SOCIAL AND POLITICAL FACTORS IN THE DEVELOPMENT OF TOXICOLOGY

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Summary

The aim of this thesis is to investigate some of the factors that influence and direct the development of science. It takes the case of toxicology and focuses specifically on the social and political factors that have shaped its development to the present day. This is examined within a framework derived from some of the current issues pertinent to the sociology of science and science policy, which are particularly concerned with the role of external goals in the creation of scientific knowledge.

The emergence of toxicology is explored from its origins as the study of gross poisoning. The popularity of using poisons as tools for murder and assassination is seen as presenting toxicology with its first social goal. Developments in experimental toxicology during the nineteen and early twentieth centuries are investigated, as is its relationship to other emerging sciences at this time. Finally the emergence of the science in Britain since 1945 is explored, its institutionalisation and social and cognitive organisation are examined with particular emphasis on the commercial aspects of the science.

The external goals for toxicology are defined in social and political terms, as the need to control human exposure to poisons, and the particular regulations that exist to control the availability of toxic chemicals. The emergence of such policies in Britain is presented, with the major conclusion that in general the control of toxic substances has moved from being backward looking, controlling known gross poisons, to incorporating a requirement for a predictive evaluation of new chemicals before marketing.

In this context the interaction of science and policy is investigated, focusing on two aspects in particular. These are the scientific committees which have been established to advise government departments on questions relating to toxicology, and the different guidelines that have been produced to aid the safety evaluation of new chemicals. It is concluded from the research findings that social and political factors have had an important influence on the direction and development of toxicology as it is found in Britain today. They have directed both the social structure of the science, and the type of knowledge that it generates.

Keywords:

policy: sociology: toxicology: hazards: science.

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Introduction

This thesis developed from research that was undertaken by the author in the Technology Policy Unit, at the University of Aston in Birmingham between 1979 and 1983. The idea developed from a short thesis which had previously been written in partial completion of an M.Sc.degree at the University on the Social Aspects of Science and Technology. This was a case study of the emergence and development of a particular research institution concerned with toxicology - the British Industrial Biological Research Association (BIBRA). This study supposed that in the case of toxicology there are well defined social problems which influence and direct the scientific research programme. This work forms the origin of the Ph.D thesis which explores the role of social factors in the development of toxicology. Preliminary investigations along these lines revealed the long history of toxicology, which is represented in the recent past by political requirements for information on safety in the use of novel substances synthesised by the chemical industry. It remained, then, to establish a theoretical basis for such a thesis. Relevant literature was found both in the field of the sociology of science and in the work relating to the analysis of science policy. Previous studies were limited, however, rarely considering how the development of a scientific field can be influenced by political requirements for knowledge, the question which seemed most relevant to this study.

Recent developments in the sociology of science have started to investigate the relationship between the social and cognitive aspects of scientific specialties, based on the premise that these two factors are interrelated. To investigate the emergence of a new scientific specialty, both these factors must be taken into consideration. The work that has been done in this area, however, tends to focus on the

development of science within an academic context. Far less attention has been given to the emergence of new specialties within an industrial location. In contrast the science policy literature has failed to develop general theories relating to the role of science and technology in the policy area, but is dominated by case studies of the development of particular policy questions. In order to investigate the influence of political goals on the emergence of a scientific discipline, in this case toxicology, literature on the development of policy goals for science has been used together with work which relates to the direction of scientific knowledge by goals external to science.

The aim of this thesis is, then, to evaluate how autonomous the development of scientific knowledge is from the direct influence of social requirements. There are aspects of toxicology which make it a good candidate for a study of this kind. There is a well defined social and political goal in the desire to ensure the safety of new chemical products. The development of this goal can be investigated, through policy programmes that emerge to control the safety of toxic chemicals. A specific study of policies which require toxicological knowledge will provide a general view of the State's attitude to the control of new chemical products, whether there is a general toxicology policy or whether each policy question was generated and resolved in its own idiosyncratic way without reference to the experience of other types of control. The increasing involvement of scientists in policy formulation and implementation are studied as the problem shifts from the need to control the availability of substances known to be harmful to predicting those that will cause harm.

Policies in this area depend heavily on expert committees. Thus specific Departmental approaches to the appointment of committees and the institutional affiliation of scientists involved are questions of concern.

Where these committees produce test guidelines for different products, this should illuminate whether there is consensus or conflict over safety evaluation of substances or whether different departments vary in their approach to regulation. Finally, the State is primarily responsible for funding scientific research, so it is important to see how requirements for toxicological knowledge are transmitted to those bodies in government with the responsibility of distributing funds. If decisions are made on rational criteria, toxicological research should be encouraged in this area to solve some of the regulatory problems in using it.

Political goals it is argued are set, for the field of toxicology, by social requirements, expressed in the political arena, and mediated between policy and science through expert committees and experimental guidelines. The impact that this has had on the scientific area can be understood by investigating the development of toxicology as a scientific specialty. This involves an historical approach to the changing concepts in the field. Substances which exert an acute toxic effect have been known since ancient times, but the desire to use such substances for beneficial reasons gave this knowledge new meaning. The desire was then to find a dose which did not cause harm to the person using the substance. This raised the problems of defining acceptable risks, and also created scientific controversy over the effects of repeated dosing. Intimately related to these intellectual problems is the problem of detection techniques, which although rudimentary in the last century, have now been refined to take very sensitive measurements. It was the rapid development of the organic chemical industry which gave toxicology its subject matter, and prompted the development of animal testing models.

In Britain, toxicology began its formal social institutionalisation after the Second World War, but such initiatives were confined to the governmental and industrial spheres, with less interest shown by the

academic community. This implies the existence of conflicting research goals in the area, set by commercial and governmental needs, possibly conflicting with scientific research goals.

In undertaking this thesis a number of methodological approaches have been used, which can be divided into two general categories. The historical material, that is the information up to 1939, is obtained from both primary and secondary sources. The primary sources comprised mainly journal articles, books and published governmental reports. Secondary sources used were mainly articles and books on the history of medicine, although some unpublished theses were consulted. The major limitation with the material used in this part of the thesis is that it is constructed from information available in English, while much of the interesting activity took place in other European countries. In addition, the further back in history the story is traced, the limitations of the source material increase, especially from primary sources.

The second category is that which looks at developments in Britain since the Second World War; other methodologies had to be used to supplement the available published material. A review of the published material on toxicology in books and journals was made, but it became obvious that this did not accurately reflect the fact that toxicology is mainly undertaken in commercial laboratories. Some of the information in this section, then, was gained by correspondence with toxicology laboratories in various firms, and from interviews with a number of scientists active in industry. In addition unpublished reports from the Medical Research Council Toxicology Research Unit are used. Other unpublished sources of information are the British Toxicology Society, and the Public Records Office, Kew, and interviews with various people. Published government reports are also used.

Finally, information on the development of animal tests in the U.S.A. was supplied by correspondence with scientists who were members of the F.D.A.Division of Pharmacology during the forties.

A thesis of this type, however, is limited by access to data. Information from industrial and commercial laboratories on toxicology is often not kept separate from the total cost of the development of a product, and long term records are often not available. In addition, some multinational firms undertake all their safety testing in one country - and so do not appear on British records. Much commercial information, also, is confidential unpublished work. There are problems in defining the scope of the scientific area, as it includes the whole range of work done on toxicological problems from technicians working in industry to academic research scientists.

In doing a case study of this kind it is hoped to produce new generalities on the interaction between science and government, but as there is a dearth of existing work on this question, one case study cannot go far in this direction. The case of toxicology is quite specific in that it does not contribute to profitability of a company, but depends on specific expenditure to ensure safety. Thus the attitude of industry to toxicology may be different than its attitude to those sciences which enhance innovation. So conclusions from this study may not be applicable to all industrial sciences, nor even to toxicology outside the British situation, in a different political environment. Methodological constraints restrict the type of questions that can be answered by such a study, while there are theoretical constraints in trying to match two independent areas where the theoretical work has developed within different conceptual modes.

Previous work on toxicology is limited in scope, although there are some interesting researches that can be referred to. A useful

introduction to the history and social aspects of toxicology is given in 'Toxicology and Society', a thesis by David Eva submitted to the University of Manchester.[1] Other work on the science investigates the conflict that was produced over the question of lead toxicity by scientists from different occupational and disciplinary backgrounds.[2] There are a number of studies which focus specifically on the question of the development of governmental policy in this area, in particular for food additives[3] and pesticides.[4] The work by Johnston, Eva, and Gillespie on aldrin and dieldrin highlights the problems of interpreting information gained from safety tests.[5] Investigation of the British policy towards carcinogens has been undertaken by Green and Irwin,[6] and an interesting study of the interaction between theories of the causation of cancer, and American and British policies toward the control of industrial carcinogens can be found in J.S.Williams' thesis on occupational carcinogens.[7]

This thesis can be seen then as adding to the range of literature available on these questions. It is divided into three parts, the first being concerned with the theoretical framework within which the case study is to be evaluated. Part two surveys the general historical background to toxicology, from its pre-scientific origins as the study of poisons, to the emergence of forensic toxicology in the nineteenth century. The international aspects of scientific development are considered, with the relationship of toxicology to other emerging scientific disciplines. In addition this part of the thesis surveys the emergence of specific legislative controls over poisonous substance in Britian. It ends with a consideration of the development of specific animal tests to predict the toxicity of chemicals by the Division of Pharmacology of the Food and Drug Administration.

The third part concentrates on the trends that have emerged in Britain since the Second World War. In particular it looks at the

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emergence of the social and institutional structure of the science, and the related cognitive developments. External policy goals are defined for toxicology, for the types of chemicals which are required to be tested on animals before marketing. Thus the establishment of a policy towards pesticides, food additives, drugs and industrial chemicals is examined in detail, as all these cases have specific governmental guidelines on safety testing published about them. The establishment and development of these guidelines, then, is examined in detail, as these are the particular external directives for the science. In addition the scope of the toxicological community is identified and this is compared with the background of the governmental advisory scientists who evaluate the data and set the guidelines. Finally, the conclusion attempts to identify the trends within the process of the political and scientific interaction, and elucidates the actual impact that these external goals have had on the direction and development of toxicology

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PART ONE

THEORETICAL CONSIDERATIONS

CHAPTER ONE

SOCIAL AND POLITICAL ASPECTS OF SCIENCE

Social and Political Aspects of Science

There is a traditional view of scientific knowledge which holds that it is objective, factual and certain. In effect science is a system autonomous from, and not influenced by, wider aspects of society. Thus when society uses scientific knowledge for a social end, for example in public policy, an uncontestable package of "facts" may be obtained and utilised. It follows from this that any controversy that is generated over science policy arises only from differences with the social values of the scientists involved and not from queries about the existence of certified knowledge.

This basic assumption has been extremely influential in both the sociology of science and the literature on science policy. In the former case the Mertonian school has developed an important strand in the sociology of science, focusing on the social organisation of scientific specialties, rather than on their cognitive structure.[1] In the policy arena this concept led to the spectre of 'technocracy', where scientists, as the guardians of knowledge, wrest political power from those elected to exercise it.[2] Political decision makers are expected to devolve policy problems to those with the technical skill to solve them. Thus political and ideological decision making rests increasingly on objective facts, and there is 'a considerable narrowing of the scope of conceivable alternatives in public policy and on attenuation of the differences which distinguish capitalist and socialist systems'.[3]

Although this is still an important view of scientific knowledge, particularly within the disciplines of philosophy and the history of science, it has been widely criticised.[4] An alternative approach can be based on some of the more recent work which has developed the Kuhnian thesis of the development of science. This explores not only the

social organisation of scientific specialties, but also their cognitive content, and the utilization of knowledge by the political sphere. This approach recognises that scientific knowledge can play a unique role in the solution of social, economic, and political problems, but it cannot be considered as entirely independent from this utilization for social ends. Science and politics interact in the modern world, and it is the function of this thesis to explore the ways these can direct, influence and shape each other.

Much has been written on both science and policy as separate issues, and they can be considered in this way, with political goals regarded as one input to the development of scientific knowledge, and vice versa. It is interesting, however, to focus specifically on the point of interaction between science and policy, to investigate when this developed, how it has changed, and whether it can be directed in the future. Such questions have begun to be raised in the literature, although much of the preceding literature, being highly specific in nature, does not easily lend itself to a more general reinterpretation. A review of some of the relevant concepts in the areas of the sociology of science and science policy follows, with a more detailed consideration of theoretical points which arise from their points of interaction.

1.1. Science and Technology in Government Policy

Within the general area of science studies there is a more specific concern with the way that questions involving science and technology have become taken up in policy making at the governmental level. Not only are most of the resources for scientific research distributed from Governmental sources, but also many areas of policy making depend on the provision of expert technical advice to policy makers. These two processes are linked through the necessity of utilizing scientific knowledge to implement Governmental objectives.

There is a problem in drawing general conclusions about the role of science policy in an administrative system, when focusing on specific case studies. It may be possible to avoid this problem by looking in a more general way at a set of policies, which, although set in very specific conditions are linked by an underlying theme, which necessitates a similar approach to their implementation. Thus it can be asked whether there is a British policy towards the control of basic chemicals, how this policy emerged, whether there are detectable differences in approach between political parties and if international considerations have influenced the development of such a policy in Britain. These questions allow the investigation of the actual role of scientific knowledge in policy formulation.

In the literature, science and technology tend to be considered as apolitical factors in that political attitudes to these policy questions are not divided along the usual partisan lines, in fact the literature rarely mentions the political context in which decision making occurs.[5] But as Brickman suggests 'it is fundamental to ascertain the impact of political variables on the science policy process'.[6] One concept of the role of science and technology in policy making arises from the idea that they are apolitical factors. Brickman outlines the view that they are part of the distributive policy of a government, that is, a small part of its resource and policy making function, which by definition does not impose on any other political interests. Thus the political decision making involved in questions of science and technology is minimised as, 'these are policies that are virtually not policies at all but highly individualised decisions that only by accumulation can be called a policy'.[7] This can, in fact, describe the existing attitude to science policy making, particularly where it is fragmented, and found

as parts of policies, not obviously related to science and technology. In this approach, then, 'science policy' remains mostly an aggregation of specific measures and programs where governmental action on one has little bearing on another'.[8]

Brickman identifies a number of problems with the distributive theory. In actual terms all distributive policies are redistributive in the long term, because certain policies will affect particular interests. This means that a part of a science policy will be regulatory in nature. It is also important to recognise that there are international influences on decisions which alter aspects of partisan policies. Finally, party political considerations will play some part in decision making about science and technology.[9] The benefit of this approach is that it opens up the analysis of science policy to comparative analysis with other governmental policy, as there is clearly a need for more extensive and careful comparison between science and technology and other areas of public policy.[10]

Another way of analysing science and technology policy is to investigate the different political systems from which it arises, to compare policies on a country by country basis. Thus it should be possible to relate international differences in politics, to individual differences in political organisation and attitude.[11] This latter type of analysis has, however, received little attention up till now, by science policy analysts.

The problem is to attempt to analyse science policy in terms of distinct approaches related to ideological or political differences found in partisan politics. There are, however, problems in defining the concept of political ideology in terms of which social and political matters will have priority. There are also difficulties in defining the scope of science policy, as there is not a homogeneous policy

directed towards science and technology, rather these are utilised in a wide range of policies in a non-uniform way. Support for basic research, for industrial stimulation and social regulation all contain parts of the national science policy, so it is not possible to consider all these as part of one policy towards science and technology. Even taking a basic "budgetary" view towards expenditure on research and development, the industrial sectors involved vary too widely for support to be perceived as part of a unified policy. Furthermore, Brickman does not think that this is the most useful tool for analysis,

> Budgetary figures indicate neither the extent of controversy which preceded allocative decisions, nor the distribution of benefits and costs accruing from different courses of action nor the process by which policies were set.[12]

Science and technology are obviously then, not value free. It is, however, quite commonly assumed that they function autonomously from the political system. This does not account for their role in policy formulation as there is always a choice involved in allocating resources between scientific areas. The "autonomy" of science is, then, a product of its internal organisation, and the desire of the scientific community to remain independent of political direction, while retaining political influence. Brickman comments,

> the scientific community has acquired an exceptional degree of influence in the public administration of its own affairs, justified by their esoteric nature, the profession of value free norms, and the promise of social benefits.[13]

It is clear that, 'traditional politics and ideologies have played an undeniable role in science and technology decision making',[14] but that, 'no single explanation or analytical approach among those considered adequately accounts for the degree and nature of the involvement in politics'.[15]

In analysing a policy issue in which science has played a major part, there are two aspects to the problem which must be considered. The distribution of government funding between competing scientific specialties for research grants, and the utilisation of scientific knowledge in policy formulation. Thus we are interested in all aspects of scientists involvement in the political arena, from the role that they play in allocating research funding between research areas, to their concern in identifying and publicising problem areas which require a political solution. Finally, their involvement in policy formulation and their part in implementing the accepted solution.

1.2. Policy For Science

This is mainly concerned with the distribution of resources between established scientific disciplines within the university system, for basic research. Within science there is a hierarchy of specialties which affects the distribution of funding, and one problem which has been identified is that the cross fertilisation between disciplines is not facilitated by the distribution of research support, neither is a multidisciplinary approach.[16] It has been suggested that the support of pure science is equivalent to the state support of cultural activities such as art or music. As the scale of the funding is much larger than would be expected if this were true, it is valid to ask how far the support of pure science coincides with state objectives. State intervention can suppress a discipline developing, but cannot direct the way in which it does develop.[17] If the research has to be seen to be relevant to the funding institution for results, this is especially relevant as more basic research is being undertaken within non-academic organisations. There is, then two types of research, 'open' research, which is the traditional research of the academic, chosen for its interest and relevance to a particular subject. The other is 'oriented'

research where objectives for the research are set by the sponsoring body. This latter type may well attract far larger funds than academic research, but there is some controversy over the type of knowledge that can be directed in this way.[18]

As there is inevitably an element of choice involved in the prioritizing of research projects and the distribution of funds, criteria which can be used to distinguish between potential projects are attractive. An early model was suggested by Alvin Weinberg,[19] who suggested that the decision to fund a research area should be based on the assessment of both the internal evaluation of the field, and external criteria, such as the relationship to desirable technology, so that,

> A field in which lack of knowledge is a bottleneck to the understanding of other fields deserves more support and should be pushed more urgently than a field that is isolated from other fields.[20]

Internal criteria, being identified as whether a field is ready for exploitation, are left to the scientific experts to assess, independent of any external interference.

Despite the apparent rationality of these criteria, this system has been critized as being impracticable. Concepts like national prestige are impossible to measure, and this system cannot indicate what part of the budget should be allocated to fundamental research, whether it is regarded as valuable in its own right, or as an imput to production.[21] In effect, Saloman considers,

> It is science fulfilled as a technique which interests the state and justifies in the eyes of public opinion the money spent on research, and not science as culture aimed at the enlargement of knowledge for its own sake.[22]

Once the problem of the allocation of resources has been resolved, the best means for their distribution must be resolved. Nelkin explores

the relative merits of a centralist versus a pluralist approach, as different governmental structures lead to different systems of allocation of resources, so :

> Government efforts may take several forms: grants, contracts to support research in private industry, or non-profit institutions, special purchasing procedures, or measures to disseminate technical information.[23]

As governmental intervention is important over the whole range of scientific and technological research and development, the balance between supporting basic research which has no obvious practical value, and large "mission oriented" projects, which have a specific practical objective must be achieved. There is the question of who should set the priorities in science, the policy makers or the scientists with conflict between control and autonomy. Essentially the success or failure of a policy depends on how the affected interests respond.[24] Non-technical factors are also an important aspect of decisions about the allocation of resources. Saloman makes a distinction between

> tactical choices which deal with scientific problems and projects within a given field and are basically dependent on internal scientific criteria and strategic choices which concern areas of great priority and must be guided by objectives external to the scientific community.[25]

Nelkin identifies three major external objectives which merit some attention :

1. National political goals
2. Perceived urgency of the problem
3. Technological opportunity.[26]

National political goals are a set of objectives which will dictate how resources are allocated - for example the desire for weaponry has ensured major expenditure. The perceived urgency of the problem to

be resolved is related to the processes whereby problems are brought to political attention and are taken up in the political arena. This can be a long struggle if the problem in question is not illustrated by some event of public concern, or where no special interest group exists to press the case as public needs often become equated with organisational imperatives that follow from existing arrangements.[27] Technological opportunity exists where the political desire to solve a problem coincides with the scientific and technical ability to provide a solution. In the cases of successful matching of these two factors, the most successful policies are made.

It can be seen then, that state aid for scientific research is not solely decided and allocated on rational grounds of choice between competing research projects as 'the use of science and technology is influenced largely by the degree of political consensus about specific problems'.[28] Thus some projects are more likely to attract funding than others. Scientists themselves are involved in this assessment in terms of their choice of research area and research discipline. Chubin and Connolly suggest that this choice on the part of the researcher is not a straightforward assessment of the internal state of the science, but that 'these scientists select their projects under the influence of a complex of organisational, cultural, political and intellectual conditions'.[29] In effect researchers choose their topics 'in pursuit of a bounded self interest',[30] in which they move from topic to topic, following a particular 'research trail'. To carry on scientific research, a scientist needs 'legitimacy, funding, access to local resources and training capacity'.[31] In this way research areas can be built up, and, Chubin suggests, a hierarchy of scientific specialties builds up, with the scientific elite controlling the distribution of funds to each individual project, and the continued support of an individual

trail,

> both the individual researcher and those powerful gatekeepers of the relevant hierarchies who control funding publication, and acclaim, acquire a reputational interest in the continuance of the trail.[32]

But funding is obtained most easily for those areas that are already established

> A research proposal is most readily prepared, and most readily accepted, in an area with which one is most familiar.[33]

This has the result that the development of science is by both its internal logic, and its social organisation, rather than being subjected to assessment from external, socially linked criteria, it is in the hands of a few scientists

> The elite legitimates and funds .... the scientific elite plays a functional role in the amelioration of political pressures and the evolution of research .... The elite can, in short, determine what problems are chosen and whose trails are sustained.[34]

An interesting example of the strategic importance of a well placed individual can be seen from the role played by Frederick Lindemann in securing resources for the development of solid state physics.[35]

1.3. Science For Policy

Although these two areas are interdependant, it is not always easy to assess how they relate, nor how research needs are transmitted from one position to another. The object of study here is in the role of science in policy making ranging from defence and R&D policy to regulative and social policy. Here, scientists are important as having specialised knowledge and are particularly utilised as expert advisors, but as Sayre notes,

> the scientific community is most often used as a strategic phrase intended by the user to imply a large number of experts where only a few may in fact exist or to imply units of view where disagreement may in fact prevail.[36]

Weingart has attempted to address the problems of the use of science by the state,

> We .... limit ourselves to the analysis of the process of programme formulation and implementation in the political system and try to account for the various factors that determine that process, i.e. the use that is being made of scientific knowledge and the danger that occurs in the perception of problems.[37]

This is undertaken by investigating how policy programmes evolve with respect to political goals and scientific information, and how these policies are implemented. The basic change in the function of the state is seen as being a move from a 'laissez faire' attitude reacting to disasters after they have occurred to being more interactive in character, in actively interfering to control undesirable effects in character, in actively interfering to control undesirable effects of the economic order.[38] This has affected the information required by the state before action can be taken,

> the execution of comprehensive programmes calls for the anticipation of first and second order consequences and this, in turn, makes it necessary to obtain as much systematic information as possible on those areas which are affected .... The change in the nature of governmental function, therefore, implies an extension of the utilization of systematic knowledge.[39]

Weingart outlines three types of relationship between science and the state: funding for research institutes to support the development of a region or the production of qualified manpower, science used to legitimate or give greater credibility to political decisions, and science being also important for its knowledge value as it is used for its information producing function.[40]

The first aspect of the utilization of science and technology in policy formation is its role in the actual establishment of a problem as one requiring political action. Weingart points to acknowledged problems, such as social legislation, that are regarded with different priorities by governments with different ideological commitments. Another problem is the state of the knowledge in the area, as this can be constantly changing and policies based on it may be invalidated, (also knowledge may be lacking, and so special conditions must be created to produce it), although ideologies influence to an extent what knowledge is being perceived and how it is interpreted.[41] It is suggested, then, that scientific knowledge can highlight a problem for policy and also that scientists may be involved in bringing the problem to public awareness through public action or opposition. Scientists also may form part of a governmental committee to investigate and give policy recommendations on an area which has been perceived as requiring attention. In short,

> We proceed from the assumption that a problem may be perceived either within the governments i.e. the administration itself, or by the scientific community (in the widest sense of the word), or by the public ....[42]

In order to explore the role of science and technology in policy formation Weingart suggests that it is necessary to analyse the contribution of the relevant institutional sectors. In particular to analyse the establishment and implementation of governmental programmes, why they are established at a particular time and what inputs ensured that the problem emerged and was taken up as a political question.

Where implementation of a programme leads to an increasing interest in promoting or reorienting a sector of scientific research it is necessary to investigate the success of the new programme, or to assess the reasons for the failure.[43]

There is some question over whether the use of science in formulating policy is compatible with democratic aims in society, because 'expert advice concerns policies which affect many persons other than scientists'[44] also, Macrae states that,

> The politically most significant area in which science and democracy can conflict is that of "science in policy" - i.e. in public policy affecting major aspects of society other than science. Democratic governments make use of science in many types of policies. They concern themselves with it both as direct sponsors .... and as regulators of the private sector - controlling food, drugs, the environment, and the effects of economic changes.[45]

This is highlighted due to the increasing complexity of problems needing political solution and the inequalities of knowledge between scientists and the public in general. Scientists' knowledge, however, is very technically specific and narrow, while policy recommendation requires a broader analysis of the impact of the policy.

A major task for governmental agencies is in the control of the disbenefits to society from industrial processes. This particularly takes the form of regulative control. Nelkin identifies three major themes in such control. "Participatory control", involves all affected groups. This is particularly a reaction to problems arising from existing technologies or processes, usually environmental or social in impact. In the United States one response has been the proliferation of citizen group involvement, often on an ad hoc temporary basis, which react to decisions already taken by industry or government on a technological issue. Such groups often lack expertise and can, therefore, be unsuccessful as 'complex data supporting a particular development cannot be challenged without counter expertise'[46] Despite scientists' traditional dislike of being involved in partisan issues, Nelkin also points to the development of public interest science, particularly where scientists themselves have taken a stand over a public issue.

The second form of control is of the type that is a reaction to recognised problems caused by technologies. In particular, 'administrative and legal controls are used to influence scientific and technological development ...'[47] The responsibility for carrying out these controls may be delegated to a regulatory agency, which, Nelkin states,

> are traditionally expert and non political bodies with both judicial and legislative responsibilities .... They regulate industrial practices by setting rates and safety standards and issuing permits, and they influence the development of technology by controlling prices, profits and entry into the market.[48]

The courts are more commonly used in settling issues concerned with science and technology in the United States than in Britain. There they are accessible to private citizens who wish to interfere in a decision, and it has been noted: 'Citizen initiated law suits have increased in response to problems associated with technology, and litigation has been a major means to restrict and direct technological change'.[49] In particular the courts can define responsibility for damages caused by technology. They can impede the development of technology by imposing injunctions on it, and finally can back up administrative and regulatory action. Regulation can take place through the influence of market incentives, such as taxation or fees and penalties, or through minimum standard setting although 'Direct government controls over both research methodologies and applications raise difficult policy problems. Compulsory controls elicit accusations of government paternalism and overprotection'.[50] The third type of control assessed by Nelkin is anticipatory control , designed to be applied before decisions in new technologies are taken, these particularly involve techniques such as forecasting, futures research and technology assessment.

A brief note should be made here about risk analysis. There is much written about the analysis of risks and how they can be ranked, and quantified. Numbers like the fatal accidents frequency rate developed from work on the assessment of the safety of nuclear reactors. In Britain, in the regulatory arena such evaluations tend to be made implicitly by advisory bodies, rather than explicitly stating what criteria have been used. Such decisions are mainly made on the philosophy that if specific safety standards are met, this is actually an integral part of the assessment of risks.[51] More important to the analysis of science for policy is the role of scientists as "experts" in the parliamentary system.

1.4. The Role of Expert Scientific Bodies

The growth of the involvement of science and technology in governmental decision making, means that technical advice must be provided to the state in some way. In particular this is provided in the form of advisory committees staffed by scientists with backgrounds in relevant disciplines. There are various allegations about the representation on such committees, and whether the advisers are drawn from an elite within the scientific area. The possibility has been suggested that such bodies are appointed with the view that they will agree with the particular partisan policies that are being put forward, rather than being expected to give objective advice. This point of view acknowledges the political and social components that are present when decisions involving science and technology are made, as 'it is, moreover, often the prestige of scientific knowledge rather than scientific knowledge itself that politicians and others draw upon to justify their positions and to discredit their adversaries',[52] whereas there may be controversies with the scientific camp, as Calder suggests,

> experts are not easily manipulated in areas where their knowledge is on well established grounds and a professional consensus exists about what is right and wrong ... expert knowledge can vary widely in the grey areas of policy where there are options and room for interpretation.[53]

Appointment to an advisory committee may be regarded by the scientific community as one of the rewards for success, although successful advisers are those who keep a foot in both camps, and, 'the adviser is, in any case, almost certainly a 'reliable fellow' who will neither cause needless embarrassment, nor argue about purely political matters'.[54]

Once policy goals have been settled, if they are clear, uncontroversial, and there is a scientific consensus in the field, expert advice will be sought. Although disagreements among scientists in scientific questions give more freedom to politicians and administrators to interpret scientific opinion and to select measures to be used,[55] 'Scientists also have different political views and, rather than attempting to be neutral experts, there is the possibility that they might agree on the assessment of evidence and on factual consequences of each of the preferred alternatives of policy but ..... disagree on the policy to be chosen.' [56] The basis of expert disagreement has been attributed to the relative internal development of the scientific theory in the field. As Ravetz states,

> Indeed, as we move away from the established physical-chemical sciences, into those concerned with the natural environment such as ecology or into fields dealing with the interaction of human bodies with alien substances and species such as toxicology and epidemology we find ourselves among 'less developed sciences'. There, methods, theories and even basic facts are still in dispute.[57]

Hence knowledge in these areas is open to dispute among the experts and there is a high risk that the advice they give will not be the best. Ravetz again, has pointed out,

> In poorly developed disciplines scientists may find themselves in radical disagreement over the most apparently elementary matters of fact. For where an effect is imperfectly understood, different theories may even call for quite different sorts of data so that there is little comparability of information from various sources .... The relative weakness of the scientific evidence makes it more difficult for a scientist to resist political and other attachments and demands, and there is a tendency for each scientist to argue 'scientifically'[58]

Whether this is a function only of the less precise sciences, or is found even with the advice of hard scientists is a question for investigation. It has already been pointed out that no technical decision is made without social and political dimensions. It is, however, interesting to explore the problems that do arise from non precise sciences and to investigate the particular aspects of advice which is given in this context. It is important to see how the changing situation of scientists, employed in a partisan context, raises problems for impartial expert advice. This is a problem that Ravetz has commented on,

> Much scientific knowledge is produced through the investigation of problems chosen for their relevance to industry, commerce, government and military security. The institutions sponsoring such research will impose various controls of many sorts and degree of rigour on the publication of results. The scientist who makes public the results of his research without permission, may find himself in violation of his conditions of employment, or of a commercial contract, or some particular statute, or even an official secrets act.[59]

An adviser, chosen for his or her expert knowledge must be viewed, in certain situations, as working in a partisan environment or on one side of a controversy and therefore not with the impartial nature of the traditional 'objective scientist'.

> Therefore we observe that the interpretation of any statement of a scientific character is subject to influence by the role which the author and his interlocutor accept .... The fact that a person has qualifications as a scientist, or that he holds an academic appointment does not by any means ensure that he is genuinely acting as a consultant.[60]

There are a number of issues in which the recognition of the character of expertise is important, as the idea of scientific rationality is useful for politicians wishing to depoliticize problems and define decisions as technical questions. Thus Nelkin believes that disputes between experts play a role in exposing the political nature of decisions over technology;

> when expertise becomes available to both sides of a controversy, it further polarises conflict by calling attention to areas of technical ambiguity and to the limited ability to predict and control risks. The very existence of conflicting technical interpretations generates political activity.[61]

Thus, in order to challenge a decision on science or technology, access to technical expertise is essential. This is important as scientific experts are not only seen to have a certain authority based on assumptions of the nature of science, but also legitimate decisions.

