapter Three of this thesis represent a further significant leap, enabling the manipulation of DNA for human purpose.[2] In a wider political and social context, however, there was more than a 'moment of drama' to their revelation and subsequent development. James Watson was again to play a central role and in 1979 was to suggest:

> "... our national leaders should announce that they will help push DNA research as fast as our national and corporate treasuries can permit." 3

There is no doubt that the new techniques caused tremendous excitement amongst scientists in related fields, particularly once the 'moratorium' was lifted and the work could begin in earnest. However, what also became clear was that despite the earlier expressions of concern, many scientists feared unnecessary hold-ups in the subsequent exploitation of genetic manipulation. It became apparent that groups of scientists went on the defensive against what they perceived to be increasing bureaucratic involvement. Although this was a generally international phenomenon, it was particularly evident in terms of a fear of legislation being drawn up to impose regulations and control procedures. This focuses the issue

primarily in the United States, where legislation seemed for a time very likely, but also in Europe, within certain individual states,[4] where issues of legislation arose. The European Community, under actions of the Commission, was faced with the possibility of a Directive necessitating legal controls for member states. This chapter, therefore, must consider the issues involved in the legislative options, and indeed the consequences of the attempts.

A second important issue arising within the transnational response to the origins of concern also needs elaboration, namely the question of attempting to assess the actual degree of risk involved in recombinant DNA activities. Indeed, the Berg letter itself suggested the need to "evaluate the hazards", before continuing with the work. In time, after Asilomar II, attention came to centre on explicit, if somewhat controversial, attempts to design risk assessment experiments and criteria of evaluation applicable to classes of experiment. It is apparent that as moves developed to devise legislation in the United States, activity aimed at assessing risks also increased. The linkages between these two processes need to be considered. Thus in analysing the issues involved in the recombinant DNA debate, it is necessary to examine the alignments of the important actors in relation to these moves.

Risk assessment was, however, only part of a wider politicised process of 'risk-benefit assessment under uncertainty', which in the case of recombinant DNA was a transnational activity. It is argued that the two dimensions of legitimately achieving a socially acceptable balance between conjectured risks and benefits, on the one hand, and determining equally acceptable control procedures, on the other, comprises the heart of the debate surrounding recombinant DNA techniques.

1. RISKS AND BENEFITS: PROCESSES OF ASSESSMENT.

a) Risk Assessment.

In the case of recombinant DNA, risk assessment referred to both biological hazards *per se* and their potential reduction through the application of containment safeguards, at the laboratory level. Such safeguards have been described in the guidelines developed by various states, and they invariably include physical containment techniques. Those guidelines drawing on the approach of the United States, also included the recommended use of biologically enfeebled host-vector systems, argued to reduce further overall risk. Thus, assessment of the risks involved in various types of genetic manipulation experiments applied from unsafeguarded to highly contained work. In general, however, risk assessment is a problematic area.

Conventionally, risk assessment in scientific and technological activity is seen within a framework of rational estimation of the probability of undesirable consequences occurring at different stages in scenarios which represent potential paths to disaster. Irwin, Smith and Griffiths provide a useful summary of the numerous methods developed within the broad field.[5] They mention the methods of safety audits, hazard surveys, the use of hazard indices, operability studies, failure modes and effects analyses, and event and fault tree analysis. Most emphasis, however, they put on event and fault tree analysis, a process of creating logic diagrams representing sequences of events which may propagate through a system. A diagram resembling a family tree results, where 'and/or' possibilities branch off. It is then necessary to allocate the probability of each individual event occurring before the total probability of various sequences of events can be estimated. Difficulties may arise in miscalculating probability estimates or in omitting potentially logical sequences of

events, either as a single chain of events, or chains in combination. Obviously the more empirical knowledge acquired through experience in a hazardous activity, then the more detailed the events sequences and probability estimates might be.[6] These procedures are a guide to risk reduction, by assisting in the identification of potential causes of hazard and, by implication, in the application of monitoring and control procedures.

Of crucial importance in any examination of the issues surrounding recombinant DNA techniques is the understanding that the origins of concern were conjectural in nature. From the very beginning, a number of scientists perceived some potential sequences of events which might lead to undesired hazardous consequences. Two things are, however, of note: firstly, these perceived sequences were sketchy in outline, later becoming a central topic of discussion at Asilomar II and elsewhere; and secondly, there was a complete lack of an empirical basis for estimating realistic probability assessments. Moreover, the conceptions of the hazards involved were such that the conjectured scenarios suggested low likelihoods of undesirable consequences, but potential, nevertheless, disastrous outcomes. In these circumstances, risk assessment would be particularly fraught with analytical difficulties.

A central concern of many involved was the development of safeguards applicable to different types of experiment in relation to some estimate of risk. The estimates of risk were, on the whole, based on the application of concepts relating to differences between prokaryotes and eukaryotes and the perception that risks diminished in relation to the evolutionary distance of the source DNA from man. However, across the international range of guideline approaches, different degrees of emphasis were put on the risks of particular types of experiments in relation to

the current wisdom. The point is not to delve into the details of such differences of conceptualisation and assessment, but to indicate the consequences of, on the one hand, the perception of a need to make some sort of risk assessment, and, on the other, the very fact that uncertain procedures of assessment and categorisation create problems of legitimacy.[7]

The process of risk assessment took place in many forums, some not commonly acknowledged as part of that process. For example, the publication of the initial letters of concern (Singer and Söll and Berg et al.) were in their own way a reflection of first steps in estimating risks. More formal deliberations followed suit, but not always without bias. These included both domestic investigations and, more important here, they also included international, or more accurately, transnational, assessments. Of note is the general attempt to provide 'rational' assessments of the level of risk. Scientists are thoroughly familiar with a perception of rational science, deducing chains of logic derived from experimental hypotheses and inductively compiling supportive or disproving data. It would not, therefore, be surprising to find appeals to 'rationality' and 'common sense' becoming synonymous. To the scientific community, generally, the way to advance forward with controlled use of the recombinant DNA techniques was seen in relation to rational assessment of risk and with regard to levels of containment applicable to postulated levels of such risk.

An interesting interpretation of the problems of risk assessment attempts can be made in terms of the later criticisms of those scientists who condemned their own early actions. In arguing that they should not have been so bold in their statements, they have made the point that there was little or no evidence to support such statements. What is really at issue is that there was no evidence sufficient for the task of rational risk

assessment where rationality involves complete knowledge of alternatives upon which to base choice.[8] A substitute for definitive knowledge would, for the purposes of risk assessment, include probability estimates of some sophistication. In the earlier years of the recombinant DNA issue, knowledge upon which to make probability allocations was very limited. Instead, the biological proximity of man to the donor organism was used.

To complicate the problem further, the years since concern was first voiced have brought further information, not least through using recombinant DNA techniques, but not enough to suggest that all work is safe. At the very beginning, there was a perception that large-scale disaster might occur, if only at very low levels of probability indeed. Conceptualising such risk is very difficult and not easily estimated. Much of the subsequent debate after guidelines were introduced centred on the degree by which they might be lowered. Some types of experiments, however, are likely to remain in high risk categories, even if lower level containment allocations are revised. At no stage in the process of relaxing guidelines, or in the early expressions of concern, has reliance been put purely on risk assessment in an empirical sense. Theorising and conceptualisation are equally legitimate research activities and can provide a sufficient basis to make calls for caution. Conjectured risks need not have empirical or probabilistic support in order to deserve attention. The key to the whole problem is that the issue was characterised by uncertainty.

It a criticism, therefore, has been that the early calls for caution should have been based on more 'evidence', then equally valid is the proposition that containment should not be relaxed on the basis of insufficient evidence or evidence given too much weighting.[9] Early expressions of concern called for caution and active attempts to assess hazards further. For some years, the assessment process was largely conjectural in its own

right, but increasingly supported by new theories and models of genetic functions. Empirical evidence has never been in abundance. These issues can be discussed further in the context of a brief résumé of the risk assessment process as seen by those involved.

Both the RAC in the United States and GMAG in the United Kingdom were involved in what could overall be described as a transnational process of risk assessment. The charter of the RAC and the terms of reference of GMAG both explicitly required these bodies to assess risks or hazards in relation to precautions.[10] For example, between revisions of the US guidelines, the RAC sponsored risk assessment experiments and investigated potential host-vector systems, while GMAG eventually adopted a new categorisation system more closely related to the technical risk assessment procedures identified above.

In 1982, Sheldon Krimsky (both a non-scientist representative on the RAC and a lobbyist within the Coalition for Responsible Genetic Research)[11] produced what is undoubtedly a detailed and informed analysis of the varied approaches to risk assessment adopted at different institutional levels within the United States. His analysis is instructive in terms of the US policy process involved and the use of new information on the part of scientists. In particular, he examined the impact of a workshop held to investigate the potential of converting E. coli K-12 into a pathogenic organism.[12] Held in Falmouth, Massachusetts, in June 1977, it was influential in leading to the reduction in the strength of the US guidelines. However, it was also somewhat controversial. The meeting was organised under the auspices of the US National Institute of Allergy and Infectious Disease (NIAID) and the National Institues of Health (NIH). The aim was to include scientists from wider fields than those who were using recombinant DNA techniques, who would be experts qualified to discuss

infectious diseases.[13] Two early reports of this workshop both emphasised its unanimous conclusion that it was "virtually impossible to convert E. coli K-12 into a pathogen of epidemic consequence by insertion of random bits of eukaryotic DNA".[14] A report by a COGENE representative, A.M. Skalka, and a letter by S.L. Gorbach, the workshop chairman, to the Director, NIH received early and widespread attention and provided support to those wishing to relax precautions. Krimsky, in retrospect, however, has raised many questions of the accuracy of Gorbach's early letter which gave a strong impression that E. coli could not be a vehicle for hazard. By breaking the arguments down, Krimsky addressed the logic of the statements made by Gorbach and indeed the accuracy of his summary,[15] in relation to the loose definitions of concepts involved. Some points are of note: the technical interpretations of results were questioned to some degree; the argument which was produced by Gorbach related to pathogenicity comparable to existing E. coli pathogens, and therefore precluded new E. coli pathogens; it was left unresolved whether E. coli K-12 carrying genetic implants could pass its genetic information to natural indigenous organisms within the human gut, should it successfully escape containment. The point is that if such technically based questions of definition, scope of inquiry and extensions of investigation were shielded behind a veil of strong assertions of safety, then risk assessment of this nature has questionable legitimacy. Krimsky has shown that the logic explicit or implicit in the assumptions and conclusions was weak. But the whole endeavour was presented as authoritative and the 'results' were rapidly and internationally disseminated in the context of Gorbach's letter and Skalka's report for COGENE.

Following Falmouth, an important international meeting was held between 26th-28th January 1978 at Ascot, England. Sponsored by the NIH and the European Molecular Biology Organisation (EMBO), it was reported in the US

Federal Register.[16] Scientists from twenty-seven countries attended as relevant experts rather than as representatives of governments or policy-making groups. Expertise included clinical infectious disease, public health, medical and diagnostic virology, the biology of virus infection, biochemical virology and plant, insect and veterinary diseases. Only five of the participants were actively engaged in recombinant DNA work. The results of this international investigation were, like the Falmouth workshop, influential, not least in the relaxation of US guidelines in 1978. In particular, it was observed from a study of the mechanisms necessary to transfer viral DNA (inserted into E. coli) through bacterial replication that such a transfer of viral DNA would be unlikely. A worst case, of viral DNA having become established in wild type E. coli and disseminated through the bowel flora of vertebrates, was postulated. Access of viral DNA to cells of the vertebrate host was considered in terms of the mechanisms and the nature of the inserted viral sequences. Although access to the host vertebrate cells was considered possible, production of infectious virus particles by bacteria was considered impossible on the basis of bacteria not having the necessary enzyme systems found in vertebrates. From this limited ability merely to gain access to host cells, but not to have the DNA replicated in E. coli, the report concluded that the containment should be no more than that required for use with the same virus involved in non-recombinant DNA work. It suggested prudence in adopting any higher containment, for use with the virus itself, if it were greater than existing recombinant DNA guidelines requirements. The European Science Foundation endorsed the recommendations of the Ascot workshop, emphasising the report's reference to the need to ensure proper training of personnel as a safety feature. COGENE considered the workshop a successful risk assessment exercise.[17] Never criticised like the Falmouth exercise, the NIH/EMBO joint effort was laudible. However, it is of note that it was some five years after the first expressions of concern.

In the United Kingdom and the United States, guidelines were revised, but with much more controversy in the United States. In the US case, containment categories were relaxed, while in the UK a conceptually different system was developed, owing much to fault tree analytical procedures. Controversy in the United States centred on the degree of relaxation at each stage. Following Falmouth, the revision of US guidelines was to take a year, and the debates involved reflected widely differing viewpoints between practitioners and other interest groups. All this was undertaken with a backdrop of impending US legislation and with revelations of guidelines violations, both discussed below.

Detailed recommendations for revision of the US guidelines came from the RAC and were passed on to the Director, NIH. Much of the proposed revision concerned the greater faith in the restricted ability of E. coli K-12 (an EK1 vector) to become pathogenic after DNA insertions. These proposals were published for public comment in September 1977, in the Federal Register,[18] and a public meeting of the Advisory Committee to the director was convened on 15th December. Interested groups made statements and all the correspondence received since the publication of the proposals was available at the meeting. Ironically, however, the proposed revisions were not to be introduced to the planned timescale. Seven months after the meeting, a further set of proposals was published, this time including a chart comparing the original guidelines, the 1977 proposals and the latest considerations.[19] Despite all the criticisms of the first set of proposals[20] and the procedures for making revisions,[21] the 1978 proposals were even more lax, by now being subsequent to the NIH/EMBO workshop.[22] A further impetus to downward revision was an explicit comparison with guidelines from other states, noting that some experiments banned in the US were allowed in other states, or at least were subject to lesser controls. No reference was made in the Federal Register, however, to

requirements in other states which were more stringent than those of the United States. Many states were well behind both the US and the UK in establishing initial guidelines, never mind revisions.[23]

After a one day hearing on 15th September 1978, the revised guidelines were published on 29th December 1978, to come into force on 2nd January 1979. Krimsky, however, has taken the analysis of the misrepresentation of empirical work further in examining the build-up to still more revisions in 1980, in particular emphasising the role of Wallace Rowe, a member of the RAC.[24] Rowe has consistently argued for extensive relaxation of the guidelines and in 1979 led calls for the exemption of most E. coli K-12 experiments.[25] His proposals were seriously considered by a RAC working party, but were opposed by other respected scientists. Rowe had marshalled as much 'evidence', including results of his own work, as he could find that E. coli K-12 was safe. An interesting misuse of some evidence, however, was noted by Roy Curtiss. Curtiss observed that much of the evidence gathered related to biologically enfeebled laboratory strains of E. coli K-12 (EK2 systems) and not to the wild type strain of E. coli K-12, which it was also proposed to exempt. More subtly, however, Curtiss also noted that much of the data had already been presented as a justification of the 1978 relaxations and should not therefore be used to justify a further round of relaxation.[26] In addition, Curtiss noted that data were emerging suggesting that host strains survived better than was previously thought in hostile environments. The main direction of his argument was uncertainty, a view shared by other interest groups opposed to such wide exemptions.[27] Of note was the observation made that such proposed exemptions would come before risk assessment experiments being organised by the NIH itself were complete, and which were designed to investigate E. coli further. A final point, noted by many, was to relate to the vote taken by the RAC to accept the proposals, including the

exemptions. It seems that the ten to four vote occurred when a majority of RAC members were not present.[28] As a consequence, the Director, NIH did not exempt E. coli K-12 work, but accepted recommendations on containment levels.

The point of the above discourse on risk assessment in the context of US guideline revision is to question the ability to be rational when faced with uncertainty or incomplete information. Much of the emphasis in relaxation of guidelines related to lack of evidence 'to the contrary'. That is, it was argued by many that work with recombinant DNA techniques over the years had not revealed any real hazards. However, specific attempts to identify hazards were a very small proportion of the total work, thus suggesting that inductive logic was important in altering perceptions of risk. Because something had not happened, the view strengthened that risks using E. coli were not likely to manifest themselves, a questionable process of logic. Some also began to argue that because recombinant activity could occur in nature,[29] with exchanges of genetic information between species involved,[30] then some earlier fears were unjustified. Even if genetic information can thus be transferred, it is not an argument to say that because a process occurs in nature it therefore does not require regulation when duplicated by man. Nature over the centuries has shown that it can be dangerous in terms of viruses and pathogens. Until the mechanisms leading to new viruses, for example, are fully understood, we cannot assume that genetic transfer is harmless,[31] and such work by man alters the rate of transference. Nevertheless, use of recombinant DNA techniques did reveal that eukaryotes were more complex in terms of their mechanisms of expression than prokaryotes, greatly reducing the likelihood, at least, of eukaryotic DNA accidentally becoming expressed in a prokaryotic host.[32]

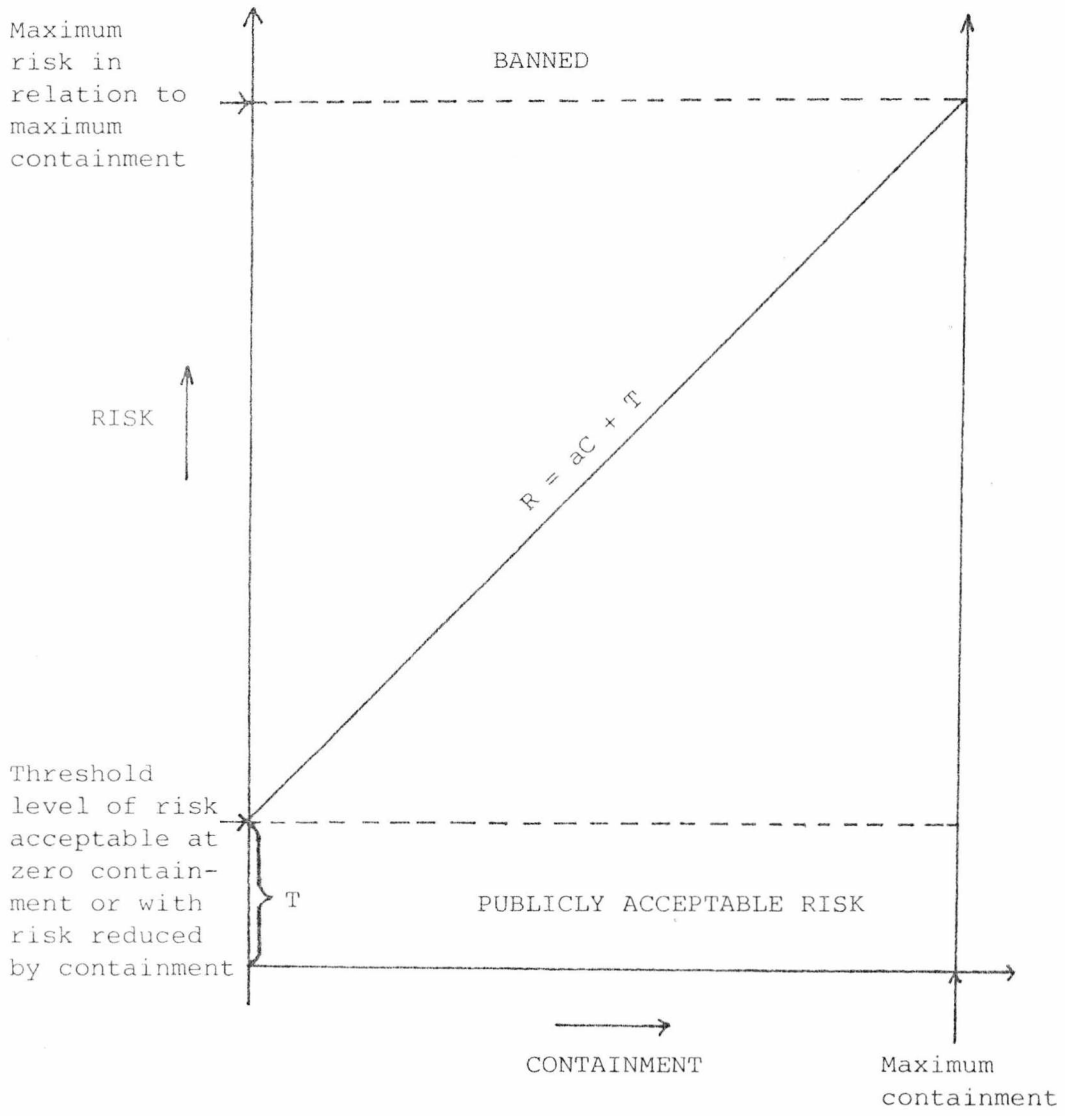
Much of the above provided an input into the deliberations in other states. Indeed, overall, the recombinant DNA guidelines of different countries have tended to be relaxed over time.[33] This process of guideline reduction has been a transnational phenomenon, with the risk assessments discussed here having international impact. Falmouth results were disseminated bi-laterally through scientists' contacts and multilaterally through COGENE and other organisations. The NIH/EMBO workshop held at Ascot was itself an international consideration of risk.

In the UK, GMAG for its part published a proposed radical change in its assessment procedures in November 1978. It adopted, however, the US approach to announcement in that the proposals were first published in Nature for the purposes of stimulating comment and were followed by a public discussion.[34] GMAG's new assessment method was based on a categorisation first outlined by Sydney Brenner, and was firmly rooted in the rational fault tree analysis method, as briefly outlined at the start of this section. Initially introduced for a trial run in parallel with the existing procedures, the Brenner proposal broke with the foundations of both the NIH and earlier Williams guidelines. The existing approaches were based on a broad, if not rudimentary, assessment of the "evolutionary relatedness of the cloned DNA to human DNA".[35] Brenner's suggestion was that the possible pathways by which a manipulated organism could penetrate a human host, gain access to susceptible tissues and express products should be estimated. In order to begin assessment of experiments proposed, additional information was sought from the experimenter. Proposals would have to include probability estimates of each of the following factors: access factor, or the probability of escaped manipulated organisms entering the body; expression factor, or the likelihood of expression of the foreign gene into protein; damage factor, or the probability of physiological damage in the recipient's body.[36] GMAG recognised the difficulty

of giving precise figures, but it argued that it would nevertheless like the local safety committee to provide "approximate orders of magnitude". A GMAG technical panel would make further assessment before GMAG allocated containment requirements. Because many researchers might not be interested in trying to achieve expression (merely wanting to obtain quantities of genetic material for analysis) then they would find the containment downgraded from the earlier guidelines,[37] but industry, which invariably would want to try for expression, would be penalised relative to those other experimenters. Nature produced an interesting critique of the new procedures, recognising the obvious difficulties of making probability estimates, but noting that although tests of individuals' allocations of risk differed markedly, their rankings were remarkably consistent.[38] It is the assignment of such probability estimates that is the main difficulty, although other writers have explicitly discussed similar fault tree type analyses.

Francis Rolleston, responsible for regulating Canadian recombinant DNA work in 1979, argued in a science journal that risks and containment must be considered together in a more logically consistent way than to date in national guidelines.[39] Internal consistency, he argued, would relate problems associated with offering alternative containment requirements for a particular experiment (for example EK1 plus P3 or EK2 plus P2 in the US context) and the need for an overall reduction of any experiment with appropriate containment to below a threshold of risk. External consistency was needed to make recombinant DNA risks comparable to those accepted in other areas of human activity. Rolleston forcefully argued that such an exercise of assessment must involve both scientists and technical experts, on the one hand, and the public, on the other. Scientists would assess risk and containment requirements on a basis of containment reducing the risks to below a threshold. The public would have to be involved in

establishing what the acceptable threshold was, at both the minimum level and in relation to maximum containment where certain experiments may need to be banned because containment is not adequate to bring the risk below the threshold. In diagrammatic form the argument is perhaps clearer. Diagram 1 was derived from Rolleston's analysis, where he made a model based on the equation for a straight line.



Key: R = Risk
C = Containment
T = Publicly decided threshold level of risk
a = One to one relationship of increased risk requiring increased containment (a = 1)

DIAGRAM 1

Rolleston's analysis makes a powerful an logical argument for a mix of rationality and public participation. He acknowledged the limits of empirical allocation of risk but defended the procedures of relative rankings of risk as applied by the Brenner approach.[40] Others have either tried to show that overall risks for individual experiments are very low, or have applied fault tree assessments to designing containment facilities for laboratory use.[41] The point, however, is again stressed that much of this assessment benefitted from hindsight and the actual experience of using the techniques. At the period of initial concern, data were limited and the theoretical conjecture was prior to the later models of gene expression derived from use of the techniques. Nor at that time had some risk assessment experiments, previously called for, been concluded.[42] Nevertheless, as Krimsky has suggested, subsequent data have been questioned in terms of interpretation and presentation. Risk assessment, as a rational approach, requires considerable knowledge to undertake. To apply it then for the purposes of allocating safeguards as a replacement to conjectural containment levels requires much empirical experience. Control systems had been established very rapidly in the US and the UK, and elsewhere, in response to conjectured risks and quite legitimately in view of the authority of those who expressed initial concern.

Three problems, however, have arisen within the recombinant DNA issue area, derived from the above. Firstly, there were many non-scientific groups which took up the role of monitoring the activities of the scientists from the point of view of public fears in a case displaying characteristics of uncertainty. Secondly, some states were much slower in applying guidelines, such that when first round revisions occurred in the United States, their guidelines seemed to be too high. It is argued here that a 'lowest common denominator' process of revision then occurred transnationally.[43] Thirdly, however, it is possible to suggest that the international scien-

tific community was displaying elements of both explicit and tacit bargaining. Much promotion of the results of the Falmouth exercise in particular was evident. Scientists encouraged the use of research data to reduce guideline restrictions and, as seen below, to counteract calls for stringent legislation. Tacit bargaining reveals itself in the common assumptions and interrelated activity which, without organisation, occurred transnationally. On the whole, scientists wanted their techniques to appear safe, and therefore welcomed supporting evidence with little questioning. They also responded to reductions in one state by calling for reductions in their own states, aware that this was part of a future downward movement, as they perceived it.

Scientists in the traditions of their inquiry wanted evidence to be the basis of rational risk assessment. But given some evidence, many began to talk about the 'burden of proof' now falling upon those who would continue regulation. It could be argued that if Popperian falsification was the norm, these problems would be lessened.

b) Risk-Benefit Assessment.

Analysis so far has shown that with regard to recombinant DNA techniques assessing risks has been full of difficulties, both conceptual and empirical. This was particularly the case during the period when concern emerged. However, it is argued that many of the scientists and the organisations representing them tended to see the requirement of risk assessment as an exercise involving rational calculations and assessment of albeit often limited information. Conjecture, with some justification, was not seen as an adequate basis to maintain strict control. Yet the picture is not complete without considering the issues concerning the relationship between risks and benefits.

By the 1980's benefits had already accrued in a wide variety of areas of application, if only at the level of greatly increasing knowledge and understanding. Many reports have appeared in the pages of respected journals discussing the imminent arrival of new commercial products, or processes of production for existing products. Industry very rapidly adopted genetic manipulation and in many states (although notably the United States) forged strong links with research laboratories in universities. Overall, genetic manipulation has been subsumed, at the industrial level, under the broader concept of 'biotechnology'.[44] Such has been the recognition of the importance of the techniques that the European Community has considered sponsoring research and the United Nations Industrial Development Organisation (UNIDO) in 1981 suggested the idea of an international centre to spread the techniques to the third world.[45] Finally, in 1983, one thousand delegates attended the 'Biotech '83: Europe' conference, the third of its kind.[46]

As with risks, it is important to note that the scale of the potential benefits involved was also highly conjectural in the early years. It is argued here that an important element of the whole recombinant DNA issue area was that a process of assessing risks against benefits was involved. However, such risk-benefit assessment was never implemented in any rational sense, as often considered by economists in cost-benefit exercises, where economic and social costs are set against benefits in a rigorous analytical fashion, although not without difficulties.[47] In the case of recombinant DNA, as with many issues of possibly hazardous activity, no centralised assessments of risks in conjunction with benefits were indeed undertaken, although the Ashby Report in the UK made some tentative conjectures, as did the NIH Environmental Impact Statement. The few attempts made were little more than lists of conjectured benefits and risks, with conclusions to the effect that the benefits were likely to be very great, therefore

the work should continue.[48] This observation, however, is meant less as a point of criticism than an observation that the task would be somewhat difficult if attempted, given the degree of conjecture involved.

In effect, the whole transnational debate was a social and political process of assessment. Indeed, it was a process far removed from the niceties of rational assessment, as we have defined that term. At the level of assessing risks against benefits, it was a selection of interest groups, press coverage, and public responses, supported by some 'allied' scientists providing the necessary technical comprehension, which forced the issue into the open. Involved scientists from early on invariably saw a future view of increasing benefit, set against a future view of declining risk, a powerful argument for the work to continue, and acceptance of short-term safeguard constraints.

More important perhaps than the details of perceptions of hazards and benefits was the more general observation of the uncertainty which predominated when the decision structures were built and operationalised. Participation and the identification of roles became as key an issue as the content of the decisions. Much of the politics involved represented a search for legitimate structures and decision-systems. Superimposed on all this was the nature of inter-system interaction. A key factor of note was the response in one system if another changed its assessments. It became quite apparent that scientists and industry closely monitored the international process of guideline relaxation and the moves towards legislation as they affected individual states. Indeed, threats of moving abroad to use lower guideline levels were at times used as political ammunition. A Swedish firm for example in 1979 threatened to go abroad if permission to use recombinant DNA techniques was not granted.[49] Earlier in 1978, a US scientist, Stanley Falkow, returning from an international

symposium in Milan, wrote to the Director, NIH in response to a request from the Director to consult colleagues on risk assessment evidence. However, he also returned his comments on relative guidelines:

> "Aside from these positive aspects of my travel, I confess that, in another vein I found the meetings most distressing. It is painfully obvious that because of the very restrictive nature of the NIH guidelines, as well as the bureaucratic wall that the guidelines have spawned, American biologists can no longer expect to keep pace with either Western European or East European science." 50

Falkow was commenting when the NIH guidelines were more stringent than, for example, the UK guidelines. Sir John Kendrew made the following point after the US revisions of 1978, and in the context of the Wye College conference of 1979:

> "When we had the conference at Wye in Kent with the international group of scientists involved last April, many of the Americans came over having got their revised guidelines and really trying almost to steam roller us into acceptance that all the regulations should be swept away." 51

Some, however, welcomed the NIH revisions as an opportunity to press for UK guideline reductions. An influential report on biotechnology has stated:

> "We recommend that GMAG considers urgently the possible prejudicial consequences to British industry if controls on genetic manipulation in the United Kingdom are more severe and restrictive than in other countries." 52

The same report noted that although GMAG's flexible approach made UK controls less restrictive for some work than the NIH guidelines, overall they were more restrictive. This illustrates an important point. Pressures for relaxation of guidelines did not only operate on the basis of comparing guidelines packages, but often identified particular experiments

or types of experiments treated more severely in the home guidelines. The lowest common denominator effect was to create pressure at revision times for selecting the level lowest in a survey of guidelines in a collection of states. In addition to this, industry and scientists were well aware of the competitive pressures involved in promoting recombinant DNA research. European states in particular were often host to comparisons between the rates of development in biotechnology internationally. Tied to observations of the relative position of domestic research were requests for national support in promoting the technologies involved. In turn, these requests for support influenced calls for guideline relaxation.

International organisations were well familiar with these competitive pressures and responded in the important fashion of advocating international harmonisation. The ESF, EMBO and COGENE were all to a greater or lesser extent interested in the degree of harmonisation needed. EMBO proposed either the use of the UK or US guidelines as a package; while the ESF accepted this, it explicitly recommended the UK approach for Europe. A COGENE working group compared all guidelines and the European Community attempted to bring harmonisation through a Directive.[53] Harmonisation might have ameliorated the competitive downward relaxation of guidelines, and thus the complaints of domestic controls restricting international competitiveness.

There is some evidence that a perception was to emerge later that international harmonisation might in fact be too inflexible and, to some, undesirable. Certainly it has been shown that this charge was addressed against the proposed Community Directive. More subtle, however, was a general reaction in the May 1980 meeting of COGENE to a question from a representative from the World Health Organisation. V.R. Oviatt passed on a suggestion that the WHO might devise international guidelines in asking

if it might be more appropriately a COGENE function. The general feeling of the meeting was that such activity would only serve "to preserve guidelines".[54] In discussing controls, the question of harmonisation will again be addressed.

Thus, as with the attempts at risk assessment per se, risk-benefit assessment as a transnational social and political exercise was characterised by uncertainty, particularly in the early years of concern. Over time, the risks have been perceived to decline, while the social and commercial benefits have begun to appear, albeit more slowly than initial expectations led to believe. Benefits must not be seen in too narrow a sense. It is necessary to take the wider view of the importance of science leading to new knowledge, the utility of which need not be immediately apparent. Academics have a long tradition of seeing knowledge in its own right as important. However, set against this, it must also be realised that a number of groups within the politicised debate have expressed fears of dangerous knowledge. Could recombinant DNA techniques not be abused? Thought has already been given to the question of deliberate misuse in the context of future biological weapons. Another expressed fear has been concerned with long-term use in influencing human development. Roy Curtiss, a key figure in the early expression of fears and also a key figure in establishing safe hosts based on E. coli for use in research, has noted that the issues of knowledge may involve choices outside the scientific community:

> "I have spent two and a half years of my scientific life in taking the cautious approach to provide safer systems for cloning and to establish to my complete satisfaction, at least, that no harm will come from this research unless it is a conscious decision of society to use the knowledge gained from recombinant DNA research for purposes over which the scientific community has no control." 55

More abstract considerations of long-term social risks and benefits, have been evident from at least as early as the Davos symposium held prior to Asilomar II in October 1974.[56] Further serious consideration in an academic context occurred at a conference on the "ethical and scientific issues posed by human uses of molecular genetics",[57] held in May 1975. Possibilities of misuse and possibilities of human gene therapy for correction of certain genetic deficiency diseases were considered.[58] Largely beyond the focus of this thesis, these issues nevertheless are relevant to wider social and political assessments of scientific knowledge, of which genetic manipulation has provided a further case study.[59] Given that there are political issues involved in risk-benefit assessment overall, the purpose of this thesis is to elucidate the transnational characteristics of decision-making, participation, and the international difficulties in operationalising controls. The above analysis gives an indication of issues which were both evident within the historical development and discussion of recombinant DNA techniques and the question surrounding the limits of rational decision-making and assessment as theoretically postulated here. Risk assessment and risk-benefit assessment have both occurred; the former was awkwardly attempted in a rational method, while the latter could not be anything other than a wider social and political activity with strong international inputs. It is argued here that the scientific community, often with institutional support, attempted to enhance the importance of the expert and his role in rational assessment.