> Technical expertise is a crucial political resource in conflicts over science and technology. For access to knowledge and the resulting ability to question the data used to legitimate decisions is an essential basis of power and influence.[62]

A few studies have been done to explore whether advisory committees are actually appointed only from a small, visible elite group of the scientific community. Mullins has studied the advisory structure of the U.S.Public Health service, with the expectation that such committees were controlled by an elite,

> Specifically, we should expect that (1) a limited number of persons hold positions within the advisory system, and (2) as far as is possible, new appointments will be made from the pool of scientists with prior or present service.[63]

The study, however, does not find these expectations fulfilled. In Britain, Blume found the membership of the Advisory Committee on Scientific Policy (ACSP) to be balanced in favour of Oxbridge and London trained doctoral graduates, and he identifies a high number of prestige scientists who serve as multiple chairpersons of committees.[64] Hook, however, does not find evidence in Britain that advisory committees on questions of technological risk are appointed from a small elite although he has some evidence to support that of the multiple chair-people.[65]

There is some support for the view that there is creation of an elite in a scientific field, particularly from Mulkay, who sees these groups acting as a 'buffer' between the social and political arena and the internal organisation of the science.[66] He maintains that advisory bodies create an institutionalised link between government and the research community,

> The advisory system has been arranged hierarchically; committees at the lower end of the hierarchy being concerned with relatively specific, scientific issues, such as the evaluation of funding of particular research proposals, whilst those at the higher end deal preponderantly with decisions involving social, economic and political, as well as purely scientific considerations.[67]

Mulkay holds that it is the elite who are involved in this activity. Thus the elite exert some influence on governmental policy both towards academic science and in policy areas concerned with science. As the elite are undoubtedly academic scientists they may be expected to be particularly concerned with the distribution of resources between academic fields and desirous that this is done only on scientific evaluation of the worth of competing projects to research goals, rather than on their practical or commercial merit, 'in general it appears that there is a pronounced bias in Britain in favour of fields

with high scientific status but low economic relevance'[68]

Thus the elite has much control at the level of the choice of projects to fund, although the wider political context supports the backing of promising projects in economic terms, and try to influence this in funding allocation,

> it is clear that politician and civil servant play a decisive role, for example, in determining what proportion of total public expenditure is to be devoted to scientific research.[69]

Scientific advice is desired for the technically specific expertise of the scientists. They have the means not only of defining problems in a certain way, but also of implying a certain range of solutions within such problem definition, and Weingart suggests this to be the source of their power,

> If it is true .... that scientific, technical and professional knowledge has assumed considerable functional importance and legitimating power, it will also have a growing impact on the structure and contents of political problems. It may therefore be inferred that knowledge conveys political power insofar, and only insofar, as it becomes a major ingredient in the definition of political problems.[70]

The traditional conception of the scientific adviser as being consulted for knowledge,

> depends on the assumption that politics and science values and knowledge can be neatly separated .... (and) the instrumental function of knowledge alone in its role in determining problem solutions, does not convey power because it leaves the scientist in a state of dependancy on those who do or do not call on them for advice.[71]

The true situation, according to Weingart is that power lies with those who control the access to knowledge,

> because a certain body of knowledge will then assume an orienting function which entails the acceptance of implicit assumptions, the predetermination of the possible range of solutions, the exclusion of other knowledge and thus alternative problem perceptions and solutions.[72]

Weingart identifies two reasons why the impact of scientific expertise has not given scientists political power. The institutions in which scientists are now employed are much wider than narrow academic places, so such knowledge that is required for policy making is located within this wide base. A consequence of this is that the scientific community can no longer be regarded as a homogeneous body, as 'alliances and fractions emerge which run along the lines of political convictions rather than systems of knowledge.'[73]

In policy formulation, Weingart postulates the emergence of 'hybrid communities' by investigating 'the formal representation of scientists and other experts' in policy-defining bodies, and the differential impact of types of knowledge held by these groups on the definition of problems.[74] The traditional academic advisers increasingly share the platform with experts from different institutional affiliations. It is those expert groups from different institutional background that are termed hybrid communities, and,

> Their function is to help define policy programmes and correlate policy measures, all of which feed back into the perception and definition of the policy problems themselves. The significance of the 'hybrid communities', therefore, lies in their cognitive function as brokers of expert knowledge and political values.[75]

In order to corroborate the idea that experts from different institutional backgrounds shape the definition of political problems, it is necessary to investigate the role of scientific knowledge in defining the problem. Robbins and Johnston illustrate the fact that disputes between experts may not only occur because of political differences but also because of genuine disciplinary based differences in approach towards the creation of scientific knowledge,

> Recognition of the socially constructed nature of scientific knowledge requires that an analysis be made of the factors which affect the particular knowledge the scientist adviser chooses to draw upon in presenting his advice.[76]

In addition to this, it is not difficult to show that even where the advice is consistent, different governmental administrations can reach contradictory conclusions on the acceptable policy solution.[77]

These approaches are beginning to challenge the positivist attitude towards scientific knowledge and its use in policy formation. The black box conception of scientific knowledge has been shown to give a false idea of its role in policy formation, and the actual production of the knowledge itself must now be investigated. The interests and institutional affiliations of the advisers can alter the advice that is given, and genuine conflicts of knowledge within the scientific area should be explored where there is a controversy over a technical matter.

1.5. Britain

It is necessary, therefore, when investigating some particular aspect of science policy to take into account the country in which the policy is made. It is important to be aware of the fact that policy is made by specific governments in specific contexts, so that differences between political systems will arise even when there is consistency from scientific advisers.

In investigating a particular scientific area which is heavily used in policy for regulating industrial behaviour, and is also a developing scientific area in its own right we are looking at the interrelations of both policy processes for science, how these interrelate within a particular system and how governmental priorities are set.

It is useful, therefore, to look at the British system for establishing policies, and the provision of technical advice to British

ministers.

In Britain policy making is a prerogative of the elected governments, but pressure groups have an increasing role to play in its formulation. Only a small number of statutory instruments receive parliamentary scrutiny, while the Cabinet has a major role in decision making. One area of concern is the alleged lack of information available to the British Government. Smith states,

> That there exists in British government a need for such information, especially on the consequences of public policies is obvious .... The Treasury has also admitted that adequate information on the output of public expenditure programmes .... has not been available to policy makers.[78]

and also,

> Information problems in government occur at all stages of the policy process, from the appraisal of problems through the production of the results from possible lines of action to the evaluation of the effects of chosen policies on the original problem. Since most perceived problems are already under the influence of some existing policy, it is possible to conclude that there is a great need for what ought to be termed 'output' information as distinct from 'input' information.[79]

The problem of information is particularly distinct in relation to scientific and technical matters. In order to cope with the growing need for this information a number of changes have been made to facilitate its use. Committees dealing with defence and civil policy were set up after the war, Government departments appointed advisory councils to keep in touch with research undertaken in the universities, and 'the use of experts or expert committees to advise government has increased enormously the number of political decisions based on evidence not subject to informed public or parliamentary criticism'.[80] So the position is, that Members of Parliament are often ill informed about decisions taken with technical information which is not generally available, particularly when a report has been commissioned but not

published. Albu holds that,

> The truth is that, over a number of years, Members have allowed the executive to acquire nearly a monopoly of the information on which policy is based. As a result, the executive has now developed an attitude of almost insolent secrecy.[81]

Another means of obtaining information is through Select Committee reports which are usually taken seriously by Departments even if all the recommendations are not accepted. Committees can set up sub-committees on specific issues. Political parties may have their own committees on scientific matters, and there have been some all party groups concerned with scientific and technical matters. Other means of transmitting information are through parliamentary debates and through questions in parliament. Scientists' trade unions provide some information for speeches.[82]

One important aspect of the administration of science and technology policy in Britain is the interdepartmental differences in responsibilities. It is such that a department may find itself with a contradictory brief - such as to both promoting and regulating a certain industry. This could influence the choice of people to sit on advisory committees, as Smith and Pitte note,

> Members are usually selected by the Minister concerned who is not, of course, bound by their advice and recommendations .... A department may try to obtain a politically neutral endorsement from its immediate environment for something it wishes to do or has made up its mind to do.[83]

Advisory Committees may receive their powers from the source of their appointment which is either from parliament, via the passage of statutory acts, through Royal prerogative, or conventionally through their appointment by ministers. There are two major types of committees - standing committees which are appointed on a continuing basis, and usually deal with general matters, and ad hoc committees appointed to

deal with specific problems, which are dissolved when the problem is solved. Royal Commissions are formally appointed, but departmental committees may be informally set up, although the differences in types of appointment are not clear. The Home Office and Scottish Office appoint most of the committees, which are independent, while some departments notably, Health and Agriculture appoint more joint committees. Propensity for setting up committees seems to depend, among other factors, on the suitability of this type of investigation to the work of the department. Some departments have a 'tradition' of setting up committees, while large departments with bigger areas of responsibility and larger budgets set up more committees. In appointing members to a committee it is hard to discern a common policy. Some people are met informally, some are appointed to discharge a political debt, or choice of member may even be left to an official. Those most commonly appointed are elderly men with previous experience of committee work. Members of the judiciary are most often appointed with academics, businessmen and retired civil servants. All committees have a secretariat for organising meetings and drafting reports. Some have assessors when the committee needs expert advice of its own as to examine witnesses and produce brief technical reports. The chairman is responsible for carrying out the mandate. Most reports are published within 1-3 months of submission.[84]

Distribution of funds for science is through the system of research councils which have the responsibility for deciding between competing research areas, as Allen suggests over the past 15 years, industry and the public sector have withdrawn from major areas of basic science and, increasingly, as the economic problems crowd in on the U.K. the Research Councils and the universities and the polytechnics have an even greater responsibility for the prosecution of basic research.[85]

In practice it is the Advisory Board to the Research Councils which makes the tactical choices in the policy for science. The most important review of this system was carried out by Lord Rothschild in 1971. In his subsequent report on government funding for research and development he introduced the concept of accountability, the 'customer-contractor' principle.[86] While this was primarily concerned with the funding of applied research, it is important to note that projects funded by the Medical Research Council were encompassed by this principle.

The British 'science for policy' is more difficult to track down as it spans virtually every department in the administrative sector, and is channelled through a plethora of committees. Chicken, in his study of hazard control policy in Britain, identified the major groups involved in policy formation.[87] He found policy making dominated by the civil service, with demand for new policies often originating from within the departments concerned. In developing a policy use is often made of independent committees - and this is often the point where interest groups can have the most effect on policy. The involvement of political parties, parliament and the cabinet is small in this area. When the hazard is identified, the solution involves control via a legal framework or a specialised inspectorate to establish and enforce the controls. Consultative bodies and research may be initiated. In general older hazards are not as tightly controlled as new ones, and this difference is greater than the difference between public and privately owned industries.[88] In practice it can be difficult even to determine whether a hazard has been coherently defined as a policy area, given the traditional ad hoc approach to British policy making. For example see the problems faced by Green and Irwin in attempting to define a British Carcinogens policy.[89]

In conclusion, certain general statements about the role of science

policy in the general activities of the state can be postulated. These may be expected to hold true for states with a liberal-democratic government, and, as some theorists predict the convergence of policy issues in an industrial environment centred on technological innovation, for states with other forms of government.[90] This then raises the question as to how significant differences in policy formulation and solution can arise in different countries. The specific social and political environment must be understood when science policy issues are under investigation, although wider international influences may have a profound effect on such issues, and this must also be taken into account.

The political requirements of science are well established, but how these affect the development of science itself is a legitimate area for investigation. Such an investigation is the responsibility of the sociology of science. The dominant tradition in this area has focussed on the social organisation of scientists, leaving the analysis of the development of scientific knowledge to the philosophers and historians of science, a division which is still much in evidence.[91] This split has, comparatively recently, been challenged by sociologists of science. With the publication of 'The Structure of Scientific Revolutions' in 1962, T.S.Kuhn emphasised the role of the scientific community in creating scientific 'facts'.[92] Thus science lost its status as 'objective knowledge', and the door was opened for an analysis of the contribution of social factors to the establishment of scientific theories,[93] in fact 'by emphasising the cognitive aspects of science and linking changes in cognitive structures to socio-psychological phenomena, Kuhn legitimated sociologists' revolt against Merton'.[94] There is no agreed way, however, of approaching such a study of a scientific area, and many of the myriad of case studies in the area have been undertaken to satisfy a certain theoretical orientation.[95] Reviews of such case studies could be useful

in extracting some consistent features in the development of scientific knowledge, but these tend only to elucidate the variety of approach in the area.[96] In effect the question to be answered is, what is the relative importance of factors internal to science (its social and cognitive organisation) to external constraints, economic, social and political which impinge on the development of knowledge.

1.6. The External/Internal Debate in the Sociology of Science

Much of the previous work in the sociology of science has been classified into two different approaches: the externalist and the internalist approach.[97] The former, Johnston states:

> accepts the production of scientific knowledge as largely unproblematic, a somewhat mysterious and ineffable process, and concentrates on the operation of the scientific institution; questions of interest include the appropriate forms of education for scientists, the application of scientific knowledge and the appropriate relationships with government necessary to ensure adequate financial support.[98]

In this it encompasses such work done in fields such as science policy, the economics of research, the relationship between science and technology, social responsibility and communication processes in science.[99] Blume characterises this research as that which explores

> permeation of those values, prejudices, loyalties, affiliations characteristic (to use no more precise term) of the environing society, into the social processes of scientific activity[100] .... (the externalist perspective) focuses upon the institutionalization, social relations and social functions of science in different societies and upon the relevance of political, economic and other social factors for the functioning of the scientific system.[101]

In this category Blume puts the work on the stratification system in science, work on 'politico-scientific' roles, work on advisory bodies, honorific awards and the evolution of the institutional structure of science. The existence of elites within science is a problem for this area.[102]

The externalist view of the development of scientific knowledge is that, 'the explanation of scientific advance can be traced to the technical needs and processes of the time and the economic structure in which we are all embedded'.[103] In particular the Mertonian view of the development of science is criticised. Mulkay objects to the concepts of norms and values as guidelines in the execution of 'scientific method'. The demonstration that conflicting norms could equally well be applied to certain instances of scientific activity, led to the suggestion that the model adhered to by Merton and his followers amounts to nothing more than professed 'ideology' of science, forwarded by the elite within science to serve their own social interests and protect their autonomy. They promoted the idea of scientific knowledge as a valuable commodity, which necessarily leads to practical benefit and left free from outside regulation.[104]

The internalist approach 'includes those studies which take as a central question the production of scientific knowledge'.[105] Thus it explores developments in the sciences by investigating the role of the social organisation of the scientists, and the structure of the knowledge itself. Of particular interest to the internalist approach are the perceived differences between sciences at the disciplinary, specialty and research area levels, and the relationship between these three levels. Disciplines can be seen as the framework for scientific communities, while not entering the process of knowledge production.[106] They are one level of organisation in science related to a particular way of perceiving a field, as 'disciplinary ideals refer to particular ways of doing science and integrating the results. To be a member of a discipline is to adhere to a particular approach to scientific understanding applied to an aspect of reality'.[107] Research areas can be seen as a commitment to a set of research practices

and techniques and specialties to particular explanatory models and definitions.[108] Differences, then, between fundamental organising principles may well give rise to different types of knowledge, institutionalised in different ways, so that 'the more developed and articulated in an ordering principle the clearer will research based on it be differentiated from that of other disciplines.[109] Although individual research areas or specialties will not all be equally developed or articulated.

Essentially disciplines can be seen either as 'developed' with a well defined central 'core' of important problems, or weakly developed lacking 'a clear formulation of the ordering principle'.[110] Both types have their own particular characteristics, different relationships with research areas and specialties, and distinct social and intellectual organisation within the field. In weakly developed or 'polytheistic' disciplines, new problem areas are frequently added,[111] while 'institutional allegiance activity are likely to prevail over common disciplinary perspectives'.[112] This means that the elite of the field are likely to be drawn from those people who have institutional authority, moreover Whitley characterises these as,

> When disciplinary spokesmen and authorities are required these are probably selected from those with organisational authority. Such groups are likely to be ad hoc, fragile and briefly dependant for their constitution on external pressures and goals.[113]

In more developed (or umbrella) disciplines, the elite will have far more intellectual authority and serve primarily to legitimate areas of high prestige in the discipline by the allocation of resources.

In effect, this type of analysis has started to question some of the problems in conceptualising the nature of science, taken to be embodied in the paradigmatic theory of Kuhn, in which it is implied that all sciences follow the same pattern from exploratory research to a fully articulated paradigm, which implies, 'if the sciences are structurally identical, and

those which are paradigmless are only 'young' sciences, then progress is only possible through the adoption of the type of paradigm existent in the paradigm science i.e. physics'.[114] Whitley questions the legitimacy of such a generalisation, which implies that physics and chemistry should be 'taken to be the "paradigmatic" disciplines against which all other cognitive structures must be measured'.[115]

Following the identification of two major disciplinary types in science, the major questions regarding their degree of social and cognitive institutionalisation can be formulated. More generally science itself can be seen as split correspondingly into two types, restricted and unrestricted, related to 'varying degrees of closure, coherence and articulation'.[116] A range of general statements can be made of these two types. Restricted sciences are characterised by high theoretical specificity, with a high division of labour and clear differentiation of research topics. Work is organisationally distinct with cognitive boundaries reinforced by social ones. The social structure in the field has a high degree of formal hierarchy. The importance of research tasks is well delineated, and there may be migration of scientists to less prestigious areas. Differentiation in intellectual structures are paralleled by the social structure, journals, conferences and seminars all form a hierarchy, and research principles are reflected by publication in 'core' journals.[117]

In the unrestricted sciences a broader specification of objects and techniques is found with a low differentiation of labour. Day to day research incorporates wider, more general considerations and acts of personal judgement are more commonplace, although large amounts of work may be purely technical, while the work of technicians is less formalised and may be more dependant on individual understanding of work. Although it is not obvious how research problems are selected and legitimised in this case, or to which disciplines a problem belongs, so that

social and cognitive identities are vague.[118] In fact for the unrestricted sciences, Whitley suggests,

> The lack of a clear institutionalised cognitive framework for the discipline which defines the dominant approach and sets standards to permissable work is likely to lead to an emphasis on technical criteria of adequacy and have relevance in technical skills.[119]

In this view, then, cognitive institutionalisation is related to the coherence of the theoretical basis of the science and social institutionalisation is the ease of demarcation of the members of the community. Methods of communication throughout the community are related, and cannot be understood in isolation from one another. In this model, in areas which are not highly institutionalised research areas may become important as a source of cognitive and social identity.[120]

This opens a new range of problems which places the generation of new knowledge to the fore. Whitley holds that a relevant study now

> is concerned with understanding how different forms of knowledge arise, are accepted and change relations between such knowledge and the wider culture. This study involves the analysis of how dominant ideas in a culture are related to metaphysical assumptions in the different sciences and of economic and technological influences on the development, quantitative and qualitative, of different specialities. How different cognitive enterprises, or scientific activities, are selected and modified and their results arrived at is part of the sociology of science, as are the relations between different types of cognitive enterprises and their degree of institutionalisation and legitimation.[121]

The way to proceed with this programme then is to describe units of organisation, their boundaries, in the sciences utilising such notions of discipline, specialties and research areas where they are useful, as these are the places where changes take place in commitment

to cognitive structures, and social groupings; the view being that as intellectual structures are linked to social organisation, then to understand the development of science it is necessary to understand the development of its social/cognitive organisation, in order to substantiate the view that scientific knowledges vary and these variations are linked to differences in the way scientific work is organised,[122] and that research situations are structured in ways which limit scientific choices. Thus the important aspect to focus on is the way in which work is organised by different scientific organisation. Some basic influences on the professionalisation of scientists can be identified, such as their educational establishment, subsequent employment in full time research, the career structure for the particular science, the administration system for grants, existence of specialist expertise, and degrees of autonomy and independence from economic considerations.[123]

One area of research which has emphasised the role of the social structure of science has been that concerned with the emergence and development of new specialties. In particular models developed by Mulkay and Mullins have stressed this aspect. Mulkay argues that 'the formal organisation of science is only loosely related to the actual social relationship through which new knowledge is generated',[124] and informal networks of these 'invisible college' type, are important for four reasons. Scientific research activity tends to be highly specialized, and as researchers can only absorb technical information from a limited number of sources, they choose to communicate only with people engaged on a similar problem to their own, or with scientists with whom they are sharing a costly piece of apparatus. An informal communication network without clear boundaries may then develop.[125] Mulkay sees the growth of a research network as consisting of three phases. The first is characterised by the perception of a new problem area by scientists, already engaged in a neighbouring

specialty of unsolved problems, unexpected observations or unusual technical developments, the pursuit of which lies outside that area.[126] Entry to a new field may also have important career implications related to the perception of the scientific potential of the new field. At this stage there is a small amount of social organisation, research may be undertaken at a variety of geographical locations, the research may be mainly exploratory using fairly obvious techniques, and consequently there may be many multiple discoveries in this stage with competition for resources such as suitable techniques, students, research funds and publication outlets - usually in general purpose journals, before more specialist ones are established. Early publications are a vehicle for 'negotiations' between the authors to define the central problems in the area. In addition scientists from an adjacent area may give their support to the new field and therefore help to legitimate it.[127]

The second stage of development is characterised by a sharper delineation of the area, it obtains its own journals, teams of researchers working at the same site give continuity to scientific aims and standards. An elite begins to emerge, both as contributors to 'core' works and teachers of research groups, while the amount of work produced increases exponentially, as the opportunity for novel innovation decreases as the area grows. By the end of this stage the area will be well institutionalised cognitively and socially with an acknowledged elite structure, and stable recruitment of resources and students.[128]

The final stage may be characterised by routine research, which may eventually lead to a proliferation of anomalous results and a revolution in the Kuhnian sense, or possibly a more fruitful migration of scientists, concepts, theories and techniques into a neighbouring

area, with the resultant decline of the original network.[129]

This model is not considered to be incompatible with Kuhn's theory of scientific development as both models focus on the connection between cognitive and social differentiation, and agree on the function of the education system on science and on the existence of pressure towards intellectual conformity. They differ in that the model of branching sees revolutions in science as one possibly for the development of knowledge, most likely from within the most highly institutionalised science.[130] Critics of the model suggest that it is merely describing the function of normal science, which has been commonly misunderstood as conformist behaviour, due to the lack of consideration of how new problem areas emerge.[131] Mulkay however, stresses the emergence of new areas as part of a complex social process and in contrast to Kuhn, is demonstrating flexibility rather than conflict and resistance within a paradigm, which is his main thesis.[132]

An alternative model to the development of new specialties in science is described by Mullins in his studies of the phage group and of ethnomethodology in social science.[133] He defines a specialty as

> an institutional cluster which has developed regular processes for training and recruitment into roles which are institutionally defined as belonging to that specialty. Members are aware of each others work, although not necessarily deeply involved in communications with one another.[134]

In his model a new area, or paradigm group is characterised by a minimum of two scientists, possibly in contact, interested in the same question. This develops into a communication network of scientists interested in the new area. Further development leads to a cluster, if luck, leadership, a substantial problem and institutional stability are present, but 'many networks of interaction die out before they have a chance to form clusters'.[135] The cluster stage develops

into a specialty with communication, co-authorship, apprenticeship and colleagueship.

Law believes that this model depends on the Kuhnian conception of scientific knowledge, but is concerned more with social organisation than cognitive developments.[136] He makes a distinction between technique or method based specialties, theory based specialties and subject matter specialties, as units for analysis.[137] Law holds that this is a development of the Kuhnian thesis, as Kuhn

> does not deal in general terms with areas of work methods or theories that are thought of as highly preferred .... an understanding of the structure of such more or less preferred areas methods or theories allows the sociologist to distinguish between different types of paradigm bound specialties and specialties at different stages of intellectual development.[138]

The fact that so much attention has been spent on analysing the emergence of new specialties has been criticised by Geison.[139] He proposes that a more basic unit for analysis are research schools, which are

> small groups of mature scientists pursuing a reasonably coherent programme of research side by side with advanced students in the same institutional context and engaging in direct continuous social and intellectual interaction[140]

while a specialty,

> comprises several separate research schools and a research school very rarely exists (and perhaps never survives) in total isolation from other research schools that, together, constitute a specialty[141]

His criticism is mainly directed towards the Mulkay and Edge study of the emergence of Radio Astronomy,[142] which he holds can be more fruitfully seen as a study of the interaction of two research schools,[143] although the authors seem to equate scientific change with the development of new specialties.[144] He presents two schema of factors which influence the success of research schools,[145] but also notes the

limitations of confining analysis at this level including the imprecision of the terminology, and absence of analysis of scientific creativity.[146]

In these analyses of innovation in scientific knowledge mention must be made of the role of citation analysis in attempting to quantify such changes, in delineating specialty boundaries, highlighting core articles and pinpointing the research community. Such methodology is important in the quantification of the sociology of science, but is still in the developmental stage, and has not yet taken over from more descriptive work.[147]

1.7. Goals in Science

The internal/external dichotomy in the sociology of science allows a third approach, more recent in its construction, bringing together cognitive, internal and external factors.[148] Shapin dubs this the 'instrumental model' in which :

> the generation and evaluation of knowledge is treated as goal-directed. Knowledge is not regarded in this literature as contemplatively produced by isolated individuals; it is produced and judged to further particular collectively sustained goals. Knowledge in this perspective, is always tailored to doing things.[149]

In the model research can be directed by external social or political requirements, but at the point of production of the knowledge internal and external factors interact in a complex manner with experimental results. It is through the development of this perspective that some insight might be gained, not only of the success of science in constructing explanations of observed phenomena, but also of its authority in society and its practical successes on which industrial society depends. This is essentially a development of the Kuhnian view of science.[150]

An aspect that needs consideration is the variation in the establishment of goals within science, as these are always determined by the state of knowledge of a science, by interaction with the socio economic factors involved, and with scientists themselves. In the process of goal setting, goals are continually being revised and redefined.[151] It can be argued that both the academic scientist and scientists working in an industrial situation have research tasks which are prescribed for them, although there are many different levels at which goals are specified, and they are in operation at all times. Goals may be suggested by social, economic or political needs, or closely linked to an evolving body of knowledge being constantly altered in response to changing variables such as theory changes, or resource allocation.[152] There is also the question of the transformation of goals into useful research programmes (or goal mediation) which may well lead to conflict between different groups of scientists for priority in incorporating the particular goals into their discipline. Alternatively, industrial goals are strongly determined by economic considerations. Finally it is necessary to look at the process of goal evolution, how goals succeed each other and the factors involved in this process.[153]

This analysis - that all modern science is goal directed implies that a completely general analysis of science in an industrial society is possible, and the concepts of goal establishment, mediation and evolution are useful as a basis for exploring the interaction between scientific, technical, political, economic and social interests in the shaping of objectives for science.[154]

The foregoing description of the incorporation of goals into research is an attempt to broaden the analysis from a consideration only of academic research which sees external goals as impinging on to science. It suggests that, in all research situations, there is a constant interaction between the research problems under consideration

and economic social and political factors which are influencing the development of this knowledge. Rather than being a function of the knowledge itself both are mediated by each other.

The most well developed model for examining the incorporation of goals into the construction of scientific knowledge is that developed by the Starnberg Group, the model of finalisation.[155] This is primarily concerned with the introduction of goals into the cognitive development of the sciences and their subsequent impact on the development of scientific theory. The basis of the finalisation thesis is essentially based on science policy studies of seven research areas, in Germany. Finalisation depends on a developmental view of science which borrows from Kuhn the idea of phases; pre-paradigmatic, paradigmatic, and post paradigmatic. The thesis looks at the possibility for orienting science towards external aims in each of these phases, and at the factors internal to science itself which makes a field either receptive or resistant to these attempts to direct it. The process of political goal formulation is considered, with the difficulties of transferring problems from the political to the scientific community.[156] In essence the finalisation theses states that under particular conditions non scientific considerations can be incorporated into scientific developments, 'finalisation is a process through which external goals for science become guidelines of the scientific theory itself'.[157] Thus it is conceived as a process particularly distinct from the mere generation of 'applied science' from an established body of knowledge. As Bohme, van den Daele and Krohn state,

> It is our assumption that the category of 'finalisation' will serve to reveal the structure of those scientific developments which are characterised by their linkage with social, military and economic purposes, but which are not adequately described by the traditional category of applied research.[158]

A number of conditions are held to have necessitated finalisation.

Artefacts, required increasingly for economic, military and medical purposes, have become dependant on scientific inputs, and these often require specific scientific developments, rather than merely utilizing research results. This is only possible in areas where the existing theory has developed to a stage where it gives rise to reliable predictions, and has also given rise to techniques on which modern society is now dependant. In effect, these conditions 'serve to demarcate finalisation in science from other, earlier forms of mission-oriented science'.[159] It is thus suggested that finalisation is an historical evolution of science, first appearing in agricultural chemistry around 1850, and which has not yet developed within disciplines such as biology, physiology and psychology.

In order for a scientific area to become receptive or 'open' to external direction, internal resistance which orientates and legitimates research programmes must be overcome. The Starnberg Group see two possibilities for this. In the first case an area with a well developed theoretical core can afford to take up research problems not necessarily related to the 'logic of inquiry', that is the further development of the internal scientific paradigms. Alternatively in a relatively new area, causal relationships may be taken as a 'black box', understood only to the point where they may be utilised for external purposes, a process termed 'functionalisation'. The first of these conditions is seen as the legitimate area in which the possibility of external direction of science is possible and towards which every scientific discipline will inevitably move. The concept of phases within science is described thus by the Weingart, van den Daele and Krohn,

> The exploratory phase characterised by classification procedures and by trial and error strategies. Theoretical approaches are pluralistic and the theoretical problems do not constitute a unified research programme

> The phase of paradigm articulation. Here, explanatory problems dominate research. The constellation of problems raised within the discipline is derived from attempts to simplify make consistent and universalize the theoretical models
>
> The post paradigm phase - in which, after relatively uncontroversial theoretical explanations of simple models have been developed, theoretical conceptions for more complex phenomena are worked out. In each of these three phases different internal rules of disciplinary development are effective and these create different conditions for external orientation.[160]

External demands have an entry point into science in both the first and last phases. Although the first phase is that which gives rise to functional research. Here research follows no particular methodological programme, discovery being the main goal of inquiry, while the available techniques determine research strategies. Where the basic theoretical development of a science is missing, however, attempts to orientate the field towards basic external goals is, in the long term, seen as pointless as a 'black box' model of science is looked upon as being merely the 'pre-form' of the scientific explanation itself.[161] The general factors concerned with the functionalisation of research involve defining strategies that give rise to a programme of empirical research such as pharmaceutical screening programmes. It is also possible for external goals for science to contribute to the articulation of the internal theory development where the problems in both cases are equivalent, that is 'when the subjects of exploratory research are politically defined'.[162]

In the second phase of paradigm articulation, this is the only case where external interests cannot be introduced. The field is seen to be entirely dominated by the internal dynamics of the developing field, except where 'internal research fronts coincide with external problem orientations'[163] A fundamental theory emerges as a result of a number of fruitful theoretical approaches. This is the only legitimate pursuit

of scientists in this phase, theory development is seen as 'the only effective guideline of scientific advance and the only one meaningful for the progress of knowledge'.[164]

When this stable internal core has been completed, the discipline will be conclusively demarcated from any other. Most external goals can be incorporated into research planning, free from any fundamental conflict with the internal needs of science. This is the phase characterised by the Kuhnian 'normal science', where the theory is seen to be 'specialised, differentiated, and modified in order to extend its range of applications'.[165] Thus, particular problems of political or social interest may themselves define the specific research fronts of this discipline. A science which has reached the stage of maturity within its theoretical development can be recognised, because, for fundamental theories, 'their characteristic feature is that they can no longer be improved by minor modifications. Substantial changes, however, give rise to an entirely new theory',[166] although it is recognised that the theories may contain 'open' or unsolved problems which may restrict the solution of external problems from existing resources within the field.[167]

In complex systems, this kind of understanding can be useful as, where control and regulation of the system is an important factor, this is possible as 'the lack of explanatory power of the science does not preclude the utilisation of its findings for specific purposes (of control)'[168] Where very complex systems are under scrutiny, then, a functionalistic analysis could be useful for science policy regulators. Although there is a danger too that the basic theoretical developments within the field may be bypassed for short term gains, as the Starnberg Group suggest,

> The difficulties arising from this kind of external orientation - which is possible without investing in theory - may correspondingly become apparent in the capacity it is producing: the increase of planning capacity combined with an accumulation of relative ignorance will augment the system's susceptibility to crisis. It is not clear, moreover, whether functionalisation does not excessively exploit the scientific resources, i.e. that use is made of the available knowledge without it being possible to provide for coming needs in science by timely investments.[169]

This forms the basic framework of the theory, although there are two areas left to elaborate on. These are the actual process of goal selection and elucidation and the particular factors influencing the uptake and orientation of the science towards the problems that have been formulated. In order to define the question in reasonable manner, the external influences may be considered specifically to be particular policy problems rather than taking account of the entirety of the possible social influences on science.[170] Thus there are two aspects to be considered, both the social processes, and cognitive limitations within science and also the system of problem perception and goal formation within the political dimension.