2. THE IMPLEMENTATION OF SAFEGUARDS.

a) Guidelines.

Internationally, the use of guidelines has been widespread amongst states within which recombinant DNA techniques have been used or are likely to be used. International organisations encouraged the dissemination of

information concerning guideline considerations in different states. However, guidelines and their means of implementation need to be seen as a 'package'. This is especially the case when considering the adoption of pre-existing guidelines as developed in other states. Of particular importance were the approaches of both the United States and the United Kingdom, not least because of their influence in other states. For the US model, the guidelines were set in great detail centrally through a fully constituted committee (RAC) and approved by the Director of the main research funding body (the NIH). Local safety committees (IBCs) would then monitor the implementation of the centrally established guidelines covering types of experiment. In the UK, guidelines were again centrally established, but in much looser form, mainly detailing containment categories. A central committee (GMAG) administered and revised the guidelines, but with an explicit function of allocating all experiments being proposed, in the whole state, to containment categories on the merits of each case, and in relation to the Williams Report recommendations. Local safety committees again monitored adherence and containment facilities. The key difference is the means of allocating containment, either for each case on its merit by a central committee, or the application locally of very detailed, but less flexible, guidelines for types of experiment.

In reviewing the activity in other states, the impact of these two models was illustrated. States either adopted one or other of the guidelines as packages or developed their own, sometimes as a compromise. Yet in most instances the agencies responsible for funding or directing research were involved in establishing a central committee along RAC or GMAG lines. Some GMAG style committees (in terms of composition) were used to administer NIH style guidelines.[60] The problem they were facing was, however, defined in a similar way in each state. If the work was to continue and risks were

to be minimised then there needed to be some means of relating individual experiments to containment, either in a physical context or in combination with biological containment. The United Kingdom had downplayed the latter, preferring to use the much more familiar physical methods. Much of the avowed safety of the US approach derived from assumptions of the limited survival ability of E. coli K-12. However, the greater flexibility of GMAG established a Safe Vectors Subcommittee and produced a list of approved disabled host-vector systems,[61] and use of these in experiments would be a factor in allocating physical containment.

A key difficulty concerned the range of researchers covered. In the United States, industry responded to the guidelines only on a voluntary basis. Under regulations based upon the Health and Safety at Work Act, however, industry in the United Kingdom was required, like other groups undertaking genetic manipulation, to submit experiment protocols to GMAG for approval. Much of the basis for proposed legislation in the United States and elsewhere was to extend guideline coverage to all groups likely to want to undertake work.

In the discussion following, it will be necessary to consider further aspects of the implementation of safeguard procedures derived from guideline deliberations. At this stage, it is worth re-emphasising the point that apart from the perceived limited duration of the moratorium there was never any real question, internationally, of the work not continuing. To a great extent, the lead taken by the United States and the United Kingdom was sufficient reason, on the basis of their apparently detailed investigations, for general acceptance of the principle of continuing the work. Safeguards were seen as part of a way to progress with research. There was little consideration of any other alternatives in either of these states, and this in turn was the norm elsewhere. Underlying the institu-

tional responses was the scientists' opinion expressed at Asilomar II that not only should genetic manipulation continue, but that it should be assisted forward with appropriate safeguards as soon as possible. Guidelines were the method devised, and thus subsequent debate centred both on their stringency and on their conformity by all undertaking genetic manipulation.

b). Legislation.

Earlier in this chapter it was suggested that threatened legislation was part of the backdrop to the deliberations on risk and risk-benefit assessment. Although not the only state to consider the possibility of legislating to extend guideline coverage over all using recombinant DNA techniques with some degree of enforcement, it was a particularly intense exercise in the United States. However, scientists and industry in all states concerned watched the events in Washington closely. What happened in the United States could happen elsewhere, although it should also be remembered that, in contrast, some states such as the United Kingdom, Sweden and Switzerland had existing statutes which could assist guideline implementation. Nevertheless, complaints from industry of the need to comply fully were evident in the United Kingdom and Sweden. Not least was the fear of prior disclosure of sensitive information which might affect patent applications or assist competitors.[62]

Much of the literature commenting on genetic manipulation emphasises the experiences in the United States and delves deeply into the issue of legislation. From an international perspective, the United States case should not be overemphasised, other than in the context of it altering perceptions seen elsewhere. Indeed, in the United States itself, the principle of legislation need not have been a problem. It has, on at least one occasion, been strongly argued that the proposals for legislation

in the United States were not to 'control' scientists and industry in the content of their activity, something the scientists feared. Burke Zimmerman, of the US Committee on Interstate and Foreign Commerce, has argued that legislation was not to be an attack on "freedom of inquiry". Legislation was not the response to the perceived hazards - that was in fact the establishment of the NIH guidelines - but was the response to the exemption of some researchers (those not NIH funded) from sanctions.[63] This may not have been the intention, but it certainly could have been a result had some of the legislative proposals ever been passed, and Zimmerman does acknowledge that some drafts went beyond caution and a legal extension of the NIH guidelines.

The discussion of the Federal Interagency Committee deliberations of 1976/77 introduced the institutional considerations on the need to extend coverage of the guidelines. Senator Kennedy, who was eventually to introduce the government bill, had earlier shown sufficient interest to write, with J.K. Javits, to the US President,[64] requesting executive action. The government bill, simultaneously introduced in both Houses by Kennedy and Representative Paul Rogers, was the result of the Interagency Committee, which included representatives of the President's office.

However, the problem in the United States was that by this time (April 1977) a number of other bills were also being introduced. Whereas the Kennedy-Rogers bill was initially a sober attempt to extend the guidelines to all sectors of the research community and to the uses of the products of genetic manipulation, some of the other bills greatly worried the researchers. Such was the concern that many scientists offered support or at least acceptance of the proposals in the government bill,[65]

In addition, however, to more stringent alternative bills, the Rogers bill

suffered amendments taking the penalty for violations from $5,000 a day to $50,000 a day.[66] Other bills introduced a particularly controversial suggestion, that local government could go beyond Federal legislation and, if it wished, impose harsher restrictions. Local and very vociferous debates, often given extensive coverage in the United States and elsewhere, had already given the scientists cause for concern.[67] Consequently, scientists turned from offering limited support for legal extensions of NIH guideline coverage to become active lobbyists against restrictive penalties and local regulations. After much lobbying and with the withdrawal of Senator Kennedy's support for the original government bill, legislation was left to decline slowly in likelihood and recede completely in 1979. It also left industry with only voluntary compliance.

The success of the organised lobbying by the scientists and groups like the American Society for Microbiology (ASM) and the Harvard based 'Friends of DNA',[68] was intrinsically linked with the emergence of risk assessment activity purporting to show a decline in estimated risk. Gorbach's letter written immediately following the Falmouth workshop was very influential, despite some attempts by a number of participants at the workshop to show that Gorbach both overemphasised the degree of consensus and extended it to some areas where there was insufficient evidence for a consensus to emerge. In addition, work in the laboratory of Roy Curtiss, an early advocate of caution, led him to reach a change of heart and to publish both his results and the process of his conversion.[69] These views greatly impressed themselves on the legislative process, with suitable lobbying in support.

Much of the problem with the process of US legislative activity centred on the range of differences in the dozen or so proposed bills. Kennedy's bill became associated with establishing a nuclear energy style commission

to oversee all work, while Rogers developed his bill to place regulatory authority under the Department of Health, Education and Welfare (HEW). The Rogers bill was favoured by scientists until an amendment made local extensions of control more likely. Other bills proposed, for example, only a few authorised research institutions, investigative commissions of inquiry and higher fines. With the environmentalist lobby pushing for local controls, and thus further opportunities for public participation, the whole issue of US legislation was very controversial. With the success, however, of a now politicised and more adept scientific community, one final approach to legislation emerged. Zimmerman tried to create a bill which the main institutions would support. It extended the coverage of the NIH guidelines and placed regulation under the HEW and was designed to be a two year interim piece of legislation. Harley Staggers introduced it but it died of lack of interest. The ASM and the Director, NIH among others supported it to a degree, but the environmentalists opposed it, hoping for something stronger in the next session. Norton Zinder has summarised his view of the attitudes of the scientists in saying:

> "I believe the scientific community would have accepted the simple codification of the NIH guidelines into the law of the land. These bills were far from that. They set up vast bureaucracies, cumbersome licensing, harsh penalties and tedious reporting procedures." 70

In examining the legislative proposals, US industry, despite earlier reticence about guidelines, fully endorsed the idea of Federal legislation. The principle of extending cover of the NIH guidelines to all users of recombinant DNA techniques was quite compatible with their promises to comply with them on a voluntary basis anyway.[71] Most of the debate surrounding US legislation was before industry became involved beyond the laboratory level, where industry was in any case well used to safe practice. It made sense to comply voluntarily in that any future realised

hazard could be legally defended on the basis of adherence. However, the vociferous lobbying in the United States over the nature of legislation was on the part of the scientific community in general, rather than political pressure from industry which would have exposed it to further questioning of its activity and motives from environmentalists.

It is argued here that in a climate of uncertainty, and misperception at times of what individual bills proposed, an unnecessarily complex process of political conflicts led to a lack of action. However, 'no action' was by 1979 considered a significant victory by the scientist activists opposed to harsh legislation. Those pressing for strong legislation gained early momentum from spectacular press coverage promoting unfounded levels of fear. Challenged by the language of scientific theories and empirical evidence supported by equally strong lobbying, they eventually lost out. Ironically, the issue of regulation resurfaced in the 1980s when commercial uses and experiments became more widespread and proposals to release genetically altered organisms into the environment were formulated and approved.[72]

The degree of borrowing of US and UK guidelines has been examined, emphasising the package approach. In addition, however, consideration was given by some states to the possible use of existing legislation (as in the UK) or the development of indigenous legislation as in the Federal Republic of Germany. It is of importance that the political prominence of US attempts at legislation were well reported in the international science press and through the various international organisations. In Europe, however, the issue of legislation was brought fully to the international level through the proposed European Community Directive.

Much opposition from groups within the member states eventually led to the

rejection of the actual Directive proposed, although the principle of harmonisation was quite acceptable to many. Indeed the challenge to the Directive were much the same as the general challenges to legislation. The Community proposal would have required some legislation in all member states, including the UK, but with little built-in flexibility for future revision of the procedures involved. As in the domestic debates, the problem was raised that too stringent an approach might lead to competitors outside the European Community operating under much more relaxed restrictions. This perception, as seen elsewhere, assumed future guideline relaxation as the dominant trend.

It seems that one of the main difficulties with all approaches to legislation from the local city level through the national level to the international regional level, as attempted, was the inability to present an appearance of sufficient flexibility. Whatever one thought of the risks involved, it was apparent that if allowed to continue the work would progress rapidly. Thus, attempts to mould a more slowly moving bureaucratic response, while keeping up to date, and in a generally controversial area, were full of difficulties. A number of points are of note in this context:

i) The inflexibility of the bureaucratic process supports the argument that the initial actions of the concerned scientists were creditable and rapid in response, particularly in that they took their concern to the international level from an informal stance.

ii) Such was the novelty of the recombinant DNA case that existing statutes in most states were inadequate. Technological hazards are difficult to generalise, but perhaps there is greater need to make such attempts to limit future problems.

iii) At the international level, competitive advantage may accrue to states willing to accept higher levels of perceived risk. This makes

any international harmonisation difficult.

iv) Even if regional harmonisation is achieved in a legalised fashion, there are still likely to be voices of discontent if guidelines elsewhere are either lower or are more flexible in making revisions.

v) The more international the coverage, the greater will be the difficulties in achieving harmonisation in the first instance and legal standardisation in the second.

c) Monitoring and Punishment.

Had legislation been more widely adopted internationally, then provisions for monitoring and enforcement would have become more stringent. In particular, the punishment for infringement through carelessness or wilfulness would have taken on a more explicit use of the concept of deterrence. However, in the context of a general failure of legislative proposals, it is necessary to provide some analysis of the actual nature of ensuring compliance among researchers to the appropriate guidelines.

An assumption made from the start in most cases of establishing safeguards was that scientists involved would not deliberately violate recommended containment on specific experiments. Many saw the recommendations literally as 'guidelines' of most appropriate containment, particularly when initial documents based on Asilomar II recommendations were applied. Caution in the early days characterised the scientists' approach to the issues, making the need for agreed precautions dominate the agendas of discussion rather than means of enforcement. Critical in understanding this perspective is the central importance in science of peer review. Openness in publishing results and sharing the products of research, for example genetically manipulated organisms, would make secret violations of limited utility. Knowledge of the facilities in different laboratories could quite easily be related to requirements for different types of

experiment. Indeed, the greater the potential violation, the more likely this would be observed when results were shared. It was indeed this principle which in retrospect confirmed adherence to the moratorium.

As long as there was a consensus on the nature of the risks and the need for guidelines both for safety and to allay public fears, then perhaps the above approach could arguably suffice. Given disagreement between members of the relevant scientific community, then the strains on such monitoring might show. A number of violations did indeed occur. In September 1977, Nicholas Wade reported an early breach of the NIH guidelines by researchers at the University of California, San Francisco. The research group broke the guidelines by using a vector before it had been certified by the Director, NIH. They repeated the experiment when they "realised their mistake" using a certified vector. Wade noted that the team completed the whole experiment (the production or expression of the rat gene for insulin) only three weeks after the new vector they used was certified. Some confusion may have emerged as a result of a failure to realise the differences between the RAC's recommendation for approval of the vector and the Director, NIH's certification. The former had occurred by the time of the experiment. Of importance in this whole episode was less the risk of hazard than the competitive advantage over other researchers strictly abiding by the rules.[73]

In early 1980, Samuel Kennedy carried out a genetic manipulation experiment using Semliki Forest virus in contravention of NIH rules, in his laboratory at the University of California, San Diego. As with the case above, the guidelines were later changed to allow the experiment in the conditions of containment which Kennedy actually used. Kennedy claimed that he thought he was using a different virus, Sindbis virus, both viruses having been sent to him in the same package in 1977. The issue came to

light when four graduate students in his laboratory suspected the real virus and approached Kennedy. Kennedy in fact denied their charge. Subsequent to their approach, Kennedy gave a seminar presenting data which the students interpreted as confirmation of their suspicions. Two days later the students informed the chairman of the biology department and they then 'resigned'. An independent review was ordered and the Semliki virus was identified.[74]

The NIH ordered the local biosafety committee to investigate, the report of which argued that Kennedy either deliberately used the virus or lapsed in memory or record keeping. As a consequence, an NIH review committee continued investigation, but decided that no further action could be taken against Kennedy, who by then had resigned his post and was no longer working with NIH funding.[75]

However, the most serious violation of guidelines to date was international in scope and involved Martin Cline of the University of California, Los Angeles. Of importance was his use of recombinant DNA techniques to alter bone marrow removed from two human patients which, after alteration, was replaced. He aimed to treat a gene deficient disease known as thalassaemia which interferes with the produciton of haemoglobin, causing anaemia. All experiments involving human DNA were banned. Under the NIH rules he could not have obtained approval,[76] but, to compound the problem, Cline, who was NIH funded, undertook the work abroad. One twenty-one year old girl was treated in Israel and another girl of sixteen was treated four days later in Italy. It has become clear that at least in the Israeli case, the hospital authorities were misled, believing that Cline intended to use unaltered bone marrow cells. Indeed, the Israeli authorities in the hospital took great care to make sure that Cline had no intentions of using genetic manipulation, and were consequently upset. In both cases

the girls were neither significantly improved nor harmed by the work. The point was that Cline saw the work as the next stage in progress from research with animals and took the decision to experiment abroad.[77]

Cline, chief of the division of haematology-oncology, resigned his position like Kennedy, but remained as professor of medical oncology. The NIH response to the violations after an investigation was to require all future recombinant DNA work by Cline to need special permission, and that review committees assessing his future proposals be furnished with details of his violations.

These three cases have indicated that violations can and have occurred, in one instance internationally. Although the penalties brought against each scientist were not punitively harsh, they were all presented with wide publicity of their actions and subsequently open to opinions of their peers. Indeed in Cline's case the peer assessment was formalised by an NIH recommendation, accepted by Cline, that the three institutes, at that time funding Cline to a total of $600,000, might decide whether any of his current research money might be withdrawn.

With strong competition in science for both recognition and finance, peer censure is a strong deterrent. Had the violations been more serious, or in Cline's case some years earlier, then the response might have been greater. Nevertheless, there is some indication in the NIH leniency that it was reluctant to adopt a punitive role. Legislation in the US and other states might have added the possibility of fines.

Most states relied on both peer review pressures and the threat of cutting future funding or withdrawing licences as the means to ensure compliance. It could be argued, however, that as scientists perceived risks to decline,

then they would perhaps be more likely to violate guidelines if they saw them as too stringent. Curtiss said as much with regard to impending US legislation if it were to prove too restrictive.[78] In the UK, however, the Health and Safety at Work Act could provide legal powers in the event of violation. However, as the Birmingham smallpox outbreak showed, getting a court judgement might be difficult. British industry, it is of note, was equally liable to sanction, unlike that of most other states.

Monitoring of recombinant DNA work was usually the responsibility of a local safety committee (reliant on peer review and administrative direction) and a central mechanism of some sort which could control sanctions, where they were applicable. In conclusion, it could be said that as far as scientists in the public sector were concerned, compliance was under sufficient control, whereas for industry the sanction would more likely be the firm's reputation. However, for any violations in the confines of a laboratory in industry, there was no guarantee that the results of internal inquiries would ever emerge. It is, however, likely that inquiries would have occurred to avoid more seriously damaging recurrences. As most states had no explicit controls over recombinant DNA work in industrial laboratories, the final safeguards were probably the use of existing statutes against pollution, the threat of well-publicised law suits for compensation, and so on. Nevertheless, it has been a weakness at the international level that industry has avoided the restraints faced by other researchers, except on a voluntary basis.

d) A Note on Deliberate Misuse.

In this thesis, the aim has been to identify some of the transnational issues associated with the operationalisation of control over the use of recombinant DNA techniques when they were conjectured to involve hazard. The deliberate misuse of the techniques could be construed as a potential

hazard, yet nowhere was the issue seriously considered by those involved in developing procedures to ensure safety levels in the work. The early concern shown by Pugwash has been noted and reference has at times been made to the issue in passing. At this stage some update on the current situation is of relevance.

It was reported that in mid-1982 a group of genetic engineers began campaigning against the use of recombinant DNA techniques in biological warfare weapons. One cause of this was that the United States military establishment advertised in journals for an experimenter to clone a gene related to the production of a chemical neural transmitter which nerve gases attack. A second cause for concern was that after, as it was believed, a number of scientists refused the work, it was accepted by a team under John Baxter of the University of California, who also received funds from the Howard Hughes Research Foundation. The point here was that the US guidelines only compulsorily apply to NIH sponsored work.[79] Richard Goldstein, a genetics expert, and Richard Novick, an official with the Public Health Research Institute of New York City, mailed a proposal to colleagues and the RAC including this comment:

> "The use of molecular cloning for the deliberate construction of biological weapons is the most serious biohazard imaginable for this technology and ... it constitutes an egregious misuse of scientific knowledge." 80

In February 1984, the RAC passed a proposal to allow two microbiologists in the medical corps of the US Department of Defense to clone a toxin found in an E. coli strain, with proporties similar to a bacillus responsible for a type of dysentery. Separate from the chemical and biological research units in the US defence authorities, this group nevertheless brought attention again to the issue of biological weapons derived from recombinant DNA.[81]

Over the last few years much press coverage has directed attention to renewed interest in biological weapons research, ostensibly for 'defence' purposes. The Superpowers have both made accusations and counter accusations regarding research with biological weapons and there is no doubt that the recombinant DNA techniques would be useful in this.[82]

Future concern within the field of International Relations and other social sciences might specifically examine the military and potential terrorist activities to which the recombinant DNA techniques could be put. Weapons need not be designed to kill, but with modifications to organisms causing milder afflictions it could be possible to develop a whole range capable of debilitating an enemy. Alternatively, E. coli could be used as a host-vector to manufacture with much greater ease many known toxins currently difficult to obtain in quantity.

3. THE TRANSNATIONAL PERSPECTIVE.

Many of the issues analysed in this chapter have involved questions considered to a greater or lesser degree by actors within the overall issue area. An attempt has been made in this thesis to emphasise the neglected international elements. This section, however, explicitly outlines the actual transnational framework appropriate to the recombinant DNA issue area, essentially a mapping exercise, and will make some comment on communications content.

a) Communications Systems.

In the chapters examining the institutional responses of the United States and the United Kingdom, the main patterns of interaction between the component units were outlined.[83] It has been argued consistently that the US and UK examples can be seen as systems in their own right, as they

developed and operationalised decision processes, for handling the experimental work, relatively independently. From these approaches, models of safeguard packages can be identified which other states wholly or partially may have drawn upon. From this it remains to point out that the regulatory process within each of these other states for day to day decision-making can also be seen as a system. However, to comprehend fully the framework within which the recombinant DNA debate occurred, it is necessary to identify the pattern of international contact. Chapter Seven described the main international organisations involved which can be seen to have communicated both amongst themselves and with states' decision-systems and Diagram 2, below, provides a visual summary of the main communications linkages.

Linkages were essentially at the domestic level, the transnational level, or the transgovernmental level. When including the European Community we can also talk of intergovernmental linkages. Two states are represented as decision-systems, and the EMBO-ESF interrelationship is taken to be a system in its own right.[84] A network of complex communications channels emerges in this description, enabling information to disseminate (whatever its origin) rapidly through the whole system. Although presented as a two-state model, the simplifications involved are intended to enable it to apply as a characterisation of most states involved in recombinant DNA work comprising the whole system. The 'heavy' lines of communication represent the heart of the transnational and transgovernmental framework, suggesting established communications channels between groups within different states. Emphasis is on operational control and the exchange of safeguard information, and this is reflected in the identification of the important channels. Linkages are either direct or between international organisations, and these organisations themselves interact in important ways.

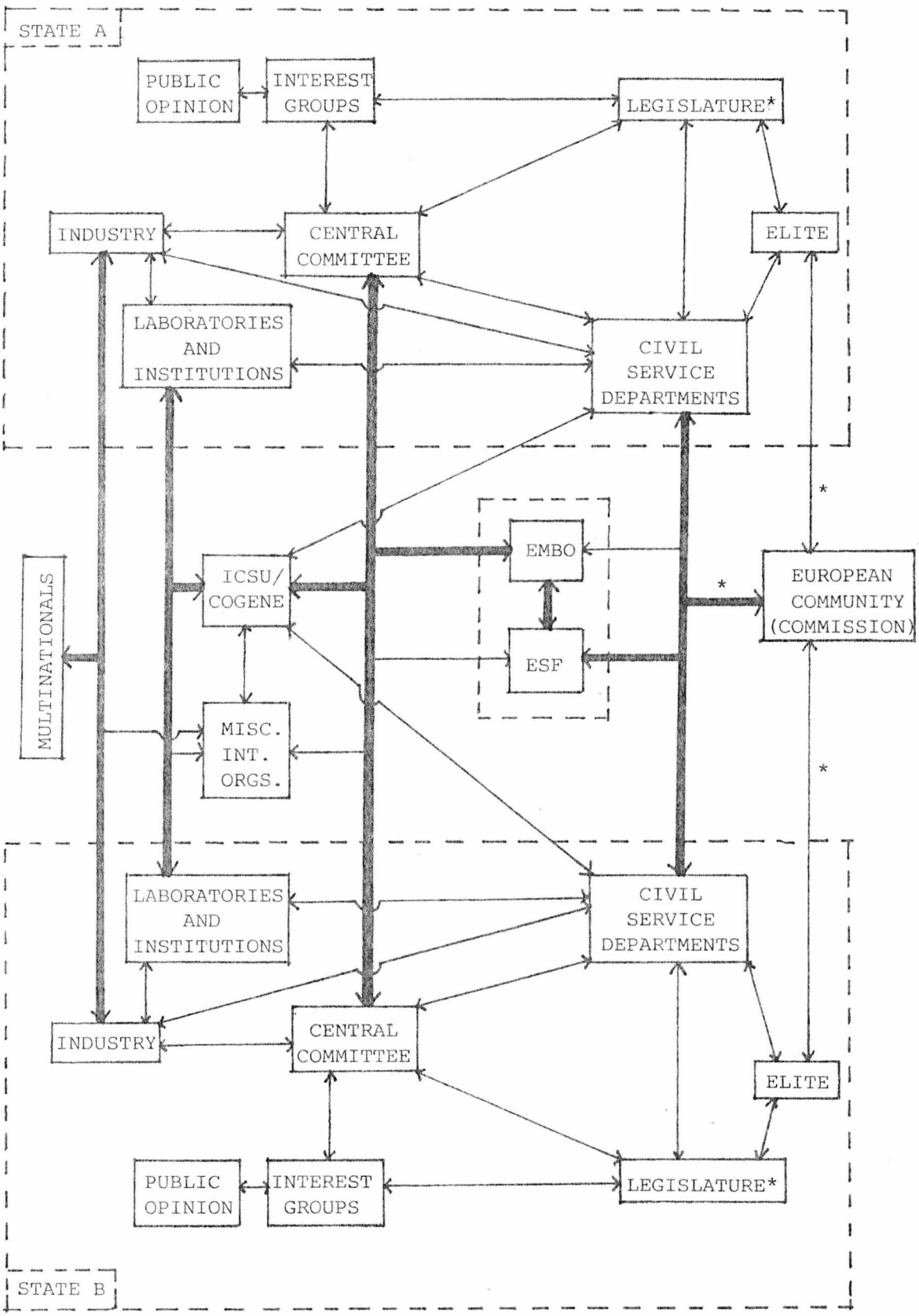


DIAGRAM 2. Simplified Two-State Communication Model for Recombinant DNA Issue Area.

Key:

⟷	Main Domestic and Minor Transnational Links
⟷ (thick)	Main Transnational (and Transgovernmental) Links
*	Where Applicable
- - - -	System Boundary

In a negative sense, it is of note that a number of transnational links are weak in relation to the importance of certain domestic groups. Interest group activity was not especially noticeable at international levels, although these groups could be vociferous within states, and most notably, in the United States. Indeed it could be suggested that the scientific community, which is highly international in outlook and characterised perhaps as an 'invisible college',[85] was much more suited to developing transnational standpoints and strategies. Common ground on the part of the scientists involved was more easily identified through the central roles of their international organisations. Lack of direct communication at the level of governmental elites was also noticeable. This was not too surprising, however, as policy formation and implementation occurred on the whole at departmental levels of the civil service and not at cabinet levels. In terms of policy making, both within Europe and across the Atlantic, transgovernmental linkages were of importance. This was encouraged by the ESF in particular, with representatives from North America also present at its Liaison Committee meetings. Atlantic links were, in addition, fostered through joint activities such as the NIH/EMBO workshops on containment and risk assessment.

Communications involve message content, as discussed below, but need to be considered also in terms of message origin. Information disseminated through the transnational network had various origins and, in addition, various points of compilation and interpretation. Much of the content of messages had origins within the procedures for operationalising controls within states. Working parties, central committees, research laboratories, interest groups, industry and individuals all fed messages into the transnational network. Basic information, although important, was perhaps less influential than information after analysis and interpretation, an exercise carried out more formally within institutions with information

research facilities. These included domestic departments and central committees, but more significantly from the perspective here they included the important international organisations. In addition to ensuring the dissemination of basic information, international organisations offered comprehensive reports, advice services and policy recommendations, all of which reflect key roles.

In a climate characterised by uncertainty, the roles of interpretation and collation of information are very important. Political advantage can accrue from control of sophisticated information, even if the actor involved would rather not see the issue as political. Good communications links involve a degree of 'tuning' or empathy between sender and receiver. Within the transnationally dispersed scientific community, with its entrenched culture and mutual hospitality to colleagues, such 'tuning' was very fine. Rose and Rose observe:

> "It is the belief of many scientists that science is international, that research knows no frontiers. The scientific enterprise, they claim, is pushed forward by many workers, in all parts of the world, each adding their individual contribution to the sum total of the published and freely available knowledge. A statement of this sort can be found in most books about science - provided they are written by academic scientists." 86

Although it can be questioned whether scientists completely avoid the pressures of nationalism, especially in large-scale prestige science, it could be argued that for the genetic manipulators the common fear of excessive regulation enhanced their unity of purpose. Like the research scientists, it could be argued that common perspectives were held within the respective industrial and regulatory communities, although weaker in the latter where the policy issues were concerned. Industrialists tend to be open to each other's interests in as far as they are not directly competitive, as in developing patents. However, in the period of develop-

ment of concern, industry was only showing initial interest, and its real importance did not emerge until later, in the context of extending guideline coverage and in the development of commercial products.

When the whole issue of conjectured risks came to light, organisations, both domestic and international, responded rapidly. Many set up committees of inquiry on either a formal or an ad hoc basis. It is interesting to note that many of these committees comprised representatives drawn from a common pool of talent, and certain individuals such as John Tooze and Sir John Kendrew had important positions in more than one international organisation. With the dramatic impact of the initial announcements of concern, consideration of future operational procedures and the nature of risk were much to the fore. However, in later years when risk assessment information and containment allocations were disseminated, the effects were more cumulative. Incremental response occurred rather than sudden response, but showing general trends in terms of direction, for example both the reduction of containment requirements and the establishment of a degree of harmonisation. Thus in Deutsch's terminology 'unstable equilibrium' existed in the early years, where important information injected into the transnational system would engender considerable response.[87] Responses were most rapid in newly created decision-systems such as the RAC, the working parties, and specialist committees within institutions. A lagged response occurred in the more established bureaucracies (other than to set up further groups under their auspices), For example, the World Health Organisation, the United Nations and the European Community were slow to isolate[88] the recombinant DNA issue area. Not least in importance, legislatures were rather hesitant in deciding on activity.

Deutsch also drew attention to the 'selectivity' of the receiver. Patterns of information exist within organisations into which new messages

have to be inserted. Specification of information, therefore, becomes important. In the recombinant DNA case study, certain types of information were rapidly accommodated in some institutions, while other types were not. Messages relating to promoting and encouraging research were readily incorporated into the decision frameworks of institutions whose raison d'être was specifically the promotion of such research, or perhaps even the funding. The concerns of industry took longer to emerge in the operationalising institutions, partly due to the time-lag before the techniques became utilised by them, and partly due to differences in their interest. Specific fears and viewpoints held by interest groups opposed to rapid guideline relaxation were not disseminated as effectively through the science-based institutions.

In summary, it could be suggested that a learning process became evident in terms of science institutions adapting to increased politicisation of issues. As a result of this, a complex network of communications channels emerged, proving to be adaptive to the issues seen as important by the actors themselves. These channels of communication can be characterised by the degree of directness involved in linkages between groups, as suggested here, and by the content of the messages carried, discussed below.

First order links existed where groups of importance communicated directly, such as central committees, important research institutions, policy-making departments and international organisations. These links were rapid and the content of messages could be more 'personalised'.

Second order links were also important, but involved intervening actors. These would have included, for example, links between central committees via an international organisation such as EMBO, or via personal communication between individual scientists. A further important example might

refer to government departments linked through a policy-based international organisation such as the ESF or the European Community. Multilateral rather than bi-lateral considerations would have predominated in this context. Of note at this level was the compilation of information by important organisations.

Third order linkages, although of less importance, nevertheless existed. In these, communications occurred with two or more intervening organisations. For example, an NIH policy document obtained by one laboratory could have been passed to another, before being given to a different central committee or laboratory.

By way of reminder, the perspective adopted here is to see organisations as decision-systems in their own right. Thus the patterns of interaction described here suggest multilevelled overlapping systems, which preceding chapters have attempted to isolate and describe. Within this communications network much of the information and many of the political viewpoints were disseminated and important decisions made.

b) Communications Content.

Much of the content of communications to enter the channels outlined above concerned technical information. New host-vector systems were made widely known as were results of experiments of importance, new products of genetic manipulation, patent applications, proposed experiments, risk assessment activities and results, and research materials were shared. The content of different states' guidelines and technical comparisons were common in the international institutions. Newsletters and conferences supplemented the other channels of communication in transferring and exchanging such information. A particularly important practical approach to safeguards concerned the sharing of information on and the organising of

training courses for scientists not experienced in safe laboratory practice in microbiology. Science in general is based on the dissemination of such information, and for many of the international institutions involved this was their main function.

A second area of information content can be related to issues of policy. Much exchange of viewpoints, supported perhaps by technical information, was evident concerning issues such as guideline relaxation or stringency, harmonisation of guidelines and important national practices, legislation and approaches to it, monitoring and participation. In terms of participation, attention was put on the involvement of representatives of the 'public', industry, specialist scientists in disease-related fields, and trade unionists. Policy considerations tended to involve the giving of advice by those compiling reports on international practice, although in the European Community policy discussions included the possibility of imposing constraints. Institutions making recommendations either made general suggestions for all concerned, or made detailed suggestions to those who specifically solicited advice. States developing guidelines and procedures for operationalising them could consult other states and organisations for assistance. Government departments to some degree operated in a transgovermental context, keeping regular contact with colleagues in other states. Within Europe, the ESF offered a valuable forum for eighteen member states to compare policy through research council representation.

Transgovernmental relations across the Atlantic were partly formalised through NIH and Canadian participation in ESF meetings, but often they were more bi-lateral. In the case of the United Kingdom this was certainly true, where department officials used their personal contacts, for example in the HEW. On one occasion the DES took the opportunity to arrange an

impromptu two hour meeting with D.S. Fredrickson, the Director, NIH, while he passed through Heathrow en route elsewhere! Shirley Williams, while Secretary of State for Education and Science, kept informal links with the US Secretary of Health, Education and Welfare, Joseph Califano, whose department was responsible for the NIH. Representatives of GMAG have also visited the United States.[89]

Policy considerations, therefore, were evident in the communications either directly between officials of government departments (or 'quangos') or through meetings of international bodies, most notably the ESF and within the Commission and Economic and Social Committee of the European Community. Thus the national policies developed within the many states involved benefitted from an awareness of procedures and plans within other states. Although Community legislative instructions never emerged as a Directive, the ESF by 1980 was of the view that similar safety precautions were suitably evident within its membership.

Of course it is also evident that within the transnational framework a number of possible policy questions, argued here to be of importance, were given little, if any, real consideration. For example little attempt was made to compare formally the issues involved in the recombinant DNA case with general social policy towards risk in technology as a whole, although some brief thought along these lines was evident in the European Community investigations.[90] Part of the reason for this was the way the recombinant DNA case was taken up by agencies with remits concerned with relatively narrow fields. Biomedical research funding groups often developed the first responses, and became involved in control policy, through holding the purse strings. Those agencies with wider remits tended to compartmentalise issues and usually established a special committee for recombinant DNA work, for example the ESF and the International Council of

Scientific Unions (ICSU and its special committee, COGENE).[91] Comparison with other technological risks and their similarities or differences were not widely considered, although the UK Health and Safety Executive approached the safeguards issue from a wider perspective than the NIH, for example.

A second important omission was a lack of in-depth consideration of potential deliberate misuses. Some mention in passing occurred in the NIH Environmental Impact Statement and in the Ashby Report. It seems that the view was that the International Biological Warfare Convention covered the techniques and such issues were really beyond the agencies concerned with basic laboratory research.

Long term possibilities in terms of the social perception of the future of recombinant DNA techniques and their use in gene therapy and other human applications were not examined in the main agencies involved. There was, in general, a shortage of ethical considerations of this order.[92]

Most of the institutions involved in the case study had fairly specific orientations in both technical and policy terms. Nevertheless within these narrower perspectives a vast amount of communication occurred.[93] A very sophisticated transnational system linked many domestic groups with other national and international bodies. Transgovernmentalism was important and recombinant DNA provides a useful case study of this general phenomenon.

Much of the mapping exercise reinforces, in addition, the insights developed by Evans concerning interorganisational relations.[94] Key organisations like the ESF and COGENE (ICSU) provided support analysis for other organisations. They investigated various technical and policy

issues, in order to make comparative analyses of use in various domestic institutions and other international institutions. Both 'wheel' analogies and 'chain' analogies apply as Evans outlined them and, as he suggests, 'boundary' personnel are also of note. 'Focal organisations' or focal systems perhaps can be identified within and between states. Diagram 2 in effect provides a visual representation of important 'nodal' points of decision-making within the whole transnational system. Complex problems introduced at different points may lead to technical analysis and decisions may result, for example a series of recommendations on biological containment. Alternatively, policy decisions may focus on different nodes.

However, the Evans model and many of the functional assessments of organisations can overemphasise a structural and communications based interpretation. Much of the orientation of organisations, within and between states, and groups of scientists and non-scientists can be seen to be overtly political. That is, 'political' in the sense of values in conflict with those values held by other groups. It is ironical that because of the difficulties of rational or straightforward 'technical' solutions to the issues, arising out of conjectured hazards, the scientists themselves began to learn the basics of politics. Beliefs and wishes at times became partial substitutes for empirical evidence. But more subtly, canvassing for support on viewpoints, or even support in applying pressure on policy-making agencies, occurred within the transnational communication system. Sir John Kendrew drew attention to the scientists from the US attempting to "steam roller" those of the UK into accepting lower guidelines, during the COGENE and Royal Society co-sponsored meeting at Wye College. Indeed this whole conference was widely criticised on the basis of those not in attendance, mainly the press and scientists who were still advocating great caution. Common viewpoints were reinforced at Wye

and in other forums in the transnational system. Thus, political standpoints were implicit.

However, politics was not confined to this level of analysis. National standpoints on issues such as the European Community proposed Directive were fed into the departments representing the member states. Indeed, France and Denmark were particularly opposed to interference in domestic science, and in Denmark's case they saw it as an issue outside Community economic consideration. In terms of promoting research by the European Community, France and Germany were hesitant over the duplication of research which could be organised nationally. Political issues, expanded upon further when looking at participation in the next section, were therefore important within the transnational communications system outlined here.

4. DECISION-MAKING.

From the analysis so far, a number of important actors have been identified: international organisations; government departments; 'quangos'; central committees; scientific professional organisations; industrial firms; industrial professional organisations; laboratories and key individuals; trade unions; and interest groups such as environmentalists. Some of these need further elaboration in their importance.

In the United States the environmentalist lobby was most vociferous. A wide range of groups were involved, some representing coalitions.[95] Many of these groups latched on to the recombinant DNA developments; at least one important Friends of the Earth representative, Pamela Lippe, had transferred her interest from the nuclear energy debate. Much of the lobbying by such groups was to develop during 1976 and 1977 with concerted efforts

notably between Friends of the Earth, the Sierra Club and the Environmental Defense Fund. The former People's Business Commission has more recently attracted attention to itself from a religious and ethical standpoint, under the newer title of the Foundation on Economic Trends.[96] These groups found some effectiveness in the United States, in helping to force the NIH Environmental Impact Statement after the first US guidelines and in pushing for developments in proposed legislation. To some degree they assisted in the sensationalisation of the debate which also involved inaccurate press reporting. Part of the problem was that in the early period of the recombinant DNA debate these groups lacked the scientific knowledge to appreciate fully the nature of conjectured risks. Nevertheless, divisions at that time within the scientific community fuelled their concern. Their aims tended to centre on the need to increase caution in experiments, increase controls including satsifactory cover of industrial activity and increase the involvement of public representatives. More openness was advocated and if necessary their aims should be ensured through legislation, including the right of local extensions of federal controls. Yet there was little direct communication between US groups and interest groups in Europe. However, in as much as US activity set possible precedents, their role was important.

Generally in Europe the debate was less publicised, and the UK as one of the two leading states in developing controls offers quite a different model in this respect. Part of this reason is the different political system, less dependent on the politics of lobbying, but also because of a wider involvement of non-scientific groups from the start. Much pressure had been directed against the Williams committee and the 'establishment' by a particular trade union, the Association of Scientific Technical and Managerial Staffs (ASTMS). The union was very influential in getting GMAG established in the format of mixed representation, and was also to

prove to be critical of DPAG and its role in the Birmingham smallpox outbreak, to the extent of leaking the Shooter Report to the press. Donna Haber, a divisional officer, has been a central figure, having pursued a number of activities in relation to laboratory workers' interests. She sat on GMAG, gave evidence to the European Commission, and organised an open conference on 'Genetic Engineering' in October 1978, bringing many sides in the debate together.[97] It was interesting that Haber was one of the few dissenting voices raised at the Wye conference with regard to the secrecy of the meeting and the need for scientists to make their change of heart appear legitimate by being more open.[98] In the UK a further body calling itself the Genetic Engineering Group of the British Society for Social Responsibility in Science submitted a memorandum when the Select Committee on Science and Technology took evidence. Indeed, they noted the inability or unwillingness of UK institutions to promote open discussion.[99]

In France, the press and public response to the issues has been characterised by Philippe Kourilsky as relatively vocal and equally ill informed. Internal controversy within the Pasteur Institute provided a background to this activity leading to a degree of controversy in France. Similarly, Japan was characterised by early press reports and an atmosphere of hostility to the work in 'non-professional circles' and in the Netherlands political parties took stands in a long running controversy. Overall, however, the most extensive involvement of lobbying interest groups was in the United States.

Industry to a degree organised its responses through professional organisations, notably from the points of view of the containment requirements for work, potential competitive disadvantages if domestic restraints were too stringent, and the problem of confidentiality in having to reveal

experiment protocols (for example in the UK). The nature of US and European legislation (including Community level requirements) also invoked response.

Collectively all of these actors and the form of their interactions constitute a transnational system in the terms of Keohane and Nye, within which a number of important issues relating to concerns of legislation, guideline relaxation and communications content have been focused upon. It is now necessary to return formally to the main elements of decision-making systems, as outlined in Chapter Two, where eleven headings were used to structure the conceptual breakdown involved in addressing analytically the problems. The first two, communications and communications content, have been used to flesh out the transnational system in the section above. In moving towards some conclusions the remaining concepts will now be considered.

a) Systems Interaction and Boundaries.

The case of recombinant DNA as illustrated in this thesis has shown that it is a truly international issue area. It is quite apparent that a state centric approach, whatever the merits this approach may have, does not fit the basics of the case. The approach supported here is based on an assumption of overlapping and interacting systems at many levels of analysis. Some comments are necessary regarding the identification of the systems involved. It was argued that one method would be to define systems in terms of their collective roles. On this basis the decision-systems within individual states deserved attention, and in particular the influential examples of those of the United States and the United Kingdom. These were, however, all open systems, although in the cases of the US and the UK their early developments of operational procedures and guidelines were relatively independent.

Regionally, it became apparent that international European interactions were important, centred on both the ESF and the European Community, in many ways the former being the more important. Policy, politics and technical exchanges operated where central committees, government departments and other interested groups, including key individuals, all interacted. Also within Europe a sub-system was evident with regard to EMBO and ESF co-ordination of technical information and policy.

At a more international level, it is clear that organisations such as COGENE (ICSU), again EMBO, and others were part of a more loosely defined international science community who were interested in recombinant DNA techniques. It is argued here that the interactions between these diverse groups were regularised sufficiently to see them as a system, a most transnational one at that.

A system can also be seen to characterise the decision-making procedures of individual institutions themselves, going back to the roots of organisational decision-making as outlined. All of the institutions at all levels involved formalised procedures, which in many cases led to appropriate specialist subcommittees, centred on different roles, such as: national guideline implementation; transnational risk assessment; transnational guideline comparison; policy and guideline harmonisation; information and material compilation and dissemination; political consensus formation; arranging international workshops and conferences. Weak systems at best existed in terms of co-ordinating transnational opposition to the research as practised.

However, to a large extent the boundary problem is made more difficult by the central roles of key individuals in terms of communication paths. As mentioned, some individuals, as a survey of the memberships of various

committees will show, were active in a number of forums. In many ways this is to be expected when the appropriate administrative expertise and scientific background capable of adapting to the science of the new techniques was rare, given the relatively few scientists initially active in the field. Thus, membership of domestic central committees could overlap with international committees, and indeed some key individuals were members of more than one at the international level. It can be argued that many therefore had strong boundary positions within which to gain influence in disseminating information and to influence policy. John Tooze, for example, was cautious in his early arguments for harmonisation and sensitive to the expressions of concern. He was also more in favour of effective harmonisation through discussion and recommendation rather than legislation or a Directive of the form the Commission produced. By no means was he in favour of great stringency.

In sum, many overlapping systems existed which reflected interaction at different levels, mainly transnational or transgovernmental. However, organisations themselves can be seen as open decision-systems operating in this environment, in part characterised in terms of interorganisational relations.

b) Complex Decision Problems.

It has been suggested that complex decision problems involve values which are affected by choices taken in a zero-sum trade-off sense. Thus one set of values is satisfied at a corresponding cost to differing sets. The existence of the trade-off of values may, however, be a consequence of misperception, where in effect positive-sum outcomes might be possible. Uncertainty can be taken to be a further characteristic, as can the dispersal of the power to make the decisions over a number of actors or organisations.

It is quite evident that the nature of the key decisions in the recombinant DNA case study were politicised and values were clearly in conflict. During the period when concerns were voiced and guidelines were developed, committees investigated the issues, took divergent evidence and made recommendations. Scientists themselves at Asilomar II and elsewhere expressed the need to examine in detail all of the issues. There may have been a loose consensus at Asilomar II, but it became apparent that not all the scientists were agreed on the degrees of risk which could be conjectured and the actions which should be taken. Interest groups took up discussion based on these divisions, called for openness, for further pause, and for legislation. Government departments which were involved held different views from those of scientists concerning the imperatives for work to progress as rapidly as possible, and administrators perceived the requirements of submitting protocols or memoranda of understanding as less disruptive than scientists and industrialists. A very important value held by some groups was purely and simply the right to participate in decisions, regardless of what the decision itself was. Decision-making issues liable to involve conflicts therefore included:

i) Should the work continue? (That it should was an assumption for many.)

ii) What degree of containment was necessary? Should it be a mixture of physical and biological?

iii) What type of monitoring mechanism was required?

iv) Where should the authority lie?

v) Who should participate in decisions?

vi) How could industry be covered?

vii) Would legislation be required? If so, in what form?

viii) How much risk assessment would be necessary to support the relaxation of guidelines?

ix) By what degree (in relation to viii) should guidelines be relaxed?

x) How much national effort should be put into promoting genetic manipulation?

xi) How could international harmonisation be achieved?

xii) What parameters of inquiry should exist in examining recombinant DNA issues? What about ethical, moral and religious issues?

Much of the basis for values coming into conflict related to the overall uncertainty. Firstly, the scientists admitted to their uncertainty when they announced their fears, and secondly, perhaps more important in explaining some conflicts, was that even if scientists were becoming less uncertain, those who lacked the technical knowledge were not. The credibility of scientists was challenged further by some misuses of information and by guideline violations. In terms of undertaking risk assessment, or risk-benefit assessment, the problems of uncertainty have already been outlined. At best, attempts to be rational have occurred within certain limitations. 'Bounded' or 'limited' rationality better describes the incremental decision processes in operation which led to 'satisficing' type outcomes.

An example of bounded rationality can be seen in deciding the form and content of the guidelines. Lack of comprehensive information led to a search for suitable criteria for allocating safeguards. The limits of rationality were particularly evident with the final recommendations of the RAC for the 1976 US guidelines. Three sets of draft guidelines were considered in parallel with paragraphs considered for no more than ten minutes, and votes taken on proposals. Controversial proposals and counter proposals had led to the various drafts which the RAC compared and recommended upon. A degree of rationality may have applied in attempting to make an optimum choice, but the nature of the decision process limited it.

Decisions concerning proposals for legislation at all levels in the transnational system involved political lobbying and conflicting values. Rationality gave way to, at best, 'satisficing' procedures. Such a decision problem also indicated the diverse power held by various bodies involved. 'Friends of DNA' lobbied in opposition to 'Friends of the Earth' and other groups. In Europe, the Commission's Draft Directive failed due to a lack of political consensus and strong lobbying of representatives by industry and scientists. Nevertheless, out of these complex processes decisions were made and implemented. Guidelines were developed and applied in many states, but these decisions in general could not be technically described as 'rational'. Conflicting values are not readily amenable to rational trade-off, yet despite this many asserted the dominant role of the scientific 'expert' even when some issues were not directly scientific choices.

c) Uncertainty Avoidance.

The literature on decision-making procedures has suggested that uncertainty leads to the response of organisations trying to avoid or bypass it. This is not necessarily a criticism, but more an observation on decision strategies. Short-run decisions were very evident in the case of recombinant DNA. Guidelines were designed as cautious, such that, as Brenner suggested, future revisions should be downwards. Revision was to be frequent to accommodate both new information and short-run feedback from scientists using the containment and developing empirical evidence. However, not all feedback from the scientists' tentative and temporary action was positive or reinforcing from their point of view. Although well thought out, the temporary measures outlined in dramatic fashion by the Berg letter and the Asilomar II meeting led to an upsurge of press and public interest, especially in the United States. This reaction in turn led to an abortive attempt to draft a second 'Berg' letter, almost

four years after the first, this time summarising reasons for relaxing early concerns.[100] By then the threat of legislation was at its height. Yet many considering legislation on their part tried to build clauses into proposed bills limiting the lifetime of the legislation to perhaps two years, in recognition of the need for future reappraisal. Indeed, the European Community Draft Directive similarly proposed a regularised revision of the situation. In effect, it was the very strength of the early perceptions of uncertainty which complicated the decision processes and engendered a diversity of opinion.

Aware of the problems of past uncertainty, some of those advocating guideline relaxation tried to show that the scientific community was now certain in its view of the safety of the techniques. This view was in part based on the risk assessment activity considered above. In a political context, however, many non-scientists interested in the issue area could not readily adapt to the transition from expressions of uncertainty, leading to incremental decision-making, to expressions of near certainty concerning the safety of the work (given precautions).

All in all, the scientists showing early concern acted in a way that would allow subsequent information to alter the tentative decisions taken. Their mistake was in failing to appreciate the much wider politicised responses relating to non-scientists and uncertainty. On the other hand, many institutions responded by recourse to implementing standard procedures. Committees of investigation made recommendations which were sent to a higher level for approval and which were then implemented by adapting existing mechanisms. Within and between states institutions responded by compartmentalising the issue area before subsequently introducing innovations such as GMAG and RAC type central committees. In turn, central advisory committees often established specialist working groups

which created further compartmentalisation. Over the years the uncertainty of the issue has been played down where possible or contained within incremental decision procedures.

d) Organisational Search.

Drawing on theoretical concepts, it has been suggested that political and technical difficulties could arise from the methods which organisations use in their search for alternative courses of action. For example, simple-minded rules might be applied, or alternatively elaborate measures could be taken to justify decisions already made.

Decisions were taken within systems of interaction displaying different degrees of 'organisation' within the transnational framework. Berg's small committee informally consulted colleagues and made once-off decisions relating to their letter and the Asilomar II conference. They had few rules to go by. At the other extreme, consensus pressure for guideline relaxation was applied by a transnational community of scientists, partly as a result of tacit bargaining. Such output from a loose system again does not really reflect organisation.

Yet at many levels organisations, either pre-existing or new, took important decisions some of which involved little consideration of alternatives. The charges against the US NIH Environmental Impact Statement regarding its very limited survey of alternatives could apply to most agencies in the other states which developed safeguards. It is clear that it was never seriously contested that genetic manipulation should continue. Within states and internationally, decision alternatives were developed within parameters of what was acceptable to the community involved. This was most noticeable in terms of voluntary guidelines. If they were too strong, the 'threat' was that there would be limited

adherence to them. The raison d'être of some organisations such as the ICSU, EMBO and the ESF was the promotion in general of scientific study and the exchange of information. Transgovernmental and domestic governmental decision-making was very influenced by the inputs of such organisations and the science community in general. Wider alternatives than guideline provision and appropriate implementation were not considered in departmental decision-making contexts. Nevertheless, wider discussion did occur within other institutions such as pressure groups, but perhaps more importantly in the many legislative hearings, commissions of inquiry or parliamentary study groups - the reports of which have provided valuable source material for this thesis.

In sum, large-scale risk-benefit assessment was never related to policy decisions. Within the communications networks, the fact that information was provided or collated by like-minded groups reinforced the overall limited selection of policy options. Opponents to these groups were never so politically well organised or motivated outside, perhaps, the United States. Indeed, it could be argued that some groups actively tried to neutralise considerations of certain options by strongly supporting an alternative. For example, many researchers opted to support relatively lax US legislation proposals partly to enhance their own credibility and partly to divert attention away from consideration of the more extreme proposals. In an earlier example, many scientists supported guidelines in fear of legislation.

Within some states, many decisions acquired a momentum on the basis of what was happening elsewhere. The least common denominator effect of guideline relaxation could be seen to be a politicised example of this phenomenon. In general, decision groups within states had certain favoured comparisons with other states (such as lower guidelines elsewhere) brought

to their attention by interested parties. Internationally it is of note that most states' policies came from a limited range of options considered. A notable exception was with GMAG type assessment procedures. The case law approach in this body meant that a continuous adaptation was possible in as far as allocating containment was concerned, and a number of states were to copy this.

e) Organisational Learning and Feedback.

The cybernetics term 'feedback' has become a standard concept in the approaches to decision-making analysis. In particular, the perceptions of positive and negative feedback are of note here, suggesting insights into the possible effects of decision outputs. Concern centres on the ability of decision-systems or organisations to adapt or alter course as a result of learning from previous actions they have taken.

With regard to early expressions of concern, it has been the argument in this thesis that domestic institutional and international organisational response has been generally rapid and, on the whole, very commendable. Certain responses, however, eventually led to scientific bodies developing political awareness as their actions and those of other groups brought wider social and political involvement in the issue. To be fair, the many organisations introduced serious programmes of risk assessment and set up working parties in response to apparent information shortfalls, and the new technology was rapidly assimilated into the wide ranging activities of the larger institutions. Over time, the 'load' on key decision-systems built up, particularly in both providing technical support and surveying national policy options. Ad hoc committees tended to become replaced by more formally constituted and briefed committees. Some problems were apparent, however, in what Deutsch termed 'lead'. Predicted future responses to the actions did not meet the subsequent reality as legislation

seemed imminent following much wider than expected interest group and bureaucratic scrutiny. Nevertheless a rapid response was evident at least in key sections of the scientific community, supported by professional organisations, to avoid excessive bureaucratic requirements.

Central committees were designed to be reasonably flexible in their responses (something which ironically was questioned by those who wanted more rigid formality[101]). By their very nature they were exposed to a wide range of inputs from many groups, often of conflicting viewpoints. In GMAG style groups, the greater degree of viewpoints was internalised through the appointment of a range of representatives.

Over time the main goals of a number of organisations and the methods of achievement became modified. From recommending the adoption of guidelines and appropriate training programmes, emphasis shifted to advocating relaxation and the avoidance of legislation. Groups in opposition modified their goals from the restriction of the use of laboratory techniques in general to raising wider ethical, moral, religious and future use issues. It would have been surprising, however, if changes in the state of the art had not engendered organisational changes. One problem has been noted. To some degree information can be seen to have been selected to support specific viewpoints as shown with the use of the Falmouth data. Thus, feedback could be subject to the same biases in selection as new information in general.

f) Cognition and Perception.

As far as individuals and small groups are concerned, it has been argued that cognition and perception are recognised to be of influence, if analytically beyond the scope of this thesis.[102] Individuals undoubtedly had divergent perceptions concerning a variety of issues: the conjectured

risks and benefits; the appropriate actions to take; who should participate. These issues are closely related to the questions referred to in examining the concept of complex decision problems above. In many ways the analysis of the central issues of risk, risk-benefit assessment and legislation have utilised source material revealing differences of perception. Uncertainty has undoubtedly raised numerous problems enabling different perceptions to emerge and for them to alter over time. Associated with such changes in perception have been shifts in the conflict of values. For example, the change of perception on the risks of using recombinant DNA on the part of many scientists was interpreted as simply self-serving by others, which intensified the values in conflict. Values are addressed further below.

As far as 'cognition' and 'perception' apply to organisations, then the processes of decision-making were undoubtedly influenced. In terms of limited or bounded rationality, biases in perception were in part responsible for the specific pattern of the fragmentation of problems and apportioning of responsibilities, leading for example to the dominance of organisations which were charged with promoting science.

g) Values.

As with cognition and perception, the concept of values is also taken fairly loosely. The heart of politics is the conflict of values, relating to the establishment of norms or standards through processes of persuasion. A number of stances related to values held by groups of individuals and the membership of organisations can be identified. The following list suggests some of the values or norms called for explicitly or implicitly through the nature of activity:

i) Freedom of science and the free right of unrestrained inquiry.

ii) Progress is both necessary and possible.

iii) Science should be socially responsible, responsive and accountable.

iv) Activities likely to cause harm to others should be restrained.

v) Openness in decision-making and rights of participation are desirable.

vi) Freedom of the press to report science developments.

vii) Rights of development of new research through open competition between companies and states.

viii) The right to inspect for compliance with rules.

ix) The right to introduce legal sanctions against creators of hazard.

These values have all been evident in the debates surrounding the issues of recombinant DNA and they are closely linked to perceptions and subsequent political actions. Common values were quite evident in scientists carrying out research (the tenets of academic freedom, for example) and pressure groups calling for extremes of caution (social responsibility in science for example).

Thus values were important and often substituted for shortages of empirical evidence or for lack of comprehension of empirical evidence. Differing values could also be seen at the heart of interpretations of the desirability of scientists vetting the safety of colleagues' work, and the production of risk assessments at a time when legislation threatened. Finally, at the international level some conflicts emerged between harmonisation and national independence.

Norms and values can change, leading to splits among previously united groups and activities associated with the canvassing of support. Scientists unsure of political activity learnt from what they perceived as tactical mistakes, and became more adept at using the transnational framework of communications to develop new strategies and to win the support of their colleagues. A particular difficulty for the well established

figures was to overcome the post-Vietnam idealism of some of the younger workers. Generalisations of the actions of scientists should not over-emphasise their unity.

Not all the activities in terms of the values held by actors were overtly conflictual with other groups. Often personal values shielded those who held them from different values, by affecting their perceptions and conditioning the continuation of certain behaviour in ignorance of possible reactions from others. This perhaps characterises the attempts of the scientists to keep the risk assessment activity within the field of their expertise. Indeed, the whole transnational social and political set of interactions relates to a process of establishing what the norms associated with genetic manipulation experiments of different types ought to be.

h) Conflict.

The issues surrounding recombinant DNA have on occasion been referred to as a 'debate'. In many ways this is not an inaccurate description of the levels of conflict involved. Values undoubtedly came into conflict over the many issues involved, and from time to time the exchanges became heated. Physical violence or coercion were not features of the methods used in attempting persuasion. Rather the conflicts involved occurred within established political frameworks and through the media. At times the term competition was perhaps more applicable. Yet conflict did occur, values clashed, and attempts at persuasion were at an organised level.

However, it is argued here that much of the conflict was misconceived due to problems of perception and to failures of legitimacy, Scientists, for example, had brought their conjectured fears to international attention after serious deliberation. They expected, from their perceptions, to

receive a sober and analytical response, investigating the risks and developing appropriate measures of caution. Scientists fully expected to remain in the central position, discussing internationally and assessing risks perhaps under the auspices of government departments. Calls for 'rationality' were common. At Asilomar II the realisation dawned that they would have to take such actions rapidly or find themselves the victims of their own authoritative statements. Legislation, turmoil and harsh constraints might follow.

The authoritative expression of concern was followed by a rather arbitrary set of guidelines to let the work continue and to produce some guidelines lest someone else should. Conflict to a large extent focused on two levels of uncertainty:

i) It was quite apparent that scientists were divided on the nature and degree of hazard, despite appearances at Asilomar II.

ii) Non-scientists appreciated the authoritative nature of the scientists publicising their conjectural fears, but did not understand the science. Their uncertainty was further enhanced by the divisions among scientists and their subsequent actions.

Conflict arose out of uncertainty. It was compounded by the time-lag before public, interest group and legislative activities emerged. As non-scientist groups found their feet in the science of the issues (or found scientists to support them) and began to comprehend the nature of the risk conjectured, some scientists were making new discoveries. Evidence, albeit limited, emerged to show reason for conjecture that the hazards might be less than first thought. To some scientists this and further evidence made them begin to believe that their early actions were hasty. To non-scientists coming to terms with the issue, this seemed a turn around, and they suspected that scientists were attempting to avoid the

opening up of their activities to scrutiny.

From such beginnings the misperceptions and the outright politicking took root. Scientists wished to maintain authority, but could not understand the political requirements of legitimacy. Bureaucratic imperatives and vocal criticism from interest groups widened the calls for participation. Much of the value differences became apparent at transnational levels as the whole context of the debate became more complex.

Part of the complexity was that some scientists learned some lessons of basic politics (as they saw it) and became active in defending their values and beliefs, if necessary at the cost of dependence on empirical evidence. Overall, such uncertainty raised an important issue in the United States, which was often better resolved abroad. Demands for participation in decision-making arose, centred on the requirements of legitimacy. Both scientists and institutionalists were defensive against these.

In many ways the nature of the conflict within the recombinant DNA debate was unfortunate, particularly when combined with domestic and international imperatives towards competition. Yet it all reflected a process of attempting to establish appropriate and legitimate norms. However, that which appears legitimate need not be that which with subsequent analysis is most appropriate. Further comment on the nature of conflicts based on legitimacy can be addressed in considering participation.

i) Participation, Decisions and Non-decisions.

It has been argued in this thesis that participation in decision-making is a basis of power. Although analysis of the domestic processes of decision-making in issues surrounding genetic manipulation may have some

characteristics of elite structures, at a transnational level more pluralist participation was important. A corollary of the notion of power lying in participation is the act of excluding other groups. Thus the conceptions of organisation as the 'mobilisation of bias' and the possibility of 'non-decision-making' need investigation.

It is clear that groups like environmentalists, trade unions and representatives of industry wished to be involved in any major policy decisions. Environmentalists wrote many letters in the United States to the Director, NIH, trade union representatives acquired positions on GMAG, industry lobbied bureaucrats on the European Community proposed Directive. What is also evident is that the scientific community would have preferred more specialist committees to assess 'rationally' the hazards and the appropriate containment. Legislation to cover industry would have been acceptable, but the fear held by many scientists was of legislation also interfering with their own work.

Professional decision-makers in departments responsible for domestic policy were in positions to establish procedures from the beginning. However, the conjectured hazards were announced by scientists in an authoritative but technical way. In effect the administrators were asked to assist further consideration of issues, a request which eventually led to working parties in many states calling witnesses and drawing up reports. Guidelines were drawn up by scientists but administered by departmental professionals, scientists and local institutions.

Although the issue of participation was much publicised in the United States, it was less of an issue in Europe and the United Kingdom. Partly the smaller scale of activity in many states made the issue less obvious, and partly the nature of the United States political system facilitated

lobbying at local and national levels. With regard to legislation and local regulations, the environmentalists in the United States had some influence, but only acquired through intensive activity on their part, and some misinformed sensationalist press coverage.

On the other hand, the GMAG model was established to include wider participation. As the Williams Report suggested in 1976:

> "We recommend the establishment of a Genetic Manipulation Advisory Group (GMAG). Since a central advisory service will need to command the respect of the public as well as of the scientific community, including scientists in industry, the membership of the GMAG should include not only scientists with knowledge both of the techniques in question and of the relevant safety precautions and containment measures but also able to take account of the interests of employees and the general public." 103

Ironically GMAG was to be much more secret in its operations, and some problems arose concerning which trade unions should be included and who should represent the public interest. Yet much of the problem concerning coverage of industry was overcome in the UK at least by use of existing statutes. France went somewhat further, after a controversial beginning involving much public and press concern, in establishing two central committees, one similar to GMAG and one to examine ethical, moral and wider social issues. Japan overall took a very wide and interdisciplinary perspective. Altogether at least eleven states by 1980 included public interest representatives on their central committees. Even the United States moved the composition of the RAC more towards wider participation.

Perhaps more important in examining the issue of participation, there is need to consider the mobilisation of bias in terms of limiting wide discussion. It is clear that the scientific community and the administrators favoured keeping the issue from becoming too controversial. A

useful mechanism in achieving this was to emphasise the technical nature of the issues. A certain knowledge was needed even to understand why scientists had shown concern and what the guidelines were trying to do. Openness was possible without great publicity. Existing norms of behaviour were used as much as possible to minimise disruption. The press could be labelled 'ill-informed' or 'sensationalist' and scientists could urge colleagues to be very careful what they said. This was taken too far concerning the international Wye conference when only three journalists could attend given the last minute decision not to ban journalists. Prevailing values were reinforced and emphasised where necessary. For example emphasis on the 'freedom of science' as a traditional right was used to justify the assumption that the work would continue even at the height of uncertainty, and to organise response to threatened legislation.

The whole policy of developing risk assessment experiments, drawing up and revising guidelines, was an attempt to reinforce the traditional conception of the expert suited to evaluate complex issues. Yet little attention was addressed to potential misuse or to the possibility that some scientists might not be trusted to play by the rules.

Indeed, the question of potential misuse was riddled with examples of non-decision. As discussed elsewhere, the Berg letter omitted a draft paragraph on potential misuse and, although the Ashby working party acknowledged such possibilities, it declined to comment further, weakly arguing that this type of hazard was not within its remit. All of the main international organisations gave little public consideration to this issue, or indeed to the future ethical questions which might arise in human genetics.

Thus, scientists and science organisations feared controversy and having

to justify publicly what they 'knew' was safe practice. Administrators showed little interest in going beyond the more limited issues of public health and safety. Governments remained somewhat distanced from the issue. Yet in retrospect, had the risks been theoretically upheld, then certain groups, including the general public, would have been shortchanged in terms of participation. Incremental decision-making was chosen rather than wider and more long-term risk and policy assessment. Public inquiries were not generally considered necessary. In many ways the issue has died, and the question of participation has receded somewhat. Yet the potential hazards have not completely gone away, but have changed as the issue area modifies itself extensively, within the context of industrial biotechnology.

In summary, the analysis in this thesis suggests the following points concerning participation, bias and non-decisions as notable:

i) Although recombinant DNA techniques were originally conjectured to have potentially disastrous hazards at very low subjective probability levels, outside the United States the diversity of interest groups was limited.

ii) A number of groups were involved which were not fully satisfied in terms of the degree of participation in decision-making which they would have liked. Pressure or interest groups concerned with more general environmental or social responsibility in science issues were critical of those who were in the decision-making systems. An exception, however, was that trade unions were more active this side of the Atlantic than in the United States. To an extent they had a base of wider power to argue their way into the process if not invited outright. GMAG type committees also appeared more legitimate to those interest groups which were monitoring the debate, including the press.

iii) Some scientists advocating much more caution than colleagues were

often not invited to international or national conferences, or to participate in organisational decision-making.

iv) Experts in general hazard controls were seldom consulted, although the Health and Safety Executive of the United Kingdom used its trained inspectors.

v) Many institutions which responded to the statements of concern by scientists were responding from the perspectives of the general aims of the organisation. As many were involved in encouraging research, although a moratorium occurred, they saw the work as too important not to continue. They saw the benefits in the general sense of important knowledge as well as important practical benefits. Some groups advocating caution emphasised that practical benefits could perhaps be achieved using different techniques. Some wanted benefits and risks to be compared. Trade unions, environmental groups and industry equally revealed biases derived from their general aims. At the international level some evidence of 'nationalism' influenced the stands taken by states in transgovernmental deliberations on harmonisation and promotion.

vi) Many of the issues raised in the above discussion on 'complex decision problems' were sublect to the mobilisation of bias as an organisational phenomenon. This was particularly so where scientists were both dominant and worried about challenges to their dominance as with possible legislation in the United States and elsewhere. However, it is also important to note that in interaction with other actors or organisations there was mutual awareness of biases. In reconciling values and different perceptions, including those concerned with who should make risk and containment assessments, these biases were both politicised and counter productive.

vii) Failure to participate is not quite the same as having interests ignored. It is important to say that some concerns were explicitly

addressed even in the absence of direct representation of supporters of those concerns. Scientists involved in decision-making and assessment work were aware of the more generally expressed viewpoints, as were the members of government departments. However, much of the politics of participation was based on the maxim that not only should things be done, but they should also be seen to be done. Wider participation and less heated exchanges of perceptions might have enabled greater legitimacy to emerge. In Europe, more discontent arose from representatives of indistry, especially in the United Kingdom, fearing condifentiality being breached and loss of competitiveness to countries like the United States where industry could more easily maintain secrecy - evoking in turn a different issue there.

viii) In examining 'communications content' above, a number of omissions were indicated. Their lack of discussion in institutional agencies and scientific organisations does not belie their importance. They may therefore be taken as possible examples of non-decision and often deliberate exclusion because of their potential controversy, or their irrelevance to beliefs held.