The political sphere can be seen as reacting to the disfunctional effects thrown up by science and technology in a complex industrial system, by progressively entering into public action, both future oriented and complex, by systematic planning. Legal acts are therefore becoming more dependant on a flow of scientific information. There are a number of ways in which this information is developed and utilised. It can accrue as a 'side effect' of a public sponsored research institution or a university department, or used as legitimation of a political decision. Finally it may be the product value of science which is required, where science is serving in its problem solving capacity.[171] There are a number of constraints on the formulation of an issue into a

political problem. The values, norms and ideology of the government excludes some issues from the political sphere, as does the particular structure of ministerial and interdepartmental divisions. The existence of systematic knowledge about a problem alters perception of it, as an issue likely to have a solution through the application of scientific research.[172] The success of such policy formulations then, can be measured by 'the institutionalisation of research governed by goal definitions which stem from science policy programmes![173] A problem undergoes a number of transformations before it is formulated at the level of a scientific research programme. It is first defined as a political problem or goal which then may become a problem for science policy. If the problem solution depends on scientific research, the political goals have become defined as technical problems which must then be linked to existing research areas. It is here that the external goals are taken up as scientific problems.[174]

Actual transfer of political goals to the scientific community is undertaken through a number of advisory bodies which may comprise of a mixture of scientists, politicians, civil servants, industrialists and possibly other interest groups. The existence of these bodies, along with funding programmes, setting up of research centres, research co-ordinating and the establishment of new departments or chairs may all be indicators of political direction, although they must be identified separately from traditional forms of support.[175]

It is possible to specify more distinctly the factors which are involved in making science receptive or resistant to the internal-isation of political goals. The most obvious of these is the actual cognitive structure of the discipline, which sets limits to the technical level and development of a discipline beyond which it cannot be influenced by external requirements. The cognitive level affects the co-operation possible between disciplines, the differentiation between specialties

and the evaluative mechanisms within the science itself.[176] Different methodological approaches exist, such as description, qualitative experiment, measurement, interviewing, and orientation around techniques. These variations can be taken as differences in objectives between the sciences and may be linked to the phases of development. The latter is also linked to the level of theoretical development achieved, which influences the degree of openness of the science to external goals.[177]

Factors influencing the relationships between scientific specialties and their parent disciplines, are important in the transmission of research practices, instruments, techniques and methods, the comparability of criteria of relevance and the interaction of results. These factors are characterised by the background shared by other disciplines, the specificity of the subject area in relation to the established classical disciplines, its interdisciplinarity, its dependance on discoveries in other fields and its general reductionist or antireductionist stance.[178] Also important is the process of a specialty. This depends on the autonomy of the specialty, which defines its limits with respect to other specialties and research areas. A number of factors may indicate the extent to which institutionalisation has taken place. The formation of an autonomous system of evaluation and reputation, a communication system, representation on supporting bodies, utilisation of expertise in the area by public bodies, its incorporation as a formal qualification for certain occupations and its use in governmental and industrial research programmes. In addition, the social integration of the field will be set by the structure of formal and informal organisation that is the areas in which the specialty is institutionalised, and degree of the division of labour in the field as well as the emergence of schools or opinion leaders, with associated elite formation. The final aspect in the institutionalisation of a scientific specialty is the existence of a system for the training of students, dependent on the existence of the area in the curriculum, the

existence of a career structure, the reversibility of a decision to enter the area, the continuity of resource allocations.[179]

The inclusion of these type of considerations into ideas about the function of political goals in science, seems to refine the concept of resistance to external direction, both in the cognitive and institutional sphere. Receptivity to external direction is seen to be greater if the field has a well developed theoretical and technical base, and also depends on the possibility of developments within the specialty that could incorporate the external requirements. Here finalisation is seen as the extreme case of receptivity in science.[180] This receptivity, however, must be seen to be complicated by institutional resistance, both from the type of institution - for example industrial laboratories - and the complex social system within the established sciences, which provide manpower, and tend to direct the best researchers to the perceived prestige areas within science, and in general away from multidisciplinary research which political problems tend to require. This indicates that 'there is quite a distinct relationship between a field' internal development and the development of a hierarchic system of reputation and evaluation'.[181] Institutional resistance would therefore be seen as difficulty in recruiting sufficient manpower for a particular programme, and lack of response to funding programmes, or the possible substitution of personal interests as research programmes where goal direction is thought to have taken place.[182]

The finalisation thesis has been criticised on a number of grounds. Not least of these is the dependence on the concept of the paradigm, which is problematic in that it is vaguely defined, and used with great generality.[183] The term finalisation is itself used in a number of ways so that external goals may be conceived as anything from 'social economic and military purposes', to concepts introduced from one discipline into

another.[184] The greatest weakness of the theory is its monism. It is assumed that all sciences have the same type of developmental path, passing through each phase, without offering an explanation of 'how or under what conditions a science may move (or fail to move?) from one place to the next'.[185] It also gives undue emphasis to the role of theories as the important aspect of science, without suggesting criteria by which finalised, or closed, theories can be recognised. It is necessary to take into account not only the institutional structure where the research is done, but also the function of goal conflict between institutions.[186] It is questioned whether such 'theoretical maturity' is necessary for finalisation, as there are examples of fields sponsored very early in their development purely for the techniques they give rise to, and subsequently develop consistent theories. Finally, it is not clear in what particular ways finalisation in science differs from applied or mission oriented science, as decisions to find large projects may take only extra-scientific factors into consideration.[187] Thus it seems that the question of the direction of science by external goals has not been answered as 'the real problem is that cognitive factors, even if socially defined, will not completely describe events - we still have these external factors getting 'into' the science'.[188]

1.8. Scientific Knowledge in a Non-Academic Context

The previous models are limited by their concentration on science as an autonomous activity driven by the interests and perceptions of the scientists involved. This case may exist in universities and academic institutions where scientists are free to choose the problems they wish to work on. By far the largest concern has been with the internal and external factors which relate to the production of pure or basic research, a notion which always involves some kind of assessment of autonomy, or freedom of the researchers involved. Far less attention, as yet, has

been given to the effect of these influences on scientists working in industrial or commercial organisations, nor to their possible conflicting professional or scientific loyalties when faced with requirements outside their usual day to day tasks, or how these are resolved.

This concern with university research has led to the relative neglect of other forms of scientific knowledge, particularly that which is technology oriented. In fact, this is notable only where it coincides with the academic world. Mulkay notes,

> it is, of course, true that there is an increasing number of 'technological sciences' which are explicitly organised around problems arising in the pursuit of practical objectives. These sub-disciplines are often located mainly within the academic community, whilst retaining close links with industry.[189]

The vast majority of scientists, however, work in a multiplicity of non-academic organisations with different goals, expectations and research needs. This area has, in the main, been ignored by sociologists, although it is to the credit of the Starnberg Group that their focus on external goals in science has opened the way for asking about the role and function of science in a non-academic context.

From the work that has been done, particularly on scientists in industry, it is not difficult to extract an 'orthodox' model which suggests that fundamentally scientists in industry are misplaced, and there is a basic conflict between their values and needs, and the expectation of management.[190] This latter is seen as having a prime motive to make money, and that control and supervision of employees is important in reaching this goal. Scientists are seen to require freedom to choose their own research problems, to communicate with other scientists, have freedom from accountability and the need for independent verification of their work.[191] These two 'ideologies' are drawn from traditional concepts of the areas and they have been explored more fully by

Kornhauser. He sees four main areas of conflict. In the setting of research goals, the scientist is seen to favour basic research and freedom to chose, rather than the applied, commercial objectives sought by management. There is seen to be a conflict between the 'hierarchy' of the industrial laboratory and the equality of the 'profession' of scientific collegeship, while the rewards from each profession vary between promotion and commercial incentives to publication and intellectual honours. Arising from this Kornhauser sees the breakdown of communication between the two groups.[192]

More recent work has questioned the assumption that industrial scientists have internalised the supposed ethos of pure science, and suggest that new employees in an industrial laboratory undergo a process of 'enculturalisation' during which they embrace the needs and aims of the laboratory, and often express a preference for applied research.[193] They are not concerned with creating a reputation external to the organisation, tend to lack a professional consciousness, and believe that they should follow their own self interest in career terms. They are more likely to see the relevance of professional institutions than more basically oriented organisation, while there is no evidence to support the 'two culture' conflict model of the traditional literature.

Industrial science is essentially seen as diverse, fragmented and amorphous in nature, in fact 'holistic generalisations of any kind about the nature of the industrial scientist have a limited heuristic value'.[194] Both the content of the work, which may be basic, applied, development, design or interdisciplinary, and the context, the nature of the work situation, vary enormously. In addition, the education of undergraduates may vary between university and between departments as the 'ethos' of science is modified between scientific and engineering schools and between technical and pure science based universities.[195] When employed within an

organisation, the scientist is generally not perceived to have any managerial role at all, but merely to be expertise 'on tap', although this position is not necessarily accepted by laboratory workers as being desirable.[196]

It can be seen then, that the industrial scientist is not just an academic scientist out of context, but a completely different kind of professional altogether, because of the different orientation of their particular work situation, and the different kinds of scientific problems on which they work. This brings into focus a far more general reason for being concerned with the impact of external goals on science, as this is the condition under which most of the practitioners work. In this case, it may be fruitful to look at the development of science as a profession, and the conditions under which this has taken place. It is necessary to see that scientists are not employed primarily to generate scientific knowledge, but to utilise it, either as an educator, provider of commercial innovations or weapons for war.[197] During the twentieth century there has been an increase in patronage for science - both by the state and by industry, and it is precisely this which has encouraged the growth and fragmentation of science, due to the necessity of responding to the specific requirements of the patrons. This can backfire due to the influence they may have over basic research, according to Robbins and Johnston;

> When patrons are sufficiently powerful, for example the state or large corporations they may initiate and support the emergence of new specialties in academic science. These specialties arise specifically to create knowledge and manpower to fulfil need defined by such patrons.[198]

This may lead to a proliferation of organisational contexts, if government agencies are considered, and also the increasing tendency for state sponsored work to be carried out within existing university departments.

Scientists in each organisation will, because of its position have a different concept of the professional role due to their particular knowledge concerns, and work organisation. Growth of governmental bodies has occurred in a wide variety of areas, with a variety of organisational structures.[199] In terms of knowledge problem selection and possible techniques, selection may be directed by the local goals of the organisation. Such differentiation may inhibit the transfer of trained personnel, concepts and techniques from one research situation to another. This combination may disperse the perception of shared values across science, and thus decrease integration of new knowledges produced.[200]

We expect, then, to be able to identify different attitudes, problems and research practices contingent on the particular institution in which the scientists are located. This implies that an analysis of institutionalisation must be incorporated into any description of the development of a scientific area.

1.9. Science in Policy : Policy in Science

The effects of the interaction of the political and scientific sphere obviously has important consequences for both systems. Policy makers are dependent on the structure of scientific knowledge for its utility value in solving problems, while scientists are dependent on governmental support for research projects. Thus some mechanism must exist which enables political requirements to be transferred to the scientific community, and the resulting knowledge communicated to government, which in turn alters political goals. Not only will advisory committees be important in bridging these communities, but there must also be ways in which political goals from departments are transferred to funding bodies within government, and there will be a resistance or receptivity to these goals within the scientific field depending on the internal constraints of the specialty concerned.

The literature has identified a number of aspects that can be practicably studied. On the policy side, when deciding on research funding priorities, what type of projects are chosen, withwhat type of support? How are strategic and tactical choices made between specialties and research areas, and what is the role of national prestige urgency and technical opportunity in these choices? What are the political constraints on funding, and are the constraints organisational, cultural, political and intellectual imposed by the scientists? Finally, how is funding for a new research area obtained?

There are a number of ways in which scientists can be involved in the establishment of a public policy. In identifying and establishing the problem in the political arena which depends on political priorities, the state of the knowledge and the role of scientists and other pressure groups in highlighting the area. Scientists may discover the problem in the course of their work, may be called upon to give evidence to an advisory committee, or may themselves be asked to become a member of a fact finding committee. In the formulation of the policy there are certain options which will be influenced by political, social, economic and technical factors. Has the scientist a role in making the decision between policy options? What is the contribution in this decision from different institutional sectors? Also is there a role for the scientist in administering the final policy, either as a member of an expert committee or in full time paid employment within the civil service? Finally how successful is the policy, and what are the reasons for its failure if this is so? Is the control, participatory, reactive or anticipatory? Do advisors committees, have actual decision making power, or are they legitimatory? Does the state of knowledge have an impact on the policy, if there is consensus or conflict in the field, or if there are commercial or defence secrets? What role has science and scientists in reviewing the administration of the policy, or suggesting new areas for

investigation or of altering the type of control? Finally who are the scientists consulted by the government, what is their institutional and disciplinary background and how is this related, directly or indirectly to the problem under consideration, and can they be said to represent an elite within the specialty concerned?

Within the sociology of science, there appears to be many ideas that are not co-ordinated or related to each other. Many of the concepts used are vague and ill-defined so that it is not easy to cross compare ideas, or bring them together in a way that would suggest a framework within which a case study could be located. There are three main areas to consider, the internal development of a field (social and cognitive), the external factors which may have a bearing on its social or theoretical development, and the process of knowledge generation within non-academic institutions.

An alternative approach is to explore the development of the specialty, (or research school). Mulkay treats the growth of research areas in this way, conceiving three particular phases through which they pass, the exploratory phase, a phase setting the core theory and a final phase characterised by routine research with possible migration of scientists to a new area. This basically suggests an alternative theory to the concept of revolution in areas with a fully articulated paradigm. It looks at the emergence of research areas as part of a complex social process focussing on the informal communicative networks which develop at the beginning of a new research area. In each of the three phases a number of conditions are suggested which describe the level of development of the research area. These conditions may be useful if it is desirable to utilise the finalisation thesis at the research area level. Finalisation also relies on a three phase model of development, but does not state at what level of organisation the model applies. It also relies primarily on analysis of the cognitive structure of a field, so

that any input by social constraints would improve the analysis. A consideration of the external goals of a field would, in its turn, improve the internalist stance of Mulkays thesis.

On the question of goal orientation we are left with two possibilities, either that this is an impossible exercise until a science is ripe or at its most receptive for external orientation, or that it is a common experience of many sciences especially characteristic of those which develop from within industry, where methods and techniques emerge first, and theoretical explanations are articulated at a later time. Here the concept of functionalisation may be useful. Related to this is the question of the transformation of political, social or economic goals. More importantly it is worth considering how these areas relate and interact with each other if we want to consider the total development of a field.

It is still worth trying to relate the work that has been done to a more useful programme. Whitley suggests an essentially static model, which postulates basically two types of science, which he calls restricted and unrestricted, and are related to the organisation of the field at the disciplinary, specialty and research area level. The suggestion is that the type of knowledge structures generated the coherence of the theory related to the social institutionalisation of the field, the division of labour within it, the type of elite formed, and the resistance to outside pressures and goals. The suggestion is to study the day to day tasks of the scientists, their educational background, the career structure for their particular science, and other social factors, in order to assess the particular levels of social and organisation of the field, and from that the type of science it is. A similar set of requirements may be employed in elucidating the concept of resistance and receptivity science. This is linked to a developmental model of science, and is concerned with the conditions of

finalisation in science. The concepts do have some similarity, however, and in both it is the social and cognitive factors internal to the scientific area which are focused on, formal training and qualification on the one hand and the interrelation between specialties, methods and theories on the other. Another way in which this type of analysis can be of use is in consideration of specific institutional settings external to the academic community, and in considering the specific types of knowledge generating from within governmental and industrial settings, as these will be expected to vary with institutional constraints such as lack of communication within the community; specificity of concepts and techniques not transferable to other areas of research; and resistance in publishing; the transfer of goals, first into a manageable social problem, and then into a scientific or technical one. Thus it is as worthwhile to look at the emergence of these goals as it is to investigate their solution. The hypothesis here is that, at least in the case of political problems, their perception will be as much mediated by the structure of the political situation, departmental concerns and organisation, as they will by the actual structure and knowledge within the scientific field. There may be, then, institutional resistance as well as cognitive resistance to the uptake of external goals. Alternatively the impact on the research situation where there is a clash between the goals of the research organisation and political requirements may be of significance.

In summary, the important factors involved in the consideration of the interaction between the scientific and policy fields can be identified:

a) the social organisation of the science and its institutional base

b) the cognitive structure, is it restricted or unrestricted

c) factors important in the emergence of the new area, how social and cognitive factors are interlinked

d) the institutional contexts, and professionalisation of the scientists, particularly in a non-academic context where scientific fragmentation may be apparent

e) the role of scientists in identifying policy problems

f) their role in delineating and deciding between the possible policy solutions

g) their role in implementing the final solution

h) the means by which goals external to the scientific field are translated into scientific objectives and are taken up as research problems.

An emphasis has been put on the role of expert committees in mediating between the two arenas. It is important to investigate the actual function of such committees and the extent and limitations of their power. Finally, a study that is concerned with a specific national context must also take into consideration whether international factors impinge on political and scientific institutions. It is these considerations, concerned with the interaction between the emergence of a new specialty, and the impingement of political objectives on it, which this thesis attempts to examine.

PART TWO

THE EARLY HISTORY OF TOXICOLOGY UNTIL 1945.

CHAPTER TWO

THE EMERGENCE OF SCIENTIFIC INVESTIGATION AND SOCIAL CONTROL OF POISONS.

The Emergence of Scientific Investigation and Social Control of Poisons

The science of toxicology is concerned with the deleterious effects of chemicals on living matter. As there is a number of naturally occurring chemicals of animal, plant and mineral origin which are toxic to humans it is not surprising that the knowledge of lethal poisoning is very ancient. Arrow poisons have long been used by primitive tribes for hunting and warfare. There is evidence that the Egyptians, Hindus, Arabs and Greeks had knowledge of these poisons, as well as of specific antidotes.

Knowledge of poisoning survived in Europe throughout the middle ages, where it was used for criminal purposes, especially for political assassination. Developments in analytical chemistry during the eighteenth century provided the first possibility of detecting toxic substances in biological matter. This was an important tool in the hands of the legal profession, as the cause of death could accurately be determined, and the legal control of poisonous substances could be effective. There were few attempts at governmental regulation of poisoning before the nineteenth century, during which questions of criminal and accidental poisoning became more recognised as more pressing social problems. In the first half of the century following a long campaign by the Pharmaceutical Society, an act was passed to control the sale of Arsenic.

Developments in other scientific areas opened another role for toxicology. Early physiological, pathological, and pharmacological studies utilized known toxic substances in experiments on animals. These were to shed light on the abnormal responses of biological mechanisms. This work was done with materials which are highly poisonous, causing death from small doses. Another feature of toxic materials which took much longer to become recognised was that of chronic

poisoning, where harmful injury is caused from repeated doses of the substance. Knowledge of this type of harm from occupational exposure is very old, with regard to metals such as lead and mercury. Nevertheless wider acceptance of the concept of chronic toxicity took a long time to become realised, with continuing debates within the medical profession on the subject. In the eighteenth and early nineteenth centuries the problems of industrialisation, bad sanitation, overcrowding and infectious disease were more immediate issues with regard to public health.

2.1. The Ancient Knowledge and Use of Poisons

The word toxicology, meaning the scientific investigation of poisonous substances is itself a tribute to the ancient knowledge of toxic substances. An early Greek meaning of the word was 'the poison for smearing arrows with', while the Greek root toxicon or toxos means an arrow.[1] The earliest record of the use of poisons is in open warfare using arrows tipped with snake venom. Later this was mixed with putrid blood or animal matter, and superseded by the juices of plants.[2]

The earliest written record relating to the use of poisons in medicine is Egyptian, dating from 1500 B.C.[3] It includes references to lead, antimony, copper and opium, as well as hemlock and aconite, the latter used originally as a Chinese arrow poison.[4] It is probable that the Egyptians used prussic acid as a form of capital punishment, under 'the penalty of the peach'. This acid could be extracted in a dilute state from certain plants, one of which was the peach.[5]

Other ancient civilizations also had their own poison lore. The ancient Hindus had knowledge of poisons and antidotes, recorded in the Vedas which were written about 900 B.C. Specific direction in the detection of poisoners is given:

> He does not answer questions or the answers are evasive. He speaks nonsense, rubs the great toe along the ground and shivers. His face is discoloured. He rubs the roots of his hair with his fingers and he tries by every means to leave the house. The food which is suspected should be given to animals. It is necessary for the practitioner to have knowledge of the symptons of different poisons and their antidotes, as the enemies of the Raja, bad women and ungrateful servants sometimes mix poison with food.[6]

Both Meek and Wynter Blyth refer to the suggestion that the practice of the self immolation of the Hindu widow on the burning pyre of her husband was introduced to discourage domestic poisonings.[7] The Chinese and the Greeks used poisons for suicide, and also in the latter case as a state method of execution.[8]

There was, then, extensive knowledge of the use of poisons as a means of death, used for state execution, warfare and for murder. A range of animal, plant and mineral substances were known, but it was the Greeks who began the process of a systematic classification of poisons. Hippocrates, who lived about 400 B.C., suggested the first principles of toxicology by attempts to control the absorption of a poison in cases of therapy and overdose,[9] which are different concepts of poisoning than the property of causing death. He also recognised the occupational hazards of certain trades. In the fourth century (B.C.), for instance, he recorded the effect of lead poisoning in mines. Another Greek scholar Pliny referred to the effect of mercuric sulphide or cinnabar as an occupational poison.[10] The work of Theophrastus (370-286 B.C.) contains references to many poisonous plants.[11] With Hippocrates, he was concerned with wresting medicine from mythology and replacing it with a more rational tradition, and they taught that diseases were caused by disturbances in the balance of the four humours.[12]

The major Greek work which was specifically concerned with the question of poisons, however, was written by Nicander of Colophon

(204-135 B.C.)[13] He wrote two poems concerned with poisons and their antidotes, "Theriaca" and "Alexpharmaca". They are concerned with animals; the poisons of venomous snakes scorpions and insects. Nicander was a poet and not an authority on current medicine, and the poems themselves contain a certain amount of exaggeration. It is thought, however, that his home in Asia Minor was near that of Apollodorus author of 'On Poisonous Animals', and that he was acquainted with the ancient literature of the Near East. These other texts did not survive and the poems became accepted knowledge by the Roman authors Philumenus, Pliny and Galen. They became a major source of information on poisonous animals until the Renaissance.[14]

The first attempt at drug control was by Dioscorides (40-80 A.D) a physician in the court of Emperor Nero. His 'materia medica' was a therapeutic guide for physicians on the selection and administration of commonly used substances.[15] He classified poisons into three categories; those from animals, plants and minerals,[16] and enlarged the list of known plants compiled by Theophrastus.[17] He also described a method for the preparation of opium.[18]

By the time of Galen (129-200 A.D.), little more knowledge of poisons had been added. His concept of the mechanism of poisoning was that toxic substances acted on the Hippocratic 'humours', like a magnet on iron, and so altered the balance of the humours on the body. The treatment of poisoning, was therefore, to administer a substance with the opposite effect.[19]

This Greek knowledge became widely disseminated. It was known to Ibn Wahshija, author of the treatise on Arabic Toxicology, the 'Book of Poisons'.[20] It also spread to Rome where poisons were used widely for political and domestic purposes. In 82 B.C. Sulla issued the first law against poisoning, the 'Les Cornelia', under which

punishment consisted of deportation and confiscation of possessions. Nevertheless, poisoning remained widespread. Nero had his own professional poisoner in his household, an infamous woman named Locusta. These two prepared a poison to kill Britannicus, the rightful heir to the throne, by testing on a kid and a boar.[21]

In this early period the social origins of toxicology are apparent. Knowledge of the existence of substances which could aid or cause death in an enemy is very old, and associated with this are various techniques for the extraction and administration of poisons. In a more controlled way similar substances were administered for therapeutic reasons and as antidotes to poisons. The Hippocratic theory of medicine gave rise to hypothesis on the mechanism of toxicity, but most of the documentation that remains refers to listing properties, means of identification and primitive classification of known poisons. An association between certain occupations and poisoning had been noted, but this was not generalised into a theory on the effects of repeated exposure to toxic materials. The crude use of animals to test the potency of a preparation, is interesting, if not important from a scientific point of view as there were no measures for standardising preparations in this way.

2.2. Murder and Medicine in the Middle Ages

Criminal poisoning was a successful method of murder for many centuries because there were no techniques for demonstrating the existence of a poison in the body. Unless the murderer was caught in the act of administering the substance, no evidence of the deed would exist. The development of techniques for chemical analysis during the eighteenth century was a great advance for toxicology. It opened the possibility for toxic materials to be separated from biological matter

and thus provide concrete proof of poisoning. It also opened the possibility for exploring the action of toxic materials on the body.

Political poisoning regained its popularity in Venice during the fifteenth century, as a means to implement government policy. The secret archives of the Venetian 'Council of Ten' contain details of the assassination of key political figures, the motives, fee paid, and the outcome.[22] The notoriety of the Borgia family in Rome is well known, and their skills in the preparation of poisons were directed mainly towards wealthy cardinals and bishops.[23] During the seventeenth century in Italy a number of women were convicted of selling and administering poisonous substances, which appears to have been a popular way of disposing of unwanted husbands.[24] In France poisoning became a fashionable form of murder. Meek describes some of the rumoured methods of administration,

> In 1572 there were 30,000 sorcerers in Paris, most of whom dealt quite openly in poisons, love philters and abortifacients. The work of Porta and Cardan popularised the knowledge of poisons, both mineral and vegetable. There were secrets for poisoning gloves and clothing. Books were soaked in deadly drugs and became fatal to the reader, knives were so skilfully drugged that on cutting a peach one side only was poisoned, the other being eaten by the murderer to allay all suspicion ....[25]

Poisonings were so common in France that in 1679 a special judicial commission the 'Chambre Ardente' was appointed to try such cases, but it was notably ineffective as many of the nobility concerned had powerful political influence. The major protection for the criminal was the absence of any method of detection or control. The effects of poisons could not be separated from cases of death by natural causes.[26]

Although poisons were used in this negative way some substances

were used for therapeutic purposes. A major figure of the sixteenth century who was concerned with healing was an alchemist popularly known as Paracelsus.[27] He broke with the traditional herbal remedies by using metallic and chemical substances in medicine. In relation to toxicology Paracelsus expounded some important views. He believed that focus should be put on the toxic agent as a chemical entity, and that experimentation and examination of the response to chemicals were essential. He considered that some agents acted with a specificity of effects, and there should be a distinction between the therapeutic and toxic properties of chemicals even though this might only be according to the dose. The factors articulated by Paracelsus echo some of the current concerns of toxicology, including the relationship of chemical structure to toxicity and the relationship of dose to response.[28] He was also interested in the relationship between occupation and disease, and from the observation of miners in the Tyrol realised the deterious effects of certain metals.[29] The pottery trade was known for the dangers of lead glaze, and the classic symptons of lead poisoning were described by Francois Citois of Poiton in 1572 as colic, pallor of the face, disturbed mind, vomiting and pain in the abdomen.[30]

The age of the alchemists was not to last, as a new rational philosophy, mechanistic and empirical in nature started to develop during the sixteenth and seventeenth centuries.

2.3. Science and Empiricism

The transition taking place was highlighted by William Harvey[31] who demonstrated the circulation of the blood through the body in a manner of strict empiricism while adhering to the medical theories of Aristotle and Galen, and rejecting the mechanistic theories. In the field of chemistry J.B.van Helmont was a major transitional figure.[32] He adhered to the Alchemical view of the developmental nature of matter,

but supported an empirical approach to chemistry. His attempts to link this theory with precise observation of the action of gases in chemical reactions helped to develop the base from which the developmental theories were, at last, replaced. An important transition, according to Toulmin and Goodfield, can be identified:

> The change over from a developmental to a static conception of matter was as profound as the change from a geocentric to a helio-centric astronomy and its effects were as far reaching[33]

The seventeenth century gave rise to many embryonic ideas which science would develop. The simple microscope became available and observations were made which could not be interpreted for up to two centuries.[34] Boerhaave was teaching the application of chemistry to medicine, and that direct observation was the 'touchstone of certainty'.[35] The link between science and social issues was made by an Italian physician, Bernardino Ramazzini, who observed occupational diseases. He was particularly concerned with the relationship between certain trades and occupational poisoning, and his treatise on diseases of tradesmen published in 1700 contains vivid descriptions of poisoning associated with certain trades. It was translated into English, German and French. He also suggested ways of avoiding diseasethrough cleanliness and better posture, and urged that medicine should be used for a wider social benefit,

> it is but reasonable that medicine should .... display itself in a particular manner (a thing hitherto neglected) for the safety of trades-men, that they may follow trades without injuring their health.[36]

The new mechanistic principles of the body as a machine was embodied in a treatise published in 1702 by an English physician, Richard Mead. In his 'Mechanical Account of Poisons' he aimed to improve the available information on the known poisons,

> I do not promise methodological and finished treatise but only some short Hints of Natural History and Rude Strokes of Reasoning, which if put together and rightly Improved, may perhaps serve to furnish out a more tolerable Specimen of the doctrine of poisons that has yet been Published.[37]

He believed that poisons contained crystalline particles which acted mechanically on the solid particles found floating in the blood, vessels and nerves.[38] The range of poisonous substances he included resembled those identified by Nicander, with one essay devoted to the viper, the spider and mad dog, which, he suggested, produced symptoms which were similar in that 'they induce a particular Delirium sui generis, attended Partly with Maniacal, partly with Melancholy symptoms'.[39] His third essay is devoted to poisonous minerals and plants, because 'the Force of these is chiefly confined to the stomach and Primae Viae'[40] in which he described specific experiments on the effects of minerals fed to dogs. These poisons were classified due to the similarity of their effects on the body. The dominant thought in chemistry was still the alchemical theory of the spontaneous generation of matter from within the earth, and this was demonstrated in the final essay 'of Venemous Exhalations from the Earth, Poisonous Airs and Waters'. These 'exhalations' were supposed to be especially rife in mines and pits, and were taken into the body with the breath. This form of poisoning he illustrated by many incidents related by acquaintances. In accepting the new philosophy, Mead could not disperse with the accumulated wisdom of the past, particularly with old views of chemistry in the absence of a new theory to replace them with.

Mead devoted a whole essay to the effects of opium and highlighted an issue that would become a central concern of pharmacology, the mode of therapeutic action of the drug, rather than its toxicity:

> True indeed it is that we do every Day find This to be, in a small Dose one of the most Noble Remedies in the World. But it is not worth the while to engage in the Controversies warmly debated by some Authors, how Far Poisons are Medicinal; since it is notorious enough that medicines do sometimes prove Poisonous. And take the matter as we please, it may serve to very good Purposes to understand the manner of Operation of so Celebrated a Drug, and help us in a great Measure to ascertain its Use in different Cases, and if we are beforehand rightly appraised of its Nature and Way of Acting.[41]

Throughout the eighteenth century methods of chemical analysis improved.[42] Joseph Black developed calorimetry and worked on the nature of gases. He was an atomist and supported the static rather than the developmental theory of matter. Other chemicals began to be isolated. Scheele discovered arsenic acid and several other organic acids, including prussic acid, but did not recognise this as the poison.[43] Around 1780 he discovered that arsenic hydride gas decomposed on heating to deposit the metal. The work of Joseph Priestly brought great advances in chemistry, and his work was characterised by its systematic quantitative character. Methods of organic and volumetric analysis were introduced with new techniques of chemical separation. Developments in the quantitative aspects of atomism by Proust and Berthollet culminated in Daltons atomic theory in 1803.

The most important development as far as toxicology was concerned, was an article published in the Edinburgh New Philosophical Journal in 1836 by James Marsh, an assistant to Faraday. Entitled 'Description of A New Process of Separating Small Quantities of Arsenic from Substances with which it is mixed', it became a revolutionary tool in the hands of the medico-legal profession. For the first time true evidence of poisoning by arsenic could be obtained from biological matter. The test was derived from the experiments of other chemists on arsenical hydrogen, a gas which decomposed on heating to deposit arsenic. Wynter

Blyth commented,

> like many other useful processes, it seems to have been evolved by a combination of many minds. It may, however, be truly said that Marsh was the first who perfected the test and brought it prominently forward.[44]

2.4. Occupational Poisoning and General Health

During the eighteenth century knowledge of the effects of lead poisoning increased. Observations by George Baker, published in 1767 attributed the occurrence of 'Devonshire colic' to the existence of lead in cider vats.[45] The first observations of the relationship between occupation and cancer were made by Percival Pott. In his book Chirurgical Observations published in 1775 he pointed out the relationship between cancer of the scrotum and the occupation of chimney sweeps. He suggested that 'the disease of these people seems to derive its origin from the lodgement of soot in the rugae of the scrotum'.[46] An unusual feature of the disease was that it affected only British sweeps. This gave rise to suggestions that some peculiar feature of English life was to blame, such as less frequent washing, or that protracted exposure to soot, due to the habit of separating it from rubble to sell, was a causal factor.[47] In this suggestion was the idea that there was a relationship between dose and response with regard to the development of cancer, a fact that had already been established for therapeutic preparations.

Occupational poisoning was not a major cause of disease during the eighteenth and early nineteenth century. Infectious diseases such as typhus fever, typhoid, influenza and whooping cough took the greatest toll of life.[48] Edward Jenner made the first cowpox vaccination against smallpox in 1796, and this was the first demonstration that diseases could be brought under scientific control. This was a time of transition from a reliance on the old established knowledge to a modern scientific

attitude. Developments in chemistry opened the way for the study of acute poisons. While the low level of general health obscured the contributions of chronic toxicity, with the growth of industrialisation and the consequent growth of urban areas, problems associated with public health, such as overcrowding and bad sanitation, multiplied. In 1832 Charles Turner Thackrah an apothecary from Leeds published his work on the comparative health of the urban and rural populations.[49]

Between the fifteenth and the end of the eighteenth centuries profound changes had taken place within European society and its science. The popularity of widespread criminal poisoning, which had almost become institutionalised, or at least socially acceptable for the elite in society, was declining, and, it appeared, would now be brought under control. Within the alchemaic system a number of important issues had been articulated, such as the relationship between therapeutic and toxic doses, the mode of action of poison and the relationship between disease and occupation. These issues remained unresolved, and were intensified by the public health problems connected with industrialisation. Toxicology was associated with general social problems that it was, as yet, unable to solve. Its internal, theoretical articulation was oriented towards the new mechanistic philosophy, but was still dependant on the concepts of alchemy. The modern chemistry had provided rapid technical improvement, but innovations in the theoretical thought were still to develop.

2.5. The Emergence of Forensic Toxicology

The development of chemical techniques laid the foundation for the study of the action of chemicals on biological systems. The prerequisite for such an advance, however, was that a link should be made between chemistry and medicine, and this was achieved by a French scientist M.J.B.Orfila, who was qualified in both subjects. A dedicated

experimentalist, he also provided a definition of toxicology, and his own classification of poisonous substances. Two other French experimentalists, Francois Magendie and Claude Bernard both utilized poisons in their work, while toxicology was taken to Edinburgh by a student to Orfila, Robert Christison. An extensive theoretical model of the action of chemicals in the body was published by Liebig in 1842, drawing on his knowledge of chemistry, fermentation and the 'vital principle' of organic systems.