In general the important insights developed in decision-making analysis concepts are relevant to this study. Characteristics of bounded rationality or satisficing, complex decision problems, weaknesses in organisational search, feedback, cognition and perception, values, conflict and participation have all to a greater or lesser degree been useful in helping to identify aspects of the recombinant DNA issue area.

Elements of the pluralist perception of power and decision-making are therefore very relevant, but so too are the conceptions of elite structures - especially insofar as existing frameworks were simply adapted, or issues

were handled without political conflict. However, the processes of decision-making are to an extent compromised by elements of bias and non-decision, supporting the insights of Bachrach and Baratz and others discussed in Chapter Two.

5. CONCLUSIONS: A RETURN TO THE HYPOTHESES.

Finally, to conclude this thesis, it is necessary to return to the original hypotheses as outlined in Section A. It has already been stated that these derived from preliminary examination of the case study, with some background from an analysis of nuclear energy. From time to time commentators on, and participants in, the recombinant DNA issue area have made comparisons with events heralding the dawn of the nuclear age. The conclusion here is that such comparisons are not entirely applicable. Nuclear energy research, development, control and exporting were all much more the central concern of governments. The example is one of 'big' science rather than 'high intensity' laboratory science. It is also important to note that nuclear energy from the beginning was a component of a weapons programme. Although genetic manipulation may lead to new weapons, they would not be the first weapons of mass destruction, and they would involve different political issues. Some of the hypotheses underlying this study have thus proved less relevant than was initially conceptualised at the start of the study, and this needs to be taken into account (refer to pages 94-95).

a) Hypothesis One.

Constraints of a politicised nature have undoubtedly influenced the operationalisation of control options. In a negative sense it could be argued that governments, scientists, professional and international orgainsations all tried to limit the political context of the debates over

the technology. Full open forums, such as public inquiries, were not usually seen as relevant, although in the United States many open meetings and legislative hearings were held. Non-decision and organisational bias emphasised the value of the role of the research expert in determining both risk categories and implementation procedures, such that in many states involved scientists either allocated containment or set guidelines.

At the governmental level, political will was not sufficient to achieve a policy of harmonisation of control, although this partly resulted from the pressures of domestic and transnational groups. In a number of states controls were never applied in any compulsory fashion to industrial or privately funded researchers because of the political and technical difficulties associated with introducing legislation. Constraints on controls increased both as a result of new information suggesting less risk, but also because of successful political lobbying by representatives of involved scientists.

The nature of political activity and its subsequent effects of control implementation differed between states, the US and the UK providing some striking contrasts. However, control options were in their own right imperfect, partly due to political compromise where values clashed. The lack of harmonisation led to problems of legitimacy for individual guidelines or even containment on specific experiments. Monitoring was weak on centrally organised inspection, putting much emphasis on local safety committees. Central expertise could have developed, as with the HSE in the UK, in more states. Punitive measures for possible violations were very weak in an institutional sense. Had the techniques proved to be more hazardous than was the case, then in most states punitive deterrents were weak, relying more on peer censure and possible loss of research funds.

b) Hypothesis Two.

This hypothesis as it stands holds superficially. However, to an extent it is a little misleading. Many control options in retrospect could be seen to be applicable. Differences of emphasis on inspection, central regulation, range of coverage, punishments and so on would have been possible, as would a complete ban. Extensive differences between states, however, might have arisen causing further problems of moving work to where there were the weakest restraints in a foreign state. The problems of harmonisation which did exist indicate that more restrictive controls would have been much harder to apply internationally, unless the lead was intergovernmental. The latter option would have been politically very difficult because of the complexities of achieving international agreement, and the likely inflexibility of modification with future knowledge.

In effect, the development of controls was much more characterised by transnational incremental and satisficing decision-making, notably in the first year of concern. Both risks and benefits were conjectured and it was assumed (for better or worse) that the work would continue. Thus, voluntary suspension of work gave way to tentative but quite restrictive Asilomar II guidelines. These in turn prompted more formal development and tentative implementation of controls. With new knowledge and experience in using these guidelines and controls, modifications were made. Under uncertainty, such incrementation is quite creditable given the difficulties of rational assessment. The real political problem was one of legitimacy concerning who should be involved in this process of policy decision-making. The controls were much more commendable in the way they were established than in the way they were relaxed through a more politicised process.

c) Hypothesis Three.

Because of uncertainty and the nature of incremental decision-making, this hypothesis rings very true. That is not necessarily a criticism, however. With the initial uncertainty surrounding the conjectures of potential risk, those scientists who announced in an authoritative fashion their fears were not unnaturally expected to continue to examine the issue. These individuals and those they in turn alerted operated within institutions with which they were familiar. Scientists who had knowledge sufficient to conjecture hazard could be expected either to have or to develop insights to increase precision.

Administrative and government sponsored reactions such as NIH sponsorship or working parties such as the Ashby and Williams committees depended to a large extent on the expertise of the few scientists at that time familiar with the newly developed techniques. During the period of the international moratorium, there was no real difficulty in such an approach, although perhaps wider consultation could have been made with experts in infectious disease.

Problems in utilising existing systems really only emerged when it was decided to end the moratorium and allow work to proceed under guideline constraints. Administration of guidelines by agencies sponsoring research led to charges of conflicts of interest. At such a stage there is a strong case to say that central control should be somewhat separated from organisations whose normal bias would be towards protecting and encouraging science activity per se. Such early action could have avoided the problems of not all researchers being accountable to guidelines and perhaps could have been structured and operated to enhance legitimacy.

Risks being both uncertain and of very low conjectured probability

(despite possible consequences) brought caution of a different sort. Scientists reasonably successfully argued against what they would see as excessive control over an activity to which only conjectured risks applied. Finding resources to cover a conjectural set of risks through new agancies would be politically difficult to justify.

In many ways the outcome was a compromise. Innovations were introduced but to a limited degree. Thus the practice of having a central committee to provide advice was implemented, supported by encouragement of risk assessment effort. An existing structure was used as far as possible, and adapted in an incremental fashion, domestically and transnationally.

d) Hypothesis Four.

It is argued here that this hypothesis not only holds, but stands as a very strong criticism of the operational activities. Although in many ways the recombinant DNA techniques were to introduce conjectured risks of some novelty, there might have been much to learn by opening the issue out for response from experts in hazard control per se and to experts in specific if physically unrelated hazards. Procedures to engender confidence, to operationalise risk assessment and to gain new insights could have emerged. Such criticism is not merely directed against recombinant DNA, but against the general tendency of societies to compartmentalise such issues rather than to centralise all hazard and potential hazard policy. If this had been the case, a more appropriate agency might have already existed for assimilation of the problems. Susan Wright has criticised the failure in the United States to use what provisions did exist. In the UK it became apparent that although the Health and Safety at Work Act could be used, it nevertheless required a redefinition of 'work'. The UK overall was more fortunate in having the HSE, although this comprised only part of the institutional response. Nevertheless,

some UK comparison with dangerous pathogens in general has been noted. Japan was, however, more exceptional in locating recombinant DNA issues within more interdisciplinary studies of technological impact on society.

e) Hypothesis Five.

On the whole, this hypothesis proved too difficult to operationalise fully. Communications were very good between the various institutions involved, at the level of transmitting information. They were less extensive and less formal at the level of policy discussion, especially in international terms. Although disaster can be related to communications in many cases after the event, this is more problematic before the event. Yet examinations of communications networks can try to identify weak points and points of inflexibility. As far as recombinant DNA is concerned, communications were very good, bar one proviso. Some of the information transmitted reflected political biases. The Gorbach letter was a good example of the insertion of biased information (his mis-interpretation) into a general system. Politicisation grew out of the clashes of values involved. More legitimate structures of decision-making might have lessened such problems. Some messages were not widely disseminated if they were minority views, such as the views of scientists advocating above average caution. In an early example, however, of what could be done through individual initiative Roy Curtiss took it upon himself to distribute one thousand copies of his famous sixteen page letter supporting the Berg letter. Wider participation might have altered the balance of message content in the communications network. However, wider participation might not have resolved the safety issue. Some scientists with information suggesting more caution would perhaps keep quiet fearing excessive politicisation. To an extent, these comments are speculative, but it is hoped they are of relevance.

f) The Hypotheses.

These hypotheses acted as a general guide to the investigations underlying this thesis. The above comments, and those in Chapters Five and Six, are drawn from a subjective analysis of the case of recombinant DNA in the 1970s. Today the issues are different, as the techniques are giving rise to industrial processes and products, a view that cloned pathogens are often safer in new hosts has emerged, and long-term ethical and moral issues are gaining prominence. Not least the techniques discussed here have been combined with older techniques in what has now come to be termed 'biotechnology'. Future research lies in these directions where the international perspective could again be applied.

The case has raised a number of substantive issues specific to the international sphere, elucidating aspects of the recombinant DNA debate as well as reinforcing the need for International Relations to accommodate approaches encapsulating many levels of analysis, actors and issues. In general terms it is hoped that if any future technological developments display conjectured or real risks comparable with those discussed here, then studies of this remarkable technology will lessen the problems to be faced. As far as the future of genetic manipulation is concerned, with wisdom in its application, great benefits are now ensured, in terms of further knowledge and very real and practical applications.

Introduction.

1. Aldous Huxley, "Foreword" (1946) Brave New World, Penguin, Harmondsworth, 1932, pp.9-10. Huxley noted that in his book the only scientific advances he specifically described were those involving the application to human beings of the results of future research in biology, physiology and psychology.

2. See, for example, J. Glover, What Sort of People Should There Be? Penguin, Harmondsworth, 1984.

3. The methods involved are described in depth in Chapter Three.

4. Discussed in Chapter Four.

5. For convenience, when the academic field is being referred to, the upper case 'International Relations' will be used, and when reference is to the activity of the real world, then the lower case 'international relations' can be distinguished.

6. See, for example, V. Rittberger, "Science and Technology in the New International Order: Problems Facing an International Development Strategy of the United Nations", in O.R. Holsti, R.M. Siverson and A.L. George (eds.), Change in the International System, Westview Press, Boulder, Colorado, 1980, pp.83-102. Rittberger's emphasis is on the role of technology in the development process. See also E.B. Skolnikoff, "The International Functional Implications of Future Technology", in D.S. Sullivan and M.J. Sattler (eds.), Change and the Future International System, Columbia U.P., New York and London, 1971, 1972, pp.59-79. Skolnikoff examines technology and its impact on the environment, in outer space, the oceans, and with regard to natural resources, emphasising international decision-making as increasingly more appropriate than national approaches. For a broad discussion of the general importance of technology to international relations in the context of modernization and change, see E.L. Morse, Modernization and the Transformation of International Relations, Free Press, New York, 1976, and E.L. Morse, "The Transformation of Foreign Policies: Modernization, Interdependence and Externalization", World Politics, Vol. 22, No. 3, 1970, pp.371-392. To Morse, the more 'modernized' a society becomes, then the higher is the ratio of the uses of inanimate sources to animate sources of power. Note that the developments discussed here might eventually compromise this definition as new forms of animate sources of power arise from biotechnology.

7. See, for example, H. Rose and S. Rose, Science and Society, Penguin, Harmondsworth, 1969.

8. See, for example, M. Willrich, Global Politics of Nuclear Energy, Praeger Publishers, New York and London, 1971, and M. Willrich (ed.), International Safeguards and Nuclear Industry, Johns Hopkins Press, Baltimore, 1973. See also C.K. Ebinger, International Politics of Nuclear Energy, Sage, London, 1978 and H.R. Nau, National Politics and International Technology: Nuclear Reactor Development in Western Europe, Johns Hopkins Press, Baltimore, 1974. In general, however, most International Relations authors have emphasised technology in its military context, although by no means all. See, for example, D.H.

Blake and R.S. Walters, The Politics of Global Economic Relations, Prentice-Hall, Englewood Cliffs, N.J., 1976, pp.143-167.

9. See E.L. Morse, Modernization and the Transformation of International Relations, op. cit.

10. See H.R. Nau, op. cit., pp.22-23. See also J. Vogler, "Technology and Change in International Relations: On the Independence of a Variable", in B. Buzan and R.J. Barry Jones (eds.), Change and the Study of International Relations: The Evaded Dimension, Frances Pinter, London, 1981, p.143.

11. See, for example, G. Boyle, D. Elliott and R. Roy (eds.), The Politics of Technology, Longman, London, 1977. This reader covers various aspects of social control, the role of government, public involvement and decentralisation, all in relation to the point of view of bringing technology under control. See also R. Johnston and P. Gummett (eds.), Directing Technology, Croom Helm, London, 1979; D. Nelkin (ed.), Controversy: Politics of Technical Decisions, Sage, Beverly Hills and London, 1979; and D. Elliott and R. Elliott, The Control of Technology, Wykeham Publications, London, 1976.

12. R. Williams, "The Development of Nuclear Technology"; J. Hartland and M. Gibbons, "Blind Landing Systems: Government-Industry Interaction in Innovation"; P. Stubbs, "Technology Policy and the Motor Industry"; B. Gillespie, "British 'Safety Policy' and Pesticides"; and E. Yoxen, "Regulating the Exploitation of Recombinant Genetics", all in R. Johnston and P. Gummett (eds.), op. cit.

13. See R. Johnston and P. Gummett, "Introduction", in R. Johnston and P. Gummett (eds.), ibid., pp.9-10. They borrowed from the work of R. Roy, "Social Control of Technology", Control of Technology, Unit 1, Open University Press, Milton Keynes, 1978.

14. Or "the science of the industrial arts". See R. Johnston and P. Gummett (eds.), op. cit., pp.9-10.

15. H. Rose and S. Rose, op. cit., pp.1-3.

16. H. Rose and S. Rose, ibid., p.2.

17. In general 'lead' times between theoretical research and final technical realisation have tended to reduce in modernized societies across a number of fields.

18. See Chapter Three, pp.137-139.

19. See J.R. Ravetz, "DNA Research as 'High-Intensity' Science", Trends in Biochemical Sciences, Vol. 4, No. 5. May 1979, p.N97.

20. See H.P. Green, "The Recombinant DNA Controversy: A Model of Public Influence", Bulletin of the Atomic Scientists, Vol. 34, No. 9, 1978, pp.12-16. Low probability, high consequence disaster is further discussed below, pp.11-14. See also C. Grobstein. A Double Image of the Double Helix: The Recombinant DNA Debate, W.H. Freeman & Co., San Francisco, 1979, p.21. A number of pressure groups considered elsewhere in this thesis were influenced by prior concern with nuclear energy as an issue.

21. The nature of perception of risk is considered in Chapter Eight.

22. Nau, in examining European nuclear energy, adopts a state-centric approach, although he acknowledges that 'new' technologies might be examined with more relevance by approaches disaggregating the state. See H.R. Nau, op. cit., p.35.

23. Or indeed in the sense of efficiency used in non-liberal economic thought. That is, there must be considerable motive in developing the technology on a large scale.

24. Uncertainty in the scientific community was reflected in a voluntary deferral of certain genetic manipulation experiments. Subjective fears of catastrophe as a possibility apply more widely than just in the scientific community, as subsequent decision taking involved many actors. Although catastrophe as a possibility has all but disappeared as a perception in the scientific community, its utility here as a concept is valid, as emphasis is on the consequences of initial uncertainty and the wider impact of scientists in the early stages of the field voicing their concerns. These concerns and actions are developed in Chapter Four.

25. Reference to such material will be made in passing. Scientists and journalists have also contributed assessment, sometimes in book form.

26. Not without debate concerning their adequacy, and their own histories of the development of such controls, more often after the acquisition of data. It is interesting that in the 1980s the chemical industries and recombinant DNA techniques have become more integrated with the emergence of biotechnology. New issues of control are therefore in evidence where chemical firms might develop industrial-scale biotechnology processes.

27. J.D. Watson and J. Tooze, The DNA Story: A Documentary History of Gene Cloning, W.H. Freeman & Co., San Francisco, 1981, p.vii. Watson along with F. Crick won the Nobel Prize for the discovery of the double helix structure of DNA.

28. P. Berg et al., "Summary Statement of the Asilomar Conference on Recombinant DNA Molecules, May 1975", submitted to the Assembly of Life Sciences of the National Academy of Sciences and approved by its Executive Committee on 20 May 1975. Reprinted in C. Grobstein, op. cit., pp.113-117 (quotation p.113). The Asilomar Conference is discussed in Chapter Four. Note that this conference was aware that excessive caution was desirable with possible future relaxation.

29. For a very thorough analysis of the relationship between disaster and previously accepted precautions, see B.A. Turner, Man-Made Disasters, Wykeham Publications, London, 1978. For an assessment of studies on disaster in International Relations, see R. Kent, "Reflecting on a Decade of Disasters: The Evolving Response of the International Community", International Affairs, Vol. 59, No. 4, 1983, pp.693-711. Both of these authors emphasise the tendency of studies to centre on the consequences of disaster.

30. See B.A. Turner, op. cit., pp.8-48.

31. B.A. Turner, ibid., pp.83-84. Turner makes a conceptual distinction between 'natural' and 'man-made' disasters, but acknowledges that in

many real cases involving multiple causes these categories may overlap. This thesis focuses on a conception of disaster where human effort is aimed at minimising the risks of particular hazards.

32. Turner provides a breakdown of stages of disaster development under the following headings: Initial culturally accepted beliefs; Associated precautionary norms; Incubation period; Precipitating event; Onset; Rescue and salvage; Full cultural readjustment. Beliefs and precautionary norms reflect the interest here, but influenced by Turner's overall analysis. See B.A. Turner, ibid., p.85. Changes in conceptions of risk make the earlier estimates of risk seem excessive.

Chapter One.

1. On the scope of inquiry, see, for example, P.M. Morgan, Theories and Approaches to International Relations: What are We to Think? Transaction Books, New Brunswick (USA) and London, 1981; A.J.R. Groom and C.R. Mitchell (eds.), International Relations Theory: A Bibliography, Frances Pinter, Nichols Publishing Co., London, New York (respectively), 1978; N.D. Palmer, "The Study of International Relations in the United States: Perspectives of Half a Century", International Studies Quarterly, Vol. 24, No. 3, September 1980, pp.343-364; T. Taylor (ed.), Approaches and Theory in International Relations, Longman, London and New York, 1978; and J.E. Dougherty and R.L. Pfaltzgraff, Contending Theories of International Relations: A Comprehensive Survey, 2nd Ed., Harper & Row, New York, 1981. On the relationships of theory in International Relations and empirical inquiry see, for example, C. Reynolds, Theory and Explanation in International Politics, Martin Robertson, London, 1973; K.N. Waltz, Theory of International Politics, Addison-Wesley Publishing Co., Reading, Mass. and London, 1979; and R.J. Lieber, Theory and World Politics, George Allen & Unwin, London, 1972.

2. See, for example, A. Ryan, The Philosophy of the Social Sciences, Macmillan, London, 1970. Ryan provides a useful analysis of the contributions of the likes of Kuhn, Popper and Winch. In general, see the literature on the philosophy of science and social science. An in-depth study of such material is beyond the scope of this study, but the issues involved are noted.

3. C. Reynolds, op. cit. and K.N. Waltz, op. cit.

4. K.N. Waltz, ibid., p.11.

5. See A. Rapoport, "Various Meanings of Theory", American Political Science Review, Vol. 52, December 1958, pp.980-982. These points are summarised in R.J. Lieber, op. cit., pp.6-9.

6. See K. Knorr and J.N. Rosenau (eds.), Contending Approaches to International Relations, Princeton U.P., Princeton, N.J., 1970. Both sides of the ensuing debate are represented in this volume.

7. Although recognising the merits of techniques of content analysis, it is argued that they are inappropriate due to the array of different types of documentary evidence and the variety of national cultures involved. See below, pp.96-97 for a description of sources in the sub-section on operationalisation.

8. See, for example, R.O. Keohane and J.S. Nye, Power and Interdependence: World Politics in Transition, Little, Brown & Co., Boston, Toronto, 1977, pp.23-37. They see an alternative model of international relations, which they term complex interdependence (discussed below) to be seen like the traditional model as an ideal type with relevance for different issues. See also G.T. Allison, Essence of Decision: Explaining the Cuban Missile Crisis, Little, Brown & Co., Boston, 1971. Allison takes three 'models', including the traditional approach, and examines their explanatory power concerning a specific case study. His line of argument is that each gives a different insight, rather than that any is right or wrong. Indeed, his analysis highlights the level of analysis problem, previously discussed by Singer. See J.D. Singer, "The Level of Analysis Problem in International Relations", in K. Knorr and S. Verba (eds.), The International System: Theoretical Essays, Princeton U.P., Princeton, N.J., 1961, pp.77-92. See also R.E. Jones, The Changing Structure of British Foreign Policy, Longman, London, 1974, p.70. Jones describes the traditional approach as covering a segment of the data of foreign relations and is essentially a special and not a general interpretation of those relations. Note that the terms 'realism' or 'politic realism' are often associated with the traditional orientation.

9. See R.O. Keohane and J.S. Nye, op. cit., pp.23-24 and R. Harrison Wagner, "Dissolving the State: Three Recent Perspectives on International Relations", International Organisation, Vol. 28, No. 3, 1974, p.437.

10. The term 'system' is frequently used in a general sense to refer to a system of states. Much literature has been devoted more specifically to the concept of system, and this is discussed below. For the moment, the term is taken to mean 'units in interaction', those units here being states.

11. See I. Clark, Reform and Resistance in the International Order, Cambridge U.P., London and New York, 1980. Clark refers to the "tradition of despair" deriving from the work of Rousseau (while Kant's writing gave rise to the "tradition of optimism"). See also T. Taylor, "Power Politics", in T. Taylor (ed.), op. cit., pp.125-126 and P. Savigear, "European Political Philosophy and the Theory of International Relations", in T. Taylor (ed.), ibid., pp.32-53. For a useful overview on the development of thought relating to international relations, see F. Parkinson, The Philosophy of International Relations: A Study in the History of Thought, Sage, Beverly Hills and London, 1977.

12. See, for example, H. Bull, The Anarchical Society: A Study of Order in World Politics, Macmillan, London, 1977. The concept of 'power' has been central to much of the traditionalists' approach, although a fully satisfactory definition of the concept has been somewhat elusive. See, for example, J.E. Dougherty and R.L. Pfaltzgraff, op. cit., notably their chapter entitled "Power and Realist Theory", pp.84-133. Many definitions refer to power along the lines of it as the ability of a state to use resources (tangible or intangible) to influence the behaviour of other states. This is further complicated if potential and applied power are conceptually separated, and if systemic features such as 'balance of power' are considered.

13. See J. Vasquez, "Colouring it Morgenthau: New Evidence for an Old Thesis on Quantitative International Politics", British Journal of International Studies, Vol. 5, No. 3, 1979, pp.210-218.

14. Many criticisms have been levelled against the narrowness of the traditional focus, broadly agreed with in principle by this author, although the arguments are beyond the scope of this particular study. See, for example, E.L. Morse, Modernization and the Transformation of International Relations, Free Press, New York, 1976. See also J.W. Burton, World Society, Cambridge U.P., Cambridge, 1972, and J.W. Burton, A.J.R. Groom, C.R. Mitchell and A.V.S. de Reuck, The Study of World Society: A London Perspective, International Studies Association Occasional Paper No. 1, University of Pittsbergh, Pittsbergh, 1974. Defences against such criticism have been made by, for example, K.N. Waltz, op. cit., and H. Bull, op. cit.

15. For overviews of systems theory approaches, see, for example, R. Little, "A Systems Approach", in T. Taylor (ed.), op. cit., pp.182-204; R.J. Lieber, op. cit., pp.120-145; J.E. Dougherty and R.L. Pfaltzgraff, op. cit., pp.134-180; and C.R. Mitchell, "Systems Theory and International Relations", in A.J.R. Groom and C.R. Mitchell (eds.), op. cit., pp.33-47.

16. Balance of power mechanisms for example have been studied extensively by systems theorists such as Rosecrance, Kaplan, Waltz, Singer and Small.

17. See R.J. Lieber, op. cit., p. 122 for definitions.

18. R. Little, op. cit., p. 195.

19. Not least a certain impetus to seeing world problems from such viewpoints derived from resource questions associated with the finite limits to growth writings of the early 1970s. See, for example, D.H. Meadows, D.L. Randers, J. and W.W. Behrens, The Limits to Growth, Potomac Associates, London, 1972, and R.A. Falk, This Endangered Planet: Prospects and Proposals for Human Survival, Vintage Books, New York, 1972. See also E.L. Morse, op. cit., pp.1-21. Morse surveys the relevance of such work to international relations. The 1974 oil crisis furthered such attention.

20. The permeability of the state and the identification of a wider pool of issues do not, however, suggest in themselves the most appropriate mode of analysis. Systems theorists and non-systems theorists have produced relevant frameworks. For example, the systems analysis of J.W. Burton and the analyses of interdependence by R.O. Keohane and J.S. Nye. See below. Keohane and Nye note, in providing an alternative approach to that of the traditionalists, that no longer can a hierarchy of issues dominated by security be assumed. See R.O. Keohane and J.S. Nye, op. cit., pp.24-27.

21. See R.J. Lieber, op. cit., p.121 and C.R. Mitchell, op. cit., p.35.

22. J.W. Burton, op. cit., p.36.

23. Systems analysts and decision-making analysts tend to take holistic views, while originally behaviouralists were concerned with a more atomistic approach, breaking the whole into component parts. However, many systems-based analysts at least adopted the same methodology, to

operationalise their research, as the behaviouralists, notably the so-called 'scientific' method. See R. Little, op. cit., pp.182-183.

24. See B.P. White, "Decision-Making Analysis", in T. Taylor (ed.), op. cit., p.146 and R. Harrison Wagner, op. cit. White, however, locates the approach within the wider approach of Foreign Policy Analysis.

25. C. Hill and M. Light, "Foreign Policy Analysis", in A.J.R. Groom and C.R. Mitchell, op. cit., p.154.

26. See P.M. Morgan, op. cit., pp.135-158. Morgan provides a useful summary of systems concepts in terms of their applications to decision-making.

27. P.M. Morgan, ibid., p.136.

28. Note that as far as the traditional model of International Relations is concerned, the concept of rationality has been attributed to states acting as purposive units. Graham Allison has effectively summarised this aspect of the traditional model in his influential work on decision-making under the rubric of the Rational Actor Model. See G.T. Allison, op. cit., pp.10-35. See also note 8 above. For a general discussion of the concept as used in social science, see A. Heath, Rational Choice and Social Exchange: A Critique of Exchange Theory, Cambridge U.P., Cambridge, New York, 1976.

29. G.T. Allison, op. cit., p.30.

30. G.T. Allison, ibid., pp.29-30. Allison develops the above in terms of a complex model of rational action in International Relations.

31. See, for example, D. Laidler, Introduction to Microeconomics, Philip Allen, Oxford, 1974, or any competent economics text on microeconomics. Economists make assumptions such as choice consistency on the part of consumers. For example, if good X is preferred to Y, and Y preferred to Z, then this will always be the case; from this X will always be preferred to Z even in the absence of Y being available. This can then be extended to a model of utility maximisation where choices consisting of comparing the utilities of bundles of goods can be made. Rankings need only be ordinal.

32. See G.T. Allison, op. cit., p.31.

33. See R. Harrison Wagner, op. cit., p.436 and T. Taylor, op. cit., p.126.

34. See C.M. Price, Welfare Economics in Theory and Practice, Macmillan, London, 1977, pp.99-102. Because such difficulties exist in cost-benefit analysis, Price argues that this type of analysis is perhaps most useful for comparing alternative projects. See also E.J. Mishan, "The ABC of Cost-Benefit", in L. Wagner and N. Baltazzio (eds.), Readings in Applied Microeconomics, Clarendon Press, Oxford, 1973.

35. See Allison's summaries of organisational theory and decision-making in foreign policy and bureaucratic politics between participants in decisions. G.T. Allison, op. cit.

36. See the growing literature on psychological aspects of decision-making. For example, I.L. Janis, Victims of Groupthink, Houghton-Mifflin, Boston, 1972 and J.H. de Rivera, The Psychological Dimension of Foreign Policy, Merrill, Columbus, Ohio, 1968. See Chapter Two, below, pp. 78-81.

37. See, for example, R.J. Lieber, op. cit., pp.18-37; P.M. Morgan, op. cit., pp.107-133; J. Von Neumann and O. Morgenstern, The Theory of Games and Economic Behaviour, Princeton U.P., Princeton, N.J., (referred to by Lieber); A. Rapoport, Fights, Games and Debates, University of Michigan U.P., Ann Arbor, Mich., 1960. Types of situation examined involve: two-person, zero-sum; two-person, variable-sum; n-person, zero-sum; n-person, variable-sum. The latter is the most desirable, although most difficult.

38. See R.J. Lieber, op. cit.

39. See A. Rapoport, Fights, Games and Debates, op. cit., p.215 or R.J. Lieber, op. cit., pp.33-34.

40. Even though a moratorium on work was self-imposed, it was never thought permanent. Involved non-scientists did not fit this pattern of view so closely. In a number of states, notably the United States, impending legislation produced similar and largely unco-ordinated response (although not entirely unco-ordinated).

41. G.T. Allison, op. cit., pp.67-100.

42. A useful survey of these can be found in S. Smith, "The Utility of Foreign Policy Approaches: Bureaucratic Politics", in M. Clarke and B.P. White (eds.), Foreign Policy Analysis, G.W. & A. Hesketh, Ormskirk and Northridge (UK), 1981, pp.75-93. See also R. Harrison Wagner, op. cit.

43. J.W. Burton, "International Relations or World Society", in J.W. Burton, A.J.R. Groom, C.R. Mitchell and A.V.S. de Reuck, op. cit., p.13.

44. Such as the promotion of scientific research, safety in the workplace, environmental protection, developing industrial products, the standardisation of international practices, etc.

45. See A. Heath, op. cit., p.88. Heath argues that such an approach is appropriate where uncertainty is due to lack of knowledge, and where this can be lessened through successive searches. See also J.D. Steinbruner, The Cybernetic Theory of Decision: New Dimensions of Political Analysis, Princeton U.P., Princeton, N.J., 1974, p.45.

46. See G.T. Allison, op. cit., pp.144-184. See also M. Halperin, Bureaucratic Politics and Foreign Policy, The Brooklings Institution, Washington D.C., 1974. See S. Smith, op. cit., for critiques.

47. R.O. Keohane and J.S. Nye (eds.), "Transnational Relations and World Politics", International Organisation, Vol. 25, No. 3, Summer 1971. Republished in book form as R.O. Keohane and J.S. Nye (eds.) Transnational Relations and World Politics, Harvard U.P., Cambridge, Mass., 1972. Page references are to the latter.

48. R.O. Keohane and J.S. Nye (eds.), ibid., p.xii.

49. See J.A. Field, "Transnationalism and the New Tribe", in R.O. Keohane and J.S. Nye (eds.), ibid., pp.3-22.

50. From R.O. Keohane and J.S. Nye (eds.), ibid., pp.xiii-xiv.

51. O.R. Young, "Interdependence in World Politics", International Journal, Vol. 24, Autumn 1969, p.726. There are many definitions used in the literature, but this one is sufficiently general to make the point. For discussions of the term, see E.L. Morse op. cit., pp.114-150; D.A. Baldwin, "Interdependence and Power: A Conceptual Analysis", International Organisation, Vol. 34, No. 4, Autumn 1980, pp.471-506; and R.O. Keohane and J.S. Nye, Power and Interdependence, op. cit.

52. See R. Rosecrance, International Relations: Peace or War, McGraw-Hill, New York, London, 1973, pp.136-140. It is also fashionable to talk of interdependence involving the 'sensitivity' of one state to events occurring within other states, and the 'vulnerability' implying the degree of effect remaining after efforts have been made to minimise 'sensitivity', These tend to be state-centric assessments, and are not of great relevance here. See R.O. Keohane and J.S. Nye (eds.), op. cit, and D.A. Baldwin, op. cit.

53. See the works of Johan Galtung and Andre Gunder Frank for example.

54. R. Harrison Wagner, op. cit., pp.440-445.

55. This is acknowledged in R.O. Keohane and J.S. Nye, Power and Interdependence, op. cit., p.25. See also R.O. Keohane and J.S. Nye, "Transgovernmental Relations and International Organisations", World Politics, Vol. 27, No. 1, October 1974, pp.39-62.

56. R. Harrison Wagner, op. cit., p.440.

57. Taken to include interdependence, transgovernmental relations and other associated concepts.

58. See K. Skjelsbaek, "The Growth of International Nongovernmental Organisation in the Twentieth Century", in R.O. Keohane and J.S. Nye (eds.), Transnational Relations and World Politics, op. cit., pp.70-92. See also the discussions on functionalism in this chapter, below, and on cybernetic theories of decision-making in Chapter Two.

59. Keohane and Nye also consider the possibility of one government influencing other governments through the use of new transnational instruments, such as the use of private investors to support foreign policy abroad. Such state-centric decision-making is not very relevant to the concerns of this thesis.

60. See the discussion on functionalism, below.

61. Keohane and Nye compare the traditional approach and an extension of their ideas which they term 'complex interdependence', in R.O. Keohane and J.S. Nye, Power and Interdependence, op. cit.

62. D. Crane, "Transnational Networks in Basic Science", in R.O. Keohane and J.S. Nye (eds.), Transnational Relations and World Politics, op. cit., p.237. N.B. IGO refers to International Governmental Organisation.

63. See, for example, F. Parkinson, op. cit., pp.143-166 for an overview of nineteenth and early twentieth century thought on the subject. See also A.J.R. Groom, "The Advent of International Institutions", in A.J.R. Groom and P. Taylor (eds.), , International Organisation: A Conceptual Approach, Frances Pinter, London, 1978, pp.11-27.

64. A.J.R. Groom, op. cit., p.12.

65. Integration can be seen to refer to the process whereby two or more states form a new entity or political community. See C. Pentland, "Functionalism and Theories of International Political Integration", in A.J.R. Groom and P. Taylor (eds.), Functionalism: Theory and Practice in International Relations, Crane, Russak & Co., New York, 1975, p.11.

66. See C. Pentland, ibid. See also M. Hodges, "Integration Theory", in T. Taylor (ed.), op. cit., pp.237-256; F. Parkinson, op. cit., pp.143-166; and A.J.R. Groom, "Integration", in A.J.R. Groom and C.R. Mitchell (eds.), op. cit., pp.140-152.

67. C. Pentland, op. cit., p.15.

68. D. Mitrany, A Working Peace System, Quadrangle, Chicago, 1966.

69. A.J.R. Groom, "Functionalism and World Society", in A.J.R. Groom and P. Taylor (eds.), Functionalism, op. cit., p.94.