Orfila was born in 1787 on the Island of Minorca, a Spanish Colony, and studied chemistry at the University of Valencia, where the teaching was rather backward, as 'it was still being taught at Valencia at this time that air and water were the elements'.[50] Orfila, in addition, studied the works of Lavoisier and Berthollet, and in 1806 moved to Barcelona for a more extensive education in chemistry. Five years later he graduated in medicine in Paris, but war between France and Spain removed his income and he was forced to support himself by giving private lectures in chemistry, legal medicine and anatomy.[51] It was this combination of interests which laid the foundation of his interest in toxicology. In 1816 he became a naturalised Frenchman, and he was soon appointed physician to the French Louis XVIII. He was one of the founders of the Academy of Medicine and in 1819 he became Professor of legal medicine at the Paris Faculty of Medicine. Four years later he was made Professor of medical chemistry which he held until 1831 then becoming Dean of the Faculty.[52]

Orfila carried out research entirely directed towards the question of toxicology, especially concerning legal medicine. For the known poisons, he compiled a 'systematic correlation between the chemical and biological information'.[53] and as a dedicated experimentalist, generated much information from the use of animals. In the course of his research he 'carried out countless experiments on animals and examined hundreds

of corpses in order to discover the effects of various poisons on the internal organs'.[54] An important discovery by Orfila was that poisons are absorbed and accumulated by tissues other than the stomach, and he experimented on the liver, kidney, brain and blood. He applied strict quantitative methods and devised tests to show the presence of toxic substances in the body, many of which survived late into the nineteenth century.[55] His method was to administer a known quanity of the substance under test to animals, and after death occurred, to note changes in tissues and organs, then to try and recover the substance by chemical means. The scientific value of some of these experiments was later criticised, as Wynter Blyth noted,

> Some are of little value and teach nothing accurately as to the action of poisons - as for example many of those in which he tied the gullet in order to prevent vomiting, for such are experiments under entirely unnatural conditions.[56]

Orfila was particularly concerned with the application of chemical methods for the detection of poisons to legal proceedings. His analytical approach to autopsy was used extensively for this purpose, and he was called as a witness in many cases of suspected poisoning. Some of his methods are still in use.[57] This concern with forensic toxicology led him down to a narrow concern with acute poisons, for which the end point was death, rather than an interest in all the possible conditions under which poisoning could occur. His definition of a poison emphasises those with which a small amount causes harm,

> The name poison is given to any substance which taken inwardly in a very small dose or applied in any kind of manner to a living body depraves health and entirely destroys life.[58]

In his 'Treatise on Poisons', published in French in 1813, Orfila emphasised his belief in the application of strict scientific methods to the study of poisons. The most important biological sciences he identified as physiology, pathology, morbid anatomy and analytical

chemistry, and he stressed that 'these are, in fact, the only means to enrich the science of toxicology and to raise it from the state of imperfection in which it, at present, lies'.[59] That this was a novel undertaking was illustrated by a comment from Orfila,

> I must confess I have been often discouraged by the blanks I had to fill up, and should several times have abandoned my undertaking, had I not considered that it is always useful to attempt to clear a path even when imperfectly marked out.[60]

The known poisons were classified into six classes: corrosive, astringent, acidic, narcotic, acrid and septic, and Orfila included all known poisons within these categories, not making a distinction with those which had a therapeutic use. Thus opium and nightshade were considered under class IV, the narcotics. In his book he documented descriptions of the chemical properties of the substances, and the results of the physiological experiments on animals, with doses large enough to 'produce serious accident',

> the experiments will be reported which have been made upon living animals, with the intention of ascertaining the phenomena they produce when introduced into the stomach, when injected into the veins or when externally applied.[61]

His point was, however, that simple dissection and observation of the injury produced was not sufficient to detect the substances concerned - it had to be isolated using chemical analysis,

> it will be attempted to demonstrate, from the appearances on dissection that it is impossible to be able to recognise by the simple inspection of lesions of this description, the poisonous substance which has produced them.[62]

Orfila made an important contribution to toxicology in defining the scientific problem in terms of a practical interest. He had the ability to combine the new chemistry with a range of biological information, which joined quantitative techniques, animal experimentation and

chemical analysis into scientific approach to the study of poisons. Narrowed by his concern with forensic medicine, he did not forward a general theory of toxicity, but dispelled many myths surrounding the subject.

The new techniques were not, however, accepted without debate. The Marsh test raised questions about its efficacy in cases of convicting murderers. In 1841, the British Pharmaceutical Journal commented

> Within the last year or two an unusual degree of attention and interest have been excited in reference to the subject of poisoning with arsenic. The improvements which the continental chemists have lately effected in the means of detecting minute portions of this poison - the differences which have arisen among scientific men as to the value, and extent of application of the new process of detection - and the notoriety of recent judicial investigations in which these differences have been brought prominently into notice, have all tended to spread more widely the interest felt on this subject.[63]

The doubts were such that the Paris Academy of Science and Medicine felt that the test, used as evidence in legal proceedings, was open to question, even though over 90% of murder by poisoning in France involved arsenic. They suggested,

> that the new process for the detection of arsenic by Marsh's apparatus, has been ascertained to be uncertain, and that those indications which chemists had relied upon as conclusive were proved to be quite fallacious.[64]

The original discovery made in 1801 by Tromsdorff was that arsenuretted zinc mixed with sulphuric acid and zinc in a flask would deposit arsenic on the sides. The Marsh test, developed from this experiment would render minute portions of arsenic, but it was subject to some error. Some of the leading scientists in the field, including Orfila, Liebig and Mohr were concerned by this, and they suggested that certain precautions were necessary to avoid falling into error with the test.[65]

With organic tissue, frothing often prevented a satisfactory result being reached, but it was also discovered that other substances would give results similar to those achieved with arsenic. Orfila found that the white residue of arsenic in solution in water was turned red by silver nitrate. In the course of this work the hypothesis was put forward that arsenic was a natural component of human tissue, the Pharmaceutical Journal reported,

> It was announced by Messrs. Couerbe and Orfila that they had discovered the existence of arsenic in the bodies of persons who had not been under the influence of any arsenical preparations, in fact that arsenic existed in the human body in the normal state.[66]

A debate arose between Orfila, and two other scientists Flandin and Danger who held that the carbonizing of organic matter (which Orfila had suggested to overcome the problem of frothing), actually gave rise to deposits which reacted like arsenic. This was opposed by Orfila, so the Academy of Science appointed a commission to decide the matter. The contending parties had to demonstrate experiments in front of the commission which would decide between them. They eventually concluded that when carbonisation or incineration of animal matter was incomplete, stains could appear, but these would not be confused with arsenical deposits when subject to chemical tests. The commission also gave Orfila the distinction of having been the first person to demonstrate the presence of arsenic in the organs of animals poisoned with it.[67]

2.6. Pharmacology and Physiology

While the scientific basis of toxicology was being established, advances were being made in the isolation of chemicals from plants. This was another consequence of the development of chemical techniques, and was important for toxicology in that it led to the discovery of poisonous substances that had previously been unknown. The most

important discovery was that of the organic bases, named the alkaloids. The first discovery was made in 1805 by Serturner who isolated morphine when experimenting with opium. By 1820 Pelletier and Caventon had discovered strychnine, brucine, quinine and cinchonine. Isolation of new alkaloids continued quite steadily until the end of the century.[68]

Some of these new chemicals were to be applied in medicine, and their possible use and mode of action generated scientific interest. This highlighted two other trends in the study of toxic substances, those used for therapeutic purposes and those employed in the investigation of physiological mechanisms. Orfila had given a generalised scientific definition of toxicology constrained by his emphasis on forensic medicine. Another French scientist, Francois Magendie, took up the study of toxic substances in the study of experimental pharmacology, as he was more interested in the possible beneficial effect of the new chemicals. His research on physiological actions was elucidated by studying the pathways of absorption and distribution of Java arrow poison, brought from an expedition to Borneo in 1803. Using this, Magendie successfully demonstrated its site of action on the spinal cord of dogs, and their mode of death as asphixiation. He also performed extensive studies on strychnine to continue experimenting on the spinal chord, and to test the theory that foreign materials were absorbed only through the lymphatic system. According to Olmsted these were 'the first records of attempts to administer chemical substances to living organisms in a systematic way'.[69]

Physiological investigations of this kind were taken up by Claude Bernard, a student of Magendie. He used curare and arrow poison to investigate the interaction between nerve and muscle.[70] He also explained the mechanism by which carbon monoxide is taken up by the haemoglobin in the blood. In fact Bernard is known, with Magendie and

the British scientist Blake as one of the founders of experimental pharmacology. Although Bernard held the view that 'the physiological analysis of organ systems .... can be done with the aid of toxic substances',[71] at this stage these disciplines, physiology, pharmacology and toxicology were not formally distinct.

The important branches of toxicology had been established for scientific investigation by the French scientists. These were not revolutionary new ideas, however, but the application of a rigorous, quantitative scientific method to aspects of toxicology which had long been social problems, and were now offered solutions. This is true of forensic toxicology, and the toxic effect of drugs, but the need for more basic knowledge on physiological mechanisms and the interaction of the chemical and biological underpinned all work on toxicology.

2.7. Theories on The Action of Poisons

Toxicology moved to Edinburgh with Robert Christison, who had been a pupil of Orfila. He was Professor of Medical Jurisprudence and Policy at the university, and teacher of B.R.T. Frazer. In 1829 he published 'A Treatise on Poisons', in which he gave a succinct definition of the subject, in all the forms it was then conceived,

> The object of the science of toxicology is fourfold. It supplies the antidotes for the various poisons; it furnishes the physiologist with valuable instruments of research in his investigations into the laws of the animal economy; it aids the physician in his enquiries as to the action of many energetic drugs and it collects from the numerous branches of medical knowledge as well as from collateral sciences, the materials of the most important department of medical jurisprudence.[72]

This demonstrates that, as a scientific discipline, toxicology was seen as being comprised of all these major branches. Christison himself, however, because of his association with Orfila, and the title of his post, was mainly concerned with forensic toxicology. He emphasised

the importance of this branch of knowledge is that frequency of murder, suicide and accidental death by poison .... render Toxicology, in the eyes of all well informed persons, an important, and essential part of the studies of every medical man'.[73] The credit he gave to Orfila was in systematizing the science, in applying the stomach pump to cases of poisoning and advancing the search for antidotes, while imposing old, inert remedies, advances which were of benefit to the science, because

> toxicology has advanced a step further still, and has saved the physician much necessary labour in future by laying down the general principles by which the search for new antidotes must be regulated.[74]

Christison was acquainted with the work of Magendie on the therapeutic uses of chemical substances, and realised the necessity of thoroughly investigating the toxic effects of such chemicals,

> the most energetic articles of the Materia Medica being, as already observed, poisons in large doses, it is indispensable to be well acquainted with their deleterious effects, before they can be safely employed in the treatment of diseases[75]

His observations on the scientific basis of toxicology were profound, and still apply today. He identified the main disciplines of pathology, chemistry and physiology, as basic to an understanding of it, and saw toxicology as drawing on the knowledge in all these disciplines, as a multidisciplinary science,

> the object of toxicology is to embody all this information into one science .... It ranges over the whole vast field of medical learning and draws together from a variety of quarters and principles which are seldom at any other time viewed in combination [76]

He is known for his work on the culabar bean,[77] with which he caused the death of dogs, but he also used oxalic acid, arsenic, lead salts, opium and hemlock, to investigate the toxic mechanism of these poisons.[78]

There were two main theories about the mode of absorption of

poisons, both of which had the support of scientists working in the area. These were, on the one hand that the poison was absorbed by the nerves, and passed along them to the organ that was affected by the substance, while the rival theory held that the poison was carried in the blood to that organ. In 1841 the Pharmaceutical Journal stated the problem,

> Conflicting opinions have been held and still continue to prevail, with reference to the action of poisons upon the animal organisms. Physiologists have been accustomed to ascribe the influences of poison upon those parts of the body to which it is not immediately applied, either to absorption or to a specific action upon the nerves. Hitherto but few attempts have been made to account for the phenomenon of poisoning upon chemical principles, yet the progress of investigation into the nature of those changes, which take place in the animal organism in health and disease, seems to establish a very close relation between organic function and chemical action, and the most satisfactory explanation of the operation of many poisons are founded upon the knowledge of this relation.[79]

Magendie had attempted to show that poisons are carried by the blood to their site of action, by demonstrating that no poison remained at its point of introduction, and it did not act when the circulation of the blood was affected. There was some dissent over the meaning of his experiments. As Christison noted, 'the experiment proves that the poison enters the blood and in substance reaches the trunk but it proves no more',[80] and certainly it could not be conclusively shown that the blood was the medium of transport. In fact some workers - Christison singles out a Dr. Morgan and Dr. Addison - devised experiments to show that the arterial blood of an animal under the influence of poison was not, in itself, poisonous. They also brought evidence to show that the time involved between administration of a poison and its action was unexplained by Magendie. Christison quoted their results,

> if the jugular vein of a dog be secured by temporary ligatures ... and reconnected by a table that contains woorara we find, of course, on removing both ligatures, that the poison begins to act. But it will act with the same quickness if we remove only the ligature farthest from the heart; which is incompatible with the notion that it must be carried with the blood to the brain, the organ that is affected by it.[81]

The two doctors proposed their own modified theory of sympathetic action, so that the poison still travelled down the nervous system to the organ that was affected by it. They thought that 'like other membraneous cavities of the body, the inner surface of the vascular system is supplied with an expansion of nervous filaments, on which poisons produce their peculiar impressions'.[82]

The question of the mechanism of poisoning was continued by the chemist, Liebig, who took an interest in the mode of action of poison as it related to his work on the application of organic chemistry to agriculture and physiology. His views were related to the absorption of organic bodies in the process of decay and fermentation of vegetation, and he applied this to the animal body. Liebig thought that, because of its inherent 'vitality', living matter had the ability to break up chemical bonds in food, absorb it into the blood and carry it to all organs. Vitality had "increasing mutability", an ability to reproduce itself through decay and reproduction. He thought that,

> The action of the proper inorganic poisons is owing in most cases, to the formation of a chemical compound by the union of the poison with the constituents of the organ upon which it acts; it is owing to an exercise of a chemical affinity more powerful than the vitality of the organ.[83]

Rejecting the possibility of specific action on the nerves, Liebig identified a second type of poison arising from decomposition, which did not enter into combination, but acted by virtue of their ability to ferment and decay. These he called 'organic poisons', a term which

included 'contagions and miasmas'- disease carrying vapours which were thought to be exhaled from the earth, and their mode of action he thought, was analogous to that of yeast during fermentation. This was distinct from the 'inorganic poisons', whose action depended 'upon their power of forming permanent compounds with the substance of the membranes and muscular fibre',[84] and substances such as mineral acids which he saw as causing mechanic harm, like the action of hot iron on tissue. A summary of the theoretical views held by Liebig was given in the Pharmaceutical Journal,

> When a chemical composition of simple contribution is introduced into the stomach or any other part of the organism it must exercise a chemical action upon all substances with which it comes into contact; for we know the peculiar character of such a body to be, an aptitude and power to enter into combinations and effect decompositions.
> The chemical action of such a compound is, of course, opposed by the vital principle. The results produced depend upon the strength of their respective actions; either on equilibrium of both powers is obtained, a change being effected without the destruction of the vital principle, in which case a medicinal effect is occasioned; or the acting body yields to the superior force of vitality, that is, it is digested; or, lastly the chemical action obtains the ascendancy and acts as a poison.
> Every substance may be considered a nutriment which loses its former properties, when acted upon by the vital principle, and does not exercise a chemical action upon the living organ.
> Another class of bodies change the direction, the strength and intensity of the resisting force (the vital principle) and thus exercise a modifying influence upon the functions of its organs. They produce a disturbance in the system, either by their presence or by themselves undergoing a change; these are medicaments.
> A third class of compounds are called poisons, when they possess the property of uniting with the organs, or with their component parts, and when their power of effecting this is stronger than the resistance offered by the vital principle[85]

The debate on the mechanism of action of poisons shows the lack of theoretical development in toxicology due to deficiencies in the basic sciences that it depends on. The question of whether poisons travelled via the nerves or the blood could not be determined by experiment alone without a certain amount of controversy. Liebig had suggested a general model for the action of chemical substances on biological tissue interpreted within the accepted biological theory of vitalism. His ideas are interesting in that he saw a continuity between chemical substances which produced different effects on the body, and tried to link them together with a theoretical model. The classification of poisons into organic and inorganic arose from his work on fermentation, and demonstrated that he acknowledged the existence of different types of poisoning, particularly related to disease and bacterial infection.

2.8. Early Public Health Legislation

The social problems that were created by the use of poisonous substances should be seen in relation to the public health problems that existed in the early part of the nineteenth century. The rapid spread of urbanisation in Britain was accompanied by a large scale housing shortage. To overcome the problem, in the first thirty years of the century there was much rapidly erected 'back to back' housing in the towns, which lacked drainage, sewage disposal and ventilation.[86] There was little local government concern for a public hygiene policy, as rates were paid by the occupants of better quality housing. Sewerage polluted rivers and streams were used as domestic water, and refuse piled into the streets.[87] This public health problem, coupled with the overcrowding in working class areas, meant that by 1833 the life expectancy for working people was 22 years, half that of the richer classes.[88] In addition to these problems, there was the difficulty of distributing fresh food in the towns, while unscrupulous traders offered

adulterated bread, rancid butter, and milk often infected with tuber-colosis.[89] Typhus so often reached epidemic proportions in industrial areas that it was known as the 'poor man's disease'.[90]

These conditions met with public concern in parliament, and eventually a number of reforms were enacted. The need to regulate industrial practice was embodied in the 1833 Factory Act, which was to limit the hours that children could work in textile mills. It established the right of government inspectors to enter factories, and it established an official government body for this purpose, the Factory Inspectorate.[91]

Public health reform took much longer to be enacted. It proved much harder to convince politicians of the association between dirt, bad sanitation, overcrowding and disease. Reform was made more difficult due to the lack of statistical data on the problem, and the conviction of many physicians that poverty and intemperance were the worst problems of the working class. The former problem was tackled in 1834 when John Finlaison founded a statistical society in London, which began to collect statistics on the causes of death of the poorer classes.[92]

Legge identified two other major Acts of the nineteenth century, which, with the Factory Act, he classified as the most far reaching in breaking with the non-interventionist tradition in British politics. These were the Poor Law Amendment Act of 1834, and the Municipal Corporations Act, 1835. The former was created and administered, with some difficulty by Edwin Chadwick. It established a central body, the Poor Law Commission to regulate and oversee the regional committees.[93] In the latter case, the election of local corporations was extended to all male ratepayers. Legge holds that,

> from these three acts was to grow, by extension almost the whole of the modern statutory services on behalf of the health of the people. These social reforms in industrial life promoted the new knowledge of preventative medicine.[94]

The Poor Law Commission undertook an inquiry into the relationship between sanitation and disease. The report, by Chadwick, was presented to the House of Lords in 1842,[95] and the question was given to a Royal Commission on the Health of Towns to investigate which was chaired by the Duke of Buccleuch.[96] The Commission took evidence from scientists and physicians on the state of public health, and submitted two reports, in 1844 and 1845. A Public Health Act was eventually passed in 1848, due as much to the threat of a cholera epidemic reaching Britain from the continent, as to the work of the commission.[97] The Act permitted local boards of health to be established, which could employ a qualified doctor, although the boards were not a mandatory requirement. They would be co-ordinated by a Central Board of Health consisting of Chadwick, Southwood Smith (a qualified physician) and Lord Ashley (involved in the 1833 factory legislation). This board was not very successful, but in 1855 a permanent medical officer to advise the government was appointed, and in 1858 a health department within the privy council was created.[98]

By concentrating on relating the incidence of disease to environmental conditions the public health reformers relied to a considerable extent on the new science of epidemology. The force of this was demonstrated in 1855 with the publication of the essay by John Snow 'On the mode of Communication of Cholera' in which he showed that the deaths from cholera around Broad Street in Soho, could be traced to one particular water pump which was contaminated by leakage from a local cesspool.[99] This association between contamination and disease was thought to be due to the 'miasmas', gaseous material arising from

decomposition of animal and vegetable matter, from damp and filth. This explanation was believed until the demonstration of the bacterial theory of disease later in the century.[100]

The social problem of poisoning in the early nineteenth century must be seen in relation to the overriding public health problems that existed. Bad housing, unwholesome diet and unhealthy working conditions were widespread in the industrial centres, and all took their toll on the health of the population. These were the problems that public reformers focused on when bringing the question of legislation to parliament. The regulations relating to the factory and to public health both required institutional innovations within the sphere of government. Two other aspects of the public health legislation worthy of note was that it depended on expert scientific and medical advice, and that beneficial reforms were made, despite weaknesses in the scientific theories that were accepted.

2.9. The Arsenic Act

During the first forty years of the century the question of the criminal use of poisons was an increasing cause for concern, which led to the repeated suggestion that these substances should be controlled by parliamentary legislation. The development of the Marsh test focused attention on arsenic in particular, as the number of criminal and accidental poisonings using this substance could now be accurately determined. There was an additional problem in that no acceptable general definition for a poisonous substance existed, which was raised as an objection to legislation in the area. An expert body - the Pharmaceutical Society whose membership included the pharmacy profession became an important pressure group in the area, concerned with keeping legislation within their own sphere of competence.

There were some instances of local action taken to restrict the sale of poisons. In 1845 a letter to the Pharmaceutical Journal described an initiative in Burnley where the chemists and druggists decided that poisonous substances should be marked to show the address of the vendor. They would not be sold to young children, and the druggist kept a record of the address and signature of the customer.[101] In general it was possible to buy poisons with no warning label or advice on safe doses.[102] The Pharmaceutical Journal supported the availability of such substances because of their commercial value, especially in agricultural districts where they were in general use.[103] It was maintained, however, that where a chemist knew of a less dangerous substance for the same purpose, it was his duty to suggest it to decrease the possibility of accidental poisoning.[104] The Pharmaceutical Journal felt that there was a case for the sale of poisons to be controlled by law, and in the hands of the medical profession, although the major problem was the difficulty of defining which substances should be considered poisons. The pragmatic view was that 'we must consider every substance a poison which is generally treated as such in works of Toxicology'.[105] The major obstacle to control was thought to be the commercial importance of poisons,

> Many tons of arsenic and sulphate of copper are annually employed for agricultural purposes. Many other highly deleterious substances are extensively used in the arts and manufactures and although every precaution ought to be taken to avoid accidents in the use of these articles, the prohibition of their sale, even if practicable, would be attended with very serious commercial inconvenience.[106]

The German answer to the problem was that poisons were dispensed by written order from medical practitioners. The situation in Germany was somewhat different to that in Britain, as the medical profession had a monopoly on the sale of drugs under the control of the government.

The Pharmaceutical Journal noted that it had been proposed that a list of poisons should be published annually; and that it should be illegal for any person, except a medical practitioner, to prescribe or administer any of the substances contained in that list.[107] The major problem with this approach it was forseen, was that it would not be accepted by the British public, as it would mean the withdrawal of popular remedies, and they would be indignant if they could not take a calomel pill or a dose of James' powder without consulting a doctor.[108]

The scope of the problem was illustrated by the fact that between 1837 and 1838 more than one third of all cases of poisoning were estimated to have been caused by arsenic.[109] Other substances which were in common use, that were highly poisonous included oxalic acid, salts of sorrel, salts of mercury, copper, lead, potassium cyanide, iodine, and oil of vitriol. The Pharmaceutical Journal suggested that the word poison should be marked on such articles to acquaint the purchaser of its properties. They could be distinguished by being kept in blue bottles, and marked 'for external use only'. Remedies which could not be sold through a physician should carry notification of prescribed doses.[110]

A local act - the Stockport Local Improvement Act, was introduced before parliament which included a clause forbidding the sale of arsenic, prussic acid and any other well known poison to anyone under 21 years. In addition customers would be required to register their name and address in the presence of two witnesses. Chemists in Stockport, however, remonstrated against the act, as they held that 90% of the Materia Medica were deadly poisons when taken in excessive doses. Such an act had the backing, in principle, of the Council of the Pharmaceutical Society, especially if the terms of 'any other poison' were removed. A similar act covered Manchester.[111] In France a law for regulating the sale of poisons controlled who could sell poisons,

and ensured that a register with the name and address of the purchaser be initiated. The poison had to be labelled with the name and address of the vendor. Arsenic could be sold only for medicinal purposes and there was provision for inspection of premises. A list of about seventy poisons had been drawn up.[112] The British case for some control was supported by the Pharmaceutical Society,

> We fully agree .... that much difficulty and inconvenience would attend the introduction of a comprehensive law for restricting the sale of poisons generally; but if we may judge from the cases of poisoning reported almost daily in the public papers, there are good grounds for believing that a proper restriction on the sale of arsenic by retail would be the means of preventing at least nine-tenths of the criminal poisoning which now occur.[113]

In addition to human poisoning other effects were noticed particularly of using arsenic for steeping and corn agriculture.

> For some months past in certain parts of Hampshire partridges have been found dead in the field presenting a very remarkable appearance. Instead of lying prostrate on their side as is usually the case with dead birds, they have been found sitting with their heads erect and their eyes open, presenting all the semblance of life.[114]

The Pharmaceutical Society suggested that an Act of Parliament for regulating the qualifications of Chemists and Druggists was necessary. Such an act could ensure that most active poisons were kept separately, and substances would be labelled correctly. A legal Board of Health would consult the college of Physicians before medical advice was given.[115]

The ruse of poisoning as a form of murder was giving concern, and discussions among Medical and Pharmaceutical bodies were taking place to diminish criminal poisoning with the aim of drafting a bill.

> In consequence of the numerous cases of secret poisoning which have lately become public, a variety of plans have been suggested with a view of placing some check upon this destructive crime.[116]

It was not unanimously agreed that such practice was on the increase, but that it was becoming more systematic. The Provincial Medical and Surgical Association presented a petition to parliament, which stated:

> 1. That no Druggist or Shopkeeper be allowed to sell arsenic without a licence under a penalty
> 2. That no person be allowed to sell small quantities of arsenic unless combined with some material, the administration of which with food would be at once detected by the appearance or taste
> 3. That no person be allowed to purchase arsenic unless accompanied with a witness,
> 4. And that the vendor do keep a book, in which he should make an entry of every sale of arsenic, to which the purchaser and his witness should affix their names and places of abode and that this should be attested by the vendor.[117]

But because arsenic was now easy to detect there was an accurate assessment of the quantity of deaths caused by it even though there could be another substance whose effects were worse. It was expected that chemists would oppose moves to control arsenic on commercial grounds, and because of fears that such a law might be inoperative. They could also object to singling out just one poison. The Pharmaceutical Journal noted,

> Accidental poisoning is overlooked, the education and examination of those who deal in poisons is deemed a matter of no moment, and opium, aconite, lobelia, hemlock and nightshade, with a thousand other deadly drugs, may be sold without restraint by ignorant persons, provided always that a prohibition is placed on the sale of arsenic by granting a licence to sell it.[118]

A bill introduced in 1835 was opposed by Chemists, and was withdrawn when the impractibility of the scheme was shown. The Pharmaceutical Society, acting jointly with the Medical Association set up a committee now consider the practicability of adopting measures for Preventing

Accidental and Criminal Poisoning.[119] Each member of the society was sent a questionnaire, to obtain facts about the sale of poisons over the country, although,

> It was not to be expected that all parties would at once acquiese in the propriety of a legislative enactment interfering in some degree with their business arrangements, still less was it to be expected that all would agree as to the precise nature of the regulations most calculated to produce the desired effect.[120]

Although it became clear that many members had adopted similar regulations to those being considered. At a meeting between the committee of the provincial M & S Association and the committee of the Pharmaceutical Society, 'it was generally admitted that the unlimited sale of poisons by unqualified persons was the chief source of danger.[121] The Society put forward a proposal to limit the sale by retail of certain drugs and poisons to medica and Chemists and Druggists, but there was a fear that undesirable retailers would take on such a status. The council, therefore decided to confine recommendations to arsenic.

> The sale of arsenic by retail should be restricted to medical men and chemists and druggists.
> Arsenic should only be sold to male adults known to the vendor personally on production of their written order.
> The vendor should enter the sale in a book, with the date and the object for which it is required, to which the applicant or a witness (one or the other being known to the vendor) should sign their names, unless a written order is brought in a handwriting known to the vendor, which order should be pasted into the book.[122]

It was resolved to send the recommendations to the Secretary of State, and noted that this had also been done by the provincial Medical and Surgical Association. The Society felt that the policy of co-operation had been better than the two societies opposing each other on practical grounds. The Secretary of State began to prepare a Bill on the control of arsenic, founded on the resolutions agreed by the

committees. In the House of Lords the Earl of Carlisle brought in a bill to regulate the sale of arsenic, but the Pharmaceutical Society felt it would be inoperable until there was a means of defining and regulating the qualities of chemists and druggists, but

> Several of the medical witnesses before the select committee on the Pharmacy Bill objected to the examination of Pharmaceutical chemists in Toxicology. It was alleged that this was a medical subject, and at the desire of the Society of Apothecaries the word Toxicology was erased from the bill.[123]

The Pharmaceutical Society held however, that although medical jurisprudence was a part of toxicology, it also relied on detection by chemical means, and the chemist provided antidotes to poisons. In France and Germany toxicology was taught to chemists and pharmacologists and it was felt that chemists should be acquainted with the proper doses, effects and antidotes of poisons.[124]

The Arsenic Act was passed in 1851. This Act brought in a regulation that arsenic should not be sold in quantities of more than 10lbs mixed with soot or indigo in the proportion one ounce to 1lb of arsenic unless this rendered it unfit for its purpose. A register had to be kept of sales of arsenic with the name and address of the purchaser, and its purpose. Failure to do so held a penalty of a fine of up to £20. Arsenic in medicinal products was excluded.[125] The act was intended to protect the public against fatal results from improper use by retaining a means of tracing a possessor and prohibiting its sale in small quantities for domestic use. It covers all colourless preparations of arsenic, although some mixtures (e.g. rat poison) not compliant with the act.[126]

2.10. Conclusion

By the 1830s toxicology had become recognised as a branch of science worth studying for its own sake. The experimental method was

being utilized to devise experiments specifically concerned with the mechanism of toxicity, and the ancient and alchemical remedies and antidotes had ceased to dominate the science, although some ideas still persisted. It had also been recognised that toxicology could act symbiotically with other disciplines to generally further the base of scientific knowledge. It relied heavily on the new chemical techniques, both for analysing the constituents of biological tissue, and for isolating the active chemicals present in the crude mixtures that had long been known as poisons, but it could also be utilized itself in unravelling basic physiological mechanism. This had the effect of furthering knowledge on the mechanism of action of a toxic substance, and simultaneously opened the possibility that such action may be used therapeutically in some cases. Thus, at this stage pharmacology could not strictly be considered as a science distinct from toxicology. Although the desire to discover disease-curing chemicals became to be regarded with much higher prestige, rather than the more preventative orientation of toxicology, as the disciplines became allied to medical science. At this time neither of these disciplines was distinct from physiology, however toxicology held an independent status within medical jurisprudence. This is due to the historical importance of poisoning as a method of murder, which highly motivated toxicologists to adopt the rapidly developing technique of chemical analysis to their own problems and was the source of specific research on toxicity.

The early developments in toxicology highlighted some of the problems that were to become very important in the discipline. The relevance of using laboratory animals to investigate mechanisms of toxicity was questioned (and on a more socially relevant note, the morality of using animals subjecting them to what was in some cases a very violent and painful death, was a controversial issue - to the extent that the wife of Claude Bernard became a leading light in the

anti-vivisectionist movement in France). The difficulties in generalising due to idiosyncratic effects were known, and the lack of knowledge on mechanisms of action and on structure-activity relationships were identified. Finally toxicology was given a very loose definition and several applications were seen, thus giving rise to its multi-disciplinary image which it still retains.

There were still a number of points which either became less relevant later, or had not yet been recognised. The direction of specialisation which had been started led to the development of the discipline of forensic medicine. This has its emphasis on the toxicity of acute doses of poison, and has practical uses in criminology and the clinical effects of drug abuse.

By the mid-nineteenth century, then, an international community of scientists can be identified who are interested in poisons and their action either from a chemical or biological point of view. A centre for toxicology developed in Paris, and was the beginnings of a research school, as students taught there took the study of toxicology elsewhere, in this case to Edinburgh. Independent observers had noted the existence of occupational diseases but this was not yet to be taken up as a social problem.

In the legal arena rudimentary social legislation takes place in response to the problems generated by industrialisation and urbanisation. In the Public Health field the concern is generated mainly from a civil servant, Edwin Chadwick, rather than from any scientific or medical concern, although he does have respected medical friends within government. In the development of legislation for the control of arsenic however, the Pharmaceutical Society emerges as an important pressure group, concerned to promote the interests and professionalisation of the chemists and druggists, a group under its jurisdiction. This move

was so they would retain control over the administration of arsenic, and should not be seen as completely divorced from their desire not to let the medical profession take control for the distribution of poisons.

The science is an activity developing autonomously from interference from government. It is developments within science, particularly the detection method for arsenic which allow legislation to become effective. Conversely, useful Public Health legislation is passed, based completely on a misconceived scientific theory.

Legislation is definitely used as a response to problems that are well documented, there are no adventurous moves. In particular, the lack of concern over the occupational diseases is notable, as these are well documented. In the case of cancer of the scrotum in chimney sweeps, the comparison with Germany implies that prevention of the disease could be realised.

By 1851 the science of toxicology appeared to have started to develop as a scientific specialty, and the first step toward Public Health legislation had taken place.

CHAPTER THREE

THE 'MAGIC BULLET' (1850-1910)

The 'Magic Bullet'

During the second half of the nineteenth century there were developments within many biological sciences which had an impact on the development of toxicology. Improvements in vaccination controlled some of the most prevalent diseases, and advances were made in chemistry pathology and physiology during this time. Research into pharmacology obtained a new focus as the development of Salvarsan by Paul Ehrlich created interest in finding drugs that were curative rather than merely alleviating symptoms. There were some attempts at using animals to demonstrate the toxicity of substances, but the uncertainty of the results made the methods unpopular. The question of chronic toxicity re-occurred in different issues, particularly related to the use of arsenic for various purposes, the addition of preservatives and dyestuffs to food, and the question of the role of chemicals in the causation of cancer. These were independent lines of study, however, and did not develop a coherent framework for a research programme in chronic toxicity.

A number of legislative enactments were made to control various types of toxic substance, but these in general avoided the question of scientific uncertainty by failing to define specific criteria for toxicity. Control, therefore, depended either on the technical standards that could be obtained, by prescribed lists of dangerous substances, which avoided too great a dependence on scientific advice.

During this period changes in basic sciences and techniques were taking place. Improvements were made in microscopy and histology, and new disciplines such as biochemistry and microbiology were being formed, concerned with studies of biological material at the molecular level. Older disciplines were made more rigorous. Chemistry and microscopy were introduced into medicine as a reaction against the mysticism prevalent in the discipline.[1] In 1858 Virchow published his

treatise on cellular pathology which rejected the 'spontaneous generation' theory. Advances were being made in the understanding in the role of bacteria in infectious diseases, especially due to the work of Robert Koch in Germany.[2]

There is some evidence that the centre of research in toxicology moved from France to Germany in this period. Wynter Blyth compiled a bibliography of the chief books published between 1800 and 1884.[3] Of a total of 63 books, 18 were published in France and the same number in Germany. Although all the books from France were published before 1879, three of the German books were published between 1880 and 1884. The work of German toxicologists also indicates the strength of work in Germany at this time. In 1893 Rudolf Kobert published an important textbook on toxicology. Another scientist, Lewis Lewin embraced the specialist study of pharmacology and toxicology. He was trained in both subjects and carried out extensive research in both the therapeutic and toxic properties of chemical substances, was interested in medico-legal toxicology and in the poisonous properties of therapeutic substances, such as chloroform, various alkaloids, and antiseptic. He also studied toxic chemicals in their own right and published a monograph on carbon monoxide. He developed methods of blood spectroscopy and spectrophotograph and did extensive work on poisons in the blood, and their absorption through the skin for physiological research.[4]

Some of the pioneering work into industrial poisons was also done in Germany. In 1884 the Director of Industrial Hygiene at the University of Wurzburg, K.B.Lehman, started to study the effects of gases and vapours on cats. He and his students were encouraged by German industry to investigate the relationship between aniline and bladder tumours in workers.[5] In Britain recognition of industrial diseases was slowly becoming incorporated into Factory legislation. Thomas Olivier published his survey of the area in 1902, entitled 'Dangerous Trades

The Historical, Social and Legal Aspects of individual Occupations as Affecting Health by a Number of Experts'. This, he described as the first 'adequate attempt .... to deal with the conduct of trades and other occupations in respect to the dangers to life and health to which the workers are liable'.[6] A large proportion of the book considered the effects of industrial poisoning by substances whose action had been well documented such as lead, arsenic, phosphorous and hydrogen cyanide. With lead, differences in degree of poisoning, acute and chronic, were noted, and gender differences observed, as 'women probably suffer more rapidly and certainly more severely than men .... when a white lead worker becomes pregnant it is almost impossible for her to go to the end of term if she continues to follow her employment'.[7]

Occupational poisonings were not a major area for research during this period, although developments were taking place in other areas of toxicology. Research into pharmacology, which had been associated with toxicological investigations, developed rapidly into an area of research concerned with curing diseases.

3.1. Pharmacology

The association between the therapeutic and toxic properties of substances had been known for centuries. This led to the expectation that known poisons could be beneficial at low doses. This was supported by the leading pharmacologists of the day, and many poisons, including arsenic, were freely prescribed by physicians. In 1832 hydrogen cyanide was included, for the first time, in the British Pharmacopia (where it remained until 1948) as a sedative and for the relief of coughing,[8] although it was known to be a highly toxic agent. As early as 1746 Browne Langrish had investigated the possible therapeutic effect by giving small daily doses to a dog for one month. As the subject remained healthy, got fat and increased its heart rate, the dose was

assumed to be beneficial. Hydrogen cyanide was isolated by Scheele and shown to be acutely toxic by Carl Friedrich Emmell in 1805. It was considered to be beneficial in diluted form by Magendie and became popular in London in 1820, despite opposition from physicians who objected to its toxic properties.

This state of affairs existed because there was no general theory of the relationship between chemical structure and biological activity.

It was James Blake,[9] a student of Magendie, who conducted the first systematic investigation into this relationship. He concentrated on inorganic salts, and in 1841 published a paper suggesting that isomorphic substances with a similar crystalline form showed similar physiological properties.[10] He received funding from the British Association for the Advancement of Science (BAAS) to continue this work.[11]

During the 1850s there was a rapid advance in the theory of organic chemistry. Theories of valency and structure were developed. In 1863 Benjamin Ward Richardson reported the results of his work to the BAAS on the relationship between organic structure to physiological activity. He was then awarded a grant of £10 to prepare a report on the current state of knowledge about the area, and between 1864 and 1870 he received a total of £210 from the Association.[12] He hoped that his work would produce a range of medicinally useful remedies that could be predicted from knowledge of their chemical structure.

This work was extended by two scientists working at the University of Edinburgh, Thomas Frazer, a former pupil of Christison and Alexander Crum Brown. They wanted to include a study of chemical structure into the more general question of chemical composition. This was hampered by the fact that many organic chemical structures were not known, so they concentrated on the alkaloids and their methylated derivative. Beyond extending the body of knowledge on the toxicity of these substances, no

general conclusions could be made.[13] This work, however, was the culmination of structure-activity relationships in the nineteenth century.

By the end of the century, new developments were taking place that were to change the orientation of the search for therapeutic drugs. Paul Ehrlich had begun his work on immunology, which was eventually to lead to his theories on the chemical treatment of disease. He was to break with the tradition that looked for a cure for the symptoms of disease, and to focus attention on the cause of the disease. G.O. and F.E.Clayton note that,

> The synthetic remedies were the result of two advances in science : organic chemistry and pharmacology. The limitations of pharmacology as it developed under Oswald Schmiedeberg was that it explained physiological action and measured the limits of toxicity but because its methods involved the healthy animal it failed to throw light on what Ehrlich called the main problem, namely the mechanism by which a substance cures a certain disease.[14]

By 1910 Ehrlich had discovered a specific chemical which would cure syphilis which was patented by Hoechst under the name Salvarsan in 1911. New discoveries soon followed this breakthrough as pharmacologists began to concentrate on finding specific cures for specific diseases.

The second half of the nineteenth century was a time when the philosophy behind therapeutics moved from a situation where chemical substances were administered to treat the symptoms of an illness, to a philosophy whereby the administered substance would actually cure the disease. This was via scientific interest in the question of the structure-activity relationship between chemicals and biological matter. In the former case the substances in use were often highly poisonous, so the study of therapeutics and toxicology were different

aspects of the same question. After the discovery of Salvarsan, however, much more effort was spent in trying to discover new specific cures, and there is some evidence to suggest that the study of toxic effects declined in importance. The status of toxicology can be illustrated by the amount it is taught in institutions of higher education. American evidence suggests that between 1922 and the 1950s colleges of pharmacy declined in the amount of time spent on toxicology in the curriculum.[15]

Pharmacology had, then, emerged as a discipline independent of toxicology, with a research programme directed towards investigating chemicals for a curative effect. The idea that these chemicals could also exhort a long term, chronic toxicity would have a long gestation period. This was not true, however, of all contact with chemicals. In particular more observations of the relationship between exposure to certain chemicals and the development of cancer were made during the latter part of the nineteenth century.

3.2. Cancer

The medical profession was, at best, sceptical about the possibility of chronic poisoning. In 1838 Devergie observed the presence of lead in normal tissue which started a long controversy over which chemicals were 'naturally' present in human tissue.[16] There was very little in the way of scientific explanation that could be offered for either the appearance of long term poisoning, or, what was noted more, the appearance of cancer. The Lancet noted in 1850:

> .... a very puzzling circumstance and one which is very difficult of explanation, is the fact of cancer of the scrotum making its appearance in individuals, who, having followed the occupation of sweep for a certain time, give it up and are, after many years exemption from handling soot, seized with the disease.[17]

As early as 1825, a Cornish physician, John Ayrton Paris had suggested a correlation between cancer in workers in the tin and copper mines in Cornwall, and arsenic.[18] The first observations incriminating petroleum products in the induction of occupational cancer were made by Vollman in 1874, who described three cases of scrotal cancer and other part of the skin in men employed in the manufacture of paraffin and light oil by the distillation of coal.[19] In 1895 Rehn noted the high incidence of cancer in men manufacturing magenta dye in a coal tar plant and suggested naphthylamine as the derivative involved.[20]

There were other developments in biological theory during the nineteenth century, which influenced scientific thinking about the causation of cancer. By 1890 Pasteur and Koch had set down the rudiments of bacteriology and the specificity of disease causation, when Koch published his criteria for organisms to be accepted as a cause of disease. He isolated the anthrax bacillus in 1874 and the tubercle bacillus in 1882. All the major bacteria had been found and tested in animals before 1900 while Pasteur had demonstrated the means of transport and infection through the air and their type of replication.[21]

These developments in medical science were taken up by a certain number of scientists interested in the causation of cancer, who thought this may be due to specific bacteria, 'the similarity between malignant disease and tuberculosis has lead numerous investigators to seek for an organism which would bear the same causitive relation to cancer'.[22] The major rival to this theory was that supported by Professor Virchow, that 'these growths are caused by injury or chronic mechanical irritation'.[23] This latter had long been the favoured explanation for the cause of the infamous 'chimney sweeps' cancer, It was noted by Butlin, in 1892,

> here we have a curious kind of experiment which has been conducted before the eyes of surgeons for at least 100 years and which continues to be conducted year by year upon the human body, namely the repeated application of a chemical substance or a mixture of chemical substances to a particular part of the integument.[24]

By the end of the century there was concern over the increasing mortality from cancer. Regional variations of cancer incidence had been noted, and the disease showed a strong correlation between locality and number of deaths.[25] The rate of incidence of cancer in Britain had risen from 0.56 per 1000 in 1883, to 0.87 per 1000 in 1903, although the journal, Nature, suggested that the increase could be partly explained by a more accurate diagnosis due to the experience of two to three decades of surgery.[26]

This concern existed in a number of countries, and was reflected in the institutions which carried out research on cancer, and the funding that it attracted. In 1902 there was a state subsidised cancer laboratory in America, directed by Professor Roswell Park, and in Germany there was a Cancer Committee chaired by Professor von Leyden which had grants worth 50,000 marks. Considerable co-operative work was being undertaken in France where there was a journal devoted to the results. In Britain a fund of £100,000 established the Imperial Cancer Research Fund (ICRF) for research on cancer, to be managed by five trustees, and a general committee consisting of three representatives from the college of physicians, and three from the college of surgeons, members of the laboratory committee of the two colleges and one member nominated by the Local Government Board.[27]

The ICRF launched immediately into the controversy over the mechanism of the induction of tumours. There was some support for the theory that cancer was contagious from the fact that it was more prevalent

in some geographical districts, and that secondary growths were often observed in an affected person. One of their first tasks, therefore, was to try and induce an experimental cancer in test animals - mice were used. Healthy mice were kept in contact with diseased animals, but failed to contract cancer. When cancerous cells were innoculated into healthy mice they found the resulting cancer was in the form of a transplant - the tissue introduced formed the growth, rather than the tissue of the animal, and these cancers were species specific as they could not be transferred between species.[28] Other facts that were accepted about the disease was the rapid growth of tumours, their recurrence after removal by operation, and their tendency to reproduce in parts of the body that were distant from the original site.[29]

Scientific recognition and investigation of cancer developed as a separate question from that of chronic toxicity. It was a recognised disease, with a well defined end point, which attracted both scientific interest and public funding. Experiments on animals were carried out with no question as to their relevance to scientific investigation. In addition some epidemiology statistics were kept regarding deaths from cancer, and most of the accumulated wisdom on the chemical causation of cancer derived from the observation of certain occupations.

The existence of chronic poisoning, however, was harder to demonstrate, and so did not become fully accepted as a possible poisonous effect. The common daily use of a number of acute poisons, also hindered the general acceptance of long term poisoning.

3.3 Arsenic

Despite its popularity in murder and suicide cases, arsenic was readily available for purchase, and used for a multitude of purposes. Arsenic pigments were used indiscriminately as colouring in a wide variety of goods which included tablets of all kinds, sweet wrappers,

childrens toys, soaps, sweetmeats and wallpaper. During the 1860s Paris Green (copper acetoarsenite) was introduced as a pesticide in the U.S.A. This presence of arsenic in many forms in the environment was sanctioned by the majority of the medical profession. There was no way of tracing a particular injury to the ingestion of small amounts of the poison, and there was widespread faith in the therapeutic value of repeated doses.

Concern about the chronic toxic effects of arsenic in dust from wallpaper inspired four medical scientists from Harvard to press for legislation against its use in Boston.[30] James Putnam, the Professor of Neurology at Harvard, recognised the possibility of chronic neuritis from repeated medicinal doses of arsenic, similar to that observed from alcohol and lead.[31] He was also worried that mild forms of domestic poisoning would be overlooked by doctors who were not aware of this possibility.[32] His own research showed that doses of arsenic were not totally excreted from the body, which meant that some was stored, and accumulated in the body tissues. There was also independent evidence for domestic arsenic poisoning, as reported by the Boston Medical Journal, in 1891,

> It is well known that a large amount of evidence has been accumulating during the past half-century indicating that the exposures of daily domestic life are sufficient to cause, under favourable conditions, almost every form and degree of arsenic poisoning. [33]

Putnam was also concerned with the physiological changes that indicate early signs of chronic poisoning, as Gombault had found signs of well marked change in the peripheral nerves in guinea pigs who had been given a small quantity of lead for some time, although they had shown during life no impairment of voluntary motion.[34] Experiments by W.B.Hills, associate Professor of Chemistry at Harvard Medical School, showed the slow elimination of arsenic in the urine of patients with suspected

chronic arsenic poisoning which he attributed to the existence of environmental arsenic as a pesticide and contaminent of coal dust.[35]

The effects of environmental arsenic were not missed in Britain as Dr.James Ritchie published his suspicions of arsenical wallpapers as a source of poisoning, after he had noted the disappearance of toxic symptoms from some of his patients when they removed the wallpaper.[36]

The developing science of immunology had discovered the seemingly contradictory effect that repeated small doses of a poison could increase the tolerance to it. This appeared to refute the idea of the production of poisoning from exposure to repeated small doses of a substance. The journal, Nature, reported,

> .... not only can animals be rendered resistant to cobra (and other snake) poison by the injection into them of graduated doses of the poison (so that rabbits were rendered tolerant of sixty times the lethal dose), but that the serum of such immunised rabbits contained a powerful anti-toxin.[37]

The problem of chronic injury reasserted itself in 1899 when the origin of an epidemic of 'peripheral neuritis' in Manchester was traced to arsenic contaminated beer. Dr. E.S.Reynolds, who did the analysis estimated that the arsenic contaminent had been in the beer for at least six months, as it was due to the use of impure sulphuric acid which was used to prepare sugar for the brewery.[38] This raised the old question of environmental contamination by arsenic. Tests performed by the Lancet on a number of consumer products failed to detect any signs of the metal except in glaubers salts and artificial manure.[39] The Lancet also recommended that its use in agriculture needed regulating, because farm labourers also showed signs of chronic arsenic poisoning.[40]

Later arsenic was also found in many dress fabrics introduced as a contaminent of the dye. This opened the wider questions of poisoning by inhalation and by dermal irritation, especially as methods of detection

had improved to 1/50th grain / sq.yard. Legislation in Sweden and Germany banned the import of textiles contaminated with arsenic, while the Bureau of Chemistry in Washington produced a report on the use of Scheele's Green as a wallpaper dye.[41]

The response to the beer poisoning epidemic was the establishment of a Royal Commission to investigate the amount of recent sickness due to arsenic in beer, and whether the presence of arsenic in other articles of food and drink could have this effect. This caused the Lancet to comment on the length of an inquiry on so urgent a matter, and to comment 'we care not whether such a Bill is directed to the interdiction of malt substitute or whether it forbids the sale of all food and drinks except under their proper name, so long as it meets with an urgent requirement of Public Health'.[42]

Concern about arsenic in the environment eventually subsided again, and it was still widely used in agriculture after the second world war. At the beginning of the twentieth century, however, there was a lack of scientific evidence that convincingly demonstrated that arsenic was a public health hazard. Some scientists were concerned with its effects to begin exploratory experiments on chronic poisoning, using both animals and human indicators. Another public health issue that also gave rise to concern over the question of chronic toxicity was the use of coal tar dyes and chemicals as preservatives in foodstuffs.

3.4. Preservatives and Dyes in Food

Towards the end of the nineteenth century, the addition of chemicals to food, to colour and preserve it, was becoming popular, and the question of the safety and ethics of this practice was increasingly questioned. The Local Government Board found little evidence that could help them to set tolerance levels for additives to food, and in their 1891 report they complained that, for boric acid, 'we have not sufficient information to

show whether such minute amounts as are generally added as preservatives could be regarded as having that (injurious) effect'.[43] In order to assess the expert consensus on this matter the Lancet established a Special Sanitary Commission on the Use of Antiseptics in Food, which reported in 1897.[44] The Commission sent a letter to leading medical men asking whether they thought small quantities of preservatives added to food could be injurious to health, and if there was enough evidence to warrant their control.

The replies varied widely and were notable for the lack of consensus among the members of the profession. While it was generally agreed that there was no proof of damage from the ingestion of chemicals in food, the respondents were split over the wisdom of their indiscriminate use. Sir Henry Thompson thought that there was no evidence of injury although he strongly objected to the dietic use of any medicament.[45] Dr. F.J. Allen who was the Professor of Physiology at Mason College, Birmingham, divided the types of substances added to food into those chemicals that are foreign to the animal organism; and those which are unusual, but occasionally are constituents of normal food. Of the latter he cited benzoic and salicylic acid, and suggested that the body could dispose of small quantities of this type of chemical. More dangerous he thought was the use of antiseptics such as boric acid which were foreign to the body, and would kill all bacteria indiscriminately.[46] Dr. G. Sims Woodland noted the known idiosyncracy of human response to foreign chemicals and ventured the opinion that while single doses, or doses over short periods may be harmless, the chemicals 'may have very serious effects if continued over a lengthened period, and the physiological effects of multiple doses, especially if the substances have any cumulative action, may be exceedingly harmful.[47]

An opposing view was given by Sir Benjamin Ward Richardson, who held that, 'in foods they are not only necessary at this moment, but that

when used in proper form and quantity they are perfectly correct - that is to say, they cause no injury whatever to the consumer'.[48] Dr. T.Lauder Brunton backed this view by stressing the beneficial effects of delaying the decomposition of food, while the remainder of the scientists declined to forward an opinion due to the lack of reliable information.[49]

These replies highlight the total lack of any systematic experiments that had been undertaken to ascertain the safety in use of these chemicals. There is also the absence of any suggestion that repeated small doses of a substance could lead to the induction of cancer, although this was known to be possible. The information that did exist was almost entirely gathered from humans, although animals had been used on a smaller scale as objects for experimentation. At a meeting of the Society of Medical Officers of Health on the question of boric acid added to butter and cream, in 1892, Dr. Lauder Brunton referred to experiments on dogs by Forster, who had come to the conclusion that repeated small doses were injurious to digestion. The strongest objection to its use, however, was that it concealed decomposition and rendered saleable food that would not normally be so.[50]

In contrast to the general lack of information about the effect of food chemicals on the body was the studies on coal tar dyes by the German scientist Theodore Weyl, whichwere published in Britain in 1893.[51] Weyl was concerned that legislation was being enacted against chemicals in food with no scientific basis, in a number of countries.[52] In his approach to the evaluation of substances he hoped to discover a relationship between their chemical composition and physiological action, and favoured testing the colours in their commercial form in case they contained poisonous contaminents. Weyl chose the dog as the optimum test animal on grounds of cost and reaction similar to people, although he

was aware of the problem of species differences, and he stressed the need for testing the material 'upon as large as possible a number of animals of various types and even the higher and lower plants'.[53] In the administration of the test substance, Weyl required exactly measured doses and favoured the use of controlled experiments for doubtful results. The symptoms to be investigated included changes in the urine, changes in the blood, anatomical changes, and the possibility of accumulation in particular tissues over a period of time was recognised. Weyl recognised that a weakness of animal testing was the absence of 'subjective' symptoms such as headaches, which in humans gave an early indication of poisoning.[54] This work by Weyl was important in identifying some aspects of toxicity testing that would later become important, such as measuring the accuracy of dosages, and testing on a number of species. He did not however carry out any long term experiments, the average lasting between 7-10 days, so the concept of chronic toxicity was not fully developed into a test procedure.[55] Even so, it was this work that was the major scientific source cited before the 1894-1896 Select Committee on Food Products Adulteration in Britian.[56]

There was some interest in the evaluation of the physiological effect of common preservatives in food. One of the earliest studies was to attempt to demonstrate the deleterious effect of boric acid and formalin on animals. This was carried out by H.E.Annett of the Thompson Yates Laboratory, University College, London, in 1899.[57] His intention was to investigate the effects of minute doses of the preservatives when taken habitually, recognising these as different from the toxic effects of a single large dose.[58] For boric acid, he noted an acute experiment on dogs done by Neumann in 1881, and a longer term experiment by Chittender and Giles in 1898. This involved giving differing dosages to dogs for 27-46 days. They showed that a daily intake of 5-10 grams increased the excretion of nitrogen, sulphuric

acid and phosphoric acid in the urine. Annett used four week old kittens (in groups of five, with one control) all the same weight, which he fed 40 and 80 grains of boric acid for four weeks. Those on the higher dosage died, while there were two survivors from the lower dosage group and four of the control lived (with one lost).[59]

After a similar experiment with formalin dosed for 6-7 weeks, he found the kittens had loss of appetite, diarrhœa and retarded nutrition. A result which he contrasted with that obtained by Rideal and Foulerton on three cats, a rabbit and two guinea pigs, who obtained no effect after some weeks.[60] The results of the experiments forced the conclusion 'that these chemicals when used as preservative of milk (and probably of other foods) are very injurious to the health of the consumer, and particularly so to the health of young infants'.[61] Annett then drew attention to the high infant mortality due to diarrhœa in large towns, and expressed a hope that,

> these experiments on animals will consist of the first of a large series by which "that sufficient information" as to the injurious effects of the use of preservatives in milk will be provided in order to make actions under the Sale of Food and Drugs Act possible.[62]

This matter was not so easy to settle however. Another set of experiments on preservatives in food had been undertaken by Alexander G.R.Foulerton, a bacteriologist and lecturer on Public Health at Middlesex Hospital Medical School.[63] He was concerned with ascertaining the effect on health of doses of chemicals which resembled the dietary level of intake especially on the digestive process. He therefore recommended four paths for exploration, the influence of the chemical on the secretion of digestive enzymes, the injurious effect on the enzymes themselves, the effect on the action of the enzymes and the ease of digesting the food.[64] A separate question was the action of the chemicals on the tissues of the body. From his experiments, he concluded that boric acid

had no effect on digestion, although there could be toxic effects from large doses and formaldehyde had the ability to slightly decrease the digestibility of milk. His criticism of Annett's work rested on the fact that the dosages had not been measured.[65] This led him to the policy recommendation that preservatives should be given a maximum allowed concentration in food and should be declared on the label, to give the consumer the information about which chemicals were present.

By the end of the century the attitude towards using animal feeding tests to determine the toxicity of chemical use in food was fairly negative. It was recognised that the variability in results obtained was due to the difficulty in measuring the dosage taken. This feeling was summed up by Samuel Rideal, a colleague of Foulerton, who held that 'experiments on animals have, after all, but a very slight bearing upon the problem under investigation.[66]

The emphasis was, then, on demonstrating a toxic effect in humans, and the most rigorous of such tests was carried out by the Chief of the Bureau of Chemistry of the U.S. Department of Agriculture, Harvey Wiley, in an attempt to prevent the fraudulent sale of bad food. In 1905, with the help of the Board of Health in Berlin, he devised a series of experiments to be carried out on the human body.[67] Twelve human volunteers ate food containing common preservatives at a hygienic table at the Bureau of Chemistry, while he kept a record of physiological mechanisms such as blood, temperature, pulse, excretion and weight, and he analysed the food eaten.[68] Wiley became convinced of the harmfulness of the preservatives he tested, as only three of the original twelve volunteers managed to complete the experiment.[69] His findings were subsequently rejected by the Department of Agriculture, which adopted a policy of setting liberal tolerances for food chemicals. His experiments were the first to be specifically set up to rigorously test the safety of food additives on humans.

The addition of chemicals to food had been recognised during the latter half of the nineteenth century, as a potential public health problem. A systematic scientific research programme, however, was slow to develop, and there was a lack of expert consensus on the value of the use of these substances. In the absence of any conclusive evidence one way or another, no recommendations could be given on the uses of chemicals as colouring and preservatives in foodstuffs. A few trial experiments using animals were carried out in an ad hoc way, but they could not be conclusive without techniques for measuring doses and the use of statistical controls. These experiments were open to the criticism that they were not applicable to humans, but the small amount of data that was available on human exposure to substances used in food was itself difficult to interpret in terms of chronic toxicity.

More generally, during the latter half of the nineteenth century the varying strands of the study of toxicology became more explicit. The basics of forensic medicine had already become established by 1850, and the problems of acute poisoning had become less of a social and scientific problem during this later period. It appeared as if Germany was becoming a centre for research, particularly in the fields of pharmacology and industrial toxicology. This latter aspect was particularly slow to develop in Britain, despite ample evidence of the cumulative toxicity and carcinogenicity of industrial chemicals, such allegations were slow to be investigated where these went beyond those chemicals whose toxicity was well documented.

The investigation of chronic poisoning made some headway despite the medical confusion over arsenic and lead. The first rudimentary experiments on animals as subjects for testing were made. Although these in general were impossible to use as the basis of decision making, and were successfully criticised on scientific grounds, it is interesting

that the results were used to suggest a policy recommendation. The Lancet Commission reveals not only the extreme lack of scientific evidence on the question of chronic toxicity but also the widely varying attitudes taken by members of the medical profession on the relative risks and benefits of ingesting small quantities of chemical over a period of time. The beer poisoning epidemic in Manchester highlighted the importance of the scientific questions to the public health.

The origins of scientific interest in the mechanism of cancer is seen in this period. It has a distinct beginning independent of both medicine and toxicology although drawing on both of them. The study of carcinogenesis began to become institutionalised and funded as an area of study. Experiments were carried out on rodents, although there was no evidence that positive results could be transferred to humans. There was little criticism of this work, comparable to the criticisms that were levelled at experiments on chronic poisoning in animals.

Legislation was introduced during this period which increased governmental control over certain types of poisonous substances. Gross adulteration of foodstuffs was controlled, air pollution from chemical works, the sale of poisons, and certain industrial diseases all became matters for concern. The approach to such legislation, however, attempted to avoid the basic scientific ignorance about the mechanisms of toxicity by producing legal and technical definitions of standards to be achieved.

3.5. Science, Technology and Legislation

In 1875 the promotion of basic research which related to the development of preventative medicine was considered vital enough to receive an annual government grant of £2,000 in support of pathology and medicine. This was used on research to investigate the production of tumours, which was largely unsuccessful, and did not receive universal

support, as reported in Nature,

> this grant has been actively opposed by a small minority in the House of Commons mainly upon the narrow and inviduous grounds that the medical profession was thereby obtaining knowledge and instruction which the medical profession ought to obtain at its own expense.[70]

This feature of this policy for science highlighted the problems in obtaining useful scientific information on which to base regulative policy. Compared to the other industrialised countries, Britain was relatively advanced in the reform of public health, although the question was submerged by its association with sanitary reform, 'the equation of dirt with disease had given preventative medicine a subterranean inclination, a preoccupation with providing a pure water supply and efficient sewage removal'.[71] These aims were achieved by the Public Health Act of 1875, which required compulsory appointment of medical officers of health by the Local Government Boards.[72] There were, however, other problems which required legislative intervention.

The question of factory reform was returned to throughout the nineteenth century. The first Factory Act in 1833 created the Factory Inspectorate, a centralised body to carry out the provisions of the Act. Concern about safety initially was restricted to the fencing of machinery. The 1864 Act required that there should be adequate ventilation to remove harmful gases from the workplace, and in 1891 power was given to the Secretary of State to designate dangerous trades and for the chief inspector to propose rules for such trades. After 1901 there was an expansion of regulations governing different trades, and two years later H.P.Freer Smith was appointed as an Inspector for Dangerous Trades and Dangerous Machinery. The 1895 Act had the first provisions of notification of industrial diseases, while in 1898 Dr. Thomas Legge was appointed as the first medical inspector of factories. The emphasis in the Factory Legislation was on specifying technical engineering standards

which could be obtained by industry to reduce hazards, especially in cases where a ban on the material used was considered too expensive or unnecessary.[73]

The establishment of technical standards was a useful means of incorporating a legal definition of safety into legislation, and was also used in the control of food adulteration. The history of the control of food adulteration has been well documented.[74] During the 1840s scientists employed by the Board of Inland Revenue had stated that there was no way chemical analysis could detect the adulteration of coffee by chicory. This was taken up by a medical doctor, Dr. Arthur Hill Hassall who advocated the use of microscopic analysis for the detection of adulterants.[75] During the 1850s interest in the practice of adulterated food increased, and in particular the Lancet published reports of analyses of adulterated food, while a wider public was reached through the popularisation of the issues by the Times.[76] A parliamentary Select Committee was set up in 1855, which did not obtain any parliamentary action on the question.[77] Attitudes to the question of control changed drastically in 1858 when two hundred people in Bradford were poisoned after eating adulterated lozenges.[78] In 1860 the first general act preventing the adulteration of food and drink was passed, although it soon became apparent that this lacked the administrative machinery necessary for its enforcement.[79] A number of Bills to amend this Act were submitted to parliament from 1868 and in1872 an amendment was passed to improve its enforcement.[80] The local authorities appointed public analysts to analyse food samples for adulteration. Difficulties arose, however, due to the lack of definition of adulteration in the 1860 Act. This made it easy for the trade to develop an opposition to the claims of the public analysts and this was demonstrated in court by representatives of the trade who disputed the analysts claims of adulteration.[81]

This situation led to the government sponsored Act of 1875 which sought to reach a compromise between trade practice and consumer protection, although it did not set down standards of acceptable practice.[82] In 1899 the Local Government Board established a committee to investigate the use of preservatives and colouring matters in food. In their report, two years later, they recommended that maximum limits should be set for commonly used preservatives in food, specifically formalin and formaldehyde and boric acid in cream. In 1907 the Public Health (Regulations in Food) Act gave the Local Government Board the power to make regulations to control the use of chemicals in food.[83]

This approach of defining standards by what was technically feasible avoided the more contraversial questions of basic research into health and disease. The trial of funding cancer research had indicated that as an alternative approach to regulation this would not be workable or practicable. It was possible, however, for government scientists to attempt to widen the scope of the problem under their jurisdiction, as this was tried with the question of pollution from chemical works.

3.6. The Alkali Act

While there were debates about the existence of chronic poisoning in the scientific community, it took the interests of a powerful group, the landowners, to precipitate governmental action over the practical problem of environmental pollution by chemical works. During the nineteenth century property owners spent considerable effort on maintaining the value of their land, tenants were required to keep streams and banks free of weeds and to ensure that young fish were not caught. The habits of animals popular in sport, the fox, hare and deer were studied and they were helped to survive during the winter months.[84] It is not surprising then that farmers and land owners brought their influence to bear on the government, when the rapidly developing chemical industry allowed its

waste to be emitted unchecked into the atmosphere, and to destroy the farmland and vegetation in the vicinity. In May 1862 a select committee under Lord Derby was appointed to investigate the question of chemical pollution and the committee rapidly published their report in October,[85] a fact which moved the 'Chemical News' to berate the slowness of the commissions on the sewage question.[86]

The report testified to the devastation caused by the lack of control on chemical emissions, mainly produced from waste muriatic (hydrochloric) acid from the Leblanc process, which manufactured alkali (sodium carbonate) for products such as glass, soap and textiles.[87] The committee testified that the worst example was around St. Helens, which had been changed from rich farmland to a wasteland in five years[88] while 'human and animal suffer from smarting eyes, disagreeable sensations in the throat, and irritating cough and difficulty in breathing'.[89] It was also reported that animals around Swansea had died from eating grass poisoned by sulphurous acid and arsenic waste,[90] but a bill introduced into the House of Commons in March 1863 by Lord Stanely of Alderly referred only to alkali works.[91] The trouble was said to arise both from the inadequate laws which provided no incentive for manufacturers to control their waste,[92] and also from the lack of understanding of the climatological principles at work. The first report of the Alkali Inspectorate stated,

> It was expected that the gas would pass into the atmosphere according to the laws of diffusion which were but little known .... it was even found that muriatic acid did not act as a gas at all, but after uniting with water was, in reality, an acid mist which varied according to the hygrometric state of the air.[93]

It was this acid which caused the damage to the vegetation and affected health. According to the Alkali Inspectorate report,

> When the muriatic acid was allowed to escape into the atmosphere without any attempt at condensation, it would be traced to a great distance, and as it destroyed vegetation wherever it fell or wherever it was washed down by the rain, numberless complaints arose .... generally it is found impossible to overcome the repulsion to the smell and the inclination to cough.[94]

There was, however, a complete absence of information on the effect of such pollution on health, so that legislation enacted to control emissions could not be based on considerations of health. It was still possible to seriously suggest that working in a chemical firm may be beneficial to the health of the worker forcing Dr. Robert Angus Smith, the first Chief Inspector to the Alkali Inspectorate to assert,

> the fact of any substance being in certain cases remedial (i.e. recovery of appetite) is no proof of the absence of deleterious or unpleasant qualities[95]

The resulting legislation, then, which was the first to embody the concept of a maximum limit to the concentration of waste gas, a compromise between what was felt to be technically feasible, and what was 'fair' to a growing chemical industry.[96] The 1863 Alkali etc. Works Act required that manufacturers should 'ensure the condensation .... of not less than 95 per centum of the muriatic gas evolved therein,[97] and created inspectors to be located in an Alkali Inspectorate. The major importance of this set limit was the fact that its feasibility had been demonstrated for a number of years by a firm in the St. Helens district, as testified in an extract of a letter to Dr. Smith from a Mr. Shanks,

> At the end of 1888 was erected three sets of condensers in the St. Helens district, to Crosfield Bros. and Co. Clough and Morley, all which worked well and gave very satisfactory results .... so that I speak with confidence when I say that we have not done any material damage to areas during the last twenty four years.[98]

This technical approach to the problem was supported in the choice of chemists rather than medical officers for the post of Alkali inspectors,

as these people would need specialised knowledge of the science.[99] The appointment of Smith seems to have been a compromise. Although he trained as a chemist he had worked with Chadwick on the sanitation question[100] and retained the broadest interest on all question of the administration of the Act, technical, medical and toxicological. The lack of direct communication with the main medical community does seem to have hampered profitable developments in preventative medicine, and ensured that the question of environmental pollution stayed in the hands of the engineers and physical scientists.[101]

Smith did his best to keep abreast of developing scientific knowledge, and was well aware of the inadequacy of the 95% limit, and the difficulties inherent in showing harm to have occurred. In the Third Annual Report, he stated,

> These demands would require us to go beyond the idea of the five per cent, and to inquire into the nature of the gas that in any way leaves the premises in order to find if it is agreeable to plant and animals ....
> But the difficulties of the public and the manufacturer are seen still more in the uncertainty of the evidence .... it is needful to prove as is sometimes attempted that certain persons were ill or died on account of the gases.[102]

He did not, however, suggest how this evidence would be collected. Smith was careful to include in his reports information on long term studies which were undertaken on the effects of acid gas on vegetables.[103] He was becoming increasingly interested in the question of collecting evidence of the effect of small quantities of gas on general health, from the overall effects of the environment on health. This led him to undertake considerable research on which he termed a chemical climatology,[104] by which he meant an analysis of the constituents of polluted air, with rather grand aims, stated in the Sixth Annual Report,

> The intention was to establish a method by which we could judge definitely of the condition of a place as to the general health, from the result of a chemical experiment, without waiting for the evidence in the disease or death of human beings .... I have thus extended my work from that of the inspection of alkali works to the examination of air generally for sanitary purposes.[105]

This research led him to reflect on the environmental influences on human health, and as 'medicine, to be perfect would seem to demand universal knowledge', he suggested the introduction of more chemical investigations into the sanitary and meteorological departments.[106]

As far as the concept of chronic toxicity went, Smith seems to have been thinking along the right lines, 'I am merely trying to picture to myself as a chemist the possible effects .... to see that minute quantities of matter are sufficient to do much evil, even if it be difficult to conceive it'.[107] He also made use of the available techniques for measuring damage produced by continuous exposure. He showed some physiological effects of carbonic acids, in lowering the pulse rate and increasing the rapidity in breating, when it was present as an impurity in minute amounts, 'to be of practical value we must use a million for comparison'.[108] The way was fraught with difficulty, however, and, although his research showed very vivid effects of the noxious emissions on plants and animals there seems to have been no question of extrapolating these effects to humans unless other, more direct evidence could be found to incriminate the waste. Thus while he was 'able to believe in the slow dying of trees after several years exposure to air with impurities in it much smaller than what is usually called a trace',[109] he had to admit that 'the air of Manchester is breathed by thousands of people that are in good health, and a few years experiments on the individual tells us nothing'.[110] Epidemological studies could show no increase of the death rate in towns exposed to chemical manufacturers that was significantly greater than the average

death rate in the overcrowded slums of cities due to dirt, disease and poverty.[111] The most he could conclude from the small amount of evidence available was that there was definitely no evidence for the claim that the discharged effluent from chemical works was 'a protection against zymotic diseases or lung diseases, or capable of diminishing the death rate,[112] a particularly hopeful hypothesis forwarded by some manufacturers. Smith was not entirely convinced, however, as he recognised the weaknesses in collecting such epidemiological data. He was aware of the high acute toxicity of the chemicals being used, the injury these caused the workforce, and he felt that the effects of continued small exposures to the chemicals in Alkali works were masked by the fact that the chemical workers themselves were a very transient population, which meant that they were not getting a lifetime exposure to the chemicals in their job, nor did they live in the vicinity of the chemical works for long periods of time. Smith was cautious in interpreting data gained in this way, noting that there was 'decided harm to those much exposed to acid gases but uncertainty in cases of slight exposure'.[113]

It was these considerations which led him to suggest a revision of the Alkali Act to include a maximum concentration of sulphurous acid of 0.2 grain cubic foot and to broaden the scope of the act to include industries besides Alkali works. When his position was taken by Alfred Fletcher in 1884, the interest of the Alkali Inspectors in questions of health was abandoned in favour of a stricter technical interpretation of the law.