70. On neofunctionalism, see in particular E.B. Haas, Beyond the Nation-State, Stanford U.P., Stanford, Calif., 1964.

71. There is an associated body of literature on regionalism, which for the same reasons is irrelevant here.

72. See L. Gordenker and P.R. Saunders, "Organisation Theory and International Organisation", in A.J.R. Groom and P. Taylor (eds.), International Organisation, op. cit., pp.84-107.

73. See, for example, I. Claude, Swords into Plowshares, 3rd Ed., Random House, New York, 1964. Claude's work is a classic of the more institutional studies, and includes a critique of functionalism.

74. They suggest that this would involve isolating the elements of leadership, group size, bureau characteristics and voting bodies, to understand the whole.

75. J.W. Burton in J.W. Burton, A.J.R. Groom, C.R. Mitchell and A.V.S. de Reuck, op. cit., pp.12-18.

76. See Chapter Two.

77. With states or other IGOs as members.

78. See W.M. Evans, Organization Theory: Structures, Systems and Environments, John Wiley, London, New York, 1976, pp.148-169. See also W.M. Evans (ed.), Interorganizational Relations, Penguin, Harmondsworth, 1976.

79. W.M. Evans, Organization Theory, op. cit., p.149.

Chapter Two.

1. K.W. Deutsch, The Nerves of Government: Models of Political Communication and Control, Free Press, Collier-Macmillan, New York, London, 1963, p.77.

2. B.A. Turner, Man-Made Disasters, Wykeham Publications, London, 1978, p.124.

3. See K.W. Deutsch, op. cit.

4. See K.W. Deutsch, ibid., pp.147-148.

5. See R.J. Lieber, Theory and World Politics, George Allen & Unwin, London, 1972, pp.72-73. See also R. Tooze, "Communications Theory", in T. Taylor (ed.), Approaches and Theory in International Relations, Longman, London and New York, 1978, pp.205-236. Decision-making and performance change in response to feedback are discussed further below.

6. At an early stage in the research effort, a preliminary transnational framework of communications was postulated based on an extension of a framework stated as relevant to hazard control in the UK, as formulated by J.C. Chicken, in Hazard Control Policy in Britain, Pergamon Press, Oxford, 1975. As well as providing an aid to thought, the diagrammatic framework was shown to a number of individuals interviewed. In Chapter Eight, this framework is reassessed. For my original, see Appendix One.

7. F.E. Kast and J.E. Rosenzweig, Organisation and Management, McGraw-Hill Kogusha, London and Tokyo, 1974, p.370.

8. Turner considered information filtering and associated problems in pre-disaster stages. See B.A. Turner, op. cit., pp.138-139.

9. See K.W. Deutsch, op. cit., pp.117-127. On transnational interactions, see R.O. Keohane and J.S. Nye (eds.), Transnational Relations and World Politics, Harvard U.P., Cambridge, Mass., 1972, pp.xii-xvi. Deutsch sees quantification as possible despite difficulties.

10. See, for example, R.J. Lieber, op. cit., p.76 and K.W. Deutsch, op. cit. Economic and social theories of exchange have, in particular, taken transactions to include both tangible and intangible commodities in situations of exchange, for example goods traded against credit or in social terms, advice or physical service in exchange for prestige or status. See A. Heath, Rational Choice and Social Exchange: A Critique of Exchange Theory, Cambridge U.P., Cambridge, 1976, pp.7-29.

11. Unless regional divisions are introduced. See K.J. Holsti, International Politics, Prentice-Hall, Englewood Cliffs, N.J., 1967.

12. J.W. Burton, World Society, Cambridge U.P., Cambridge, 1972, p.46.

13. As used in probability investigation. Apples are members of the set of apples, as pears are members of the set of pears, but both are members of the larger set of fruit. See J.W. Burton, ibid., p.48.

14. For example, through risk assessment experiments and international meetings and workshops. These are discussed elsewhere in this thesis.

15. See H. Rose and S. Rose, Science and Society, Penguin, Harmondsworth, 1969, pp.179-197. They are careful to qualify the limits on internationalisation reflected in industrial ties, military ties and the like.

16. See Chapter One, pp.54-55. See also F.E. Kast and J.E. Rosenzweig, op. cit., pp.141-142.

17. W.M. Evans, Organization Theory: Structures, Systems and Environments, John Wiley, London, New York, 1976, pp.149-153.

18. W.M. Evans, ibid., p.151.

19. J.D. Steinbruner, The Cybernetic Theory of Decision: New Dimensions of Political Analysis, Princeton U.P., Princeton, N.J., 1974, p.16.

20. Burton goes as far as to advocate a 'problem-solving approach' to be used in practical terms to assist in the reassessment of perceptions and the search for positive-sum outcomes in situations of conflict. Central to the approach is the actors definition of the problem underlying the conflict. See J.W. Burton, Deviance, Terrorism and War: The Process of Solving Unsolved Social and Political Problems, Martin Robertson, Oxford, 1979.

21. Such issues are returned to in the course of the thesis, with elaboration on the views held by different actors.

22. G.T. Allison, Essence of Decision: Explaining the Cuban Missile Crisis, Little, Brown & Co., Boston, 1971, p.77.

23. J.D. Steinbruner, op. cit., p.66.

24. R. Cyert and J. March, A Behavioural Theory of the Firm, Prentice-Hall, Englewood Cliffs, N.J., 1963.

25. F.E. Kast and J.E. Rosenzweig, op. cit., p.415.

26. See Chapter Five, pp. 202-208.

27. From H.A. Simon's 'satisficing' model of the firm. See H.A. Simon, "A Behavioural Model of Rational Choice", Quarterly Journal of Economics, Vol. 69, February 1955, and reprinted in H.A. Simon, Models of Man, Social and Rational, John Wiley, New York, 1957, pp.241-260. See also J.D. Steinbruner, op. cit., p.62.

28. K.W. Deutsch, op. cit., p.88. See also R.J. Lieber, op. cit., pp.74-75.

29. G.T. Allison, op. cit., p.77. See also K.W. Deutsch, op. cit., pp.187-192.

30. Turner notes that prevention of disaster would, to be truly effective, need perfectly accurate and continuous feedback. See B.A. Turner, op. cit., p.194.

31. See, for example, J.H. de Rivera, The Psychological Dimension of Foreign Policy, Merrill, Columbus, Ohio, 1968; R. Jervis, The Logic of Images in International Relations, Princeton U.P., Princeton, N.J., 1970; and I.L. Janis, Victims of Groupthink, Houghton-Mifflin, Boston, 1972. Some analysts have applied cognitive concepts at the state-centric level, for example in deterrence theory, which are not relevant here.

32. See A.N. Oppenheim, "Psychological Aspects of International Relations", in A.J.R. Groom and C.R. Mitchell (eds.), International Relations Theory: A Bibliography, Frances Pinter, Nichols Publishing Co., London, New York respectively, 1978, p.175.

33. H.A. Simon, Models of Man, Social and Rational, op. cit., p.198 and quoted in B.A. Turner, op. cit., p.133. See also H.A. Simon, "Theories of Decision-Making in Economics and Behavioural Science", in F.G. Castles et al., (eds.), Decisions, Organisations and Society, 2nd Ed., Penguin, Harmondsworth, 1976, pp.30-48 (excerpts from an article originally published in 1959).

34. J.D. Steinbruner, op. cit., p.87.

35. For example, in sociology, psychology, politics and, much more narrowly, economics. For a blend of sociological and political analysis of the concept, see J.W. Burton, Deviance, Terrorism and War, op. cit. Burton attempts to separate sociologically derived from biologically derived values, and assesses their political consequences.

36. See G. Vickers, "Values, Norms and Policies", in F.G. Castles et al., (eds.), op. cit., pp.129-141 (originally published in 1973).

37. G. Vickers, ibid., p.133. From the International Relations viewpoint, a special edition of International Organisation has examined values and norms applying internationally over certain issue areas and termed 'regimes'. However, although a useful concept, the whole regime approach, as argued by Susan Strange in that issue (edited by S.D. Krasner) is largely state-centric and not of great relevance here. See International Organisation, Vol. 36, No. 2, Spring 1982.

38. In their survey of International Relations approaches, Dougherty and Pfaltzgraff suggest that any comprehensive theory of conflict would require inputs from virtually every field of academic inquiry concerned with human behaviour! See J.E. Dougherty and R.L. Pfaltzgraff, Contending Theories of International Relations: A Comprehensive Survey, 2nd Ed., Harper & Row, New York, 1981, pp.181-182.

39. Some important approaches relevant to political and sociological analysis have been encapsulated as the debate between elitist and pluralist conceptions. A very useful summary of the debate has been compiled from original papers by F.G. Castles et al., (eds.), op. cit. In particular, see the contribution by P. Bachrach and M.S. Baratz, "Two Faces of Power", pp.392-404, originally published in American Political Science Review, Vol. 56, 1962, pp.947-952. The elitist view holds that every human institution involves relatively stable power structures related to its internal stratification. Dominant groups can thus be recognised where interests regularly prevail (after Domhoff, Aaronovitch, Miliband, Hunter and C. Wright Mills). See C.J. Hewitt, "Elites and Distribution of Power in Britain", in F.G. Castles et al., (eds.), op. cit., p.349. Pluralists see power as participation in decision-making reflecting actual activity rather than elite reputations of power (after Dahl, Lasswell and Kaplan). See R.A. Dahl, "A Critique of the Ruling-Elite Model", in F.G. Castles et al., (eds.), op. cit., pp.370-379. Exchange theorists suggest power derives from possession of a 'resource' others require and cannot obtain elsewhere, or from social reciprocity. See P.M. Blau, Power and Exchange in Social Life, John Wiley, New York, 1964 and A. Heath, op. cit. Note that Keohane and Nye considered that an effect of transnational relations would be the fostering of transnational pluralism. See Chapter One, pp.46-48.

40. Of particular influence is the work of Bachrach and Baratz, who attempt to combine elements of elitist and pluralist viewpoints, arguing that neither on its own is adequate. See P. Bachrach and M.S. Baratz, op.

cit., and P. Bachrach and M.S. Baratz, Power and Poverty: Theory and Practice, Oxford U.P., London, 1970.

41. E.E. Schattschneider, The Semisovereign People, Holt, Rinehart & Winston, 1960, p.71. Emphasis by Schattschneider.

42. See the works of Bachrach and Baratz, op. cit., and J.W. Jenkins, "The Case of Non-Decisions", extract from Policy Analysis, Martin Robertson, 1978, reprinted in A.G. McGrew and M.J. Wilson (eds.), Decision Making: Approaches and Analysis, Manchester U.P., Manchester, 1982, pp.318-326.

43. See J.W. Burton, Deviance, Terrorism and War, op. cit., pp.140-156.

Summary and Operationalisation.

1. Some modifications have been made to the original wording to improve clarity. The term 'political' is used as discussed in Chapter Two. 'Economic constraints' refers to the limitations of resources available, the allocation of which is partially a political issue. References to the likelihood of disaster acknowledge the low probability levels involved, where changes to the level of risk in real terms would be difficult to appreciate cognitively, or to estimate statistically.

2. E.H. Carr, What is History? Penguin, Harmondsworth, 1961, p.11.

3. See A. Ryan, The Philosophy of the Social Sciences, Macmillan, London, 1970, p.236 and T. Kuhn, The Structure of Scientific Revolutions, 2nd Ed., University of Chicago Press, London, 1962, 1970.

4. Notably, Nature, New Scientist and Science, all of which are aimed at international readership. All issues of Nature and New Scientist from the origins of the debate to 1981 were examined.

5. See notes to Chapter Four, p.411 note 1.

6. Mainly from the United States and the United Kingdom.

7. For example, the European Science Foundation, the Committee on Genetic Experimentation and the Association of Scientific, Technical and Managerial Staffs. International and domestic organisations are involved.

8. An historian, Charles Weiner, realising the importance of recombinant DNA, established an archive to provide an international information resource. More than 120 interviews were recorded or transcribed, and 1700 letters, 1500 documents and 11,000 articles had been collected and catalogued by October 1978. Throughout this thesis, documents from the MIT Archive, Recombinant DNA Collection will simply be cited 'MIT Archives'. For a description of the utility and work of this project, see J. Dorman, "History as She is Made", New Scientist, 10 January 1980, pp.86-88.

Chapter Three.

1. The broad category of techniques used to produce what are here described as recombinant DNA molecules perhaps engender different perceptions when labelled 'genetic engineering' or 'gene splicing' than when labelled 'recombinant DNA techniques', 'genetic manipulation' or

when in conjunction with other techniques are termed 'biotechnology'. See below, pp.133-137

2. See S.R. Kushner, "The Development and Utilization of Recombinant DNA Technology", in J. Richards (ed.), Recombinant DNA: Science, Ethics and Politics, Academic Press, London, 1978. See also J.D. Watson and J. Tooze, The DNA Story: A Documentary History of Gene Cloning, W.H. Freeman & Co., San Francisco, 1981, pp.529-583 and C. Grobstein, A Double Image of the Double Helix: The Recombinant DNA Debate, W.H. Freeman & Co., San Francisco, 1979, pp.3-16.

3. Shown at Cold Spring Harbor, by A. Hershey and M. Chase.

4. Late nineteenth century biology had already identified the role of chromosomes and had determined that traits were controlled by hereditary factors linked to chromosomes in some collective fashion. The concept of what we call a gene was therefore known, but identification of the biochemical importance of DNA is the real starting point of significance to the concerns here. The above provides a very brief summary of this.

5. J.D. Watson and F.H.C. Crick, "Molecular Structure of Nucleic Acids. A Structure for Deoxyribose Nucleic Acid", Nature, Vol. 171, 25 April 1953, pp.737-738.

6. J.D. Watson and F.H.C. Crick, "Genetic Implications of the Structure of Deoxyribose Nucleic Acid", Nature, Vol. 171, 30 May 1953, pp.964-967.

7. Precise references to the work that Watson and Crick developed upon can be found in the two papers referenced in notes 5 and 6. The importance of the suggested pairings to their analysis of the DNA structure is indicated in J.D. Watson, The Double Helix, Penguin, Harmondsworth, 1968, pp.101-104 and pp.151-155.

8. For a description of modifications on the DNA structure which could form in certain circumstances, including a reverse of the traditional right-handed spiral discussed below, see A. Scott, "A New Twist in the DNA Story", New Scientist, 22 March 1984, pp.42-44.

9. J.D. Watson and J. Tooze, op. cit., pp.542-545.

10. A complementary strand refers to the strand of bases comprising paired bases to an original strand. RNA results from bases pairing with only one of the original two DNA strands in the double helix.

11. See below, p.119ff for the importance of expression of genes in recombinant DNA work.

12. See D.A. Jackson, "Principles and Applications of Recombinant DNA Methodology", in D.A. Jackson and S.P. Stich (eds.), The Recombinant DNA Debate, Prentice-Hall, Englewood Cliffs, N.J., 1979, p.43.

13. C. Grobstein, op. cit., p.11.

14. U. Goodenough, Genetics, Holt, Rinehart & Winston, London, 1978, p.174. Note that mutations can also occur at the level of whole chromosomes, in addition to the level of the gene, the concern here.

15. See G.S. Stent, Molecular Genetics: An Introductory Narrative, W.H. Freeman & Co., San Francisco, 1971, pp.388-389. See also J.D. Watson and J. Tooze, op. cit., pp.541-542. The various forms that bases can take are called tautomeric forms. Variety is a result of different conditions existing due to a number of agents and chemicals collectively called 'mutagens'. Indeed heat is included. See U. Goodenough, op. cit., pp.174-223.

16. For a discussion of the importance of molecule size within the structure, see J.D. Watson, op. cit., pp.148-155. Purines are larger molecules than pyrimidines, and it was the problem of size that enabled Watson and Crick to reject an earlier approach to the structure of DNA which paired like bases with like.

17. See U. Goodenough, op. cit., pp.185-198. Goodenough indicates, for example, that it has been estimated that over 100 heat-induced mutations occur in a typical human cell each day, but that the vast majority are no doubt repaired, p.189.

18. See C. Grobstein, "The Recombinant DNA Debate", July 1977, in Recombinant DNA: Readings from Scientific American, W.H. Freeman & Co., San Francisco, 1978, p.132.

19. C. Grobstein, idem.

20. See S.R. Kushner, op. cit., pp.40-41.

21. C. Grobstein, A Double Image of the Double Helix, op. cit., p.13 and J.D. Watson and J. Tooze, op. cit., p.558.

22. See S.R. Kushner, op. cit., p.41 and D.A. Jackson, op. cit., p.44. Kushner also indicated that the biological function of this enzyme was not understood. See also U. Goodenough, op. cit., p.193.

23. For references to the laboratories and workers, see S.R. Kushner, op. cit., p.43. On ligase, see also D.A. Jackson, op. cit., pp.45-46 and S.N. Cohen, "Experimental Techniques and Strategies for DNA Cloning", in J. Morgan and W.J. Whelan (eds.), Recombinant DNA and Genetic Experimentation, Pergamon Press, Oxford, 1979, p.50.

24. See C. Grobstein, A Double Image of the Double Helix, op. cit., pp.12-13.

25. Escherichia coli, or E. coli for short, is one of the most thoroughly investigated bacteria, and the cell of which more is known in terms of genetic make-up than any other. It possesses a single chromosome of about 4 million base pairs, enough to encode for about 4,000 genes. About one-third of the DNA present can be accounted for as genes coding for known functions. It inhabits the human gut, and is therefore non-pathogenic to man, which is probably one reason why it was popular as an experimental subject. With relatively modest nutritional and environmental requirements, it will multiply once every twenty minutes, one cell thus potentially giving rise to one trillion cells in a period of around fourteen to fifteen hours. See N. Wade, The Ultimate Experiment: Man-Made Evolution, Walker & Co., New York, 1977, p.19; D.A. Jackson, op. cit., p.50; and, for a more detailed analysis of its characteristics, G.S. Stent, op. cit., pp.46-54. This particular organism also became the most favoured for recombinant DNA work, but its ability to exist in the human gut, in its natural form, gave rise

to fears over certain types of experiment. These issues are discussed further in Chapter Four.

26. See S.R. Kushner, op. cit., pp.42-43 and U. Goodenough, op. cit., pp.156-158.

27. See D.A. Jackson, op. cit., pp.47-49. For tables of various restriction enzymes and the sequences they recognise, see U. Goodenough, op. cit., p.226 and J.D. Watson and J. Tooze, op. cit., p.554. Complementary tails are often called 'sticky ends'.

28. See D.A. Jackson, op. cit., p.49ff.

29. See D.A. Jackson, idem and U. Goodenough op. cit., pp.147-149.

30. See U. Goodenough, ibid., p.541; D.A. Jackson, op. cit., p.50,; C. Grobstein, A Double Image of the Double Helix, op. cit., p.13; J.D. Watson and J. Tooze, op. cit., pp.559-560; and R. Hutton, Bio-Revolution: DNA and the Ethics of Man-Made Life, New American Library, New York, 1978, pp.37-41.

31. See J.D. Watson and J. Tooze, op. cit., p.559 and R. Hutton, op. cit., pp.37-41.

32. See S.R. Kushner, op. cit., pp.47-49 and J.D. Watson and J. Tooze, op. cit., pp.562-563.

33. See S.R. Kushner, op. cit., p.51 and S.N. Cohen, op. cit., p.51. See also pp.124-125 below on 'expression'.

34. See S.R. Kushner, op. cit., p.51.

35. See J.D. Watson and J. Tooze, op. cit., p.563. For a description of experimental hybridisation, see U. Goodenough, op. cit., pp.250-251.

36. It has been stated that there would be a problem of defining 'recombinant DNA'. Part of this problem is that a process known as 'recombination' exists in nature, essentially taken to mean 'any rearrangement of genetic material'. See I. Herskowitz, Basic Principles of Molecular Genetics, 1st Ed., Thomas Nelson & Sons, London, 1967, pp.90-189 and U. Goodenough, op. cit., pp.503-538.

37. See S.R. Kushner, op. cit., p.46. See also D.A. Jackson, op. cit., pp.50-51.

38. RNA from the DNA template, in codons, orders the sequence of amino acids in the process of translation. See above.

39. S.D. Ehrlich and A. Goze, "Expression of Foreign Genes", in J. Morgan and W.J. Whelan (eds.), op. cit., p.110. An exception of note, they point out, is if the product of the foreign gene is actually toxic to the host. In this case, in spite of the correct interpretation of all the signals, the expression may not be observed. On the general problems, see D.A. Jackson, op. cit., p.52.

40. S.R. Kushner, op. cit., p.38.

41. See S.D. Ehrlich and A. Goze, op. cit., pp.110-111. For example, Bacillus subtilis does not express E. coli genes and failure to recognise the start and stop signals involved is a possible reason.

42. Some simplification has been made in omitting the roles of ribosomal RNA and transfer RNA. Ribosomes move along messenger RNA and 'translate' the codon sequences into protein chains. Transfer RNA is chemically linked to amino acids and facilitates the recognition of the correct amino acid for each codon on the messenger RNA sequence. The above occurs outside the nucleus of the cell, in the cytoplasm where the amino acids are available. The three types of RNA each form from DNA in the nucleus and independently exit into the surrounding cytoplasm. See J.D. Watson and J. Tooze, op. cit., pp.544-546. See also U. Goodenough, op. cit., p.262 and pp.301-339 and S.D. Ehrlich and A. Goze, op. cit., pp.110-112.

43. The mechanism of splicing in the maturing of mRNA is not fully understood. It is thought, however, to involve sequences of nucleotides on either side of the introns (consensus sequences) to which small RNA molecules (already known to exist in eukaryotic cells) could bond. The short RNA molecules would thus cause a loop to form in the primary transcript, preceding the splicing and joining of the RNA where the loop begins and finishes, aligned by the small RNA. Introns would comprise the looped section subsequently removed. See J.D. Watson and J. Tooze, op. cit., pp.571-574. On the importance of this, see S.D. Ehrlich and A. Goze, op. cit., p.111. Note the coding DNA sections are known as exons.

44. See U. Goodenough, op. cit., pp.334-336 and S.D. Ehrlich and A. Goze, op. cit., p.113. Protection could take the form of their very configuration and/or amino acid sequence. The threat is from intracellular nucleases.

45. See J.D. Watson and J. Tooze, op. cit., pp.564-565; D.A. Jackson, op. cit., pp.51-52; S.D. Ehrlich and A. Goze, op. cit., pp.113-114; S.N. Cohen, op. cit., p.51; and W.J. Rutter, "Production of 'Valuable' Proteins in Alternate Biological Hosts", in J. Morgan and W.J. Whelan (eds.), op. cit., pp.123-128.

46. D.A. Jackson, op. cit., p.51.

47. See W.J. Rutter, op. cit., p.124. Rutter discusses hormones by way of example.

48. See S.D. Ehrlich and A. Goze, op. cit., p.113 and W.J. Rutter, op. cit., pp.124-125.

49. See "Banking DNA Sequences", editorial, Nature, Vol. 285, 8 May 1980, p.59.

50. See U. Goodenough, op. cit., p.4.

51. See National Institutes of Health, Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, Part One, US Department of Health, Education and Welfare, Bethesda, Maryland, October 1977, pp.11-12.

52. A. Campbell, "Natural Modes of Genetic Exchange and Change", in J. Morgan and W.J. Whelan (eds.), op. cit., pp.21-27. See above for a description of bacteriophages and plasmids.

53. Note that the term 'barrier' relates to genetic selection against occurrences rather than a literal barrier. A barrier cannot be

attributed with any 'purpose' in that evolution has no foresight. Nevertheless, the terms 'purpose' and 'barriers' are frequently used as convenient shorthand which is useful as long as the convention is understood. See A. Campbell, ibid., p.25. It is worth noting, however, that man is purposeful, in every sense of the word, in his use of recombinant DNA techniques.

54. G. Bertoni, "Laboratory Genetic Manipulations", in J. Morgan and W.J. Whelan (eds.), op. cit., pp.37-42.

55. G. Bertoni, ibid., p.41. Note that in vitro refers to the laboratory practices for creating recombinant DNA molecules rather than the natural in vivo processes.

56. See U. Goodenough, op. cit., p.4 and I. Herskowitz, op. cit., pp.90-189.

57. They use both terms, see House of Lords, Select Committee on the European Communities, Biomolecular Engineering, HMSO, London, 5 August 1980, p.vii.

58. See N. Wade, op. cit.

59. See S.N. Cohen, op. cit., p.49.

60. See the Advisory Council for Applied Research and Development, the Advisory Board for the Research Councils, and the Royal Society, Biotechnology: Report of a Joint Working Party, HMSO, London, March 1980. See also House of Lords, Select Committee, op. cit., which sees biomolecular engineering as a subsection of biotechnology.

61. Reference to arguments concerning in vivo or natural recombination is made elsewhere in this thesis.

62. US Department of Health, Education and Welfare, National Institutes of Health, "Guidelines for Research Involving Recombinant DNA Molecules", Federal Register, 29 January 1980, p.6724. This definition has been refined from definitions used in previous guidelines published in the Federal Register on 7 July 1976 and 29 December 1978.

63. GMAG, Second Report of the Genetic Manipulation Advisory Group, HMSO, London, December 1979, p.2. See also their First Report, HMSO, London, May 1978, pp.4-7, for a description of difficulties that were faced in narrowing the definition sufficiently.

64. See Second Meeting of the EMBO Standing Advisory Committee on Recombinant DNA, held at London on 18-19 September 1976, Report and Recommendations, Annex 2, "A Definition of Recombinant DNA Research", EMBO, Heidelberg.

65. For further definitions, see Memorandum from W.J. Gartland to the Director, NIH, 4 April 1977, "Definitions of Recombinant DNA", MIT Archives. Ten different definitions are compiled from: the NIH; UK Williams Report; GMAG; Canada; Netherlands; EMBO; two proposed definitions for the purposes of US legislation; a petition from two US bodies; and some proposals from S.N. Cohen.

66. When considering revision of the guidelines, the NIH requested recommendations and amongst others contacted Dr. J. Tooze of EMBO. It

was suggested that synthetic DNAs be included and subsequently D.S. Fredrickson, the Director, NIH, sent a document, "Selected Issues for Committee Review", to members of the Recombinant DNA Advisory Committee (see elsewhere for the history of the RAC) asking for views on the inclusion of synthetic DNA as one issue. They accepted its inclusion at their 27-28 April meeting. See Minutes of the Meeting of the ESF Liaison Committee for Recombinant DNA Research, 22-23 May 1978, European Science Foundation, Strasbourg, and Minutes of Meeting, 27-28 April 1978, Recombinant DNA Molecule Program Advisory Committee, Department of Health, Education and Welfare, NIH, Washington D.C.

67. See GMAG, Second Report, op. cit., p.13. See also R. Walgate, "GMAG Wants Self-Cloning Notification", Nature, Vol. 278, 1 March p.3.

68. GMAG, Second Report, op. cit., p.13.

69. See D.A. Jackson, op. cit., p.54.

70. A number of commercial firms have been applying recombinant DNA techniques to try to produce interferon in quantity. A very large potential market looms for this.

71. See A.M. Chakrabarty, "Recombinant DNA: Areas of Potential Application", in D.A. Jackson and S.P. Stich (eds.), op. cit., pp.56-66.

72. See B. Miflin and P.J. Lea, "The Genetic Manipulation of Crop Plants", Nature, Vol. 308, 5 April 1984, pp.498-499, for a summary of two recent symposia on the genetic manipulation of plants. See also A.M. Chakrabarty, op. cit., p.63 and B. Dixon, "Genetic Engineering in the Fields", New Scientist, 8 June 1978, pp.684-686.

73. In an example of violation of the US guidelines, a researcher, Dr. Martin Cline, attempted such an experiment in Italy and Israel. See Chapter Eight.

74. See, for example, E. Yoxen, The Gene Business: Who Should Control Biotechnology?, Pan Books, London and Sydney, 1983 and J. Boldingh, "Genetic Engineering: A Key to Innovation in Industrial R & D"; R.J. Erickson, "The Potential of Genetic Engineering Technologies in the Production of Industrially Important Enzymes"; I.S. Johnson and J.P. Burnett, "Problems and Potential of Industrial Recombinant DNA Research", all in H.W. Boyer and S. Nicosia (eds.), Genetic Engineering, Elsevier/North-Holland Biomedical Press, Amsterdam, New York, Oxford, 1978.

75. See Nature, Vol. 283, 10 January 1980, pp.119-131, for a series of articles on "The Biology Business".

76. See, for example, S. Murphy, A. Hay, S. Rose, No Fire, No Thunder, Pluto Press, London, 1984. More will be said on this 'application' of recombinant DNA techniques elsewhere in this thesis in discussions on potential risk. It is argued from the viewpoint of the author that risk is a more applicable category, dissociated as far as possible from considerations of potential benefit.

Chapter Four.

1. A number of journalistic style accounts have proved useful as background material. See M. Rogers, Biohazard, Knopf, New York, 1977; J. Goodfield, Playing God, Hutchinson & Co., London, 1977; N. Wade, The Ultimate Experiment: Man-Made Evolution, Walker & Co., New York, 1977; J. Lear, Recombinant DNA: The Untold Story, Crown Publishers, New York, 1979; R. Hutton, Bio-Revolution: DNA and the Ethics of Man-Made Life, New American Library, New York, 1978. In addition, material from the MIT Archives Recombinant DNA Collection was of great importance.

2. See C. Grobstein, A Double Image of the Double Helix: The Recombinant DNA Debate, W.H. Freeman & Co., San Francisco, 1979, p.16.

3. Indeed, between 1955 and 1961, some ten to thirty million US children received polio immunisation infected by live SV40, who have not shown higher subsequent rates of malignancy appearing. See S. Krimsky, "Regulating Recombinant DNA Research", in D. Nelkin (ed.), Controversy: Politics of Technical Decisions, Sage, Beverly Hills and London, 1979, pp.227-253 and M. Rogers, "The Pandora's Box Congress", Rolling Stone, Vol. 189, 19 June 1975, p.36ff.

4. Interview with Paul Berg by R. Goodall, 17 May 1975, MIT Archives.

5. See Interview with John Tooze by C. Weiner, 26 March 1976, MIT Archives.

6. For reference to this and many of the following points, see "Chronology", Finding Aid, Recombinant DNA Collection, MIT Archives.

7. Berg had been reluctant to address such wider issues, preferring to see the issue as one of health hazard only. Interview with P. Berg, op. cit.

8. See "Chronology", Finding Aid, op. cit., and N. Wade, "Microbiology: Hazardous Profession Faces New Uncertainties", Science, Vol. 182, 9 November 1973, p.567.

9. See Chapter Three, p.117ff.

10. See Interview with P. Berg, op. cit. The conference proceedings have been published. See A. Hellman, M.N. Oxman and R. Pollack (eds.), Biohazards in Biological Research, Cold Spring Harbor Laboratory, New York, 1973. A report of the work of A. Lewis is included.

11. Some people have argued that recombinant DNA should never have been singled out for special treatment, to face constraints greater than elsewhere. The corollary of this would be that all hazardous activity should be treated as were the conjectured hazards associated with genetic manipulation. No other activity had dramatic calls for caution by those involved, except nuclear energy.

12. See N. Wade, "Microbiology: Hazardous Profession Faces New Uncertainties", op. cit., p.566. Training in microbiological techniques was, on a number of occasions, to be recommended as a precursor to carrying out genetic manipulations.

13. J.D. Watson in discussion in A. Hellman, M.N. Oxman and R. Pollack

(eds.), op. cit., p.351. He went on to criticise the National Cancer Institute for failing to live up to its moral if not legal responsibilities.

14. Plasmid Stanley Cohen 101 or pSC101. See Chapter Three, p.120. See also S.N. Cohen, "The Manipulation of Genes", Scientific American, July 1975, pp.24-33.

15. See S.N. Cohen et al., "Construction of Biologically Functional Bacterial Plasmids In Vitro", Proceedings of the National Academy of Sciences, Vol. 70, No. 11, November 1973, pp.3240-3244.

16. See C. Grobstein, op. cit., p.18; M. Singer, "Research with Recombinant DNA", Academy Forum, National Academy of Sciences, Washington D.C., 1977; M. Singer, "Re-examination of Basic Assumptions: Chairman's Introduction", in J. Morgan and W.J. Whelan (eds.), Recombinant DNA and Genetic Experimentation, Pergamon Press, Oxford, 1979, pp.185-186. See also M. Rogers, Biohazard, op. cit.; J. Goodfield, op. cit.; N. Wade, The Ultimate Experiment, op. cit.

17. See M. Singer and D. Söll, "Guidelines for DNA Hybrid Molecules", Science, Vol. 181, 21 September 1973, p.1114. Because of its importance this letter is attached. See Appendix Two.

18. Essentially covering Methods 1 and 2 discussed in Chapter Three. The letter also called for some consideration of then current large-scale preparations of animal viruses.

19. See M. Singer, Letter to H.L. Kornberg, 6 June 1974, MIT Archives. Note that Kornberg at the time of the letter was a member of the Ashby Committee which was to examine the issues in terms of the UK institutional response. See Chapter Six.

20. Interview with P. Berg, op. cit.

21. See J.D. Watson, "Why the Berg Letter was Written", in J. Morgan and W.J. Whelan (eds.), op. cit., p.190. In attendance were P. Berg, J. Watson, D. Baltimore, S. Weissman, D. Nathans, R. Roblin, N. Zinder and H. Lewis.

22. He had also proposed such a conference to the National Science Foundation Human Cell Biology Panel the previous month, although those in attendance declined to become personally involved, except for Norton Zinder.

23. In retrospect, Watson has bitterly regretted the actions they were to take. In 1979 he was to say that more expertise should have been brought together from fields involving infectious diseases. He acknowledged that in 1974 they intended to bring the expertise together later, with the microbiologists. See J.D. Watson op. cit. Many of Watson's misgivings arose out of the dramatic events following their actions five years earlier. This, however, is a general problem with hindsight, and in decision-making generally. Decisions must be located within the context of their time. Others regretted the politicised response as well as Watson, and in 1977 they considered publishing a letter to neutralise the consequences of their earlier actions, in the light of new knowledge. See J.D. Watson and J. Tooze, The DNA Story: A Documentary History of Gene Cloning, W.H. Freeman & Co., San Francisco, 1981, pp.251-261. Those involved included Berg, Cohen, Zinder and Watson.

24. See P. Berg, Letter to H.L. Kornberg, 18 June 1974, MIT Archives. Quoted by C. Weiner in "Historical Perspectives on the Recombinant DNA Controversy", in J. Morgan and W.J. Whelan (eds.), op. cit., pp.282-283. Weiner was responsible for setting up the archive at MIT.

25. Many accounts have just repeated the order of events as they occurred. The conference was held after the letter was published, implying, as the letter called for the conference, that the conference was a result.

26. See Interview with P. Berg, op. cit. See also "Rough Chronology of Drafts of NAS Committee Statement", handwritten by R. Roblin, in MIT Archives. Note also that two of the earlier drafts, one by Roblin and one by Berg, included a paragraph on the potential use of the new techniques for biological warfare. See below, pp.164-165.

27. See C. Weiner, op. cit., p.283 and "Chronology", Finding Aid, op. cit.

28. L. Crawford et al., Letter to J. Kendrew, 7 June 1974, MIT Archives. See also Interview with J. Tooze, op. cit., and see C. Weiner, op. cit., p.283.

29. P. Berg, D. Baltimore, H. Boyer, S. Cohen, R. Davis, D. Hogness, D. Nathans, R. Roblin, J. Watson, S. Weissman, N. Zinder, "Potential Biohazards of Recombinant DNA Molecules", Science, Vol. 185, 26 July 1974, p.303 and Proceedings of the National Academy of Sciences, Vol. 71, No. 7, July 1974, pp.2593-2594. The British journal Nature, however, chose to use the more sensational heading of "NAS Ban on Plasmid Engineering" in Nature, Vol. 250, 19 July 1974, p.174. Further, Nature, in missing three words out at the start of a very important paragraph, inferred that the concern was over all work with replicating bacterial plasmids. At best it was not clear. Finally, the Nature version omitted the final paragraph for editorial purposes. This had emphasised the awareness of Berg and company of what they were asking researchers to do, and it emphasised the personal nature of their appeal. Its omission gave an impression of an edict that they had tried to avoid. Some of the initial British response not surprisingly was not very favourable. E.S. Anderson wrote to Nature, saying that the letter addressed well understood work, and that he wished "it had been presented less pompously"! It was not until September that Berg found out about the Nature version, when about to appear with Anderson on a television programme. When Anderson heard the real intent he apologised on the air. Of those who met at MIT only H. Lewis did not sign, but others did who were not there, despite the view of Berg that he wanted to avoid a petition. The letter is appended. See Appendix Three.

30. The final draft amended the request for a 'meeting' to an 'international meeting', as a result of the growing awareness of the global nature of the research.

31. A fact on which a number of commentators have noted. See, for example, N. Wade, "Genetic Manipulation: Temporary Embargo Proposed on Research", Science, Vol. 185, 26 July 1974, pp.332-334; S. Krimsky, op. cit., p.231; S.P. Stich, "The Recombinant DNA Debate: Some Philosophical Considerations", in D.A. Jackson and S.P. Stich (eds.), The Recombinant DNA Debate, Prentice-Hall, Englewood Cliffs, N.J., 1979, p.183; C. Grobstein, op. cit., p.21. Not all comments are specific to the Berg letter, but quite often reference is to the overall uniqueness of the debate.

32. Berg felt the press headlines were abominable, although the content was all right. See Interview with P. Berg, op. cit.

33. J.D. Watson, op. cit., p.191.

34. In science the incentive to publish cannot be underestimated, and the NIH examined journals published during and after the deferral. See NIH, Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, Part One, US Department of Health, Education and Welfare, Bethesda, Maryland, 1977, p.17.

35. See N. Wade, "Genetic Manipulation: Temporary Embargo Proposed on Research", op. cit., p.332.

36. K. Hasunama, Letter to P. Berg, 15 February 1975, and R. Curtiss, "Memorandum", both in MIT Archives. Curtiss who was to become quite influential over the issues, also commented on how slow to act had been the nuclear scientists in addressing the problems they had unearthed. Curtiss, indeed, became something of a specialist in long typed single spaced documents!

37. See C. Norman, "NIH Backing for NAS Ban", Nature, Vol. 250, 26 July 1974, p.278. Note, Nature had published the letter a week earlier than in the US and this report appeared on the day Science published the Berg appeal. R.S. Stone's successor as Director, NIH, D.S. Fredrickson, would play a more important overall role.

38. The committee was established under Section 301 of the Public Health Service Act (42 U.S.C. 241) which mandates the Secretary of Health, Education and Welfare (the NIH is a section of this department) to "conduct research, investigations, experiments, demonstrations and studies relating to the causes, diagnosis, treatment, control and prevention of physical diseases and impairments of man". See Charter, of the Recombinant DNA Molecule Program Advisory Committee, Department of Health, Education and Welfare, Washington D.C., a copy of which is in the MIT Archives.

39. Charter, RAC, idem.

40. S.N. Cohen in discussion at a meeting at Wye College, Kent, in J. Morgan and W.J. Whelan (eds.), op. cit., p.296. This international meeting is discussed elsewhere in this thesis.

41. See A. Ryan, The Philosophy of the Social Sciences, Macmillan, London, 1970, for an analysis of the philosophical issues as they apply to both science and social science.

42. In attendance were: Berg, Singer, Baltimore, Zinder, Weissman, Roblin, H. Lewis, R. Novick, W. Gartland, A. Shatkin and D. Brown. See H. Lewis, "Biohazard Conference Organising Committee", notes, 17 October 1974, MIT Archives.

43. The eminent British scientist Sydney Brenner and Niels Jerne, the chairman of the EMBO Council.

44. See Interview with P. Berg, op. cit.

45. See H. Lewis, op. cit. The list of participants is available in the MIT Archives.

46. For the importance of bacteria, plasmids and viruses in recombinant DNA technology, see Chapter Three. Viruses as a focus of study also reflected the interest in their links with tumours. Focus on the bacterium, E. coli, would reflect its experimental importance and its existence in humans.

47. This and other international organisations are discussed in some depth in Chapter Seven. The IAMS subsequently had declining impact in the issue area as better placed organisations became involved.

48. The meeting was organised by the Gottlieb Duttweiler Institute for Economic and Social Studies, the Swiss Society for Cell and Molecular Biology, and Forum Davos. See Applications and Limitations of Genetic Engineering: The Ethical Implications, Proceedings: Gottlieb Duttweiler Institute, Switzerland, 1974. See also R.M. Croose Parry, "The Promethean Situation: A Report of the Davos Conference", Futures, April 1975, pp.169-173.

49. For example, excessive emphasis on the achievements of Swiss science and problems of research funds. In many ways, the conference was pitched at issues which were too broad concerning science policy in general.

50. See H. Wheeler, "The Challenge of Davos", in the Proceedings, op. cit.

51. Report of the Working Party on the Experimental Manipulation of the Genetic Composition of Micro-organisms, HMSO, London, Cmnd. 5880, January 1975. See Chapter Six, pp.216-222.

52. A number of useful sources provide insights into the content, but also the mood of this conference. In particular, see M. Rogers, "The Pandora's Box Congress", op. cit., and Biohazard, op. cit. His article for Rolling Stone is acknowledged as one of the best summaries of the meeting. See also G. Chedd, "Genetic Engineers Discuss our Future", New Scientist, 6 March 1975, p.547; N. Wade, "Genetics: Conference Sets Strict Controls to Replace Moratorium", Science, Vol. 187, 14 March 1975, pp.932-933; C. Norman, "Berg Conference Favours Use of Weak Strains", Nature, Vol. 254, 6 March 1975, p.6. See also S. Krimsky, op. cit. Much material is also available at the MIT Archive regarding this conference and its preparation, including a tape recording of the proceedings.

53. See G. Chedd, op. cit.

54. S. Krimsky, op. cit., p.233.

55. Quoted in N. Wade, "Genetics: Conference Sets Strict Controls to Replace Moratorium", op. cit., p.933.

56. N. Wade, ibid., p.932.

57. N. Wade, ibid., p.933 and C. Norman, "Berg Conference Favours Use of Weak Strains", op. cit., p.7.

58. See N. Wade, "Genetics: Conference Sets Strict Controls to Replace Moratorium", op. cit., p.933 and M. Rogers, Biohazard, op. cit., p.73.

59. N. Wade, "Genetics: Conference Sets Strict Controls to Replace Moratorium", op. cit., p.934.

60. They would, however, involve the use of genes specifying toxins such as botulinus. Ironically, in later years it was argued that many hazardous pathogens could be treated more safely than in their natural form if implanted in a disabled strain of E. coli or other bacterium.

61. See C. Norman, "Berg Conference Favours Use of Weak Strains", op. cit., p.7.

62. A. Capron, quoted in M. Rogers, Biohazard, op. cit., p.78.

63. Quoted in M. Rogers, ibid., p.83. This was modified by the time the final statement was published, but the intent remained.

64. Handwritten note from M. Singer to P. Berg at Asilomar. Copy in MIT Archives.

65. See P. Berg, D. Baltimore, S. Brenner, R. Roblin, M. Singer, "Asilomar Conference on DNA Recombinant Molecules", Nature, Vol. 255, 5 June 1975, pp.442-443, Science, Vol. 188, 6 June 1975 pp.991-994 and Proceedings of the National Academy of Sciences, Vol. 72, No. 6, June 1975, pp.1981-1984.

66. C. Weiner, op. cit., p.287. Sixteen members of the press attended, both from science and daily newspapers.

67. The letter is contained in the MIT Archive. See also RAC, Minutes of Meeting, 28 February 1975, MIT Archives. Ten members of the press attended.

68. For many Eastern European and Soviet scientists, this seems to have been their first knowledge of the techniques at all, according to Kaplan. See Interview with M. Kaplan by C. Weiner, 8 March 1976, MIT Archives.

69. O. Maaløe, Chairman, Scientific and Ethical Questions Involved in the Problem of a Moratorium on Certain Biological Research, Proceedings of an Informal Session, 31 August 1974, MIT Archives.

70. M. Kaplan et al., In Vitro Recombination (Genetic Engineering), Special Report to the Plenary Session of the 26th Pugwash Conference, August 1976. Copy in MIT Archives.

71. Draft of Berg letter, MIT Archives.

72. J.D. Watson op. cit., p.191. The Fort Detrick laboratory was involved in United States research into biological weapons.

Chapter Five.

1. See S.N. Cohen et al., Report to COGENE from the Working Group on Recombinant DNA Guidelines, the Committee on Genetic Experimentation, International Council of Scientific Unions, Miami, 1980, pp.34-36. See Chapter Seven for descriptions of COGENE and the ICSU.

2. "Guidelines for Research Involving Recombinant DNA Molecules", Federal Register, Vol. 41, No. 131, July 1976, pp.27911-27922.

3. See A. Zander, "The Discussion of Recombinant DNA at the University of Michigan", in D.A. Jackson and S.P. Stich (eds.), The Recombinant DNA

Debate, Prentice-Hall, Englewood Cliffs N.J., 1979, p.5. Three members of the first Michigan committee had been at Asilomar II.

4. A P3 laboratory under the NIH guidelines, see below. Funds were first requested from the NIH in May 1975, while the intention to build the laboratory was announced to the university as a whole in April 1976. See "Chronology", Finding Aid, Recombinant DNA Collection, MIT Archives.

5. See C. Norman, "Science Vs. the Public", Nature, Vol. 262, 15 July 1976, pp.163-165. See also "Cambridge (Mass.) Blocks the Genetic Engineers", New Scientist, 15 July 1976, p.115. Vellucci banned P3 and P4 work.

6. See G. Chedd, "Threat to US Genetic Engineering", New Scientist, 1 July 1976, pp.14-15. Note that it was a UK publication, which also provided comment on the issues, p.3.

7. For the views of Friends of the Earth, as expressed by its 'Committee for Genetics', see F.R. Simring, "On the Dangers of Genetic Meddling", Science, Vol. 192, 4 June 1976, p.940. Overall, though, as the recombinant DNA debate unfolded nationally, there were some internal divisions. See Interview with P. Lippe by A Seidman, 13 January 1978, MIT Archives. Lippe was the Washington FoE representative most active in the issue.

8. See "Guidelines for the Use of Recombinant DNA Molecule Technology in the City of Cambridge", January 1977, reprinted in C. Grobstein, A Double Image of the Double Helix: The Recombinant DNA Debate, W.H. Freeman & Co., San Francisco, 1979, pp.152-157. Also in Bulletin of the Atomic Scientists, Vol. 33, May 1977, pp.22-26.

9. C. Norman, "Judgement of the People", Nature, Vol. 265, 13 January 1977, pp.98-99.

10. Respectively, the University of California at San Diego, the University of Wisconsin and the University of Indiana. See N. Wade, "Gene-Splicing: At Grass-Roots Level a Hundred Flowers Bloom", Science, Vol. 195, 11 February 1977, pp.558-560.

11. Epidemiological studies for example. See RAC, Minutes of Meeting, 28 February 1975, MIT Archives.

12. "Chronology", Finding Aid, op. cit. Activities such as Senate hearings and legislation are considered below, pp.205-207 and Chapter Eight pp. 335-341.

13. Curiously, the newsletter was to be initially distributed to those who attended Asilomar II, and after two years only to those who contributed to it at least once a year. In attendance at the meeting were representatives from the European Science Foundation (R. Litman), the NAS, the Energy Research and Development Administration and NIAID (W. Rowe). See RAC, Minutes of Meeting, 12-13 May 1975, MIT Archives.

14. See RAC, Minutes of Meeting, 18-19 July 1975, MIT Archives and N. Wade, "Recombinant DNA: NIH Group Stirs Storm by Drafting Laxer Rules", Science, Vol. 190, 21 November 1975, p.767. See also NIH, Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, Part One, US Department of Health,

Education and Welfare, Bethesda, Maryland, 1977, p.20 and Genetic Engineering, Human Genetics and Cell Biology: Evolution of Technical Issues, RNA Recombinant Molecule Research (Supplement Report II), Subcommittee on Science, Research and Technology of the Committee on Science and Technology, US House of Representatives, Ninety-Fourth Congress, 2nd Session, Library of Congress, Serial KKK, Washington D.C., 1976, p.21.

15. D. Stetten, Letter to M.H. Edgell, University of North Carolina, 9 September 1975, MIT Archives.

16. See R. Goldstein, H. Echols et al., Petition sent to D. Stetten, NIH, 27 August 1975, MIT Archives. Most of the letter has been reproduced in "DNA Committee has its Critics", Nature, Vol. 257, 23 October 1975, p.637.

17. R. Curtiss, Letter to D. Stetten, NIH, 13 August 1975, MIT Archives. See also C. Norman, "Genetic Manipulation: Recommendations Drafted", Nature, Vol. 258, 18 December 1975, pp.561-564.

18. See J. King, "A Science for the People", New Scientist, 16 June 1977, pp.634-636.

19. J. King, ibid., pp.634-635.

20. See D. Hogness, Letter to L. Jacobs, NIH, 10 November 1975, MIT Archives.

21. See C. Norman, "Genetic Manipulation: Recommendations Drafted", op. cit., p.562 and N. Wade, "Recombinant DNA: NIH Sets Strict Rules to Launch New Technology", Science, Vol. 190, 19 December 1975, pp.1175-1179.

22. See RAC, Minutes of Meeting, 4-5 December 1975, MIT Archives. See also C. Norman, "Genetic Manipulation: Recommendations Drafted", op. cit., pp.562-563.

23. An unnamed committee member quoted in C. Norman, ibid., p.562. See also N. Wade, "Recombinant DNA: NIH Sets Strict Rules to Launch New Technology", op. cit., p.1176.

24. N. Wade, ibid., p.1178.

25. See RAC, Minutes of Meeting, 4-5 December 1975, op. cit., and N. Wade, "Recombinant DNA: NIH Sets Strict Rules to Launch New Technology", op. cit.

26. See D.S. Fredrickson, "Decision of the Director, NIH, to Release Guidelines for Research on Recombinant DNA Molecules, June 1976", Federal Register, Vol. 41, No. 131, July 1976, pp.27902-27911.

27. See Genetic Engineering, Human Genetics and Cell Biology: Evolution of Technical Issues, op. cit., p.23 and Appendix 6 pp.103-108. Notified were seventeen groups such as FAS, FoE, the League of Women Voters, Consumer Federation of America, Centre for Law and Social Policy, Environmental Defense Fund, etc. See also Transcript of Meeting of Ad hoc Advisory Committee to the Director, NIH, 9-10 February 1976, MIT Archives.

28. M. Rogers, Biohazard, Knopf, New York, 1977, p.178. Included were a Chief Judge, a hospital medical director, the Provost of MIT, the Director of the Institute of Society, Ethics and the Life Sciences, a lawyer and the President of the National Consumers' League.

29. R. Sinsheimer, Letter to D.S. Fredrickson, NIH, 5 February 1976, MIT Archives.

30. N. Wade also argued that human error would be likely. He noted that of the 5000 cases of laboratory acquired infections over thirty years to that date, a third occurred in laboratories with special containment facilities. Even in the highest containment of the US Army's biological warfare laboratories, there were over 423 cases of infection and three deaths over twenty-five years. He emphasised these occurred with known hazardous organisms. N. Wade, "Go-ahead for Recombinant DNA", New Scientist, 18/25 December 1975, p.684.

31. See Chapter Three, p.124ff.

32. R. Sinsheimer, op. cit., p.3.

33. R. Sinsheimer, Letter to D.S. Fredrickson, NIH, 12 February 1976, MIT Archives.

34. See E. Chargaff, Letter to D.S. Fredrickson, NIH, 8 February 1976, MIT Archives.

35. E. Chargaff, idem.

36. E. Chargaff, "On the Dangers of Genetic Meddling", Science, Vol. 192, June 1976, pp.938-939.

37. See N. Wade, The Ultimate Experiment: Man-Made Evolution, Walker & Co., New York, 1977, pp.110-111.

38. Co-organiser of the Cold Spring Harbor petition.

39. See P. Berg, Letter to D.S. Fredrickson, NIH, 17 February 1976 and M. Singer, Letter to D.S. Fredrickson, NIH, 13 February 1976, both in MIT Archives.

40. Goldstein was making a comparison with nuclear energy. See R. Goldstein, Letter to D.S. Fredrickson, NIH, 13 February 1976, MIT Archives. Note, many other letters are contained in the Archive on the above proposed guidelines and meetings.

41. D.S. Fredrickson, "Selected Issues for Committee Review", 19 March 1976, MIT Archives.

42. See N. Wade, "Recombinant DNA: The Last Look Before the Leap", Science, Vol. 192, 16 April 1976, p.236-238.

43. N. Wade, ibid., p.236. Wade regretted that minority views such as Sinsheimer's, despite their weight, were not discussed.

44. P. Berg, Letter to D.S. Fredrickson, NIH, 6 April 1976, MIT Archives.

45. J.F. Kelly, Letter to D.S. Fredrickson, NIH, 14 April 1976, MIT Archives.

46. The number of respondents was 322 who replied to a request in the FAS monthly publication. See FAS, "Results of DNA Straw Poll from April Public Interest Report". See also Letters to D.S. Fredrickson, NIH from the following: B. Trumball, 15 April 1976; R.N.L. Andrews, 9 June 1976; L. Salzman (Friends of the Earth), 17 May 1976; A. Schwartz, S. Wright, M. Ross, R.P. Weeks, M. Heirich, 21 April 1976; all in MIT Archives.

47. See N. Wade, The Ultimate Experiment, op. cit., p.102. By this time the guidelines were published.

48. See G. Wald et al., Petition, June 1976, MIT Archives.

49. See "Guidelines ..." op. cit., and "Decision of the Director, National Institutes of Health, to Release Guidelines for Reseach on Recombinant DNA Molecules", Federal Register, Vol. 41, No. 131, July 1976, pp.27902-27911. See also C. Norman, "Genetic Manipulation: Guidelines Issued", Nature, Vol. 262, 1 July 1976, p.2.

50. "Decision of the Director ..." op. cit., p.27905. Such work was to be allowed, but with stringent precautions.

51. Classes 3,4 and 5 of the Department of Health, Education and Welfare, Classification of Etiological Agents on the Basis of Hazard, Public Health Service, Center for Disease Control, Office of Biosafety, Atlanta, Georgia, 1974.

52. Some exceptions could be considered on the last point if 'social benefits' would be great and extra containment precautions were taken. See "Guidelines ...", op. cit., pp.27914-27917.

53. See, for example, C. Norman, "Genetic Manipulation: Guidelines Issued", op. cit., and C. Grobstein, "The Recombinant DNA Debate", in Recombinant DNA: Readings from Scientific American, W.H. Freeman & Co., San Francisco, 1978, p.141 and reprinted in C. Grobstein, op. cit., pp.32-33. The latter is included as Appendix Five.

54. See "Guidelines ...", op. cit., p.27912.

55. Department of State, Telegram, June 1976, in J.D. Watson and J. Tooze, The DNA Story: A Documentary History of Gene Cloning, W.H. Freeman & Co., San Francisco, 1981, p.81.

56. See "Decision of the Director ...", op. cit., pp.27905-27906.

57. W.N. Hubbard, Letter to D.S. Fredrickson, NIH, 16 July 1976, MIT Archives.

58. C.W. Pettinga, Letter to D.S. Fredrickson, NIH, 4 June 1976, MIT Archives. Pettinga sent this letter two days after attending the meeting with Fredrickson mentioned above.

59. Genetic Engineering, Human Genetics and Cell Biology: Evolution of Technical Issues, op. cit., p.51.

60. See Chapter Four, pp.151-152.

61. See "Guidelines ...", op. cit., pp.27920-27921.

62. See W.J. Gartland, Memorandum, 18 June 1976, Appendix C, NIH, Environmental Impact Statement, op. cit., Part Two.

63. See W.J. Gartland, ibid.

64. See "Decision of the Director ...", op. cit., pp.27910-27911.

65. US National Environmental Policy Act, 1969, quoted by R.M. Hartzman, Letter to the Office of General Counsel, Department of Health, Education and Welfare, 16 March 1977, MIT Archives. Hartzman was a lawyer retained by Friends of the Earth, who were pressing for an Environmental Impact Statement.

66. "Decision of the Director ..." op. cit., p.27906.

67. "Recombinant DNA Research Guidelines: Draft Environmental Impact Statement", Federal Register, Vol. 41, No. 176, 9 September 1976, pp.38425-38483.

68. NIH, Environmental Impact Statement, op. cit., Parts One and Two, October 1977.

69. "Recombinant DNA Research Guidelines: Draft EIS", op. cit., p.38434.

70. The complete list can be found in NIH, Environmental Impact Statement, op. cit., Part Two, Appendix I.

71. NIH, ibid., Appendix J. The following laws were examined in detail: The Occupational Safety and Health Act, 1970 (Public Law 91-596); The Toxic Substances Control Act (Public Law 94-469); The Hazardous Materials Transportation Act (Public Law 93-633); Section 361 of the Public Health Service Act (42 U.S.C. Sec. 264).

72. Interim Report of the Federal Interagency Committee, in NIH, Environmental Impact Statement, op. cit., p.10.

73. L.J. Lefkowitz, Attorney General of the State of New York, Comments on the Guidelines and Draft EIS, in NIH, Environmental Impact Statement, op. cit., Part Two, Appendix K. Indeed all comments were collated in this appendix.

74. NIH, Environmental Impact Statement, op. cit., Part One, p.118.

75. On this point see S. Wright, "Molecular Politics in Great Britain and the United States: The Development of Policy for Recombinant DNA Technology", Southern California Law Review, Vol. 51, No. 6, September 1978, pp.1383-1434.

Chapter Six.

1. See S.N. Cohen et al., Report to COGENE from the Working Group on Recombinant DNA Guidelines, Committee on Genetic Experimentation, International Council of Scientific Unions, Miami, 1980, p.37. By comparison, Japan had some 35 laboratories involved, Federal Republic of Germany 10-20, Canada 10-15, France 12, Australia 16, Switzerland 18 and all other states were in single figures. The estimates are derived from responses to a questionnaire organised by COGENE.

2. See S. Wright, "Molecular Politics in Great Britain and the United States: The Development of Policy for Recombinant DNA Technology", Southern California Law Review, Vol. 51, No. 6, September 1978, pp.1383-1434. This paper discusses a range of issues of relevance to this chapter. It is of note that Susan Wright herself was an active participant in the US debate, advocating the need for controls.

3. See "Chronology", Finding Aid, MIT Archives.

4. Report of the Committee of Inquiry into the Smallpox Outbreak in London in March/April 1973, HMSO, London, Cmnd. 5626, 1974.

5. See B.A. Turner, Man-Made Disasters, Wykeham Publications, London, 1978, pp.109-117. Turner, whose definition of disaster is used in this thesis, took the London smallpox outbreak as a case study. In particular, he emphasised the problems of relevant information, held by many people, which was not effectively brought together.

6. Or, a delay over generations where the host passed the information through the strain, or related strains.

7. Report of the Working Party on the Laboratory Use of Dangerous Pathogens, HMSO, London, Cmnd. 6054, 1975. Subsequently referred to as the Godber Report, after its chairman, Sir George Godber. Godber began his investigation before the Ashby working party, but published afterwards.

8. See S. Wright, op. cit., pp.1393-1394 and Chapter Four, pp.150-152.

9. See "Genetics: Conference Sets Strict Guidelines to Replace Moratorium", Science, Vol. 187, 14 March 1975, p.932. Note that the MRC advises the University Grants Committee on, among other things, laboratory funding.

10. See E. Ashby, ABRC Working Party on Genetic Manipulation of Micro-organisms: Note from the Chairman, ABRC (GE) 74/3, 26 August 1974, MIT Archives.

11. Report of the Working Party on the Experimental Manipulation of the Genetic Composition of Micro-organisms, HMSO, London, Cmnd. 5880, January 1975, p.3. Subsequently referred to as the Ashby Report, after its chairman. See also E. Ashby, Letter to P. Berg, 5 November 1974, MIT Archives. In the letter Ashby expressed his intentions of making the report a discussion document.

12. Ashby Report, op. cit., p.2.

13. See Chapter Eight, pp.326-332.

14. The techniques of achieving recombinant DNA molecules were not discussed in any depth, but at that time referred to Methods 1 and 2 outlined in Chapter Three.

15. Including bacteriology, cancer research, molecular biology in general, virology, biochemistry. The representatives were scientists with similar interests and could perhaps be classed as a distinct sociological group. See Ashby Report, op. cit., Appendix 2, "List of Expert Witnesses".

16. Ashby Report, op. cit., pp.6-7.

17. See B. Dixon, "Not Good Enough", New Scientist, 23 January 1975, p.186. Dixon applauds the motives of the Ashby group and the effect of stimulating discussion.

18. Ashby Report, op. cit., p.10.

19. Report of the Working Party on the Practice of Genetic Manipulation, HMSO, London, Cmnd. 6600, August 1976, p.11. Subsequently referred to as the Williams Report, after its chairman, Sir Robert Williams. See below.

20. Ashby Report, op. cit., p.9.

21. In the US, for example, the National Institutes of Health (NIH) Environmental Impact Statement, of October 1977, recognised the possibilities of 'deliberate misuse', but argued that as far as weapons were concerned, the application of recombinant DNA techniques would be outlawed under the Biological Weapons Convention. Discussion was limited in effect to this observation. See NIH, Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, Part One, US Department of Health, Education and Welfare, Bethesda, Maryland, 1977, pp.38-39.

22. See B. Dixon, op. cit., p.186.

23. "Amber Light for Genetic Manipulation", editorial, Nature, Vol. 253, 31 January 1975, p.295.

24. Ashby Report, op. cit., pp.12-13.

25. E. Yoxen, "Regulating the Exploitation of Recombinant Genetics", in R. Johnston and P. Gummett (eds.), Directing Technology, Croom Helm, London, 1979, pp.228-229. Yoxen refers to issues such as the medical policy or sort of technology which might be needed in the UK and the question of socially acceptable risk.

26. DES, "Genetic Manipulation of Micro-organisms", press notice issued on 6 August 1975, MIT Archives. As press coverage to date had been thin, the notice was more widely distributed to interested parties.

27. F. Mulley, quoted in DES, press notice, ibid., p.1.

28. Williams Report, op. cit., p.3.

29. "Forever Amber on Manipulating DNA Molecules?", editorial, Nature, Vol. 256, 17 July 1975, p.155. The conference had been organised under the auspices of the Research Councils and the Department of Health and Social Security.

30. See Williams Report, op. cit., p.14.

31. The Birmingham smallpox outbreak, see below.

32. See Williams Report, op. cit., Appendix I.

33. EMBO, Second Meeting of the EMBO Standing Advisory Committee on Recombinant DNA, held at London on 18/19 September 1976: Report and

Recommendations. Obtained from EMBO, Heidelberg. See also J. Tooze, "Genetic Engineering in Europe", New Scientist, 10 March 1977, pp.592-594.

34. Williams Report, op. cit., p.8.

35. "Genetic Guidelines: Handle with Care", editorial, Nature, Vol. 263, 2 September 1976, p.1. See also E. Lawrence, "Genetic Manipulation: Guidelines Out", in the same edition, pp.4-5.

36. See Williams Report, op. cit., p.12.

37. See J. Tooze, op. cit., p.592.

38. See Chapter Five, pp.196-197.

39. See Williams Report, op. cit., pp.13-14. Two reports were eventually produced by the UK central advisory group (GMAG, see below).

40. See F.R. Simring, Letter to D.S. Fredrickson, NIH, 19 June 1978, MIT Archives. Simring was the Executive Director of the Coalition for Responsible Genetic Research. She expounded the virtues of centralised advisory groups such as that of the UK.

41. See C. Sherwell, "Heading for Harmony?", Nature, Vol 266, 3 March 1977, pp.2-4.

42. See Williams Report, op. cit., p.13.

43. See R. Freedman, "Gene Manipulation: A New Climate", New Scientist, 27 July 1978, pp.268-269. See also "Memorandum Submitted by the Genetic Engineering Group of the British Society for Social Responsibility in Science", in Second Report from the Select Committee on Science and Technology, Recombinant DNA Research - Interim Report, HMSO, London, HC 355, 1979, p.206. Both of these references cite the uniqueness of GMAG.

44. See GMAG, First Report of the Genetic Manipulation Advisory Group, HMSO, London, Cmnd. 7215, 1978, pp.vii-viii. In addition, meetings were attended by a number of assessors from various government departments.

45. See "Blind Man's Buff at GMAG", Nature, Vol. 276, 14 December 1978, p.657. For an example of Ravetz' work on risk and society, see J.R. Ravetz, "The Political Economy of Risk", New Scientist, 8 September 1977, pp.26-27.

46. A Divisional Officer of ASTMS, interviewed in December 1980. Haber was particularly concerned with ASTMS policy regarding recombinant DNA research.

47. See Second Report from the Select Committee on Science and Technology, op. cit., p.156.

48. See R. Lewin, "GMAG Cold Shoulders AUT", New Scientist, 13 January 1977, p.61.

49. See S.J. Pirt, Letter to the Clerk of the Subcommittee of the Select Committee on Science and Technology, in Second Report from the Select Committee on Science and Technology, op. cit., Appendix 15, pp.245-246.

50. See Second Report from the Select Committee on Science and Technology, op. cit., pp.154-156.

51. See Godber Report, op. cit., p.10.

52. "Unions Move in on Dangerous Organisms", New Scientist, 21/28 December 1978, p.915.

53. See Report of the Investigation into the Causes of the 1978 Birmingham Smallpox Occurrence, HMSO, London, HC 1979-80 668, 1980. Subsequently referred to as the Shooter Report, after Professor Reginald Shooter who conducted the inquiry.

54. See Nature, Vol. 277, 11 January 1979, pp.75-81. The editorial and a number of reporters examine the Shooter Report. See also E. Yoxen, The Gene Business: Who Should Control Biotechnology?, Pan Books, London and Sydney, 1983, pp.56-57. Some consideration was given to prosecuting ASTMS under the Official Secrets Act, but this did not occur. The report itself was eventually published.

55. "All Safety Nets Failed, Says Shooter", Nature, Vol. 277, 11 January 1979, p.78.

56. See, for example, R.A. Bird, "DPAG Needs Public Interest Representatives", Letter to Nature, Vol. 278, 26 April 1979, p.776; R. McKie, "Union Steps up Lab Safety Campaign", Nature, ibid., p.772; "Plenty for GMAG to Do", Nature, Vol. 276, 2 November 1978, p.1. See also E. Yoxen, The Gene Business, op. cit., p.56.

57. See A. Hay, "Health and Safety 3 Years On", Nature, Vol. 270, 10 November 1977. See also Annual Reports of the HSC.

58. Williams Report, op. cit., p.16.

59. See R. Lewin, "Genetic Engineering and the Law", New Scientist, 28 October 1976, p.220.

60. See GMAG, First Report, op. cit., pp.4-5; R. Lewin, "Genetic Engineering and the Law", op. cit., p.221; A. Hay, op. cit., pp.91-92; "Britain and US Discuss Genetic Engineering", New Scientist, 18 November 1976, p.372; P. Newmark, "UK Extends the Law to Genetic Engineering", Nature, Vol. 273, 15 June 1978, p.482; "Law Catches Up with Genetic Engineering", New Scientist, 15 June 1978, p.732. All of these recognised that the scientific community were critical.

61. Quoted in R. Lewin, "Genetic Engineering and the Law", op. cit., and Draft Regulation 2, Health and Safety (Genetic Manipulations) Regulations, 1976, HSC.

62. See a published exchange of letters between M. Ashburner and J.H. Locke (HSE), Nature, Vol. 264, 4 November 1976, pp.2-3. See also J.A.W. McDonald (HSE) Letter, New Scientist, 11 November 1976. McDonald criticised Lewin, who replied in the same issue, p.353.

63. See "Britain and US Discuss Genetic Engineering", op. cit., p.372.

64. This definition is quoted in Chapter Three, p.135.

65. HSE, Health and Safety at Work: Genetic Manipulation, HMSO, London, 1978.

66. See GMAG, First Report, op. cit., pp.8-10.

67. See GMAG, First Report, op. cit., pp.9-10.

68. See Evidence given by the HSE before the Select Committee on Science and Technology (Genetic Engineering Subcommittee) in Second Report from the Select Committee on Science and Technology, op. cit., p.68.

69. Magistrates were eventually to clear Birmingham University of specific charges regarding the blame for the death of the photographer. See L. McGinty, "An Unsavoury Outbreak", New Scientist, 31 July 1980, p.348. See also E. Yoxen, The Gene Business, op. cit., p.57. The case was brought by ASTMS.

70. See GMAG, First Report, op. cit., p.7.

71. Interview with Principal Scientific Officer from the Science and International Relations Branch of the DES, August 1980.

72. GMAG, First Report, op. cit., p.6.

73. See GMAG, First Report, op. cit., pp.24-26 and, for membership of the committee, pp.38-39. See also R. Lewin, "GMAG Falls Foul of Privacy Constraints", New Scientist, 15 December 1977, p.683.