Being a scientist of a broad mind, Smith left no question without a possible explanation, the most interesting being his hypothesis on the mechanism of toxic injury,

> There is of course another mode of imagining how a very minute quantity may injure a plant or an animal.

> If the poison be collected at one particular spot of one particular organ it may do harm in minute quantities by delaying the function or structure or both of a small part of that organ; the diseased part will then communicate injury to the rest.[114]

Smith had obviously progressed a long way in thinking about the long term effects of exposure to small doses of chemicals known to be harmful. This was due to the particular nature of the task that he had to perform as Chief Alkali Inspector. For a number of reasons he was very isolated in this research. His lack of medical training while it ensured that his work did not reach this audience, also meant that he was at liberty to speculate in directions which were not in the mainstream of medical thinking. This latter point may explain the curious lack of interest of John Simon in the Medical Department in the work of the Alkali Inspectorate.[115] Had Smith gained recognition in this way, there was a lack of technical skills available to analyse the physiological data, and attempts at chemical analysis were the most profitable techniques that he could use.

Robert Smith had attempted to introduce wider scientific questions into the brief of the Alkali Inspectorate, but had little success in this area. The control of air pollution was defined in terms of technical standards in law, and this was not changed. When the question of restricting the sale of poisons was raised again, this also was defined in such a way that the uncertainties in scientific research did not affect the statutory considerations.

3.7. The Control of Poisons

After the passage of the Arsenic Act in 1851, attention turned to the qualification of the dispensers of the substances. The first Pharmacy Act was passed in 1852, and the Pharmaceutical Society took the

position that the qualification of Chemists and Druggists should be legally defined. The question of controlling other poisons besides arsenic was soon raised, with the problems both of defining which substances were poisons, and of deciding which of these should be restricted. A letter published in the Times asked,

> Is the law expected to render a definition of what constitutes a poison in general or to give a catalogue raisonne of the drugs which are to fall under this legal designation?[116]

The Pharmaceutical Society suggested one of two approaches could be chosen :

> If the sale of poisons is to be dealt with by law, then the law must either give a list of the poisons to which it applies, in which case it must be a law for regulating the sale of certain poisons, or it must give a definition of what a poison is, and leave it to the discretion of the retailer to decide what drugs fall under that category.[117]

A Sale of Poisons Bill was introduced in 1857, but it did not meet with the complete support of the profession as it made no distinction between qualified and unqualified chemists.[118] Their view was that such an Act would be unworkable, although it was subject to discussion in scientific journals and public newspapers. The Pharmaceutical Society stated that they;

> had always advocated judicious legislation on the sale of poisons and medicines generally, but maintained that, unless judicious, and in the right direction, legislation was likely to increase the evil by directing attention to the subject and also by removing the existing responsibility from the vendors of drugs.[119]

There was general criticism of the Bill that had been introduced into the House of Lords as it implied heavy fines for chemists while other trades would be exempt. It was also proposed that sales should be made

only to adults in the presence of a witness who knew the vendor and purchaser, and that all poisons should be coloured, although the Society countered that the substance would destroy such colouring.[120] They pointed out that the Bill would need considerable revising

> The morbid nervousness which prevails at the present time about the public safety leads its votaries into some rather strange inconsistencies. The true and legitimate object of the Poisons Bill is to protect the public in England against injury arising from crime and carelessness in the use of dangerous drugs. Patent medicines are excluded from the operation of the Bill yet many of these contain powerful and poisonous ingredients in a form very convenient for the criminal and liable to accident in the hands of careless persons.[121]

In addition, any medicine could be made liable for stamp duty, and thus be controlled under the Patent Medicine law,

> But this system we are informed must not be interfered with. A considerable amount of revenue is derived from the stamps and licences and in comparison with this paramount object the public health or safety is a secondary consideration.[122]

The lack of standard prescriptions, it was feared, would leave the Chemists and Druggists to worry about poisonous dose levels. The Pharmaceutical Society completely backed the premise that such substances could be controlled but through the education and professionalisation of the Chemists and Druggists.

> It appears from the tenor of information received that the public are fortunately ignorant of the nature and mode of employment of poisons in general as such, and the committee doubt very much the policy of extending this knowledge by the publication of a long schedule of poisons with various particulars of a suggestive nature in the accomplishment of his object: while on the other hand, the chief security of the public consists in the discretion and intelligence of the qualified vendor of poisons, who in self defence, as well as

> from higher motives is constrained to adopt precautions which no Act of Parliament could define so completely as to constitute a safeguard equal to the moral responsibility now existing.[123]

They objected to the establishment of a scheduled list of poisons which had been recommended both by the Board of Health and the medical practitioners, but favoured the idea that a board of examiners should be set up to examine pharmaceutical chemists and to issue licences. They considered that the attempts at legislation, passing through the House of Lords only betrayed ignorance of such matters,

> Their Lordships had probably never entered a laboratory; certainly they had never discharged the duties of assistants in a Chemists shop or they would not betray so much ignorance on what they were legislating.[124]

This opposition to the Bill by the Pharmaceutical Society resulted in its modification to setting up a board of examiners to create a new qualification - of the 'licenced druggist'. This again met opposition from the Pharmaceutical Society, as the board of six examiners was only to have one representative from pharmacy.[125] The Bill was eventually withdrawn. In 1858 an amended Sale of Poisons Bill was introduced with a schedule of poisons, which was also defeated in part at least, attributable to communications from the Pharmaceutical Society. The Bill was passed in the Lords, and opposition became more intent to ensure that it was defeated in Commons. It was withdrawn due to the objections of the chemists, although the government were keen to introduce a new Bill in the next session, as

> While the areas of poisoning by arsenic had so much decreased in number, deaths from other poisons had become considerably more frequent.[126]

In 1864 two Bills were promoted regarding the registration of Chemists and Druggists. The United Society of Chemists and Druggists wanted control over the sale of certain poisons while the Pharmaceutical

Society wanted to restrict the compilation of prescriptions to registered Chemists and Druggists. The House of Commons Select Committee suggested that the two should try and present a more united front on the question of poisons before a new Bill could be introduced.[127]

The amended Bill framed by the Pharmaceutical Society, included a poison clause, and was supported by the United Society of Chemists and Druggists. It was passed in 1863 with very little opposition, although there was some alarm from the medical profession that qualified chemists would feel able to start practising medicine. The Act required that all chemists must submit to registration, and the sale of poisons was restricted to qualified persons. The Pharmaceutical Society was in agreement with this, as they had,

> ever endeavoured to raise their status by enforcing a better qualification, to maintain it and by promoting that union among them which has now been accomplished after many years of anxious exertion.[128]

The Act contained a list of substances that were to be deemed poisons, but the Council of the Pharmaceutical Society could make a resolution for any substance to be added to the list and submit it to the Privy Council for approval, and then it would be advertised in the 'London and Edinburgh Gazettes', after which one month was given before it became a scheduled poison under the Act. Poisons were to be labelled with the name and address of the vendor, sales were to be entered on a register, and certain substances could only be sold to persons known to the seller. The Pharmaceutical Society was charged with the administration of the Act and the examination and registration of chemists.[129] There had been some pressure within the House of Commons for the role of the Privy Council, as a governmental department, to be extended over the role of the Pharmaceutical Society, who was thought to have only the welfare of small traders at heart. This was not a popular move, however, as the Pharmaceutical Journal noted,

> .... what is proposed is to get rid of the Pharmaceutical Society in this matter, and then to enact that another gentleman, the medical officer of the Privy Council, for that will be the effect of it, shall by his own ipse dixit declare what is a poison and what is not.[130]

The services of the Pharmaceutical Society were retained, as was the approach of compiling a negative list of substances,

> Some critics have chosen to call it absurd to select just thirteen poisons for legislation and leave vastly larger numbers unfettered. We would remind them that the object was to restrict those articles most commonly used for criminal purposes, and to impose as little inconvenience as might be on the trade.[131]

A number of problems were raised in carrying out the Act. Magistrates and Coroners were ignorant of the state of the law,[132] many shopkeepers were unaware of their duties under the Act and the Privy Council were reluctant to add every new substance suggested to this list. For example, the addition of acids was refused on the grounds that it would be injurious to the freedom of the trade by creating a monopoly, it would enhance prices, there was evidence that chemists or manufacturers did not want the extra inconvenience, there was a questionable public good as these substances were rarely used as poisons, and it would affect a large number of old established drysalters who had nothing to do with medicines.[133]

It was decided, eventually, that patent medicines should come within the law, and come within the provisions of the act. The Treasury backed this, and brought a prosecution over a proprietory medicine, chlorodene. By 1891 the objectives of the law had been met to some extent. Of 876 deaths by poisoning in that year 544 of these were accidental, and accounted for 3.25% of all deaths by accident. The largest proportion was from narcotic poisons, (114 or 21% of the total), 48 (9%) by carbolic acid and the mineral acid, 2 by oxalic acid, 8 by arsenic and 7 by chloral. 16% were found to be caused by articles not on the poison schedule.[134]

The problems of definition were still not overcome, however,

> The question as to the quantity of a poison by which a preparation becomes a poison within the meaning of the Act, is one difficult to decide. The terms of the Act are absolute, and do not take accounts of quantity or proportion. Strictly speaking therefore the presence of a statutory poison in infinitesimal amount would be legally sufficient to bring a preparation within the scope of the act.[135]

The rigidity of the system was that some poisonous substances were allowed to be sold unchecked because they were not on the list, while even dilute solutions of scheduled substances had to be labelled. Other problems had come to light as the position of Chemists and Druggists changed. In 1897 of the 13,000 on the register, less than 200 had passed the examination of the Privy Council, although by 1897 12,080 had passed out of a total of 15,215, but a number of limited companies had developed to trade as chemists as these fell outside the scope of the Act.[136]

Between 1868 and 1900 there were two attempts by the Government to pass amending legislation, but these were successfully opposed by the Pharmaceutical Society with the support of chemists. The philosophy of the Society to control the distribution of poisons was summed up in 1898,

> Any further amendment of the Pharmacy and Poison laws of the country should only be proceeded with by the Government after consulting those who are most deeply interested in the matter and in any case it should ever be borne in mind that the elucidation and proper qualification of the vendor cannot be improved upon as a means of protection for the public in connection with the sale and dispensing of poisons.[137]

The control of poisonous substances that evolved in the latter part of the nineteenth century, developed in a particular way due both to the

interests of a strong professional group, and the lack of well defined scientific understanding of the nature of poisons. The Pharmaceutical Society was concerned with improving the professional status of its members through examination and licencing, and in retaining control over the scheduling of poisons. They were successful in retaining the administration of the Poisons Act, due to the reluctance of the government to include any general scientific definition of poisonous substances, and the decision to take a pragmatic course of a list of restricted substances.

3.8. Conclusion

In this period many social problems arising, in general, from contact with deleterious substances became political questions. On the scientific side the different strands of toxicology related to these problems became more defined. Many basic sciences of biology and medicine developed rapidly, which, with the development of chemical analysis had an impact on the development of toxicology. The distinct origins of the study of cancer emerged at this stage, and some experiments on animals were done to explore both cancer and the possibility of chronic toxicity. The State, in a number of countries took steps in funding basic research, notably in the area of tumour production although this was a very small amount in comparison to the charitable fund which was established in Britain to support cancer research. The scientific community itself, through the BAAS, saw the funding of research on the relationship of chemical structure to physiological activity as worthwhile.

The medical profession were very divided over the possibility of chronic toxicity, as this was an attitude taken with the background of high general exposure to low doses of chemicals such as arsenic in the environment. This was illustrated by the lack of consensus found by the Lancet enquiry into the effects of repeated doses of food chemicals.

It is notable that their chosen correspondents were highly visible medical practitioners, while the actual attempts at experimentally determining the safety in animals of common chemicals found in food were not referred to. The lack of communication between the scientific community and the State was highlighted by the lack of debate in the medical press around the problems raised by Robert Angus Smith of the Alkali Inspectorate, which were, again, essentially based around the difficulties of recognising chronic toxicity.

In addition to the problems of recognising under what circumstances known poisons were dangerous, there was the problem of restricting the availability of poisons in their known poisonous form. The passage of the Pharmacy and Poisons Act is an example of a section of the scientific community acting as a pressure group on the policy making process. As guardians of expert knowledge the Pharmaceutical Society brought pressure to bear to ensure that the control of poisonous substances remained under the control of the retailers. The legislation that was passed avoided the problem of actually defining what constituted a poison, but by putting the onus on the Pharmaceutical Society for the administration of the Act and leaving the responsibility to the society for suggesting substances that should be added to the poisons schedule. This legislation intended only to control those substances that were known to be harmful to humans, and there was no attempt at trying to systematically test them or to predict the effects of other substances.

A number of social questions had been raised which required political action. The solutions to these problems, however, tended to minimise the interaction required with the scientific community, and to keep this informal. There were some Government appointed scientists, and the use of Select Committees to investigate problems with scientific content were not unknown. The questions that had been tackled by legislation

were very diverse, and an underlying theme was not articulated. Although many individual scientists were interested in questions related to toxicology, there was not an identifiable group with a coherent programme of research that could be called a research community in Britain.

CHAPTER FOUR

THE DEVELOPMENT OF ANIMAL TESTS (1910-1945)

The Development of Animal Tests

During the early years of the twentieth century there were some developments in scientific attitude towards toxicology. In Britian pioneering experiments were done on the experimental investigation of cancer. Demonstration of the production of tumours in animals were important in legitimating the use of animal experiments in assessing the potential hazard from a chemical substance. The evaluation of acute toxicity was put on a more systematic basis during this period and research was continuing for both new therapeutic substances and specific chemical antidotes to poisons. Research was also done on industrial poisoning, although this still focused on substances which were already known to be poisonous.

In the policy field, there was little new legislation, beyond the development of controls that had been passed in the previous century. The use of poison gas during the First World War prompted the government to establish a laboratory to investigate the question of developing poisonous substances for a specific cuase. By the outbreak of the Second World War there was enough concern about the use of novel chemicals to raise the problem of the need for anticipatory controls. This question was taken up by the Division of Pharmacology of the Food and Drug Administration (F.D.A.) in America, who developed a number of statistical animal tests.

Research started on other aspects of toxicity in this period, notably on the question of developing antidotes to specific poisonous substances, and the possible synergistic action that could occur when a mixture of toxic substances was fed to animals. This research developed during the thirties, and was successful when K.K. Chen working at the Lilly Research Laboratory introduced antidotes against cyanide poisoning. He found that methylene blue detoxified 2MLD's and amyl

nitrate by inhalation of 4 MLD's of sodium cyanide.'[1] He also showed that 'a more striking antidotal effect is exhibited when amyl or sodium nitrate is supplemented with sodium thiosulphate: The combination of the nitrate and thiosulphate does not only show synergistic action but surpasses the sum of their individual values'.[2] C.I. Bliss was also concerned with synergistic action, especially of insecticides, which he carried out at the Laboratory of Insect Toxicology of the Institute of Plant Protection in Leningrad. He classified joint action into three categories, independent action, similar action and synergistic action. However, he stressed that there is no standard interpretation of this type of toxicity although 'with the development of quantitative methods for the estimation of toxicity a study of the mode of action of poisons applied jointly has acquired new potentialities'.[3] Other work on toxic mechanisms which started during the 1930s included investigation of the acute and chronic effects of lead compounds by R.A. Kehoe, for therapeutic use in the treatment of malignant neoplasms, although little was known about the toxic effects of lead, 'it may not be assumed that particulate lead compounds, injected intravenously, act in the same manner as those which are absorbed through the alimentary tract and the respiratory membranes'.[4]

As the toxicity of chemicals was emerging as a research programme of interest, the therapeutic properties of chemical substances was also attracting scientific attention.

4.1. Pharmacology

Within the discipline of pharmacology, the major research effort was directed towards the search for specific cures. It was only slowly realised that the chemicals also demonstrated important toxic effects, and these needed to be examined. The synthetic dye industry was supplying many new chemicals on which to experiment. In 1913, Browning

a pupil of Ehrlich, discovered chemicals with antibacterial properties, which were used to dress wounds during the war. In 1920 two drugs for sleeping sickness were isolated. These discoveries were made in conjunction with the refining of experimental technique, such as the use of cell culture and the use of live bacteria in a test tube.[5] By the 1930s chemotherapy had become the cheapest and most important method of treating disease, taking over from immunisation in many cases. According to Dale,

> The use of all these specific antibacterial sera, however, was to feel an increasing rival from chemotherapy when in 1935 the extension of this type of treatment to bacterial infections began with the introduction of sulphanilamide and continued with that of its derivatives; and then before these had yet been fully exploited, came penicillin and the other antibiotics from 1940 onward.[6]

The study of toxicity was still useful for elucidating physiological mechanisms. In 1910 G.Barger and Henry Dale published a paper on the 'sympathomunetic amines' these were amino acid amides which they had isolated while investigating the toxic products resulting from the putrefaction of meat. More recently, the theory of neuromyal transmission emerged from a series of studies of toxicity.[7] Such physiological investigations could also be used to investigate the possible toxic effects of therapeutic compounds, particular for their effect on animals. In 1901 Dr. Noel Paton and Dr.Eason reported to the Edinburgh Medico-Chirurgical Society on their experiments of the influence of drugs on the liver of dogs. They used morphine, sulphonal, alcohol and coal gas and tested the urine for their effect on the building of nitrogen into urea.[8] Drug toxicity was not automatically accepted, however, and it took the actual experience of chronic poisoning of people by drugs before the necessity of pre-clinical testing was accepted.

H.H.Dale recognised the uncertainty involved in clinical observations of patients being treated with drugs. This had given rise to the

suggestion that emetine exerted a local effect on the alimentary canal, and he realised that 'it was evidently desirable, therefore, that the matter should be put to the test of experiment on healthy animals'.[9] He used a small number of cats and rabbits, with a dose, which was proportionally higher than that for human administration. After a fortnight the experiment was terminated in death, and analysis showed damage to the liver and kidneys, which led him to conclude that 'with all allowance for differences in dosage and conditions, I cannot believe that the results are without significance'.[10] The full impact of poisoning by drugs was realised during the First World War when there were a number of fatal cases in the army, of men being treated for syphilis with Salvarsan and mercury once weekly for eight weeks. Other patients showed signs of toxic jaundice.[11] This led to experiments on rabbits with a range of doses, for varying lengths of time, the results of which showed liver and kidney lesions similar to those in humans.[12] The Medical Research Council set up a Salvarsan committee to investigate the situation.[13]

There was no concentrated effort, during the period, to systematically investigate the toxicity of drugs, although the investigation of chemical substances for a therapeutic effect was followed, and seemed to be a successful research programme to follow. Despite this, there was some recognition of possible effects of drug toxicity and some research done on animals to investigate this.

4.2. Acute Toxicity

A statistical test to measure the acute toxicity of drugs was developed in 1927, which involved feeding large doses of a substance to rats. This was termed the lethal dose, or LD50 test and it still retains an important role in the investigation of toxicity. Investigation of the mechanisms by which a poisonous substance acted on an

organ were, at this time, being carried out by biochemists. The concept that was used to link the relationship between dose and death was the 'minimum lethal dose' (MLD), which was the amount of a substance needed to kill a test animal. The value not only differed between species, but also from animal to animal within the same species, which prevented it from being useful in predicting a safe handling dose for humans. These problems were resolved in 1927 when J.W.Trevan published his paper outlining the application of statistical analysis to the dose-response problem.[14] He showed that on a dose/mortality curve, the relationship between the percentage of animals killed and the increasing dose was a normal distribution curve. The same data could be plotted on a cumulative graph to give a characteristic sigmoid shape. Trevan suggested that the median of this curve - the dose which kills 50% of the test group - should be adopted as the standard measure of toxicity. He called this point the median lethal dose or LD50. In his paper Trevan noted that variations in the LD50 can occur between summer and winter measurements, and an error was introduced from using a limited number of test animals. Other factors which could alter the shape of the curve included using both sexes of test animal using a mixture of toxic materials, genetic factors, and environmental factors such as temperature and pressure.

Despite these drawbacks this concept became accepted as a basic measure of toxicity, being more universal than the system of special measures for different species.[15] The concept was refined during the next two decades, and a number of competing methods for accurately transposing the data to a straight-line graph were forwarded. C.I.Bliss working at Galton Laboratory, UCL, introduced a statistical graphical method using probits. On the scientific meaning of the concept, Bliss felt that,

> .... with intact animals the experimental technique is usually not suitable for determining the exact minimum lethal dose for each individual .... As the experiment is actually conducted, the dosage applied to each separate lot of organisms kills not only those requiring at least this quantity of poison but also all more susceptible individuals ....[16]

On the statistical nature of the concept, he noted,

> The fitting of a dosage and mortality curve to a series of experimental observations, however crude or refined the technique is an attempt to infer, from a limited number of individuals, the 'true' empirical relationship of dosage and mortality for a given toxic agent in an infinitely larger population from which they represent only a sample.[17]

This imprecise method was seen as being due to the stage of development of the science, however, 'in the present stage of toxicological research, no theoretical curve has yet been established, so that every standard curve has a finite rather than absolute accuracy'.[18] Each curve was seen to be dependent on uncontrollable factors, such as difference in strain of animals, and individual physiological differences of the animals.

Work published by a number of scientists - both biologists and statisticians - highlighted the fact that they especially worried about the fundamental assumption that toxicity always followed a normal distribution curve.[19] A simple graphical method for plotting the data on to a straight line graph was devised by J. Litchfield and F. Wilcoxon of the Stamford Research Laboratory, American Cyanamid Company in 1949, was absorbed into most general usage.[20]

Despite basic reservations from scientists on the scientific validity of this measure of toxicity, it soon became a popular method for estimating the degree of toxicity of new chemical compounds. It was commercial companies, that were particularly interested in obtaining a quick graphical method for recording the results of animal tests, for reading off the median lethal dose. The test itself became enshrined

in various test guidelines, which were recommended under different legislation. The development of this test was, essentially, using a statistical approach to animal experiments because little basic research on toxicity was being performed. It did, however, illustrate a development in scientific thinking about the estimation of lethal dosages. In particular scientists realised that collecting haphazard information about the dosages required to kill individual animals of different species was not useful information in estimating toxicity in humans. Various environmental and biological factors ensured each measurement would be variable, depending on the particular time and place that the experiment was carried out. This refinement in evaluation of acute toxicity was not immediately accompanied by research into testing chronic effects, that would be developed by a separate team of scientists working in America. During the early part of the twentieth century, however, various innovations in experimental techniques paved the way for the development of chronic toxicity tests, while rising standards of health ensured that such cumulative effects would become a problem of some concern.

4.3. Chronic Toxicity

Better understanding of the effects of small repeated doses of a foreign substance on living matter had to wait for improvements in chemical detection methods and in the understanding of how toxic effects produced in animals were related to toxicity in the human body. Occupational poisonings were the occasions where such effects could be studied directly in humans, and efforts were made to make direct measurements on the human body.

In the realm of public health, birth and death rates were decreasing and the infectious diseases were being brought increasingly under control. Throughout the first half of the century real wages increased, together

with an improvement in diet and health care, although this was accompanied by an increase in degenerative diseases.[21] Safe water, sewage disposal and paved streets had been achieved by 1900, and attitudes to poverty were changing.[22] As the worst extremes of the unhealthy environment were being improved, concern for the effect of long term toxicity in humans began to develop.

During the first decade of the twentieth century a number of scientific techniques were introduced which would become useful in the determination of chronic toxicity. Otto Folin developed blood analysis[23] while in 1907 Ross Harrison of John Hopkins University developed a new way of studying organic cells. He discovered that if fragments of living tissue were placed in suitable media and kept under certain conditions, the cells would multiply.[24] The sciences of biochemistry and nutrition were both starting to develop at this time. Spectroscopy had been used for accurately determining the value of small amounts of a particular chemical substance in organic tissue,[25] but there was still confusion about the potential hazard of such small quantities. There was evidence that 'tolerance towards all poisons increases with repeated small doses',[26] and that biological material had a capacity for increasing its immunity on exposure to small doses of a toxic material. The use of animals for experimentation was increasing rapidly, almost entirely consisting of experiments on mice. Of the experiments performed in 1914, one third (24,000) were carried out by government departments. They were mostly concerned with the preparation and testing of antitoxic serums and vaccines, and for the testing and standardisation of drugs.[27]

The development of these techniques occurred when there was a growing concern about the growing use of poisonous substances. The possibility of chronic poisoning by lead had become an environmental hazard to rival arsenic. It was found in paint, metal containers, in

water pipes, and in exhaust gases as it was deliberately added to petrol. In addition lead was used in the treatment of malignant neoplasm. A number of studies on chronic toxicity of lead on animals were set up to try and estimate the maximum safe dose. These were reviewed by Torald Sollmann of the Pharmaceutical Laboratory, School of Medicine of the Western Reserve, University of Cleveland, when he conducted studies of the chronic poisoning on Albino rats by lead carbonate.[28] He identified a major shift in thinking about long term damage, moving from the idea of the accumulation of a minimum concentration of the chemical in the body before damage occurs, to the accumulation of small injuries produced by single small doses, over time.[29] A few years later a full review of the effects of lead poisoning were published by Joseph Aub, a Harvard toxicologist.[30] This evidence was alerting medical opinion to the hazards of lead and the profession was becoming critical of the liberal use of lead and arsenic based pesticides - especially in America where the tolerance was much lower than the British standard. The farmers and fruit growers were, however, highly sceptical of these fears of toxicity, as they believed that the government had a selective programme to destroy agriculture in the West in favour of that in the East. They held that there was no evidence of human illness arising from pesticide sprays.[31]

During this period, then, interest in chronic toxicity was developing particularly in America, although concern was still directed towards substances which exhibited a known toxic effect. The studies that were conducted, however, utilised animal experiments as a legitimate technique. In addition this was a period when industrial poisoning developed as a research area of interest.

4.4. Occupational Toxicology

Although cases of occupational poisoning had long been recognised

it was not until the early years of the twentieth century that institutions were established with the specific intention of keeping this problem under review. Independent research was initiated on substances which had been problematic for a number of years. In 1911, F.G.Gothlin of Upsala University determined the amount of mercury necessary to obviate the onset of mercurialism as 0.4-1 mg. taken daily for some months.[32]

The development of the organic explosives industry during the First World War gave rise to previously unknown occupational diseases. In 1917 Alice Hamilton recognised toxic jaundice due to benzol exposure in munition workers, which was confirmed by T.M.Legge. H.G.Weiskolton produced leucopenia in animals by exposure to benzene vapour, and in 1910 J.B.Andrews verified that the fumes of white phosphorus gave rise to Phossy Jaw, necrosis of the jaw bone which attacked women in the match trade. This was eliminated by using red phosphorus as a substitute, (which was developed in France) and placing a tax on white phosphorus.[33]

The first conference on industrial safety was held in Washington in May 1925. It was organised by the American Chemical Society with the chemical section of the National Safety Council, so the emphasis was on engineering solutions to the problems of injury to health by industrial chemicals.[34] In 1925, Ethyl Gasoline Corporation described their experiments with tetraethyl lead on a variety of animals, which led them to the conclusion that it was not a highly poisonous substance and only careless handling by the workforce could lead to symptoms of poisoning.[35] Other experiments with lead, by Minot and Aub, had shown quantitatively the localised storage of lead in the bones, and the effect of diet on this in animals.[36]

In the United States, Alice Hamilton pioneered the development of Industrial Hygiene Units, but emphasis on poisoning was not important until the thirties with the establishment of the American Industrial

Hygiene Association (AIHA). Information about occupational poisoning was growing but there was little incentive for this knowledge to be applied in industry. There was some pressure from the American Medical Association and the American Public Health Association that the prevention of occupational disease should become a function of the Public Health Department (which eventually formed the division of Industrial Hygiene). In 1937 the American Conference of Government Industrial Hygienists (ACGIH) was formed. This association was instrumental in collecting and publishing the available toxicity data on industrial toxins, and it published annual estimates of safe exposures to a number of common industrial chemicals. These were known as Threshold Limit Values (TLV) and were based on information collected by the Public Health Service.[37]

While these improvements were being directed towards well established industries, the outbreak of war hastened the development of a completely new industry, the nuclear industry, with its associated hazards. Paradoxically, there was a very high standard of occupational health here, due to the need to contain radioactive materials and to prevent workers developing strange illnesses. This view is held by Warren,

> The first large-scale employment of dust and fume chambers and large scale mass-testing experiments on animals for the developing of standards for industrial practice was probably initiated by the Manhatten Engineering District during World War II. It was imperative that safe operating levels be established for personnel in the plant producing atomic bomb materials of all sorts, so that plant could be built accordingly. It is interesting now to realise that, while the safety of the worker was a factor, it was not the overriding one; the prime element was security.[38]

These developments in scientific attitude towards industrial health took place in America, despite the pioneering research done by T.M.Legge in Britain in the early years of the century. The TLVs constructed by the ACGIH became the basis for the quantification of legislative control

on industrial poisons. These values are used by Britain and other European countries, although they were not based on systematic scientific evaluation. The high standards in the nuclear industry, in part at least, illustrated the concern with raising the standard of health at work. There was also, during this period, more interest in attempting to predict the carcinogenic potential of common substances used in industry.

4.5. Experiments on Cancer

Occupational cancers had been recognised for a long time, but it was not until the first thirty years of the twentieth century that a body of research began to develop about the causation of cancer. The research used experimentation on animals as a basic technique, a trend that was not without its critics. In 1919 the Society for the Prevention and Relief of Cancer published a pamphlet on cancer research and vivisection, in which it was held that animal experiments on cancer were a futile waste of money and had no bearing on the subject of human cancer. They wanted the provision of hospitals for cancer patients, an epidemological study of cancer patients and legitimate experiments, although they gave no indication of how these should be conducted.[39]

By 1915, a new direction in cancer research started, when two Japanese researchers, Yamagiwa and Ichikawa produced cancer on rabbits ears by painting them with tar. This opened up the possibility of predicting the hazard of cancer before it occurred. Knowledge up to this time had depended on the accumulation of observations of individual clinicians and pathologists, who noticed a high incidence of cancer among people with the same trade.[40] Thus, most of the knowledge of cancer originated in the most highly industrialised nations, Britain and Germany, and many foreign students came to Britain to study the question at this time, so it could be said 'the English school of cancer research commands

world wide confidence'.[41] The work of the ICRF had promoted the use of animals in research, especially in cattle and mice, and had suggested the benefit of using mice as an experimental animal for the investigation of human cancer. The long latency period and the localised production of tumours seemed to parallel the production of tumours in humans.[42] The ICRF had also discredited the parasite theory by producing tumours experimentally and G. Marshall Findley had discovered the possibility of producing cancer by painting mouse skin with tar in one application.[43]

During the nineteen twenties E.L.Kennaway, Chief Pathologist at the Cancer Hospital Research Institute, conducted a series of experiments on the production of cancer by tar preparations. These were supplied by the Gas Light and Coke Company, after a series of deaths from lung cancer in men who had been manufacturing gas from coal.[44] These preparations had the property of needing to be heated to 900° before becoming carcinogenic.[45] With the revival of interest in preservatives in food, at least one person ventured the suggestion that the increase of death by cancer could be linked to the increased use of antiseptics in food.[46] It was this concern for cancer as an occupational disease that was the motivation behind the development of research into its causation, although few occupational carcinogens have been predicted by laboratory experiments. In 1922 Leitch and Kennaway produced skin cancer by painting arsenic onto the skin of rats and mice, although they failed to discover cancer induced by oral administration.[47] By 1930 however, most of the cancers which had been attributed to arsenic had been demonstrated to be induced by some other agent. Miners were shown to be affected by tar and soot and aniline workers by coal tar derivatives. There were no observations of cancer in the makers and users of arsenical insecticides. One occupation shown to be susceptible to arsenical cancer was sheep dip workers who had a high incidence of skin and lung cancer.[48] In 1930 the

Ministry of Health circulated a memorandum on cancer as a subject for the attention of Local Authorities calling for the provision of adequate care facilities and the promotion of research.[49] Of the occupational cancers, benzene had been shown to cause leukaemia in 1928, radium was accepted as a cause of cancer in the 1940s, from experience of miners in Germany, and painters of luminous watch dials. During the thirties experimentalists began to use pure strains of rats and mice and research on the effects of co-carcinogenesis began with experiments by Deelman in 1923.[50]

The association between the development of cancer and exposure to small doses of certain chemical substances was well recognised before the outbreak of the Second World War. Convincing experiments had been carried out in animals to demonstrate that this was true, and a distinct community of scientists was developing who were interested in this problem. The wider question of public health, was not raised, however, and there was no suggestion that such hazardous materials could be monitored and controlled before they became a social problem. In the case of cancer, scientific interest and concern was not transferred into the public sphere as a policy problem at this time.

A more sinister development was that of chemical warfare which appeared during the First World War, and arose from research deliberately searching for rapidly poisonous materials.

4.6. Poison Gas

After the outbreak of war in 1914, deficiencies in the state of the British chemical industry soon became apparent. There had been little development in the organic chemical based industries. In fact, Britain had been relying heavily on imports from Germany in this area, and it was clear, according to Rose and Rose,

> ... what Britain had not got was a chemical, dyestuffs, explosives, metals or glass industry which could provide the weapons and uniforms to support the prodigious outpourings of blood the next few years were to see.[51]

To the superiority of the German chemical industry could be added their superiority in basic research, which has fostered the development of both pharmacology and toxicology as chemistry related sciences. Chlorine was the original toxic gas to be produced as a chemical weapon, and this was first used on 22nd April 1915. The effects were devastating to the allies until gauze filters were issued as protection. By June, phosgene and diphosgene had been introduced, contained in gas shells rather than being dispersed as waves. The final and most sophisticated onslaught was the development of mustard gas (dichlorodiethy [sulphide]) used in July 1917 at Ypres. This was the first use of a complex organic molecule, which attacked the skin and mucous membranes. The only response to this was to encase the whole body in protective clothing.[52]

The British response to this threat was to establish the Chemical Defense Research Establishment (CDRE) at Porton Down. It became a centre for research into chemical and biological weapons, but was also concerned with developing protective clothing and antidotes to poisoning. The CDRE was set up in 1916 to study the biological action of noxious chemicals after the German gas offensive of 1915. Experimental toxicology did not begin before 1917, 'but from then on CDRE was involved in toxicity assessment, mode of action and therapy for a very wide variety of toxic agents.'[53] This was the first institution established in Britain concerned with research on toxic agents.

The post war response to these attacks set the investigation of toxic mechanisms on a new path which utilised the most modern knowledge of biochemistry. Initially, poisons containing arsenic became the subject of interest. Work done between 1923 and 1926 by E.Walker demon-

strated that arsenicals abolish the -SH group in muscle tissue, and he suggested that chemical reaction was taking place. At the same time Voegtlin working in the U.S.Public Health department suggested arsenic reacted with certain compounds present in the protoplasm (using Ehrlich 'chemical receptor' hypothesis for drugs). He also suggested the -SH group as a specific receptor. This work prompted R.A.Peters, at Oxford, to investigate sodium arsenite as a selective enzyme inhibitor in 1936.[54]

This early work was conducted in the department of biochemistry. After the Munich crisis in 1938, the Ministry of Supply was interested in having a research programme to investigate the effect of war gases on enzymes. This idea was revived in 1939, due to the existence of Government funding, and so, 'early in 1940 a research team under the direction of Dr. M. Dixon was formed to work in this laboratory for the Chemical Defense Research Department of the Ministry of Supply'.[55] This was formed with the idea that there could be a biochemical explanation of toxicity; as Dixon and Needham reported,

> For some time past the belief has been growing that many, if not most, poisons act by attacking one or more of the essential intracellular enzymes, thus producing what Peters has termed a 'biochemical lesion', the actual damage observed as a consequence of the resulting metabolic disturbances.[56]

This group concentrated on mustard gas, while Peters continued his research on an antidote for arsenical poisoning. Expanding on the work already done on arsenic, he experimented with dithiol compounds which proved successful. All information on the research was presented in a series of confidential reports to the Ministry of Supply, the antidote being called OX217 for security reasons, and later termed British Anti Lewisite (BAL) by the Americans. The work also supported the biochemical theory of toxic action, and that a biochemical lesion in a tissue formed by the partial blocking (as by the partial deficiency) of an enzyme

can cause pathological damage is strongly supported; the poison produces an effect on enzyme deficiency.[57] It appears that the work done by the group under Dixon included some preliminary work on the inhibition of chlorine esterase by an organophosphorus compound (alkyl fluorophosphate).[58]

Research on poison gas was initiated in Britain as a response to its use during the First World War, which resulted in the establishment of a laboratory, concerned with toxicological research. During the interwar period, the action of these toxic gases received attention from academically based biochemists, and the outbreak of the Second World War brought these scientists into the service of the government in search of antidotes to these poisons. These were not required during the war, but the CDRE has remained the centre for chemical warfare research in Britain, and scientists who were working there during this time were to become important in post war British toxicology.

4.7. Legislative Reform in Britain

The legislative sphere was fairly quiet during this period, until the 1930s. A number of attempts were made, however, to review the poisons legislation. In 1901 the Duke of Devonshire, president of the Privy Council set up a departmental committee, the 'Poison Schedule' Committee to review alterations that were needed to the 1868 Act. In particular the schedule of dangerous poisons was to be considered and extended to include preparations such as clinical medicines, weedkiller, disinfectants and insecticides.[59] The Committee recommended that the Poison Schedule should be expanded, but opposition from agricultural interests, both farmers and manufacturers of insecticide and weedkillers was attempting to convince the government that the poison law should be relaxed. The Pharmaceutical Society opposed this possibility.[60] In 1906 Pharmacy and Poisons Bill was introduced into the House of Lords by the Lord President of the Council, but it was not completed in that

session. Another was introduced in 1907, which was passed the following year. The Pharmaceutical Society gave the revision a mixed reception, as,

> The list of poisons is made more definite and more rational; and the Pharmaceutical Society, subject to the approval of the Privy Council, receives for the first time power to remove any anomalies or uncertainties which the future might reveal,[61]

but it was not received totally without criticism; as some schedules had been relaxed,

> the relaxation of existing restrictions upon the sale of poisons used for agricultural and horticultural purposes will prove to be but the insertion of the thin edge of a wedge, the driving home of which cannot fail to prove an unqualified public disaster.[62]

Other problems were coming to light, especially with the development of synthetic chemicals, as the philosophy of control was built on the premise that clear evidence of fatal accidents was needed before the toxicity of a material was established. Again, the Pharmaceutical Journal commented,

> It is truly anomalous that whilst all poisons and vegetable alkaloids are scheduled poisons, substitutes for them, which are akin in therapeutic effect, and often equal or even greater basic power, are not scheduled, because their chemical relationship, if any, is distant.[63]

In 1926, the Privy Council set up another departmental committee to consider modifications to the Pharmacy and Poisons Bill, to investigate modifications to the schedule of poisons and to review the system of making and enforcing regulations.[64] In 1931 both the Pharmaceutical Society and the committee compiled a draft Bill. The committee had not considered the question of medicinal preparations. The Pharmaceutical Society favoured a system whereby all Pharmaceutical Chemists became members of the society and thus planned control on dispensing poisons, as an alternative to government control, although, 'Some may regard this direct state control as sooner or later inevitable and not in itself

necessarily an evil'.[65] The Committee made proposals for the creation of a Poisons Board, which was accepted by the Society as having the distinction of being free from bias and allegation that had been facing the Society. It would be an advisory committee with such the Home Secretary would be very unlikely to reject their advice.[66] There was at least one suggestion that it was new drugs which presented a problem and some form of pre-market testing was desirable although this was not embodied in legislation. The editor of the Pharmaceutical Journal reported that,

> ...I should like to see all new preparations subjected to the most rigorous tests of two types prior to their production; one group of tests to be made from a pharmacological standpoint, both laboratory and clinical and a second from the toxicological standpoint. [67]

A consolidating Act was passed in 1933, which established a Poisons Board with the ability to schedule new poisons from most types of use, although medicinal preparations were still seen as separate. It was seen as desirable that all medicines containing poisons should be sold only by pharmaceutical chemists, but this would only come about by an extension to the poison schedule.[68] A number of new organic drugs were being developed and the committee were to advise on the addition of these to the poisons list.[69] A number of other chemicals were controlled under the Act, including substances used in cosmetics, and general household chemicals.[70]

The 1933 Pharmacy and Poisons Act remained the basic legislation covering the availability of acute poisons until it was reviewed in 1972. The major reform had been the establishment of a standing scientific advisory committee, under the Home Office, wresting the power for scheduling new poisons away from the Pharmaceutical Society, which was seen as a partisan body. This foreshadowed developments that would become commonplace after the War.

Another area for legislative reform during this period was the Food and Drugs Legislation. It was during the early years of the present century that the problems of gross adulteration declined while that of the purposeful addition of chemicals to food was recognised. The Departmental Committee Report published might had recommended the establishment of a permanent body to review the use of colours and preservative materials in food.[71] It was not, however, until 1923 when pressure from the local authorities for effective control over chemicals in food, encouraged Neville Chamberlain as Minister of Health, to appoint a Committee on the Use of Preservatives and Colouring Matters in Food.[72] The committee recommended that preservatives should be prohibited in food and drink except in certain prescribed cases, subject to upper limits, and a schedule should be drawn up for the use of colouring matters in food. The 1925 Public Health (Preservatives, etc. in Food) Regulations, however, only banned the most grossly poisonous colours and preservatives from food. As there was still much controversy over the safety or otherwise of common food colours and preservatives, no more than this could be achieved. To illustrate this point, there was still controversy over the harmfulness of boron, such that some of the most prominent scientists gave evidence to the committee that they were not convinced that it presented a hazard.[74]

A new Departmental Committee was appointed in 1931, whose terms of reference in 1933 were directed towards examining whether new Food and Drug legislation was required. They reported in 1934, and new consolidating legislation was drawn up, passed as the Food and Drugs Act 1938. It specifically prohibited the addition of chemicals to food that were known to be 'injurious', although it did not cover substances about which there was no scientific knowledge. The Minister of Health would be able to make regulations prohibiting the addition of any substance to food.[75]

Legislative changes in Britain during this period, however, had still not come to terms with the scientific uncertainties inherent in assessing the safety of chemicals in common use. Responsibility for this assessment has still not been adequately defined, as research was progressing in an unco-ordinated manner on a number of fronts. Major advance did take place on the question of assessing chemicals for potential hazards, but these developments were taking place in the United States, rather than in Britain.

4.8. The Division of Pharmacology and the Development of Animal Tests

The major shift in orientation during this period was the change from considering chemical substances to the poisons if they were known to have a lethal effect, to the idea that poisonous effects could be predicted experimentally. This work was specifically developed by the U.S. Food and Drug Administration (F.D.A.) over a number of years. The particular tests on animals that they developed, ensured that, after the war, the F.D.A. became the centre for toxicological testing methods, something all potential policy makers would have to take into consideration.

There had been concern in America over the existence of toxic residues from common lead and arsenic based pesticides. The first incidence of seizure under the U.S. Food and Drug Act 1906 was in 1924, of a cargo of New Jersey apples which contained a high residue of arsenic. This led the Secretary of Agriculture, William Jardine to set up an expert committee to advise him on tolerances of residues in food. The Hunt Committee held one meeting only in January 1927 where they debated the effect of arsenic and lead in food. Their recommendations were that twice the world tolerance (0.021 grain/lb) was acceptable,[76] Whorton states,

> For centuries, exposure to lead compounds had been linked to the development of chronic complaints such as constipation, colic pallor and nervous disturbances including paralysis. Epidemics of lead poisoning, furthermore, were

> known to have resulted from consumption of lead contaminated foods, so one might expect the application of a salt of lead to fruits and vegetables to excite a certain amount of alarm. But as with arsenic it was agricultural rather than medical scientists who evaluated the hazard of lead residues and their concern was for acute rather than chronic intoxication.[77]

In 1935 the F.D.A. (formerly the Division of Chemistry) working under the Pure Foods Act began to assemble a number of young, biomedical scientists to form a new technical division - the Division of Pharmacology. The first director was G.G.Nelson, a pharmacologist by training, who had a two year sabbatical from the University of Michigan. The deputy director was H.O.Calvery, who replaced Nelson when he returned to the University. Calvery had a part doctoral degree in organic chemistry and had spent two years researching in European biochemical laboratories. The charter of the Division of Pharmacology included a number of directives related both to toxicology and the improvement of assessment techniques. These included the routine assay of drugs, and the development of techniques to improve such a bioassay. To conduct investigations related to the adverse action of drugs (particularly prompted by the 'Elixir of Sulphanilamide' tragedy) and other chemicals,[78] and to establish safe levels of food additives necessary for the production, preservation, storage and transportation.[79]

The main function of the Division was to build a unit to determine the safety of chemicals in food. The first undertaking was to study the safety and toxicity of agricultural chemicals which were contaminents of food, particularly materials such as lead and arsenic. This work started in 1935, although there were no established techniques that could be used.[80] Experiments were set up on groups of animals exposed to different, long term doses of the pesticides which were examined for physiological and pathological signs of change, in order to obtain ideas on what long term changes could take place at a sub-clinical level. Food consumption,

growth, activity, appearance, long levity, studies of organs and tissues, intake, storage, consumption and excretion were measured.[81] An advisory committee to the National Academy of Sciences was established to help the interpretation of the tests, which included Anton Colson, ex-director of the Bureau of Chemistry, and Torald Sollmann.[82] It soon transpired that the common agricultural chemicals were toxic to animals, but pressure from fruit farmers who used compounds of lead arsenic and fluoride on their trees ensured that the tests were ended.

They also made certain that the 1938 Food Drugs and Cosmetics Act prevented money being spent on testing these materials. All animals under chronic testing had to be killed, and the studies terminated.[83] Extra money was given to the Department of Public Health to carry out studies of people who were most directly in contact with the metals in the environment, and they carried out an epidemiological study on fruit growers using arsenic pesticides, with a ten day laboratory study on two people. They concluded that they had detected no adverse effects on health.[84]

The Division of Pharmacology however, was able to continue with the work of developing animal tests for assessing acute and chronic toxicity of substances that might contaminate the food supply, and could also be used for assessing the safety of new drug products. The first industrial laboratory was established by du Pont in 1935, but other laboratories soon followed, especially at Dow, Union Carbide, Eastman Kodak, Winthrop-Sterling, Merck and Eli Lily, and in many cases the Division of Pharmacology was consulted for advice on toxicological testing.[85]

No one however, predicted the extent to which the chemical industry would expand after World War II. A paper by Woodard and Calvery was published in 1943,[86] following a number of requests after it had been presented to the American Public Health Association meeting in 1941.[87] This was based on a number of animal studies that had been done by the

Division. The first comprehensive guide was published in 1949. There were novel concepts in toxicology developed by the Division of Pharmacology, such as acute, sub-acute, and chronic toxicity. These emerged both from in-house laboratory case studies and from informal consultation with industry, and were aided by the F.D.A. statisticians.[88] These new concepts and the test guidelines which had been developed were readily accepted by the government, industrial and academic scientists, who soon adopted them in developing their own test programmes.[89] Industrial companies co-operated with the suggested tests, as costs were quite low at the time. This also meant that university professors were willing to do animal tests for small grants, as only a few industrial companies had their own laboratories.[90] The F.D.A. was working to a budget which ensured that the requirements for tests were as minimal as possible, while suggesting methods that would yield the best evidence of safety that could be gained from contemporary knowledge of toxicology. The budgetary restraints were placed on the F.D.A. by Congress which prevented any basic research being done,[91] and this limitation of funds and personnel directed consideration towards applied science. This was relevant to the function of the Division of Pharmacology in implementing government regulations. Their aim was to test all chemicals to the best standards that could be developed, and to change standards as better methods, new knowledge was developed.[92]

The presence of recognised skilled personnel in the Division of Pharmacology ensured that they would be drawn into Wartime requirements. The F.D.A. volunteered the use of its laboratories in ways that were thought to be most useful to the war effort. Much of the work centred around the needs of the military and the use of substitute materials for those supplies cut off by the war, for example essential synthetic rubber, artificial sweetners, new antimalarials, insect repellants and new pesticides. These efforts were under the overall allocation of the National Research Council and the War Production Board. By this time

the new expertise in toxicology had already been established and was recognised by other agencies of the Government.[93]

Toxicological guidelines were requested by investigations in industry academia and elsewhere in government, and were published to fulfil these requests. They served as a basis for budgetary estimates, insurance, legal opinion and biomedical scientists not particularly well versed in toxicology.[94] Almost all scientists in industry approached the Division of Pharmacology before they undertook a toxicology study for approval on the methods used. These 'guidelines' were also useful to the international industry who wished to market products in the U.S., and they also helped other countries in developing legislation of their own.[95] Although industry realised that such a programme was cost effective, and saved a number of lawsuits for damages that would otherwise have occurred,[96] there was some criticism of the cost of a chronic study that involved many animals over a number of years. Because the F.D.A. wanted an assessment of chemical safety independent of industry, they undertook some testing, particularly with food colouring.[97]

4.9. The Evolution of Test Guidelines

The guidelines themselves covered the range of tests that were to be accepted in the post war period, and so were the result of the most comprehensive utilization of the available knowledge, reviewed in an atmosphere of open, scientific discussion. Dr. Woodard recalled,

> In my years with F.D.A. (1936-1957) there was free and open discussions at scientific meetings, informed conferences at F.D.A., participation in seminars, lectures and national meetings in which experiences, concepts etc. were shared.[98]

During the war it became obvious that some control was needed over the increasing numbers of synthetic materials which were being incorporated in foodstuffs, and resulting in the exposure of much of the population to the possibility of poisoning. By 1943, the obvious solution which

presented itself was, for public health officials to evaluate all specific and related information so as to determine the quantitative amounts which may be detrimental to the public health, and if necessary, establish tolerances and regulations.[99] This was the logical expression of the type of approach that the F.D.A. had been cultivating over the question of pesticide residue. Biological tolerances were backed up by accepted toxicological data and were also a useful compromise between conflicting interests, and the sensitivity of the detection techniques available.

The question was, how to evaluate each chemical so that a tolerance could be established. It seemed to be easy enough for the older chemicals for which there was already a large body of knowledge, but for new chemicals a toxicological investigation had to be planned which would give data that could be evaluated in a meaningful way. The first suggested procedure was for a general plan which could be adapted for the chemical under consideration;

A. Pharmacodynamics

Blood Pressure; respiration, heart rate; organ perfusion; isolated toxine preparations etc.

B. Acute toxicity

Dosage response curves on three or more species; objective symptoms; statistical calculations for comparative studies; simultaneous comparative determinations of other substances

C. Subacute toxicity

Large daily doses to one or more species for six to 12 weeks; microscopic pathology

D. Chronic toxicity

Three or more species; at least one species for life of the animal; several dosage levels graduated

to produce from no effect up to marked lesions, and possibly shortening life span; microscopic pathology

E. External effects

Sensitization; skin irritation; mucous membrane irritation

F. Special studies

Reproduction; Haematology; absorption and excretion; distribution and storage; effect of diet.[100]

The rationale behind the pharmacodynamic study was to give preliminary data for further work - the species suggested were dogs, rabbits and cats. For the determination of acute toxicity the rat, mouse and guinea pig were suggested as best suited, but rabbits and cats were also used. In the determination of subacute toxicity large quantities of test material were given to one or two species (preferably including rats), this sort of test was found to yield 'a great deal to information in a relatively short period of time. It also serves as a guide in the design of chronic experiments'.[101] Dogs, monkeys and guinea pigs were also suggested for use. The animal would be sacrificed and both gross and microscopic pathology observed.

The chronic test should be conducted on at least three species, for the lifetime of one of them. The species suggested for testing were rats, dogs, mice and monkeys, and as rats have a relatively short life a were well standardised, they were suggested as best suited for a life time study. Life time studies were justified by the experiments on liver tumour by Yoshida and by studies of the F.D.A. on glycols.[102]

It was suggested that special studies were important as it was here that 'one may often find the clue to the preventative measures which can be taken to avoid some of the results of the toxic actions of a particular substance'.[103] Reproduction studies should give information

on fertility, lactation, size of litters and mortality of the young.

As far as the interpretation of the tests went, the limitations that were recognised were concerned with the variation between species and the variation between individuals. Of the former, two different responses were identified, the response of different species to a single substance and the differences in response to different substances that is differences in absorption, metabolism, detoxification and excretion.[104]

Variation between members of the same species were identified as being due to a number of characteristics:

1. Normal distribution and heterogeneity of the population
2. Physiological condition:
   (a) Age, sex, weight
   (b) External environment
   (c) State of physical exertion
   (d) Pregnancy and lactation
   (e) Presence of food in gastrointestinal tract
3. Pathological Condition:
   (a) Renal, cardiac, and hepatic insufficiency etc.
   (b) Presence of infectious organisms
   (c) Nutritional deficiencies
4. Multiple exposures.[105]

These differences had been illustrated by laboratory experiments on animals, and led to the assertion that the test estimate of safety would arise from studies of the effect of the substance under investigation on more than one species,

> If careful toxicological experiments have been done on several species, and especially if comparative studies with known poisons have been carried out, a simple correlation should point the way for estimating the probable level tolerated by man. Direct translation from lower animals to man in terms of milligrams per kilogram of body weight is rarely possible and sometimes ludicrous.[106]

As far as the explanation for the differences in response between species

went, it was thought to be due to differences in physiology,

> Species differences are undoubtedly a reflection of differences in physiology. The ratio of body weight to surface area, relative size of organs, vital capacity, etc., vary from species to species. In the metabolic processes and detoxification mechanisms there are likewise recognised differences.[107]

Differences between individuals had been shown to follow a normal distribution from the construction of the dose response curve, and it was recognised that extrapolation from animal data to human exposure should take account of that. Other factors shown to have an effect on response were age, sex and weight, environmental temperature, physical exercise, state of nutrition and the health of the individual concerned.[108] The final toxicological possibility that was recognised was the potential action of more than one poisonous substance acting on the human body,

> In studying a toxic agent, one is likely to be considering only his own particular problem. However he should not forget that the public is exposed to other poisons every day. There is the possibility that some of these poisons may have an additive or summation effect. Therefore it becomes necessary to consider all possible sources of poisoning at the same time, in order to come to a judicious conclusion.[109]

The justification for this detailed plan of testing was that exposure to toxic substances was becoming an inevitable consequence of modern civilization and because of this it was necessary to obtain the best estimate of the level of tolerance of the chemicals involved.[110]

The role that the F.D.A. had assumed - that of protector of consumer interest was highlighted during the war. The scope of the 1938 Food Drugs and Cosmetics Act was extended during the war to prevent the free movement of contaminated food. The F.D.A. also faced the problem of replacing those of their 1200 personnel that were called for military duty. They had chemists at laboratories in sixteen stations to perform

chemical analysis, but the development of methods of analysis took place in Washington.[111] The Division of Pharmacology was entrusted with three main responsibilities; the control of drugs whose potency had to be determined by bioassay, the pharmacological examination of possible deleterious components of food, drugs and cosmetics, with particular regard to the acute, subacute and chronic toxicities, and finally the general improvement and development of pharmacological techniques for undertaking these functions.[112]

The problems of Food and Drug surveillance were increased during the emergency period by such factors as increased production development of new products and substitutes, transportation and storage problems, which 'results in spoilage, substitute foods, new solvents, and pressure for permission to use preservatives of all kinds'.[113] The Division of Pharmacology was reported to have spent 70-90% of its time on wartime problems between 1942-1944, and it was because of this that the general outline for dealing with toxic substances was constructed.[114] It was also noted that very few other laboratories had undertaken long term chronic toxicity tests. The Division was obliged to develop standard techniques for chemicals applied to the skin, as they were required to evaluate the dermal toxicity of some organic compounds.[115]

Ultimately, it was the special problems of wartime conditions which crystallised the specific issues involved in protecting public health against the possibility of exposure to biologically active chemicals, which were located within the F.D.A. due to the concentration there of trained scientific specialists. This resulted in the development of a number of principles relevant to the progress of toxicology, which were summed up as:

(1) Confirmation of our opinion that chronic toxicity studies should be extended throughout the life time of animals of at least one species

(2) Confirmation that our opinion that acute toxicity studies yield valuable information for comparison

(3) Discovery that subacute toxicity studies yield far more information than acute studies

(4) Development of techniques for studies of acute systemic toxicity by skin absorption

(5) Development of techniques for studies of subacute systemic toxicity by skin absorption

(6) Development of numerical scoring systems for eye, skin and mucous membrane irritations

(7) Development of a procedure for predicting the healing time of certain types of skin lesions after therapeutic treatment

(8) Development of techniques for determining the relative state of absorption after the application to the skin of ointments containing therapeutic agents. In the case of calomel it was found that the mercury concentration of the kidney and liver was a better criterion than analysis of blood and excreta

(9) Establishment of the advantage of modification of the diet; for example, many animals respond quite differently to certain toxic substances, depending on whether they are on high or low protein diets, high or low fat diets.

(10) Establishment of the fact that when two drugs are simultaneously administered one can alter the influence of the other

(11) Finding that there are a few if any substances which are not absorbed through the skin, even though the idea is prevalent that the skin is a relatively effective barrier to its environment.[116]

The Division of Pharmacology had made advances on many aspects of toxicological research, and had begun to consider some of the differences in testing which would be required by different classes of potentially toxic chemical. In 1944 the Council of Pharmacy and Chemistry of the American Medical Association published a report which was to serve as a guideline for investigations into the toxicity of new drugs.[117] The report was written by three members of the F.D.A - Walton van Winkle,

Robert Herwick and Herbert Calvery, with Austin Smith, secretary of the Council of Pharmacy and Chemistry. The guidelines were seen as necessary as the F.D.A. was concerned with obtaining evidence of the safety of new drugs when enforcing the Food Drug and Cosmetic Act. The concern of the Council was in rationalising the evidence needed to support the claims of the safety of new drugs. Thus the need for a universal standard by which new preparations could be evaluated.[118] A detailed survey of the nature of a pharmacological agent was suggested, while the approach to the study of the toxicity of the substance the recommendations of the F.D.A. were accepted, without alterations.[119] The evaluation of drugs, however, depended to a great extent on the evaluation of its benefit over the risk of unpleasant side effects which included quite extensive clinical trials on humans to verify that both the safety and efficacy of the drug was not species specific. As for chemicals in food the criterion was that they be biologically inactive, as it was acknowledged that 'when a chemical is added to foods, its ingestion literally is forced upon the individual'[120] In constructing guidelines for evaluating the safety of food chemicals it was recognised that they had no nutritional value, and were added for purely technological reasons. The accidental or unavoidable addition of chemicals from pesticide residues, manufacturing and packaging were also included. Thus food chemicals essentially differed from drugs, and required a different approach to safety,

> Under these circumstances, the approach to the appraisal of its safety of use is somewhat different from that of a drug. More emphasis must be placed on the development of chronic effects rather than on acute and subacute effects as is the case with drugs.[121]

In 1949 the most comprehensive set of procedures for evaluating the safety of food chemicals were published by the Division of Pharmacology.[122] This was divided into six phases. The chemical properties of a new compound would be established, its solubility, identity, purity, stability

with means of detection in microamounts. A detailed description of the procedure for discovering the acute toxicity, defined as 'the effect that a compound produces when given in a single dose or in multiple doses over periods of 24 hours of less'[123] was proposed, expressed as the LD50 under stated environmental conditions. The guidelines for evaluation required that the chemical should be given orally to groups of animals which had been fasted overnight, using at least five groups containing ten animals each, with a range of doses on at least three species of both sex. It was also recognised that additional information could be obtained from this test on the site of action and the mechanism of the toxic response.

There was no concept of a formal risk-benefit analysis at that time. Safety was defined in terms of the amount of a substance that humans were exposed to. This was intended to cover the old, the sick and the most sensitive. The 100 fold safety factor was introduced to help define a reasonable expectation of no toxic effect of a substance at the level it was found in the environment,[124] so the emphasis was on safety for intended use. Other factors which influenced decision making was the effectiveness of the chemical for its intended use, and the need identified for the product. During 1938 and 1939 the Division of Pharmacology obtained the services of Chester I.Bliss, a statistician who has been a student to R.A.Fisher of the U.K. Medical Research Council. The F.D.A. later established an independent section on statistics.[125]

The definition of poisons as those substances with an LD50 of less than 1gm/Kg and the 100 fold safety factor were estimates of safety that were based on a comparison of all known toxic results in animal studies on specific chemicals and the toxic effects of the same chemicals in humans.[126] In particular Dr. R.Blackwell Smith, assistant director to the Division of Pharmacology tabulated from the literature data where the

results in both animals and man were available, and also using unpublished data from the F.D.A. files. He found humans to be an average of 10 times more sensitive to the effects of chemicals than animals. A 10 fold extrapolation seemed to give rise to a reasonable risk, so the 100 fold safety factor (10 x 10) was reached.[127]

A new test that was suggested for inclusion in the 1949 article was that of allergic response from exposure to chemicals involved in food processing, consisting of an intracutaneous injection technique, to detect sensitization. As far as determining sub-acute and chronic toxicity 4 groups of animals containing 10 males and 10 females were suggested, consisting of three dosage levels to a control, repeated for two different species. A procedure for carrying out reproduction studies on rats to the third generation was also outlined, as part of the chronic evaluation. A novel test was proposed to discover the effect of a chemical on food consumption. This involved ten pairs of littermate weanling rats, same sex and size used for control and experimental data. In a note on the relevance of biochemistry to toxicity evaluation, E.P. Lang illustrated the essentially pragmatic approach that had been adopted,

> To some it may seem superfluous to know why a compound is toxic, for, if it is, then for all practical purposes, its use is either seriously restricted or not admitted at all. While such a clear-cut appraisal may be true for the class of compounds which are frankly toxic, and therefore of little use, it is certainly not true of that class of compounds which may be moderately toxic, but in specialised uses extremely valuable.[128]

In essence, then, this summarises the extent of the body of knowledge, developed by the Division of Pharmacology in response to both the requirement of the Food Drug and Cosmetic Act that they demand proof of safety of chemicals developed for consumer use, and the specific pressures brought on by wartime shortages, and efforts to ameliorate emergency conditions. The most important aspect to emerge was the distinction

between damage caused by acute and chronic administration of the substance under investigation. This was the first time that a rational programme for safety evaluation had been published, although the generalised tests had been carefully constructed to include all types of individual toxic idiosyncracies that had been observed from experiments with specific chemicals with the possible exception of carcinogenesis. It was realised that no test would ever give proof of absolute safety, but if tested on animal data, a probable estimate of safety to humans could be reached. Other problem areas were seen as the heterogeneity of the population to be exposed coupled with unknown, but possible synergistic effects. To account for this both the desirability of clinical studies on volunteers and the establishment of the 100 fold margin of safety were suggested.[129]

The structure of the Division of Pharmacology was that each staff member had expertise in one of the six areas of evaluation - thus in 1949 there was,

A.T.Lehmann	Chief
E.P.Lang	Chemistry, Biochemistry notably Pharmacodynamics
G.Woodard	Acute, Mechanism and site of action
T.M.Draize	Allergic response
O.G.Fitzhugh	Subacute and Chronic toxicity
A.A.Nelson	Pathology [130]

It soon became evident that the implementation of such a programme was an ambiguous exercise, due to problems of definition and interpretation. This necessitated a short article to be published by A.J. Lehmann, clarifying some of the issues that had presented problems.[131] The emphasis was placed on demonstrating the safety of food chemicals, and the interpretations biased towards this. Thus knowledge of the chemical properties, especially solubility and reactivity were important. A rough guide to acute toxicity was suggested, that substances with an LD50 of less than 1gm/Kg should be classed as poisonous and excluded from

use, although 'this value does not apply to drugs where therapeutic efficacy is balanced against toxicity'.[132]

The requirement for evidence of sub-acute and chronic toxicity had been called into question, and it was necessary to reiterate the benefits of the ninety day test in actually designing the longer tests. It was also necessary to make the point that all chemicals used in manufacture had to be tested and not only for those expected to be used most widely. There were reasons for the life time study of a chemical under test on one species, as specific forms of damage, including tumour production, had been shown to occur only after the first year of administration. They were also thought to cover the age distribution found in the general population.[133] The future trends that were identified included the extension of life time studies, possibly to a five year study on the dog, and increasing importance of the influence of some chemicals on fundamental physiological processes of the body with the possibility of developing a simple screening test based on the action of toxic substances on enzymes.[134]

The Division of Pharmacology had been responsible for devising a number of novel tests, particularly in relation to chronic effects. The 90 day or subacute test was specifically developed by the Division of Pharmacology. It was considered to be a preliminary study that could be done on a greater number of chemicals, whereas chronic studies were limited by space and personnel.[135] Urgency on a matter often forced a decision based on short-term studies. The use of such studies was given added emphasis by the work of Dow Chemicals and the Mellon Institute of Union Carbide.[136] There was also some collaboration with the Public Health Service especially over the question of the safety of D.D.T.[137]

The carcinogicity of a chemical was considered to be a toxicological measurement, which if discovered during the long term tests would

mean that chemical was unsafe for use in food.[138] It was not considered to be a separate effect, from other long term effects until the Delaney amendment was enacted by congress. The first publication that indicated chemicals could cause cancer from feeding tests was by a Japanese researcher, Kinosita in 1934, subsequently confirmed by the Division of Pharmacology.[139]

During the 1950s the job of standard setting moved from the F.D.A. which retained responsibility of enforcing standards. Pressures of the volume of work meant that scientists had increasingly less time to think about standards, setting, and an increase in the number of toxicologists in academia and industry meant the Food Protection Committee was in a good position to act as a consulting body.[140] Some members had been trained at the F.D.A.[141] In addition there was the feeling that such standards as were adopted would be more internationally acceptable if they were placed on a broader basis.[142]

4.10 Conclusion

By the end of the War in 1945 the transition from a backward looking description of poisons to the predictive use of animal tests has been made by the Division of Pharmacology of the F.D.A. Why this process took place here, is a complex question, but undoubtedly influenced by the fact of its situation as an applied research unit with its own technical and experimental facilities and assured funding. Toxicology retained an association with pharmacology through the realisation that synthetic drugs could be highly toxic, and industrial pharmacologists in the United States retained an interest in developing antidotes.