74. See D. Dickson, "GMAG: Stormy Weather Ahead", Nature, Vol. 271, 5 January 1978, p.5. See also evidence of J. Maddox in Second Report from the Select Committee on Science and Technology, op. cit., pp.39-40.

75. GMAG, Second Report of the Genetic Manipulation Advisory Group, HMSO, London, Cmnd. 7785, 1979, p.14.

76. In Second Report from the Select Committee on Science and Technology, op. cit., p.159.

77. Second Report from the Select Committee on Science and Technology, op. cit., p.vii.

78. See R. Lewin, "GMAG Falls Foul of Privacy Constraints", op. cit., p.683.

79. See Memorandum from the Association of the British Pharmaceutical Industry and Memorandum from ICI, in the Second Report from the Select Committee on Science and Technology, op. cit., pp.195-205 and 238-241.

80. With exceptions such as the tragedy surrounding the Spanish poisoned cooking oil case, where the chemistry of the poison proved extremely difficult to identify, in order then to understand the biological effects.

81. Conjectured hazards of using genetically engineered organisms in industrial fermentors, for example, were examined in a European Commission sponsored report. See K. Sargeant and C.G.T. Evans, Hazards Involving the Industrial Use of Micro-organisms, study contract 430-78-5 ECI EUR 6349, 1979, Commission of the European Communities.

82. At the time of writing, proposals to put GMAG under the HSE revived. See "Genetic Manipulation: Watchdog to Bark Less Often", Nature, Vol. 302, 7 April 1983. This was some five years after the ABPI memorandum. Further discussion of the relationship between GMAG and the HSE is presented below.

83. See GMAG, First Report, op. cit., pp.18-19.

84. See D. Dickson, "US to Increase Public Participation in Regulation of DNA Research", Nature, Vol. 276, 30 November 1978, p.30. Membership was to go from 14 to 20, with 6 public interest representatives. See also, Department of Health, Education and Welfare, Guidelines for Research Involving Recombinant DNA Molecules, Federal Register, Vol. 45, No. 20, 29 January 1980.

85. One rather ineffectual public meeting of GMAG was held on 22 December 1978. Mainly scientists attended. See E. Lawrence, "Bacteriologists Lobby GMAG's First Public Meeting", Nature, Vol. 277, 4 January 1979, p.3.

86. See S. Wright, op. cit., p.1406. See also E. Yoxen, "Regulating the Exploitation of Recombinant Genetics", op. cit., p.232. Officials were, however, willing to give briefings, for example to myself and S. Wright.

87. See R. Lewin, "The View of a Science Journalist", in J. Morgan and W.J. Whelan (eds.), Recombinant DNA and Genetic Experimentation, Pergamon Press, Oxford, 1979, pp.273-276. Lewin both criticised the scientists secrecy and commented on the lack of UK public debate, which he partly attributed to national character. He also contrasted the Official Secrets Act of the UK against the Freedom of Information Act of the US.

88. "Genetic Manipulation: New Guidelines for UK", Nature, Vol. 276, 9 November 1978, pp.104-108.

89. "Manipulating MPs", New Scientist, 22 June 1978, p.848. See also L. McGinty, "Grabbing the Tiger", New Scientist, 15 June 1978, p.730.

90. See Second Special Report from the Select Committee on Science and Technology, HMSO, Session 1977-78, HC 609, 1978. (Not to be confused with the Second Report, op. cit.) See also "Manipulating MPs", op. cit.

91. Second Report from the Select Committee on Science and Technology, op. cit., p.v.

92. GMAG, the HSE, the DES, the DHSS, the Association of University Teachers, the Secretaries of State for Education and Science and Social Services, all appeared before the subcommittee. In addition, some 30 documents were also submitted from both the above groups and many other interest groups.

93. See R. McKie, "Britain's Shadow Science Minister Believes in Experts", Nature, Vol. 278, 29 March 1979, p.387. The Prime Minister has, however, expressed that she was personally sorry that the House decided to disband the Select Committee. See the exchange of letters between I. Lloyd, a Conservative MP, and M. Thatcher, PM, under the title "Why Britain Does Not Need a Minister for Science", Nature, Vol. 281, 27 September 1979, p.249.

94. R. Lewin, "Genetic Engineering Under the Parliamentary Microscope", New Scientist, 9 August 1979, pp.430-431.

95. M.G.P. Stoker, "Introduction and Welcome", in J. Morgan and W.J. Whelan (eds.), op. cit., p.xix.

96. See Chapter Seven, pp.246-247. It was an open meeting in that it was advertised, but press attendance was limited to three individuals.

97. See "Royal Society President Questions Anti-Science Dogma", New Scientist, 7 December 1978, p.748. The other reason was fear of disaster.

98. The DES, DHSS, DoE and the Ministry of Agriculture, Fisheries and Food. The latter would find itself involved if genetic manipulation of plant DNA was proposed. It would act in consultation with GMAG adopting an HSE type role applicable this time to plants. Work with plant pathogens already required a licence by the MAFF. See "Memorandum Submitted by the Ministry of Agriculture, Fisheries and Food (MAFF) on Behalf of the United Kingdom Agriculture Departments", in Second Report of the Select Committee on Science and Technology, op. cit., pp.266-267. See also GMAG, First Report, op. cit., pp.26-29. Work involving animal DNA was covered by GMAG.

99. See S. Wright, op. cit., pp.1400-1401.

100. See Second Report from the Select Committee on Science and Technology, op. cit., pp.171-187.

101. See Second Report from the Select Committee on Science and Technology, op. cit., evidence from both the Secretaries of State for Education and Science and for Social Services.

102. See Second Report from the Select Committee on Science and Technology, op. cit., pp.94-95. Indeed, on writing myself to the DHSS to request a briefing for the purposes of this thesis, it was suggested to me that the DHSS could probably not add anything further to what I had been told in briefings from the DES and the MRC. My letter to the DHSS had made no mention of whom I had already seen!

103. For a discussion of the position of Whitehall within foreign policy making, see J. Barber, Who Makes British Foreign Policy? Open University Press, Milton Keynes, 1976, pp.47-62.

104. See House of Lords Select Committee on the European Communities, Genetic Manipulation (DNA), HMSO, London, HL 188, 1980. See Chapter Seven, below.

105. Many are collected in their Second Report, op. cit.

106. For example J. Ravetz and J. Maddox.

Chapter Seven.

1. Identification of these states was primarily based on S.N. Cohen et al., Report to COGENE from the Working Group on Recombinant DNA Guidelines, Committee on Genetic Experimentation, International Council of Scientific Unions, Miami, 1980 and Report of the Federal Interagency Committee on Recombinant DNA Research: International Activities, US Department of Health, Education and Welfare, November 1977.

2. Taken from S.N. Cohen et al., op. cit., p.37. Ireland was not included in this report.

3. See G.L. Ada, Recombinant DNA Molecule Experimentation in Australia, MIT Archives (undated, but probably late 1976 or early 1977). This appears to be a report sent to the NIH in the US to keep them informed in return for progress reports from the US.

4. See G. Maslen, "Genetic Engineering Debate Reaches Australia", New Scientist, 5 April 1979, p.6.

5. See G. Maslen, idem and B. Lee, "Genetic Engineering Down Under", New Scientist, 24 July 1980, p.270.

6. S.N. Cohen et al., op. cit.

7. Report of the Federal Interagency Committee, op. cit., p.17.

8. See S.N. Cohen et al., op. cit. and Report of the Federal Interagency Committee, op. cit., p.18.

9. S.N. Cohen et al., op. cit., p.36 and Report of the Federal Interagency Committee, op. cit., p.18.

10. See S.N. Cohen et al., op. cit.

11. See G.M. Brown, Letter to D.S. Fredrickson, NIH, 28 June 1976, MIT Archives. See also Report of the Federal Interagency Committee, op. cit., pp.18-20 and "Canada: Guidelines Recommended", Nature, Vol. 265, 17 February 1977, p.577. The draft was received at the NIH on 28 June 1976.

12. See Guidelines for the Handling of Recombinant DNA Molecules and Animal Viruses and Cells, Minister of Supply and Services, Canada, 1977, MR 21-1/1977. Because the guidelines went wider than recombinant DNA work, there were extra categories.

13. S.N. Cohen et al., op. cit., p.68.

14. See S.N. Cohen et al., op. cit.

15. See Report of the Federal Interagency Committee, op. cit., p.21; S.N. Cohen et al., op. cit.; S. Godfredsen, "Denmark Follows UK on DNA Guidelines", Nature, Vol. 271, 23 February 1978. See also Minutes of Meetings of the European Science Foundation (ESF) Liaison Committee for Recombinant DNA Research, May 1978 and January 1979. Although working documents rather than official documents, these minutes do provide useful insights in general into activities within Europe.

16. See S.N. Cohen et al., op. cit. The scientists were 3 geneticists, 1 biochemist, 2 bacteriologists and 2 virologists.

17. C. Sherwell, "Heading for Harmony?", Nature, Vol. 266, 3 March 1977, p.2. See also Minutes of the Meeting of the ESF Liaison Committee, 22-23 May 1978, p.5 and Report of the Federal Interagency Committee, op. cit., pp.23-24.

18. By 1980 the membership was 4 experts in recombinant DNA, 4 scientists

not in the field and 4 "outstanding individuals". See S.N. Cohen et al., op. cit., p.69.

19. See Minutes of the ESF Liaison Committee Meetings, op. cit.

20. 6 members from molecular biology, 3 geneticists, 3 microbiologists, 1 virologist, 1 plant physiologist, 3 infectious disease experts, 3 epidemiologists, 2 enteric bacteria experts, 1 cell culture expert, 3 from public health and 1 from occupational health. See S.N. Cohen et al., op. cit., p.69.

21. See Interview with P. Kourilsky by C. Weiner, 20 March 1976, MIT Archives.

22. The main French research body responsible for science co-ordination between the French research councils.

23. Interview with P. Kourilsky, op. cit.

24. See Interview with G. Bernardi by C. Weiner, 29 August 1977, MIT Archives and Interview with P. Kourilsky, op. cit.

25. See Report of the Federal Interagency Committee, op. cit., pp.21-23.

26. J. Tooze, Emerging Attitudes and Policies in Europe, a review prepared for the Miles Symposium, June 1976, MIT Archives, p.7.

27. See J. Tooze, ibid., pp.7-9.

28. See Minutes of the ESF Liaison Committee, 22-23 May 1978, op. cit.

29. It was thought that industry would comply with the DGRST to protect future grants.

30. See S.N. Cohen et al., op. cit.

31. S.N. Cohen et al., op. cit., pp.34-37 and Report of the Federal Interagency Committee, op. cit., p.24. See also S. Saraf, "UN Biotechnology: Let a Hundred Labs Bloom", Nature, Vol. 307, 16 February 1984, p.583.

32. See Report of the Federal Interagency Committee, op. cit., p.24 and Minutes of the Meetings of the ESF Liaison Committee, May 1978, January 1979 and January 1980.

33. Report of the Federal Interagency Committee, op. cit., pp.24-25.

34. See D. Dickson, "NIH Censure for Dr. Martin Cline", Nature, Vol. 291, 4 June 1981, p.369. The case is detailed in Chapter Eight, pp.343-344.

35. See Report of the Federal Interagency Committee, op. cit., pp.25-26 and S.N. Cohen et al., op. cit.

36. See "The Biology Business", Nature, Vol. 283, 10 January 1980, p.123. See also D. Thomas, Production of Biological Catalysts, Stabilization and Exploitation, study contract 345-77-6 ECI F, EUR 6079, 1979, Commission of the European Communities.

37. See Y. Tazima, Reports of Activities Displayed in Japan in Relation to

Recombinant DNA Research, prepared for an ICSU meeting, 1-2 July 1976, MIT Archives. For a discussion of the ICSU, see below.

38. 320 scientists had been polled and 111 responded. See Y. Tazima, ibid., p.2.

39. Report of the Federal Interagency Committee, op. cit., pp.26-27.

40. See Statement on the Security of the Recombinant DNA Researches in Japan, Adopted by the 73rd General Assembly of SCJ, 28 October 1977, MIT Archives.

41. Telegram from US Embassy, Tokyo, to Secretary of State, Washington, 24 June 1977, MIT Archives.

42. See, for example, D.F. Liberman, Memorandum to file, 11 October 1977, re: meeting at MIT with four members of Japanese recombinant DNA group, MIT Archives. In interview, a DES Principal Scientific Officer commented on the large groups sent from Japan, and queries which arrived at the DES via the Japanese embassy. The NIH also received requests for information.

43. See S.N. Cohen et al., op. cit., p.69.

44. See Report of the Federal Interagency Committee, op. cit., p.28 and S.N. Cohen et al., op. cit., p.36.

45. See J. Tooze, op. cit., p.9. and Report of the Federal Interagency Committee, op. cit., pp.28-29. See also "Terms of Reference of the Commission in Charge of Control over Genetic Engineering", MIT Archives.

46. See C. Schuuring, "Dutch Recombinant DNA Guidelines to be Relaxed", Nature, Vol. 273, 29 June 1978, p.698 and H. Friedeman, "Dutch Relax Rules on Genetic Manipulation", New Scientist, 29 June 1978, p.892.

47. See S.N. Cohen et al., op. cit., and C. Schuuring, "The Netherlands: Recombinant DNA Thrives", Nature, Vol. 283, 14 February 1980, p.612.

48. See J. Becker, "DNA Research Guidelines: Dutch Get Tough", Nature, Vol. 290, 9 April 1981, p.436. Unilever, for example, transferred some projects to Belgium and Gest-Brocades switched some resources to its UK laboratories. The main complaint was about administrative checks on research. Guidelines were particularly strict on the use of pathogenic micro-organisms.

49. See S.N. Cohen et al., op. cit. and Report of the Federal Interagency Committee, op. cit., p.30.

50. See S.N. Cohen et al., op. cit. and Report of the Federal Interagency Committee, op. cit., p.30 and Minutes of the ESF Liaison Committee Meeting, January 1979.

51. See S.N. Cohen et al., op. cit.

52. See S.N. Cohen et al., op. cit. Work at P3 itself was presumably in the category involving a Biosafety Committee.

53. See C. Sherwell, op. cit., p.3 and Report of the Federal Interagency Committee, op. cit., pp.30-31.

54. See European Science Foundation, Report 1980, Strasbourg, p.23.

55. See S.N. Cohen et al., op. cit. and Report of the 6th Meeting of the EMBO Standing Committee on Recombinant DNA, 17 February 1980, p.5. However, at one point, Sweden's approach was more stringent. See W. Barnaby, "Sweden Debates Gene-Splicing", Nature, Vol. 270, 22/29 December 1977, p.653.

56. See Report of the Federal Interagency Committee, op. cit., pp.31-32 and Report to the ICSU ad hoc Committee on Recombinant DNA Molecules on the Activity of the Commission for Experimental Genetics of the Swiss Academy of Medical Sciences, 30 June 1976, MIT Archives.

57. See R. Waldner, "Switzerland: Guidelines Emerge", Nature, Vol. 267, 19 May 1977, p.199.

58. See Minutes of the Meetings of the ESF Liaison Committee, op. cit. See also A. Hay, "Switzerland to Consider Revised Guidelines", Nature, Vol. 277, 1 February 1979, pp.341-342.

59. See S.N. Cohen et al., op. cit.

60. See S.N. Cohen et al., op. cit.

61. Quoted in S.N. Cohen et al., op. cit., p.42.

62. See Report of the Federal Interagency Committee, op. cit., p.34; Minutes of Meetings of the ESF Liaison Committee, op. cit.; and S.N. Cohen et al., op. cit.

63. Note that the US central committee, the RAC, widened its participation to include seven non-scientists, although they were in a minority.

64. See Chapter Eight.

65. The member states at the time of writing were Austria, Denmark, France, West Germany, Greece, Iceland, Ireland, Israel, Italy, Netherlands, Norway, Switzerland, Sweden, Spain and the United Kingdom.

66. See L. Crawford et al., Letter to Sir John Kendrew, 7 June 1974, MIT Archives.

67. Because a number of the smaller states represented in the EMBC opted out of the proposal, a new inter-governmental structure was proposed to deal with the laboratory policy. A separate body was therefore constituted to run the laboratory, although its membership were also delegates to the EMBC. See Interview with J. Tooze by C. Weiner, 26 March 1976, MIT Archives.

68. See Draft Minutes of the Ordinary Sessions of the European Molecular Laboratory Council, October 1974, July 1975 and November 1975, MIT Archives. See also Interview with J. Kendrew by C. Weiner, 25 March 1976, MIT Archives.

69. See Report of the EMBO Delegation which Attended the Conference on Recombinant DNA Molecules Sponsored by the National Academy of Sciences - National Research Council of the United States of America and Held at Asilomar, California, 24-26 February 1975, MIT Archives.

70. See the minutes of meetings or reports of these various bodies. Tooze also attended the crucial La Jolla meeting of the RAC where the various draft proposals for US guidelines were compared. Indeed, Tooze saw himself as having a key personal role in Europe. See RAC, Minutes of Meeting, 4-5 December 1976. See also Interview with J. Tooze, op. cit. In terms of the Evans model of interorganisational relations, Tooze would represent an important individual at the boundary of organisational systems. See Chapter Two, pp.68-69.

71. Chapter Six used this report in comparing the physical containment categories of the US and the UK. See Second Meeting of the EMBO Standing Advisory Committee on Recombinant DNA, Report and Recommendations, EMBO, Heidelberg, 1976. Subsequent meetings examined the drafts and finalised guidelines of other states.

72. These analyses have been used in this thesis. See, for example, J. Tooze, op. cit.

73. Second Meeting of the EMBO Standing Advisory Committee on Recombinant DNA, op. cit.

74. For the first workshop and the planning of the risk assessment experiment see Report of the 4th Meeting of the EMBO Standing Advisory Committee on Recombinant DNA, November 1977 and its annexe, Report of the NIH/EMBO Workshop, "Parameters of Physical Containment", March 1977, EMBO, Heidelberg. For the second workshop, see US Department of Health, Education and Welfare, "US-EMBO Workshop to Assess Risks for Recombinant DNA Experiments Involving the Genomes of Animal, Plant and Insect Viruses", Federal Register, 31 March 1978, Part III.

75. Some indication of the extent of communication can be seen in the number of letters and documents related to EMBO which are in the MIT Archive, Recombinant DNA Collection.

76. See ESF, Report 1980, op. cit. The member states are Austria, Belgium, Denmark, France, West Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, the United Kingdom and Yugoslavia.

77. See the ESF annual reports and Report of the Federal Interagency Committee, op. cit., p.39.

78. ESF, Recommendations Concerning Recombinant DNA Research, Strasbourg, 1976. See also Report of the Federal Interagency Committee, op. cit., pp.39-41.

79. A reading of the comprehensive minutes of the meetings of the ESF Liaison Committee shows it to have been very well informed and up to date. Overall trends in technical and wider issues were related to the developments in individual states.

80. See ESF, Report 1978, Strasbourg, pp.34-35.

81. ESF, Report 1980, op. cit., p.24.

82. It was observed that the ESF included social science in its view of science. From this, it could be questioned why social science was not brought to bear on the recombinant DNA issues. Like any ESF Standing

Committee, the one dealing with social science had a major co-ordinating function. Within the member states, social science attention towards the case of recombinant DNA was not great, and was not suitable for co-ordination. Having only been established in 1977, the Standing Committee on the Social Sciences was a relative latecomer and had initially to develop its priorities in both its co-ordinating activity and its promotional activity regarding potential research projects. Recombinant DNA would not have been a priority issue.

83. See Report of the Federal Interagency Committee, op. cit., pp.36-37. Note that in the UK context, it was the DHSS which was the lead department in relation to EMRC activity.

84. See W.J. Whelan, "The Purpose of the Meeting", in J. Morgan and W.J. Whelan (eds.), Recombinant DNA and Genetic Experimentation, Pergamon Press, Oxford, 1979, p.xxi. The scientific unions covered such fields as astronomy, geography, chemistry, biophysics, biochemistry, nutrition, pharmacology, immunology and such like.

85. Interview with J. Kendrew, op. cit.

86. See Report of the ad hoc Committee on Recombinant DNA Molecules, ICSU, 1976 (copy in MIT Archives), pp.2-3.

87. See W.J. Whelan, Memorandum, March 1977, MIT Archives. See also Report of the Federal Interagency Committee, op. cit., pp.41-44.

88. See NARSM, newsletter, July 1977, copy in MIT Archives. Reports by the guidelines group and the risk assessment group have proved valuable for this thesis. See S.N. Cohen et al., op. cit. and A.M. Skalka et al., First Report to COGENE from the Working Group on Risk Assessment, ICSU, July 1978. Further reports are in J. Morgan and W.J. Whelan, op. cit.

89. E. Yoxen, The Gene Business: Who Should Control Biotechnology?, Pan Books, London and Sydney, 1983, p.59. In writing to W.J. Whelan to request information, such as minutes of meetings, I was very pleased to receive a number of very useful reports and the requested minutes, but with a request that any verbatim quotation from the minutes be with the permission of Dr. Whelan. In itself, this is not an unusual or unreasonable request. However, the actual copies of the minutes have an attached note saying that they are within "the public domain" and that dissemination of news of COGENE activities is encouraged. It is, perhaps, merely a reflection of an excessive caution which manifests itself elsewhere in COGENE's activities. However, I am very grateful for the co-operation of Dr. Whelan in his quick response to my request. I have, as it happens, found no need to quote verbatim from the comprehensive minutes.

90. A.M. Skalka et al., op. cit., p.iv. See Chapter Eight on risk assessment.

91. See A.M. Skalka, "Second Report of the COGENE Working Group on Risk Assessment", in J. Morgan and W.J. Whelan (eds.), op. cit., pp.211-219.

92. See Minutes of the Second Meeting of COGENE, 5-6 April 1978, and Minutes of the Third Meeting of COGENE, 31 March 1979, ICSU.

93. See Interview with J. Kendrew, op. cit., p.49.

94. The conference proceedings have been published as J. Morgan and W.J. Whelan (eds.), op. cit. This reference has been of considerable utility as a source of material for this thesis. It includes both papers presented and transcripts of subsequent discussion.

95. M.G.P. Stoker, "Introduction and Welcome", in J. Morgan and W.J. Whelan (eds.), op. cit., p.xix.

96. See Minutes of the Second Meeting of COGENE, op. cit.

97. See R. Walgate, "COGENE Plays Up Benefits, Plays Down Risks", Nature, Vol. 278, 5 April 1979, p.496. See also Minutes of the Third Meeting of COGENE, op. cit. At this meeting COGENE members noted that the letter could be misinterpreted.

98. "Recombinant DNA - How Public?", Nature, Vol. 278, 29 March 1979, p.383.

99. R. Lewin, "The View of a Science Journalist", in J. Morgan and W.J. Whelan (eds.), op. cit., pp.273-280 (including discussion). See also R. Lewin, "Science and Politics in Genetic Engineering", New Scientist, 12 April 1979, pp.114-115 and "Environmentalists Criticise Secrecy of Recombinant DNA Meeting", Nature, Vol. 278, 5 April 1979, p.499. US environmentalist groups criticised, in addition, the $200 attendance fee.

100. "Molecular Biology: Suffering from Shock", Nature, Vol. 278, 12 April 1979, p.587.

101. During the discussion following Lewin's presentation at the meeting.

102. D. Haber in discussion. See J. Morgan and W.J. Whelan (eds.), op. cit., p.237. Haber also noted that the speakers were all known in advance to oppose guidelines and regulations.

103. See Ad hoc Committee on Genetic Engineering, IAMS, First Report to Executive Board, IAMS, 1979 and IAMS Ad hoc Committee on Genetic Engineering, "Summary Report", in NARSM, newsletter, January 1976, both in MIT Archives.

104. See Interview with M. Kaplan by C. Weiner, 8 March 1976, MIT Archives. Kaplan was head of Research Promotion and Development and, in 1974, head of the Office of Science and Technology in the WHO. He was also the senior scientific adviser to the Director General.

105. See Extract of the Report of the Advisory Committee on Medical Research, Seventeenth Session, June 1975: Assuring the Safety of Microbiological and Cell Biology Research, copy in MIT Archives. See also Report of the Federal Interagency Committee, op. cit., pp.45-46.

106. See K. Bögel, The WHO Special Programme on Safety Measures in Microbiology, 1976, copy in MIT Archives. The report was also presented to the ICSU Ad hoc Committee on Recombinant DNA Molecules.

107. GMAG, for example, was to recommend IATA and UPU regulations in the despatching abroad of recombinant DNA plasmids or cultures. See GMAG, First Report, op. cit., pp.51-53.

108. See P. Newmark, "WHO Looks for Benefits from Genetic Engineering", Nature, Vol. 272, 20 April 1978, pp.663-664. See also B. Dixon, "Scientists Back Down on Recombinant DNA Warning", New Scientist, 6 April 1978, p.3. Dixon referred among other things to a draft for a second 'Berg letter' being circulated between the original signatories. See also J.D. Watson and J. Tooze, The DNA Story: A Documentary History of Gene Cloning, W.H. Freeman & Co., San Francisco, 1981, pp.251-261.

109. See WHO, "Facilitation and Safety in the International Transfer of Research Materials: Report of the WHO/NIH (USA) Consultations", Geneva, 14-17 September 1978, appended to Report of the Federal Interagency Committee, op. cit. The WHO also sent a questionnaire in 1976 to over 200 scientists asking for views on what risk assessment work should be done. See "Summary of WHO-Sponsored Risk Assessment Survey", in A.M. Skalka et al., op. cit., p.15.

110. See L. McGinty, "Smallpox Laboratories, What are the Risks?", New Scientist, 4 January 1979, pp.8-14. See also "All Safety Nets Failed Says Shooter", Nature, Vol. 277, 11 January 1979, pp.78-79.

111. United Nations Educational, Scientific and Cultural Organisation and United Nations Environmental Programme.

112. See document relating to UNESCO International Cell Research Organisation, Meeting on 2-4 September 1975, MIT Archives.

113. See Report of the Federal Interagency Committee, op. cit., pp.44-45.

114. See S. Saraf, op. cit. and discussion on India and Italy above.

115. See, for example, T. Beardsley, "Cohen-Boyer Patent Finally Confirmed", Nature, Vol. 311, 6 September 1984, p.3. Beardsley examines the ten year legal argument surrounding a patent application to cover both process and product patents regarding techniques of recombinant DNA and the plasmid pSC101.

116. See WIPO, "Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure", Document Issued after the Diplomatic Conference held in Budapest from April 14 to 28, 1977, appended to Report of the Federal Interagency Committee, op. cit. The states involved were: Australia, Austria, Bulgaria, Czechoslovakia, Denmark, Egypt, Finland, France, E. Germany, W. Germany, Hungary, Indonesia, Italy, Japan, Mexico, Netherlands, Norway, Philippines, Poland, Portugal, Romania, Senegal, Soviet Union, Spain, Sweden, Switzerland, United Kingdom, United States, Yugoslavia. See also Intellectual Property Treaty Series No. 5 (1981) Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (with Regulations) Budapest, April 28-December 31 1977, HMSO, London, Cmnd. 8136.

117. See Chapter Five, pp.181-183.

118. A draft report was produced which, despite their view on openness, was a classified document, although available to UK civil servants.

119. See Report of the Federal Interagency Committee, op. cit., pp.34-35. See also C. Sherwell, op. cit., p.5. Other instruments available to the Commission in this respect involve: Regulations which are binding

on members with the same strength as national laws; Decisions which are only binding on named parties (individuals, organisations or governments); Recommendations which are not binding.

120. C. Sherwell, idem.

121. See Commission of the European Communities, Proposal for a Council Directive: Establishing Safety Measures Against the Conjectural Risks Associated with Recombinant DNA Work, Brussels, December 1978, COM(78)664 final, p.9 (subsequently referred to as COM(78)664).

122. See DES, "Memorandum Submitted by the Department of Education and Science", in Second Report from the Select Committee on Science and Technology, Interim Report, HMSO, London, 1979, p.149.

123. COM(78)664, op. cit., p.8.

124. COM(78)664, op. cit., pp.2-8. See also House of Lords, Select Committee on the European Communities, Genetic Manipulation (DNA), HMSO, London, HL 188, p.5.

125. See CBI, brief submitted, in House of Lords, Select Committee, op. cit., p.33.

126. See "Memorandum of Evidence from the TUC to the Health and Safety Commission Concerning a Proposal for an EEC Directive Concerning the Conjectural Hazards of Recombinant DNA Work", in House of Lords, Select Committee, op. cit., pp.35-36.

127. See J. Becker, op. cit.

128. See R. Walgate, "European Biotechnology: EEC Proposals", Nature, Vol. 286, 7 August 1980, p.548.

129. See Commission of the European Communities, Proposal for a Multiannual Community Programme of Research and Development in Biomolecular Engineering (indirect action 1981-1985), January 1980, Brussels, COM(79)793 final, p.1.

130. Commission of the European Communities, A Common Policy in the Field of Science and Technology, 1977, Brussels, COM(77)283 final.

131. A. Rörsch, Genetic Manipulation in Applied Biology, study contract 346-77-7 ECI NL, EUR 6078, 1976, Commission of the European Communities.

132. D. Thomas, op. cit.

133. See R. Walgate, "Brussels Asked to Spend £16m on Biotechnology", Nature, Vol. 283, 10 January 1980, p.125. This is part of a larger Nature report on "The Biology Business" in that issue, which owes much to the two studies commissioned by the EEC. See above.

134. See COM(79)793 final op. cit., pp.1-2.

135. A study contract was operationalised at the UK Microbiological Research Establishment, Porton Down. See K. Sargeant and C.G.T. Evans, Hazards Involved in the Industrial Use of Micro-organisms,

study contract 430-78-5 ECI, EUR 6349, 1979, Commission of the European Communities. This study excluded genetic manipulation hazards.

136. See "European Biotechnology Lies in Disarray", Nature, Vol. 290, 16 April 1981, pp.535-536 and S. Yanchinski, "Biotechnology in the Swim", New Scientist, 30 April 1981, p.286.

137. "European Biotechnology Lies in Disarray", op. cit., p.535.

Chapter Eight.

1. J. Bronowski, The Ascent of Man, BBC Publications, London, 1973, p.390.

2. 'Direct' manipulation rather than through breeding for selection or using natural processes.

3. J.D. Watson, "Let Us Stop Regulating DNA Research", Nature, Vol. 278, 8 March 1979, p.113.

4. For example in the Federal Republic of Germany and the Netherlands legislation was considered, while the UK and Sweden had useful existing legislation. See Chapter Seven, above.

5. A. Irwin, D. Smith, R. Griffiths, "Risk Analysis and Public Policy for Major Hazards", Physics and Technology, Vol. 13, No. 6, 1982, pp.258-265.

6. Despite years of experience in the nuclear industry, there are still miscalculations which occur, or misperceptions which apply. For a brief discussion of the Three Mile Island incident of March 1979 where a very serious accident occurred only just contained from becoming an enormous disaster, see P. Pringle and J. Spigelman, The Nuclear Barons, Sphere Books, London, 1981, pp.422-443.

7. See S. Krimsky, Genetic Alchemy, MIT Press, Cambridge, Mass. and London, 1982, pp.233-284. In examining the issues related to assessing risks, Krimsky notes that to many scientists originally the term 'species barriers' was very acceptable, but that with the ensuing debate about genetic manipulation, many scientists began to suggest that the term was inaccurate as in turn they tried to demonstrate that natural cell evolution could lead to similar crossings of the so-called boundaries. See pp.264-265. This terminology can also be politicised to some degree.

8. Chapter One pp.32-36.

9. Accepting, for the moment, that the existing level of containment has some legitimacy.

10. See RAC, Charter of the Recombinant DNA Molecule Program Advisory Committee, Department of Health, Education and Welfare, Washington D.C., a copy of which is is the MIT Archives, Recombinant DNA Collection. See also GMAG, First Report of the Genetic Advisory Group, HMSO, London, Cmnd. 7215, 1978.

11. See the discussion of actors below, p.359ff. Note he argues that risks in genetic manipulation are hypothetical. This is acceptable here.

12. See Chapter Three for a description of E. coli. E. coli K-12 was the main enfeebled strain used as an EK1 organism under NIH guidelines.

13. See RAC, Minutes of Meeting, 15-16 January 1977, MIT Archives. Enteric biologists and gastroenterologists were to be included.

14. A.M. Skalka, "Report from COGENE's Observer at the Falmouth Workshop on Risk Assessment", in A.M. Skalka et al., First Report to COGENE from the Working Group on Risk Assessment, ICSU, July 1978, pp.16-20. See also the official report by S.L. Gorbach, "Recombinant DNA: An Infectious Disease Perspective", Journal of Infectious Diseases, Vol. 137, 1978, pp.615-623. The formal report took a year to publish, but in the mean time an influential letter was sent by Gorbach to D.S. Fredrickson emphasising the consensus. See National Institutes of Health, Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, Part Two, US Department of Health, Education and Welfare, Bethesda, Maryland, October 1977, Appendix M.

15. Krimsky does, however, acknowledge the more circumspect report produced by Gorbach over a year after the letter.

16. Department of Health, Education and Welfare, NIH, "US-EMBO Workshop to Assess Risks for Recombinant DNA Experiments Involving the Genomes Of Animal, Plant and Insect Viruses", Federal Register, 31 March 1978, Part III. Note that an earlier NIH/EMBO workshop held in March 1977 examined the parameters of physical containment.

17. See European Science Foundation, Report 1978, Strasbourg, p.37. See also Minutes of the Third Meeting of COGENE, 31 March 1979, pp.8-9.

18. See Department of Health, Education and Welfare, NIH, "Proposed Revised Guidelines on Recombinant DNA Research", Federal Register, 27 September 1977.

19. See Department of Health, Education and Welfare, NIH, "Recombinant DNA Research: Proposed Revised Guidelines", Federal Register, 28 July 1978.

20. Many of the opposition groups were only referred to in passing by the NIH document suggesting the proposals. See, for example, R. Hartzman, Letter to D.S. Fredrickson, NIH, 30 September 1977, on behalf of Friends of the Earth, in J.D. Watson and J. Tooze, The DNA Story: A Documentary History of Gene Cloning, W.H. Freeman & Co., San Francisco, 1981, pp.266-267. For a summary of the criticisms see also N. Wade, "Gene-Splicing Rules: Another Round of Debate", Science, Vol. 199, 6 January 1978, p.30. See also S. Krimsky, op. cit., pp.233-243.

21. The lack of an environmental impact assessment with the 1977 proposals along the lines of the belated Environmental Impact Statement following the original guidelines was among the criticisms. See Chapter Five, pp.202-208. The July 1978 proposals included such a document.

22. See D. Dickson, "US Proposes Exemptions from DNA Guidelines", Nature, Vol. 274, 10 August 1978, p.411, for a summary of the revisions.

23. See Chapter Seven above.

24. Rowe has been a central advocate of the relaxation of guidelines, and

centrally involved in risk assessment work. Krimsky points out that Rowe has argued against the initial wisdom of scientists originally voicing concern on the basis that the broad range of expertise needed to assess risks was too great for many of the people involved. The logic of this is very questionable. It was precisely because of uncertainty that fears were expressed. To have continued the work without a pause to consider potential hazards under such circumstances would be much more suspect. See S. Krimsky, op cit., pp.234-235.

25. See "Scientists Debate Safety of Research on E. coli Strain", Nature, Vol. 279, 31 May 1979, p.360.

26. Roy Curtiss, Letter to D.S. Fredrickson, NIH, 4 October 1979, reprinted in J.D. Watson and J. Tooze, op. cit., pp.446-447. It referred to Falmouth data. Additional data, however, came from a 'worst case' experiment carried out by Rowe and a colleague, Malcolm Martin, similar to the experiment Berg was planning years earlier which sparked the whole issue.

27. D. Chamot, Department of Professional Employees, AFL-CIO, Letter to P. Harris, Department of Health, Education and Welfare, 26 November 1979, reprinted in J.D. Watson and J. Tooze, op. cit., p.444. See also F.R. Simring, Coalition for Responsible Genetic Research, Letter to W. Gartland, RAC, 6 May 1979, reprinted in J.D. Watson and J. Tooze, op. cit., p.438.

28. Many other letters are reprinted in J.D. Watson and J. Tooze, op. cit., concerning this episode, both for and against the revisions, and from a variety of interest groups. See J.D. Watson and J. Tooze, op. cit., pp.435-459.

29. See Chapter Three, pp.131-133.

30. See A. Campbell, "Natural Modes of Genetic Exchange and Change", in J. Morgan and W.J. Whelan (eds.), Recombinant DNA and Genetic Experimentation, Pergamon Press, Oxford, 1979, pp.21-27.

31. For example, the 'new' disease called AIDS (Acquired Immune Deficiency Syndrome) illustrates the ability of nature to present unexpected hazards.

32. See Chapter Three, p.126.

33. See the résumé of activity of activity in other states in Chapter Seven.

34. "Genetic Manipulation: New Guidelines for UK", Nature, Vol. 276, 9 November 1978, pp.104-108. For a more complete description of the reasoning behind the new approach, see GMAG, Second Report of the Genetic Manipulation Advisory Group, HMSO, London, Cmnd. 7785, 1979. The HSE also undertook its own consultations on the proposals.

35. See E. Lawrence, "Recombinant DNA Hazards May Be Reassessed", Nature, Vol. 274, 20 July 1978, p.203. See also GMAG, Second Report, op. cit., p.14.

36. GMAG, Second Report, op. cit., p.36.

37. "Rational Risk Assessment for Genetic Engineering", New Scientist,

9 November 1979, p.421.

38. "Now Reason Can Prevail", Nature, Vol. 276, 9 November 1978, p.103.

39. F. Rolleston, "There is a Frustrating Logical Gap Between the Assertion that Recombinant DNA Poses Potential Risks ... and the Containment Levels Imposed by Current Guidelines", Nature, Vol. 281, 25 October 1979, pp.626-627.

40. For an attempt to assign probabilities to a supposedly hazardous experiment, see R. Holliday, "Should Genetic Engineers Be Contained?" New Scientist,17 February 1977, pp.399-401. For a cancer-causing epidemic arising from a shotgun experiment (perhaps involving human DNA as donor) Holliday 'estimates' a total risk of 10^{-14} (10^{-11} for a single death by infection) or, as he puts it: if ten scientists in each of 100 laboratories carried out 100 experiments per year, the least serious case of a single infection (10^{-11}) would occur on average once in a million years. Deliberate malice is not included in his assessment of biological events.

41. See D.R. Lincoln, L.R. Landis, H.A. Gray, "Containing Recombinant DNA: How to Reduce the Risk of Escape", Nature, Vol. 281, 11 October 1979, pp.421-422.

42. Falmouth and the NIH/EMBO workshop assessed the evidence. In addition, the NIH sponsored 'worst case' experiments at Fort Detrick, the highest level US containment facility, while EMBO sponsored experiments at Porton Down, the UK equivalent facility. No special hazards were reported as a result of either work. See Minutes of the 5th Meeting of the ESF Liaison Committee for Recombinant DNA Research, January 1980.

43. See below.

44. For a useful overview of the industrial uses of genetic manipulation, see E. Yoxen, The Gene Business: Who Should Control Biotechnology?, Pan Books, London and Sydney, 1983. Marking the new decade Nature produced an eleven page assessment of the state-of-the-art, not least offering a comparison between countries of importance, Nature, Vol. 283, 10 January 1980, pp.119-131. See also Advisory Council for Applied Research and Development, Advisory Board for the Research Councils and the Royal Society, Biotechnology: Report of a Joint Working Party, HMSO, London, 1980. For an American perspective, see N. Wade, "Cloning Gold Rush Turns Basic Biology into Big Business", Science, Vol. 208, 16 May 1980, pp.688-691. The potential for new processes of manufacturing products such as drugs (e.g. insulin, interferon) has enabled a number of genetic manipulation based companies to raise a great deal of finance through sales of shares. For a discussion of the issues of patents, see S. Crespi, "Patenting Nature's Secrets and Protecting Microbiologists' Interests", Nature, Vol. 284, 17 April 1980, pp.590-591. See also Chapter Seven, pp.297-298.

45. See "Proposal for Genetic Engineering Centre Upsets India", New Scientist, 25 August 1983, p.528. See also Chapter Seven p.297.

46. The fourth meeting was held in London in May 1984.

47. See Chapter One pp.34-35 and see notes to Chapter One, p.397, note 34.

48. These points have been discussed in terms of the institutional responses of the US and the UK where the assumption was that the work should eventually proceed. A criticism of the NIH Environmental Impact Statement of 1977 was that in considering 'alternatives' it did not consider a halt to the work. See Chapter Five, pp.202-208.

49. See W. Barnaby, "Swedish Firm in Recombinant DNA Storm", Nature, Vol. 282, 15 November 1979, p.222.

50. S. Falkow, Letter to D.S. Fredrickson, NIH, 19 April 1978, in J.D. Watson and J. Tooze, op. cit., pp.344-345. The proceedings of this conference have been published. See H. Boyer and S. Nicosia (eds.), Genetic Engineering, Elsevier/North Holland Biomedical Press, Amsterdam, New York, Oxford, 1978.

51. Sir John Kendrew in evidence before the House of Lords Select Committee on the European Communities, Genetic Manipulation (DNA), HMSO, London, HL 188, 1980, p.22.

52. Biotechnology: Report of a Joint Working Party, op. cit., p.33. This comment was made with the qualification that the authors supported GMAG's policy of not relaxing or abandoning controls without a thorough assessment of risk and benefit.

53. See Chapter Seven, pp.299-304.

54. Draft Minutes of the Fourth Meeting of COGENE, May 1980. By 1980 the feeling was widespread among scientists that guidelines were restrictive.

55. R. Curtiss, "Comments on Callahan", in J. Richards (ed.), Recombinant DNA: Science, Ethics and Politics, Academic Press, New York, London, 1978, p.154. Many aspects of the ethics and politics of the issue area are addressed by papers in this collection, illustrating a concern for some of the wider issues of science and knowledge, somewhat beyond the scope of this thesis.

56. Discussed in Chapter Four, pp.156-157.

57. M. Lappe and R.S. Morrison (eds.), Ethical and Scientific Issues Posed by Human Uses of Molecular Genetics, published in the Annals of the New York Academy of Sciences, Vol. 265, 23 January 1976.

58. It was in the use of recombinant DNA techniques to try and treat a genetic disease that Dr. Cline violated both the US NIH guidelines and Israeli controls. See below, pp.343-344.

59. Many interest groups saw these issues heightened by uncertainty, as a cause for fear.

60. See in particular Chapter Seven pp.275-277 for assessment of the different approaches.

61. See GMAG, Second Report, op. cit., p.14.

62. Especially with industry, trade union and public interest groups with representatives on GMAG, for example. See Chapter Six, pp.238-242.

63. B.K. Zimmerman, "Beyond Recombinant DNA - Two Views of the Future", in J. Richards (ed.), op. cit., pp.273-301.

64. E. Kennedy and J.K. Javits, Letter to the President of the United States of America, 19 July 1976, MIT Archives.

65. See, for example, E.L. Hess, Executive Director, Federation of American Societies for Experimental Biology and R.F. Acker, Executive Director, American Society for Microbiology, Letter to H.O. Staggers, Chairman, Committee on Interstate and Foreign Commerce, 17 October 1977, in J.D. Watson and J. Tooze, op. cit., pp.184-185. Watson and Tooze reinforce the point, op. cit., pp.140-141.

66. If violation was wilful in both cases the fine could be replaced or supplemented with a one year prison sentence.

67. Particularly in Cambridge and Boston, Massachusetts, and New York.

68. See D. Dickson, "Friends of DNA Fight Back", Nature, Vol. 272, 20 April 1978, pp.664-665.

69. R. Curtiss, Letter to D.S. Fredrickson, NIH, (with copies to the various committees considering legislation) 12 April 1977, MIT Archives. Curtiss still remained cautious, as shown by his criticisms of US procedures at the 1979 revisions. For a general description and a collection of relating documents, see J.D. Watson and J. Tooze, op. cit., pp.137-201. For an analysis of the course of legislation and its links with risk assessment work and lobbying by scientists, see S. Krimsky, op. cit., pp.312-338. For a comparison between US moves to produce legislation and the UK use of existing legislation, see S. Wright, "Molecular Politics in Great Britain and the United States: The Development of Policy for Recombinant DNA", Southern Californian Law Review, Vol. 51, No. 6, September 1978, pp.1396-1400.

70. N. Zinder, "The Gene Scientists and the Law", in J.D. Watson and J. Tooze, op. cit., p.199. N.B. Other US agencies subsequently examined the possibility of extending regulations within their remits. For example, the Food and Drugs Administration and the Environmental Protection Agency.

71. See Science Policy Implications of DNA Recombinant Molecule Research, Hearings before the Subcommittee on Science, Research and Technology, of the Committee on Science and Technology, US Houses of Representatives, 95th Congress, First Session, US Government Printing Office, Washington D.C., 1977. In particular, see the testimony by J.G. Adams, Vice-President, Scientific and Professional Relations, Pharmaceutical Manufacturers' Association, and I.S. Johnson, Vice-President of Research, Lilly Research Laboratories, pp.371-490.

72. See S. Budiansky, "Prospect of New US Regulation: Surprise Welcome for EPA", Nature, Vol. 310, 23 August 1984, p.613. The Environmental Protection Agency proposed to issue regulations regarding the release of organisms created by recombinant DNA techniques by industry.

73. See N. Wade, "Recombinant DNA: NIH Rules Broken in Insulin Gene Project", Science, Vol. 197, 30 September 1977, pp.1342-1344.

74. C. Marwick, "Genetic Engineers in the Sin-bin ...", New Scientist, 11 September 1980, p.764.

75. D. Dickson, "Guidelines Transgressor Let Off Lightly", Nature, Vol. 290, 26 March 1981, p.281. See also "DNA Recombination Forces Resignation", Nature, Vol. 287, 18 September 1980, p.179.

76. He had tried on an earlier occasion and failed to get approval.

77. See D. Dickson, "NIH Censure for Dr. Martin Cline", Nature, Vol. 291, 4 June 1981, p.369. See also "Furore Over Human Genetic Engineering", New Scientist, 16 October 1980, p.140.

78. R. Curtiss, Letter to D.S. Fredrickson, NIH, 12 April 1977, op. cit., p.13. For a general assessment of the approaches of different states see Chapter Seven above and S.N. Cohen et al., Report to COGENE from the Working Group on Recombinant DNA Guidelines, Committee on Genetic Experimentation, International Council of Scientific Unions, Miami, 1980, pp.38-42.

79. See S. Yanchinski, "Genetic Engineers Campaign Against Gene Warfare", New Scientist, 24 June 1982, p.827.

80. Quoted in S. Yanchinski, idem.

81. C. Joyce, "Gene Cloning Could Further Biological Warfare", New Scientist, 16 February 1984, p.7.

82. For recent assessments of biological and chemical warfare see S. Murphy, A. Hay, S. Rose, No Fire, No Thunder, Pluto Press, London, 1984 and J. Elkington, "Something Nasty on the Horizon", The Guardian, 8 December 1983, p.16.

83. For diagrammatic representations, see Chapter Five, p.201 and Chapter Six, p.247 and p.249.

84. Where the ESF established or co-ordinated policy and the EMBO provided technical support. See Chapter Seven.

85. See Chapter One, pp.47-48. The UK trade union, ASTMS, did develop a number of international contacts, for example where trade unions were represented on the Dutch central advisory committee.

86. H. Rose and S. Rose, Science and Society, Penguin, Harmondsworth, 1969, p.179. In interview, a representative of the Health and Safety Executive termed the relevant community as a 'free-masonry'.

87. See Chapter Two, p.61.

88. Although the WHO showed an early interest, it was within the wider context of microbiological hazards in general.

89. See the evidence of Shirley Williams before the Select Committee on Science and Technology in, Second Report from the Select Committee on Science and Technology, Session 1978-79, HMSO, London, 1979, pp. 156-170. Supplemented by briefing, Dr E.J. Herbert, Principal Scientific Officer of the Science and International Relations Branch of the DES, August, 1980.

90. See Chapter Seven, pp.300-301.

91. See S. Wright, op. cit., for a discussion of the failure in the US

to apply the recommendations of Report of the National Academy of Sciences, Technology: Processes of Assessment and Choice, 1969. A wide range of human values should be related to new technological developments according to this report.

92. A survey of the minutes of important institutions reflects these omissions. However, in 1982 a Presidential Commission on ethical problems in medicine and biomedical research after two years produced a report entitled Splicing Life. The report argued that future developments could not be adequately safeguarded under the current procedures. Ethical questions would be involved in manipulating human genes, especially combinations of human and animal genes. The following question was asked: "Could genetic engineering be used to develop a group of virtual slaves - partly human, partly animal - to do people's bidding?" Dr. Martin Cline appeared before this committee and suggested scientific inquisitiveness might be impossible to regulate, an interesting observation from the man who broke NIH rules in practising gene therapy. See C. Joyce, "New Moves to Control the Splice of Life", New Scientist, 25 November 1982, p.486.

93. See the formidable collection of letters, for example, held in the MIT Archives.

94. See Chapter Two, pp.67-69.

95. For example, the following groups were particularly active: Friends of the Earth; Science for the People; the Environmental Defense Fund; the People's Business Commission; the Coalition for Responsible Scientific Research (with membership overlapping some of the above); and many local groups involved in university, city or state level debates.

96. Many position papers, statements and copies of letters to committees examining legislation and to the Director, NIH, are held in the MIT Archives. For an interesting account of the development of strategy and in-fighting within Friends of the Earth, see Interview with Pamela Lippe, by Aaron Seidman, 13 January 1978, MIT Archives. See also P. David, "Rifkin's Regulatory Revivalism Runs Riot", Nature, Vol. 305, 29 September 1983, p.349. Rifkin was head of the People's Business Commission.

97. Interview with Donna Haber, December 1980.

98. J. Morgan and W.J. Whelan (eds.), op. cit., pp.235-237.

99. Second Report from the Select Committee on Science and Technology, op. cit., pp.206-216.

100. See J.D. Watson and J. Tooze, op. cit., pp.251-261. A number of drafts were considered.

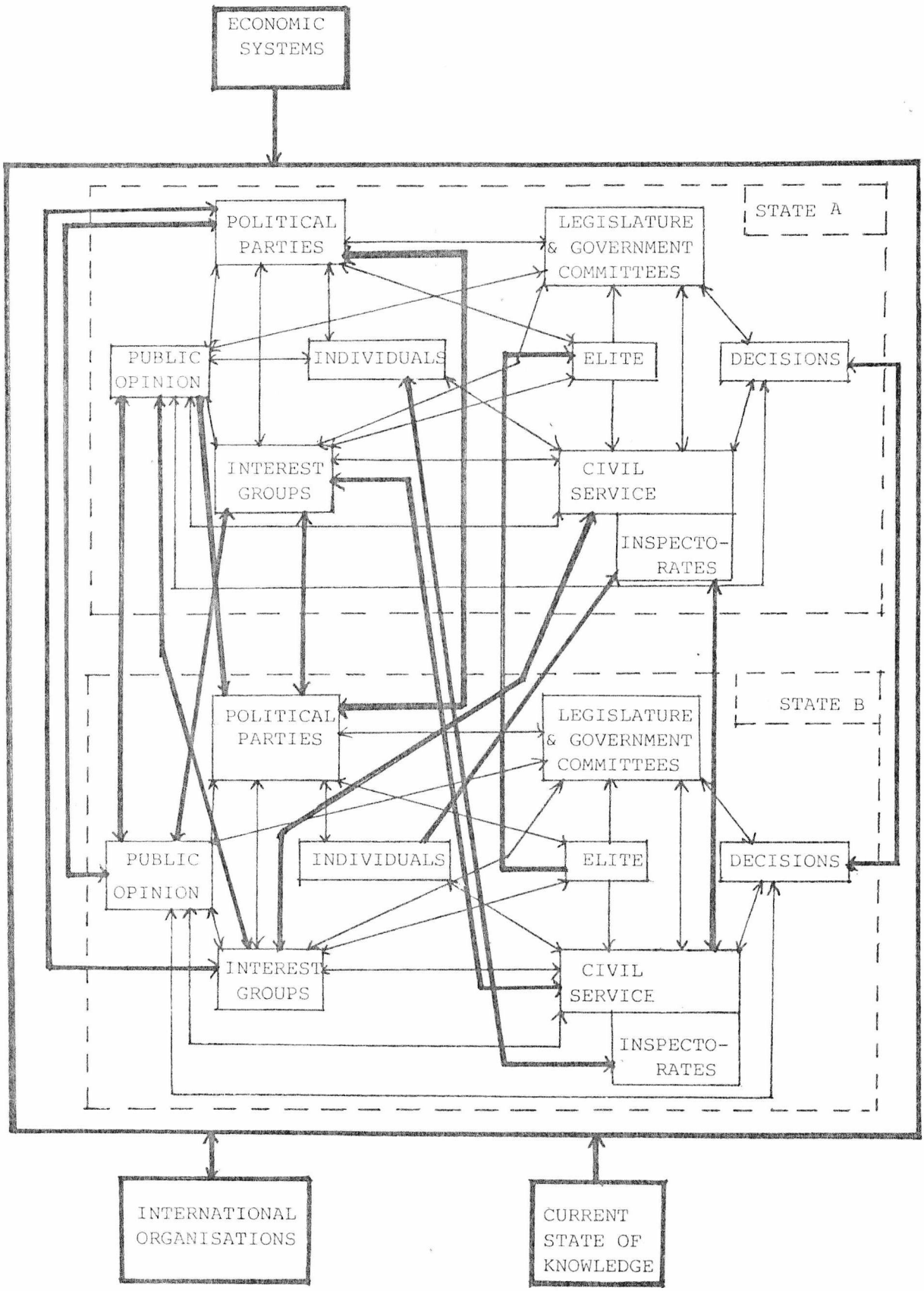
101. For example, the UK Select Committee on Science and Technology questioned the GMAG policy of excusing some members when individual protocols were examined in order to maintain confidentiality. The RAC has recently been challenged over its secrecy, which is far less than GMAG. See C. Joyce, "Battle Lines Drawn Over DNA Research", New Scientist, 29 Septmeber 1983, p.912.

102. See Chapter Two, p.78.

103. Report of the Working Party on the Practice of Genetic Manipulation, HMSO, London, Cmnd. 6600, 1976, p.13.

APPENDIX ONE.

A Two State Transnational Model (derived from Chicken's one state model).



⟷ DOMESTIC LINKS

⟺ INTERNATIONAL/TRANSNATIONAL LINKS

From: J.C. Chicken, Hazard Control Policy in Britain, Pergamon Press, Oxford, 1975.

APPENDIX TWO.

THE SINGER-SÖLL LETTER. (Science, Vol. 181, 21 September 1973, p.1114).

Letter to P. Handler, President, National Academy of Sciences, 17 July 1973.

We are writing to you, on behalf of a number of scientists, to communicate a matter of deep concern. Several of the scientific reports presented at this year's Gordon Research Conference on Nucleic Acids (June 11-15, 1973, New Hampton, New Hampshire) indicated that we presently have the technical ability to join together, covalently, DNA molecules from diverse sources. Scientific developments over the past two years make it both reasonable and convenient to generate overlapping sequence homologies at the termini of different DNA molecules. The sequence homologies can then be used to combine the molecules by Watson-Crick hydrogen bonding. Application of existing methods permits subsequent covalent linkage of such molecules. This technique could be used, for example, to combine DNA from animal viruses with bacterial DNA, or DNAs of different viral origins might be so joined. In this way new kinds of hybrid plasmids or viruses, with biological activity of unpredictable nature, may eventually be created. These experiments offer exciting and interesting potential both for advancing human knowledge of fundamental biological processes and for alleviation of human health problems.

Certain such hybrid molecules may prove hazardous to laboratory workers and to the public. Although no hazard has yet been established, prudence suggests that the potential hazard be seriously considered.

A majority of those attending the Conference voted to communicate their concern in this matter to you and to the President of the Institute of Medicine (to whom this letter is also being sent). The conferees suggested that the Academies establish a study committee to consider this problem and to recommend specific actions or guidelines should that seem appropriate. Related problems such as the risks involved in current large-scale preparation of animal viruses might also be considered.

Maxine Singer, National Institutes of Health
Dieter Söll, Associate Professor of Molecular Biophysics, Yale University.

APPENDIX THREE.

THE BERG LETTER. (Science, Vol. 185, 26 July 1974, p.303)

Potential Biohazards of Recombinant DNA Molecules.

Recent advances in techniques for the isolation and rejoining of segments of DNA now permit construction of biologically active recombinant DNA molecules in vitro. For example, DNA restriction endonucleases, which generate DNA fragments containing cohesive ends especially suitable for rejoining, have been used to create new types of biologically functional bacterial plasmids carrying antibiotic resistance markers (1) and to link Xenopus laevis ribosomal DNA to DNA from a bacterial plasmid. This latter recombinant plasmid has been shown to replicate stably in Escherichia coli where it synthesizes RNA that is complementary to X. laevis ribosomal DNA (2). Similarly, segments of Drosophila chromosomal DNA have been incorporated into both plasmid and bacteriophage DNA's to yield hybrid molecules that can infect and replicate in E. coli (3).

Several groups of scientists are now planning to use this technology to create recombinant DNA's from a variety of other viral, animal, and bacterial sources. Although such experiments are likely to facilitate the solution of important theoretical and practical biological problems, they would also result in the creation of novel types of infectious DNA elements whose biological properties cannot be completely predicted in advance.

There is serious concern that some of these artificial recombinant DNA molecules could prove biologically hazardous. One potential hazard in current experiments derives from the need to use a bacterium like E. coli to clone the recombinant DNA molecules and to amplify their number. Strains of E. coli commonly reside in the human intestinal tract, and they are capable of exchanging genetic information with other types of bacteria, some of which are pathogenic to man. Thus, new DNA elements introduced into E. coli might possibly become widely disseminated among human, bacterial, plant, or animal populations with unpredictable effects.

Concern for these emerging capabilities was raised by scientists attending the 1973 Gordon Research Conference on Nucleic Acids (4), who requested that the National Academy of Sciences give consideration to these matters. The undersigned members of a committee, acting on behalf of and with the endorsement of the Assembly of Life Sciences of the National Research Council on this matter, propose the following recommendations.

First, and most important, that until the potential hazards of such recombinant DNA molecules have been better evaluated or until adequate methods are developed for preventing their spread, scientists throughout the world join with the members of this committee in voluntarily deferring the following types of experiments.

Type 1: Construction of new, autonomously replicating bacterial plasmids that might result in the introduction of genetic determinants for antibiotic resistance or bacterial toxin formation into bacterial strains that do not at present carry such determinants; or construction of new bacterial plasmids containing combinations of resistance to clinically useful antibiotics unless plasmids containing such combinations of antibiotic resistance determinants already exist in nature.

Type 2: Linkage of all or segments of the DNA's from oncogenic or other

animal viruses to autonomously replicating DNA elements such as bacterial plasmids or other viral DNA's. Such recombinant DNA molecules might be more easily disseminated to bacterial populations in humans and other species, and thus possibly increase the incidence of cancer or other diseases.

Second, plans to link fragments of animal DNA's to bacterial plasmid DNA or bacteriophage DNA should be carefully weighed in light of the fact that many types of animal cell DNA's contain sequences common to RNA tumor viruses. Since joining of any foreign DNA to a DNA replication system creates new recombinant DNA molecules whose biological properties cannot be predicted with certainty, such experiments should not be undertaken lightly.

Third, the director of the National Institutes of Health is requested to give immediate consideration to establishing an advisory committee charged with (i) overseeing an experimental program to evaluate the potential biological and ecological hazards of the above types of recombinant DNA molecules; (ii) developing procedures which will minimize the spread of such molecules within human and other populations; and (iii) devising guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.

Fourth, an international meeting of involved scientists from all over the world should be convened early in the coming year to review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules.

The above recommendations are made with the realization (i) that our concern is based on judgments of potential rather than demonstrated risk since there are few available experimental data on the hazards of such DNA molecules and (ii) that adherence to our major recommendations will entail postponement or possibly abandonment of certain types of scientifically worthwhile experiments. Moreover, we are aware of many theoretical and practical difficulties involved in evaluating the human hazards of such recombinant DNA molecules. Nonetheless, our concern for the possible unfortunate consequences of indiscriminate application of these techniques motivates us to urge all scientists working in this area to join us in agreeing not to initiate experiments of types 1 and 2 above until attempts have been made to evaluate the hazards and some resolution of the outstanding questions has been achieved.

Paul Berg, Chairman; David Baltimore; Herbert W. Boyer; Stanley N. Cohen; Ronald W. Davis; David S. Hogness; Daniel Nathans; Richard Roblin; James D. Watson; Sherman Weissman; Norton D. Zinder.

Committee on Recombinant DNA Molecules Assembly of Life Sciences, National Research Council, National Academy of Sciences, Washington, D.C. 20418

Notes to above letter.

1. S.N. Cohen, A.C.Y. Chang, H. Boyer, R.B. Helling, Proc. Natl. Acad. Sci. U.S.A. 70, 3240 (1973); A.C.Y. Chang and S.N. Cohen, ibid., 71, 1030 (1974).
2. J.F. Morrow, S.N. Cohen, A.C.Y. Chang, H. Boyer, H.M. Goodman, R.B. Helling, ibid., in press.
3. D.S. Hogness, unpublished results; R.W. Davis, unpublished results; H.W. Boyer, unpublished results.
4. M. Singer and D. Söll, Science, 181, 1114 (1973).

APPENDIX FOUR.

EARLY CONJECTURED HAZARDS.

1. The introduction of antibiotic resistance into strains of bacteria that otherwise would not have them.

2. The creation of new combinations of antibiotic resistances in a bacterium.

3. The possibility of plasmids or viral DNAs which autonomously replicate obtaining DNA for oncogenic or other animal viruses that might be more easily disseminated to human bacterial plasmids.

4. The use of the 'shotgun experiment', where DNA is randomly fragmented, inserted into a host-vector system where the fragments might be expressed. Otherwise suppressed genes might in isolation become expressed.

5. The general use of E. coli, which naturally exists in the human gut. Risks initially thought to apply to the direct use of E. coli, after the introduction of enfeebled strains, were seen as modified to the extent that such laboratory strains might pass genetic information to wild strains in the event of human contamination.

6. Concern was expressed over the background training of the scientists who might begin to use recombinant DNA techniques. Good microbiological practice it was thought should apply.

7. The techniques might be deliberately used to facilitate the creation of biological weapons.

8. Some saw long-term evolutionary consequences, where genetically manipulated organisms released to the environment might carry new information for many generations before it is expressed.

9. The 'barrier' between prokaryotes and eukaryotes might be broken on a significant scale to produce unknown consequences.

10. Many non-scientists saw the long-term 'hazard' of dangerous knowledge arising. Genetic manipulation might in the distant future be applied to modify human development (in general, related to philosophical and ethical questions).

APPENDIX FIVE.

Excerpted from The Recombinant-DNA Debate by Dr. Clifford Grobstein.

PHYSICAL CONTAINMENT	BIOLOGICAL CONTAINMENT (FOR *E. COLI* HOST SYSTEMS ONLY)		
	EK1	*EK2*	*EK3*
P1	DNA from nonpathogenic prokaryotes that naturally exchange genes with *E. coli* Plasmid or bacteriophage DNA from host cells that naturally exchange genes with *E. coli*. (If plasmid or bacteriophage genome contains harmful genes or if DNA segment is less than 99 percent pure and characterized, higher levels of containment are required.)		
P2	DNA from embryonic or germ-line cells of cold-blooded vertebrates DNA from other cold-blooded animals and lower eukaryotes (except insects maintained in the laboratory for fewer than 10 generations) DNA from plants (except plants containing known pathogens or producing known toxins) DNA from low-risk pathogenic prokaryotes that naturally exchange genes with *E. coli* Organelle DNA from nonprimate eukaryotes. (For organelle DNA that is less than 99 percent pure higher levels of containment are required.)	DNA from nonembryonic cold-blooded vertebrates DNA from moderate-risk pathogenic prokaryotes that naturally exchange genes with *E. coli* DNA from nonpathogenic prokaryotes that do not naturally exchange genes with *E. coli* DNA from plant viruses Organelle DNA from primates. (For organelle DNA that is less than 99 percent pure higher levels of containment are required.) Plasmid or bacteriophage DNA from host cells that do not naturally exchange genes with *E. coli*. (If there is a risk that recombinant will increase pathogenicity or ecological potential of host, higher levels of containment are required.)	
P3	DNA from nonpathogenic prokaryotes that do not naturally exchange genes with *E. coli* DNA from plant viruses Plasmid or bacteriophage DNA from host cells that do not naturally exchange genes with *E. coli*. (If there is a risk that recombinant will increase pathogenicity or ecological potential of host, higher levels of containment are required.)	DNA from embryonic primate-tissue or germ-line cells DNA from other mammalian cells DNA from birds DNA from embryonic, nonembryonic or germ-line vertebrate cells (if vertebrate produces a toxin) DNA from moderate-risk pathogenic prokaryotes that do not naturally exchange genes with *E. coli* DNA from animal viruses (if cloned DNA does not contain harmful genes)	DNA from nonembryonic primate tissue DNA from animal viruses (if cloned DNA contains harmful genes)
P4		DNA from nonembryonic primate tissue DNA from animal viruses (if cloned DNA contains harmful genes)	

"SHOTGUN" EXPERIMENTS USING *E. COLI K*-12 OR ITS DERIVATIVES AS THE HOST CELL AND PLASMIDS, BACTERIOPHAGES OR OTHER VIRUSES AS THE CLONING VECTORS

EXPERIMENTS IN WHICH PURE, CHARACTERIZED "FOREIGN" GENES CARRIED BY PLASMIDS, BACTERIOPHAGES OR OTHER VIRUSES ARE CLONED IN *E. COLI K*-12 OR ITS DERIVATIVES

SOME EXAMPLES of the physical and biological containment requirements set forth in the NIH guidelines for research involving recombinant-DNA molecules, issued in June, 1976, are given in this table. The guidelines, which replaced the partial moratorium that limited such research for the preceding two years, are based on "worst case" estimates of the potential risks associated with various classes of recombinant-DNA experiments. Certain experiments are banned, such as those involving DNA from known high-risk pathogens; other experiments, such as those involving DNA from organisms that are known to exchange genes with *E. coli* in nature, require only the safeguards of good laboratory practice (physical-containment level *P*1) and the use of the standard *K*-12 laboratory strain of *E. coli* (biological-containment level *EK*1). Between these extremes the NIH guidelines prescribe appropriate combinations of increasing physical and biological containment for increasing levels of estimated risk. (In this table containment increases from upper left to lower right.)

Thus physical-containment levels *P*2, *P*3 and *P*4 correspond respectively to minimum isolation, moderate isolation and maximum isolation. Biological-containment level *EK*2 refers to the use of new "crippled" strains of *K*-12 incorporating various genetic defects designed to make the cells' survival outside of laboratory conditions essentially impossible. Level *EK*3 is reserved for an *EK*2-level host-vector system that has successfully passed additional field-testing. Because of the very limited availability of *P*4 facilities and because no bacterial host-vector system has yet been certified by the NIH as satisfying the *EK*3 criteria, the recombinant-DNA experiments now in progress in the U.S. with *E. coli* host systems are with a few exceptions limited to those in the unshaded boxes. Experiments with animal-virus host systems (currently only the polyoma and SV40 viruses) require either the *P*3 or the *P*4 level of physical containment. Experiments with plant-virus host systems have special physical-containment requirements that are analogous to the *P*1-to-*P*4 system.

APPENDIX SIX.

From: 2nd Meeting of EMBO Standing Advisory Committee on Recombinant DNA. Report and Recommendations, 1976.

Comparison of installations required for physical containment

	NIH GUIDELINES		WILLIAMS WORKING PARTY REPORT
P1	no special construction.	Category I	safety cabinet or fume cupboard with filtered exhaust. hand basin with elbow/foot taps.
P2	no special construction.	Category II	as above, in addition: remote laboratory not on publicly used corridor. negative pressure and separate or HEPA filtered exhaust. exhaust protective cabinet for aerosols.
P3	remote laboratory. negative pressure, exhaust to atmosphere (12 mm of H_2O) or gastight glove boxes.	Category III	as above, in addition: double door airlock with hand washing facilities on restricted side. negative pressure of 7 mm of H_2O and all exhaust HEPA filtered. double door autoclave or dunk tank. sealable, animal and insect-proof laboratory. all effluent sterilized. at least 24 m^3 per person.
P4	as above, in addition: negative pressure with exhaust sterilized. double door airlock with shower. double door autoclave. all effluent sterilized. monolithic construction.	Category IV	as above, in addition: shower in air lock facility. double door autoclave and dunk tank. gastight glove boxes with HEPA filters.