Toxic substances were still used as tools in the study of physiology. Developments in chemical techniques enabled the detection of small doses of a substance in biological tissue - important in the development of tests for chronic toxicity. The use of poison gas stimulated institu-

tional establishment in Britain and brought biochemical concepts into the study of toxicology. An attempt to standardise acute toxicity was made during this time with the development of the LD50 concept. Although it was intended at first as an assay for drugs, and its considerable limitations were pointed out, considerable effort was expended in developing ways to make its determination generally and easily available, particularly for use by industry.

Experiments of the production of cancer on animals produced results which demonstrated that animals could be used as models to show the potential harm of a chemical. The distinct institutional basis of cancer research begins to develop at this time. The study of industrial poisoning also starts to become institutionalised with the establishment of the ACGIH. It takes on its character as a branch of industrial health.

The important questions for legislation in this period were still the addition of preservatives and colours to food and the control of acute poisons. On the former question the situation remained that there was not enough scientific evidence to justify a change of policy from a prescribed list to a permitted one. The Government had seen fit to establish a Select Committee on the question, and they again consulted members of the medical profession for their opinion. The 1938 legislation was small improvement on this situation.

On the question of poisons, the 1933 Act established a Governmental Advisory Committee, the Poisons Board, which could advise on substances to be added to the Poisons List. At this time this legislation offered the most consumer protection, and covered a wider range of products, such as cosmetics, domestic fluids and agricultural chemicals. There were, however, no governmental mechanisms for transferring political goals (such as the desire to know which chemicals could be safely added to food)

to the research community. Even if this had been the case, however, there was no institutional basis on which to apply it. The medical profession had shown little interest in developing toxicology, and the work that was being done was tacked onto existing disciplinary work. Especially in the area of chronic toxicity there was hardly an identifiable research community in Britain.

It has already been noted that the situation differed considerably in the United States. Here, in developing the Division of Pharmacology, the F.D.A. appointed a scientific team of young scientists with a range of disciplinary backgrounds - a formula that would become characteristic of the most innovative teams in toxicology. A number of tragic cases of poisoning ensured that the team had, as part of its directive, the responsibility for investigating both the adverse reactions of drugs and the safe levels of food chemicals. Here, then, is the direct transformation of political questions into research goals for a receptive group of scientists. In addition some industrial laboratories concerned with toxicology were established, who requested help from the Division of Pharmacology, and some exchange of expertise took place. The spate of poisonings had demonstrated the inadequacy of the philosophy of prosecution, and highlighted the need for prediction. In response to this, because of its unique position, and based on primitive examples, the Division of Pharmacology began to develop its system of testing substances for safety using a series of animal tests. This was overwhelmingly the approach of applied scientists, developed from their pragmatic, day to day responsibilities, and from case studies undertaken by the team. There was consultation with industry, and the test proposals seem to have been acceptable to them. It appears that the particular form of the political requirements necessitated the 'applied' approach, but once established the Division became a centre of toxicological expertise, and was itself, able to put pressure on government and industry. In line with

approach was the rule of thumb, 100 fold margin as a safety factor, based entirely on existing data, which later, along with the LD50 was to become one of the major standards in safety evaluation.

It is undeniable that the existence of such a forum, with open interaction of scientist from different disciplinary and institutional background was extremely fruitful. It was an undeniable advance on the situation that existed before the division was created, and the scientific tests that were developed not only had a profound affect on legislation developing in other countries, but many tests have remained in use until the present day.

PART THREE

TOXICOLOGY IN BRITAIN 1945-1980

CHAPTER FIVE

THE COMMITTEE ON TOXIC SUBSTANCES IN CONSUMER GOODS (1945-1950)

The Committee on Toxic Substances in Consumer Goods

The situation in Britain in 1945 with regard to toxicology was not encouraging. Only one laboratory existed with a particular interest in the toxicity of compounds, the Chemical Defence Research Establishment. There was little evidence of a community of scientists interested in developing toxicology as a scientific discipline, as those who were interested were intellectually and physically isolated from each other. The medical profession was interested in acute poisoning, while forensic toxicologists were directed towards medico-legal work, particularly in the chemical analysis of poisons. Successive policy requirements for knowledge of chronic poisoning had not succeeded in producing either a body of knowledge in this area, or a group of scientists willing to undertake responsibility for this work. The experiments that were being carried out on the chemical causation of cancer were being done in the academic arena, and these results had not been taken up as matters for concern by policy makers.

In the immediate post-war years, the first major signs of change began to take place in Britain. The Advisory Council on Scientific Policy established a committee to review the existing policy arrangements with regard to the addition of potentially deleterious substance to consumer goods. Chaired by Professor Solly Zuckerman,[1] this committee was of major importance in highlighting the areas in which legislation on this issue was lacking, and also by making recommendations that were to be of major importance in solving the policy problems of the post-war period. There were also some important developments in the science with new laboratories being established, and the growth of industrial concern over ensuring the safety of new products.

5.1. Developments in Toxicology

The developments that occurred during this period were both in the social organisation of the science and in its cognitive development. New institutional laboratories were established, both within the industrial and governmental sphere, with very different objectives. On the cognitive side, not only were there improvements in the available techniques of chemical analysis, but also the first attempts to establish a research programme in toxicology were made.

There was evidence that some firms, at least, were considering the possibility of toxicity seriously. The chemicals firm, Proctor and Gamble Ltd., developed an interest in the question of the safety assessment of new substances after the war, when they began to develop and test radically new product formulations.[2] In 1945 a pharmacology department was opened within Allen and Hanburys Ltd. (Later to become part of the Glaxo Group), which contained a small toxicology unit of ten people, who were to investigate the safety of promising new drugs. It was not until 1948, however, that one of the most significant innovations was made by an industrial firm. The giant chemical company, ICI Ltd. opened their Industrial Hygiene Research Laboratories in Adderley Park, near Macclesfield. This was the first industrial laboratory of its kind in Britain, which had the main objective according to Dr. A.A.B. Swan, a past director

> providing a service of information and advice to production Divisions of the company on the toxic properties of chemicals to help ensure the safe operation of manufacturing process and the safe use of the companies products by other industries and by the general public.[3]

Thus it was conceived to have the dual purpose of both to ensure the safety of their employees and their consumers.

It was at this time that the major post-war expansion of the chemical industry began particularly in the area of petrochemicals and

concern for the possible hazards to health was apparent even among sections of the industry that was not inclined to establish its own research facilities. A consequence of this was that some pressure was felt by the Medical Research Council (M.R.C.) to set up its own toxicology unit, as a response to requests from industry for information.[4] There was, however, interest within the M.R.C. over the question of chemicals in food, as in 1933 a physiologist, Sir Edward Mellanby became Secretary to the Medical Research Council. Thirteen years later he discovered the association between canine hysteria and a common chemical used in the treatment of wheat flour, nitrogen trichloride, thus confirming the interest in the potential toxicity of chemicals found in food.[5]

The idea of establishing a toxicology unit also arose from another area. At the outbreak of war, in 1939 an experimental pathologist, Gordon Roy Cameron was seconded from the pathology department at University College Hospital Medical School to the Chemical Defence Research Establishment (CDRE) at Porton Down, under the Ministry of Supply. While he was there he met a young research worker, John Morrison Barnes, who had been called up from Oxford in April 1943.[6] Barnes had been working on the toxicity of tannic acid and the treatment of burns. Cameron and David Henderson of the C.D.R.E. wanted a toxicology unit established at Porton Down, and communicated the idea to Mellanby at the M.R.C. He took up the idea, and negotiated for the M.R.C. to obtain space there. In 1947 the deal was complete and Barnes was offered the job of head of the unit, which he accepted.[7] Barnes recalled that,

> This unit, established by the Council in the spring of 1947 for the experimental investigation of toxicological problems with special references to industrial hazards, has been accommodated at the Chemical Defence Establishment, Porton, by arrangement with the Ministry of Supply.[8]

The unit had 2000 sq.ft. of laboratory space, and intended to expand into hutted accommodation in the grounds at Porton where it remained until

moved to its present site in Carshalton, Surrey in 1950. In 1945 Cameron returned to University College Hospital Medical School, but retained his interest in the unit. He persuaded an experimental pathologist from New Zealand, F.A.Denz, to join and his association with the unit was stated by Barnes,

> In the early days when the unit was very small and somewhat isolated at Porton it was always a great pleasure to go up and see him - invariably with an invitation to lunch and a gossip either before or after in his room.[9]

Both Barnes and Cameron had an interest in investigating the basic mechanisms of toxicity, and were determined that this should be the focus of the unit. Barnes says, of Cameron,

> It was a great help in ensuring that the new unit was not turned into a testing laboratory, but was allowed to grow along the lines we both thought to be the right ones.[10]

The unit was, in part at least, established due to an increase in the number of requests from industry on the toxicology of new compounds, and its original purpose was, according to Landsborough-Thompson

> to assist in the solution of toxicological problems referred to the council by other bodies and to do research on fundamental problems arising from the routine work.[11]

In the same year the M.R.C. created a Toxicology Committee to advise and assist the Council in the promotion of toxicological research with particular reference to industrial hazards.[12] The Toxicology Research Unit was to carry out experimental work suggested by the committee, although the M.R.C. would not confine itself to this, as reported by the Lancet,

> In appropriate circumstances research on the subject may be promoted by the Council elsewhere either within their own staff organisation or by means of grants to independent workers.[13]

Cameron was appointed chairman of this committee, with Barnes as Secretary, thus ensuring continued close contact between the two.

The developments in the institutional structure of toxicology in Britain during this period indicate the increasing importance of the science. In particular the establishment of industrial interest demonstrated that the question of the safety of new products was being taken seriously. The M.R.C. Toxicology Research Unit was established due mainly to the interest of key individuals, strategically placed to bring the idea to fruition. Mellanby acted in the role of the organisational leader - an eminent scientist in a related discipline, who had research interests in the area of toxicology and was in a position to exert influence to establish a new M.R.C. Research Unit. Cameron was another scientist from a neighbouring discipline who had an interest in toxicology. He, however, acted as an intellectual leader, discussing research problems with the young director, John Barnes, and encouraging the unit to concentrate on basic research, rather than on safety testing. This encouragement was very important at the beginning of the Toxicology Research Unit as a scientific laboratory and ensured that there would be a balance between testing and research. There were, in fact, a number of developments in the research field that would make research into toxic mechanisms easier, and there was a small amount of interest in this elsewhere.

5.2. Basic Research

In 1947 the first edition of a book entitled "Detoxication mechanisms" was published by a young researcher Richard Techwyn Williams[14] He had graduated in chemistry at the University College of South Wales and Monmouthshire, and his postgraduate research had included the determination of the ring structure of glucuronic acid, obtained by 'feeding animals with various foreign compounds and isolating the glucuronides from their urine'.[15] During the forties he held posts at the University of Birmingham (1934-1942) and Liverpool (1942-1948), and in 1949 he moved to St.Mary's Hospital Medical School where he stayed for

the remainder of his working life.[16] During the period in question, however, he continued his doctoral work by studying the metabolism of drugs, and became convinced, that the metabolism of a foreign compound could be of particular significance to its toxicity and possible therapeutic activity.[17] The recognition of the dual possibilities that both benefit and harm could accrue from the metabolism of foreign substances was a new development in the thirties. During the last century the process of metabolism of chemical substances was demonstrated primarily by the analysis of the constituent parts of urine. The term 'detoxication mechanism' was given to the process of the metabolism of foreign substances because it was thought that the changes that the compound underwent were a mechanism to protect the body from harm.[18]

The developments in the analysis of metabolism were greatly aided by improvements in analytical techniques in the forties. During the first half of the present century the procedure was to isolate metabolites from the urine of animals who had been administered the foreign compound under investigation. The difficulties were immense, according to Young,

> Anyone who carried out investigation of this type before the middle of the century will readily recall the misgivings that attended the beginnings of the search for metabolic products, the identities of which were unknown, and which all too often were present in urine in such low concentrations that their isolation by the techniques then available might prove impossible.[19]

After the war developments in nuclear technology resulted in commercially produced counting equipment which allowed the utilization of radioactive isotope tracer techniques. The advantages of this type were that a wide range of elements which are found in radioactive form could be accurately measured and detected.[20]

A second advance during the forties was the introduction of paper

chromatography which reduced the time needed to identify the constituent compounds in a mixture of metabolites. In some cases the time saved by this technique could be weeks or months.[21]

The investigation of the metabolism of chemicals by the body was an area of research of interest to the scientists working at the M.R.C. Toxicology Research Unit. The unit began to develop its research programme by investigating the toxicity of an industrial metal, beryllium. This set the basis on which the unit would choose its compounds for research - those that presented a real threat to the health of some groups in society. The next problem to be added was investigating cases of death among agricultural workers spraying dilute solution of dinitro-ortho-cresol as a weedkiller. The third general area for research that was taken up was the toxicity of the organo-phosphorous compounds, which had initially been developed for use as nerve gas during the war, but were being manufactured as insecticides.[22] An early success was in demonstrating the action of the organo-phosphorous insecticides in inhibiting an enzyme, cholinesterase, which plays some part in the transmission of nerve impulses.[23] From this work on understanding the mechanisms of action a quick test was developed to diagnose poisoning by organo-phosphorous compounds, based on measuring the amount of cholinesterase in different organs.

There had obviously been important developments in this period, particularly in the area of chemical techniques for the analysis of compounds which made the study of the metabolism of substances easier than it had been. This opened up the possibility of metabolic studies of a large number of chemicals, which was very important for the study of mechanisms of toxicity. An important decision had been made between those substances which were detoxified or rendered harmless by the body, and those by which harmful metabolites were produced. This recognition gave an extra reason for scientists to take up the study of toxicology.

These developments were important to the emerging research programme of the M.R.C. Toxicology Unit, which from its very inception put the emphasis on undertaking basic research on chemicals which were chosen because of their social importance. This, then, both distinguished the work of the Toxicology Unit from that of the industrial laboratories that were interested in safety evaluation, and ensured that it would be independent from those industrial interests looking purely for a testing station.

Interest in the question of toxic chemicals was not confined to industry and the M.R.C. Concern in the policy arena was highlighted by the fact that a committee was established to review the existing legislation covering the control of poisonous substances, and to make recommendations on any changes that were necessary. The work of this committee marked a turning point in governmental policy, from a philosophy that controlled substances after they had been shown to be acutely toxic, to one that was more forward looking, and accepted the need for setting safety standards.

5.3. The Committee on Toxic Substances in Consumer Goods

The Committee was appointed by the Advisory Council on Scientific Policy (A.C.S.P.) on the 6th July 1949, to examine the arrangements for controlling the use of potentially harmful chemicals used in the preparation of various consumer products.[24] The appointment was made from discussion within the A.C.S.P. which arose out of a letter which the Lord President of the Council had received from the Association of Scientific Workers recommending the setting up of an efficient Consumer Research Service.[25] An earlier meeting of representatives from the Ministries of Health and Food had illustrated their growing concern over the matter. They were in general agreement that the position with respect to facilities for obtaining knowledge on the properties of substances, was very unsatisfactory.[26]

The A.C.S.P. decided that an enquiry into the standard of quality and purity which were desirable in the consumers interest, was also of interest to the question of science policy.[27] The committee was called 'Toxic Substances in Consumer Goods', and Professor Solly Zuckerman was appointed as chairman. The membership of the committee is listed in Table 5.1., and there were representatives of all the government departments concerned.

The original terms of reference were 'To examine the existing departmental arrangements for assessing maintaining the quality of standards of consumer products and to make recommendations to the Council for improved arrangements if called for'.[28] This was soon shown to be too general and the Council agreed that as the committee was defined quite specifically by its title, that the terms of reference could be made more specific, so the final brief was 'to examine existing arrangements for regulating ingredients or processes potentially injurious to health used in the preparation of foods, beverages, drugs, cosmetics, insecticides and other substances intended for use in contact with the human body: and if desirable to make recommendations for the better control of these substances and processes.[29] The chairman initially decided to adopt an order of priority in considering the harmful substances with those taken orally as being most important. The first job of the committee was to collect evidence from the department involved in administering legislation already concerned with toxic chemicals, the main ones identified being the Ministries of Health and Food, the Department of Scientific and Industrial Research, the Agricultural Research Council, Medical Research Council, the Department of the Government Chemist and the Board of Trade. The main questions to be considered were the powers of the government to obtain information on new substances being used by industry, and their ability to protect the consumer from these, whether there was a central corpus of knowledge on toxic substances and what the Ministerial

TABLE 5.1. Membership of the Committee on Toxic Substances in Consumer Goods (1950)

CHAIRMAN

Professor S. Zuckerman

MEMBERS

Sir Weldon Dalrymple-Champneys, Deputy Principal Medical Officer, Ministry of Health.

Dr. H.P.Himsworth - Secretary, M.R.C. (From 1st October 1949)

Mr. J.F.Hirst - Board of Trade

Mr. M.E.Johnston - Treasury

Mr. J. King - Department of the Government Chemist

Sir Edward Mellanby - M.R.C. (Until 30th Setpember 1949)

Mr. E.M.Nicholson - Office the Lord President of the Council

Mr. G.R.Oake - Ministry of Food

Dr. R.J.Peters - Deputy Chief Medical Officer, Department of Health for Scotland

Dr. W.K.Slater - Secretary, Agricultural Research Council

Dr. N.C.Wright - Chief Scientific Advisor, Ministry of Food

SECRETARIES

Mr. K.R.Allen

Mr. A.R.M.Murray.

facilities were for testing suspect products, or what were the total facilities in existence.[30] The evidence collected showed a wide variation in the interest and concern of the government departments.

a) Ministry of Food

The Ministry of Food was worried over the increasing use of novel chemicals in food over which there was no control, and no available knowledge about the harmlessness of these substances. The Ministry was concerned that it should be able to obtain information about novel substances that were being used as food ingredients, and that it should be able to adequately protect the health of the consumer against those which may be harmful.[31] A number of powers were in existence under which the Ministry could carry out its work. The permanent powers resulted from the Food and Drugs Act 1938, above which certain extra powers were extended during the wartime emergency. The 1938 Act was concerned mainly with the composition of food, following the tradition of avoidance of adulteration by non-nutritive or harmful substances, and resulting from this, its emphasis was on the quality of the product, rather than individual products. Relating to this legislation, its enforcement was undertaken by a number of local Food and Drug Authorities, with specialist facilities for Public Analysts and specific powers to sample food. As far as the Central Authority was concerned, the Act provided the framework within which departments made regulations for specific purposes. In actuality, the 1938 Act gave a number of legal forms of action to the Ministry. Providing there was sufficient scientific evidence that a particular ingredient was harmful to health, the Ministry could prohibit its use in all foods. More specifically the named ingredient could be prohibited from specified foods, limited to a stated maximum level in foods generally, or in specified foods. In cases where the scientific evidence was less conclusive but doubt over its safety was reasonable, the ingredient could be prohibited from use while investigations were

undertaken. Where doubt was less solidly based the Ministry could advise the firm that they would be wise to withdraw the ingredient.

At a governmental level the responsibility for regulations made under the Act fell jointly to the Ministries of Food and Health. The Food and Drug Authorities tended to be located in the councils of large towns and large urban district County Councils and the Metropolitan Borough Council. In some cases these authorities employed full time Public Analysts and sponsored their laboratories, otherwise private analytical chemists were used. Authorities could empower their officers, usually the medical or sanitary officer to take samples of food for analysis. The growing worry was that many of the ingredients used in food were not detectable by the methods used by the Public Analysts, who were also unable to supply the information required over the safety of food ingredients.

This was the basis of legislation, in addition to this during the early 1940s extra regulations were introduced relating to the standards of quality of foodstuffs, and the use of mineral oil in foods. The most important wartime order was the Manufactured and Pre-Packed Foods (Control) Order 1942. The original intention of this order was to control the price of food which used scarce ingredients, by granting licences. In the course of applying this order, the Ministry began to notice that there was an increasing use of novel ingredients being used as substitutes for more common ingredients in food. In applying for licences for their products manufacturers were required to submit their formula, and this served to bring to the Ministry's notice cases where it was proposed to use an ingredient not previously used in food manufacture.[32] The emergency wartime orders were due to be revoked in 1949 which had raised questions within the Ministry of Food as to whether the specific power of notification of new ingredients could be retained. The problem of

discovering whether these substances were harmful or not also needed resolution.

The question of harm to health not only arose from new ingredients in food, but also from new manufacturing processes. The Department of the Government Chemist had traditionally been the source of scientific analysis for government departments, but there was a lack of knowledge about whether there were alternative facilities to draw on or if new facilities were needed. They also wanted channels for making requests to scientific expertise, and means of co-ordinating the facilities available. The suggestion of the Ministry of Food was that these responsibilities should be given to a standing advisory committee, which was independent of government departments, which could be responsible for considering requests for the investigation of new food ingredients, and also for assessing the results of these investigations. This suggestion was based on experience with similar committees;

> The Ministry of Food has over a period of time had experience of basing administrative action in the difficult field of special rations for the sick or recommendation from the Special Diets Committee; and is impressed with the value of the services that may be rendered by a body which is at once authoritative in its particular field, and independent.[33]

The problems faced by the Ministry of Food were posed in a very general manner. The major example of the control of novel ingredients was over the question of mineral oils. These had increasingly been used in food because of the chronic shortage of fat during the war, to the concern of the medical profession, particularly in America, although there was no definite evidence to condemn the use of liquid paraffin. In 1948 the Ministry of Health started its own research to determine whether the regular consumption of liquid paraffin had adverse effects on nutrition, or other effects like the production of cancer. The

results of these tests showed that consumption of mineral oils reduced absorption of vitamins A and D, continued ingestion resulted in the deposition of the oil in the intestinal wall and the liver, and there was some indication of carcinogenic potential. On this evidence the Ministry of Health condemned even the medicinal use of refined liquid paraffin and its use was eventually prohibited under the Defense (Sale of Food) Regulations in 1949. Other areas of concern covered metallic contamination of foods, over which the Food Standards Committee of the Ministry of Health appointed a sub-committee in 1948. Their brief was to look at the evidence relating to arsenic, lead, copper, tin and zinc (later fluorine was included), and where toxicity was established, to advise on the minimum limits of contamination that could be achieved by good commercial practice.

The major administrative problem facing the Ministry of Food in 1949 was how much of their wartime powers they were willing to give up as there was pressure to revoke them. They intended to retain the Labelling of Food Order under section 8 of the Food and Drugs Act 1938, but this was orientated towards pre-packed food, for the information of the consumer. It still left the problem of the large numbers of new ingredients being introduced into the baking trade, especially as the Manufactured and Pre-Packed Food Order was revoked during 1949. A similar flow of information was required for peacetime purposes, but there was some doubt whether the Food and Drug Act provided powers to enforce manufacturers to declare the use of novel chemicals as food ingredients, especially if that requirement was from the manufacturers of the chemical rather than the users. Before the war the Ministry of Health had kept in touch with developments in the food industry by contact with local authorities, public analysts, food manufacturers and trade organisations. Now the option was to rely on these contacts with trade organisations and large firms, or to make regulations requiring

notification of new ingredients to the Ministry. Both alternatives required entry into a new field of administration,

> The problem raised is, of course, a novel one and has yet had little consideration, and it cannot yet be said whether the Ministry of Food could maintain under peace-time conditions sufficient administrative contact with producers and users of food ingredients to keep it sufficiently abreast of new developments without taking new powers to make notification compulsory.[34]

The Ministry favoured the possibility of voluntary co-operation with the food industry, as they already had contacts, built up over a decade. The Food Industries Council favoured voluntary co-operation, and the Ministry was afraid that a legal requirement for manufacturers to disclose new ingredients would meet with hostility, and would run into problems over the definition of 'new' or 'novel' ingredients, although they planned at a later date to introduce regulations requiring notification of new ingredients, voluntary agreements were seen as the best practicable solution,

> There is at least a reasonable possibility that adequate voluntary co-operation can be secured from the food manufacturers, because the purposes which the Ministry has in mind are ultimately in the hands of well established food firms as well as those of consumers.[35]

The evidence from the Ministry of Food illustrates that the question of novel, untested chemicals used as food ingredients had been identified as a problem area requiring governmental intervention by the government department concerned. This was mainly due to the information that had come to light because of wartime regulations that had enabled the Ministry to gain information about the substances that manufacturers were using in food products. As these regulations were due to be revoked in 1949, it highlighted the question of the type of powers the Ministry required to safeguard the public health. After considering the possibility of both voluntary and statutory controls, the Ministry

favoured the former, if it could be adequately implemented, rather than introducing new legislation.

b) Ministry of Health

The Committee was also concerned with the question of ensuring the safety of drugs, and took evidence from the Ministry of Health to review governmental powers in this area. Drugs were controlled by a number of different regulations. Before 1925 there was no legislation concerned with the manufacture, distribution or sale of biological products, then it was realised that some products were under strength or dangerously contaminated. The Therapeutic Substances Act (1925) was passed to introduce a policy of inspection and licencing of firms, insisting on high quality of staff and equipment, and the final products were tested for potency and sterility. This legislation was based on the standards already operating at the Wellcome Physiological Research Laboratories. The licences were renewed annually after the manufacturer had submitted samples for analysis and it was felt that this method of regulation was more economical than having a scientific institute as in America, where drugs were analysed, as 'such an institute in this country would represent a very great drain on scientific manpower, both in qualified officers and technicians and would moreover entail the use of a large number of persons in routine work who might be more profitably engaged in research'.[36] Thus the Therapeutic Substances Act 1925, gave the Ministry control over the manufacture of substances, whose purity and potency could not be adequately tested by chemical methods, but by biological means. The Penicillin Act, 1947 imposed standards on antimicrobial organic substances produced by living organisms. Other legislation in existence was also concerned with the standard and quality of preparations. The Pharmacy and Medicines Act 1941 required that the composition of articles on sale as medicine should be disclosed on the label. Finally the

National Health Service Act 1946 allowed some control over the dispensing of drugs, as approximately one test prescription from each chemist every 2 years could be sampled, to check on their quality.[37] Pharmaceuticals were also covered by the 1938 Food and Drugs Act which defined drugs as including medicines for internal or external use, and the standards of the British Pharmacopia were recognised for use by courts. This laid down the standards to which the official list of drugs prepared by the Pharmacopia Commission should conform. The Pharmaceutical Society published a supplement to this, the British Pharmaceutical Codes, which lacked legal status.

Much of this legislation controlled the advertisement of therapeutic substances in some way. A number of diseases could not have drugs or other treatment advertised for them. The Pharmacy and Medicines Act covered Brights disease, cataract, diabetes, epilepsy, glaucoma, locomotor ataxy, paralysis and tuberculosis. Sales of drugs were restricted to certain authorised traders. The Venereal Disease Act of 1917 and the Cancer Act 1939 banned the advertisement of treatments. The area of weakness was that there was no control over the duplication of medicines that would make it possible to discriminate between them.[38] The Ministry was eager to introduce a 'scheme for registering proprietary medicine through an independent board which would scrutinise both the advertisements and the claims of the manufacturer'.[39]

The concern of the Ministry of Health, at this time, was not over the possible toxic side effects of drugs, but over their quality and standardisation. Furthermore the Ministry felt that the area in which regulation was most urgently needed concerned the advertising of drugs and treatments, especially in the area of proprietary medicines, which could be advertised without control, so put the consumer at a disadvantage when it came to deciding between essentially similar medicines. This

problem, however, was generally agreed to be outside the terms of reference of the committee, and it was recommended in the final report that a separate body should be appointed to look at this question. In a letter from Dr. R.J.Peters, he questioned that the problem of advertising drugs should be considered by the committee,

> I would have thought that the problem of the Toxic Substances committee is to consider how to control the introduction and to avoid getting entangled in this general question of commercial probity as affecting a wide range of consumer goods .... I can imagine that the Poisons Board might well be pleased to have behind them the further support of a scientific organisation with a biological bias, towards which the committee seems to be moving.[40]

The question of the toxicity of therapeutic chemicals does not appear to have been raised as a problem within the Ministry of Health at this time, as their evidence to the Committee on Toxic Substances in Consumer Goods did not include any reference to this aspect.

c) Department of the Government Chemist

The major scientific expertise that Government Departments had to call on was located in the Department of the Government Chemist, which specialised in chemical analysis. It dated from 1842 when a laboratory was founded by the Board of Excise at Somerset House to examine excisable commodities. In 1875 Dr. James Bell, was appointed to the laboratory which was called on to undertake the examination of Food and Drugs in connection with the Food and Drugs Act 1875, and later with the Fertilizers and Feeding Stuffs Act 1893. The laboratory was therefore involved in the composition and methods of analysis of Foods Drugs and Agricultural Products. The Department of the Government Chemist was established in 1894, by the Treasury who wanted to promote the Centralisation of Government chemical work, with Sir Edward Thorpe as the first Government Chemist. Before the Second World War their work included analysing

over half a million samples a year, advisory functions and some fundamental scientific work, which included areas such as the constituents of vitamins, the role of hormones in the body, and of trace elements in nutrition. These developments indicated that the line between chemical and biochemical problems were disappearing as experiments with animals were becoming more important.

The Statutory obligations of the Government Chemist under the 1938 Food and Drug Act was to act as a referee. A court of law could direct the laboratory to examine samples for compliance with labelling claims or with the standards of the British Pharmacopia. These often required biological assays with animal experiments, which were also employed to test nutritional claims. These biologically oriented experiments were giving rise to some problems within the laboratory as 'The practicability of undertaking these tests in the Department has been under consideration for some time, but the claims by other government departments for biological tests necessitates a wider range of animal experiments than would be necessary merely to fulfil legal obligations'.[41] The department undertook a variety of work for specific departments. For the Ministry of Health this included expounding the chemical nature and estimation of complex organic compounds which had been proposed for additions to food. Chemical and physical tests were used, including spectroscopy and X-ray diffraction, while new methods were also investigated, which included microbiological methods. Other work for the Ministry of Health included the examination of drugs submitted under the National Health Service Act, to the Government Chemist, as a referee. For the Ministry of Food, the work included chemical analysis of foods, materials used in the preparation of food, and adulterants, as well as answering over a thousand queries a year on food standards. Other work included questions on pollution and agricultural chemicals for the Ministry of Agriculture and Fisheries, nutritional properties of native foods for

the colonial office, detection of trace elements for the Medical Research Council, examination of dust for toxic industrial solvents for the Ministry of Works, and examination of imported foodstuff for the Department of Customs and Excise. In addition was the job of acting as a referee for the local Food and Drugs Authorities which involved giving information on the composition of food and drugs but not advice of the possible harmful effects. Finally, some work was undertaken for the Admiralty War Department to which staff of the Government Chemist were attached for some time.[42]

The total number of scientific staff employed by the Government Chemist in 1949 was 254, who were located in the Central laboratory in London and 24 divisions of which 5 were concerned with food, drugs, agriculture and water analysis. At this time the Department was considering moving to a new laboratory to house its London laboratories, but they had not planned to extend the type of work they did to include pharmacological or toxicological work, as it would involve setting up a completely new branch for which they were not equipped and did not have the resources. The work was confined to the detection of known toxic substances while 'there remains the general question of the long term effect on the human organism of surface active materials ingested in small quantities for years on end,[43] although some ad hoc work had been undertaken on the effects of substances in the list,' the Department undertook a long term examination of the diets of R.A.F. apprentices, some years ago, for the amount of fluorine present in connection with dentition.[44]

It was quite clear from the evidence submitted by the Department of the Government Chemist that the major work undertaken was that of chemical analysis and identification rather than carrying out estimations of the safety of these substances to biological systems. The

work of the Department was not, in fact, forward looking, involved in setting standards, but, especially in the case of food and drugs was concerned with implementing pre set standards which the law required.

d) The Department of Scientific and Industrial Research (DSIR)

The DSIR had governmental responsibility for the Industrial Research Association which the committee received evidence from. Also administered by the department were various scientific establishments. The Directorate of Food Investigation was not carrying out research directly into questions of toxicity, but was aware of the need for control of the problem. They favoured a central organisation with the responsibility for biological tests, and the Food Investigation Board had been in touch with the National Research Council on the matter. The Water Pollution Research Laboratory did no work in the area either, beyond developing methods for removing poisonous materials from Water. The DSIR also had responsibility for the Pest Infestation Laboratory which did no experiments of its own on animals, but was interested in analysing residues in food, and had been in contact with the British Flour Millers Research Association and the British Baking Industries Research Association on this question. There had also been some contact with the Dunn Nutrition Laboratory at Cambridge, on the effect of fumigation on vitamin content.

A number of the research associations had done some ad hoc work in the area of toxicology, although none of them regarded this work as the main concern of the organisation, and very little of it was being done at that time. The committee, however, received evidence which summarised the activity of the research associations in this area,

i) British Jute Trade Research Association - had completed investigations into the elimination of toxic substances from materials used in wrapping bacon.

ii) Hosiery and Allied Trades Research Association - They had done some work with garments which were claimed to have caused dermititis, which led to concern over chemical residues in wool from processing. During the war they had collected information on chlorinated wool underwear.

iii) Research Association of British Flour Millers - They had been working on Professor Mellanby's results with nitrogen trichloride for some years, in order to isolate the toxic substances involved but they felt that the Milling industry would soon take up chlorine dioxide as a flour improver instead. Other compounds they had done experiments with included chlorine dioxide and potassium bromate, and they had contacted the Ministry of Health and the Medical Research Council about their work.

iv) The Research Association of the British Paint, Colour and Varnish Manufacturers -

were concerned about the problem of children licking toys, but had done nothing about it.

v) British Leather Manufacturers Research Association - did no work in the area but had in the past looked at substances causing dermititis.

vi) British Food Manufacturing Industries Research Association - They were concerned about the regulation of ingredients and processes in food manufacture although they did no toxicological work themselves, they had suggested a number of limits that should be observed for trace metals in food, based on the levels that could be obtained by trade practice. The Research Association was represented on the Ministry of Food Metallic Contamination Sub-committee,

and the Joint Committee of the Society of Public Analysts the Society of the Chemical Industry Food Group on Preservative Regulations and the Ministry of Food Scientific Liaison Panel Working Party on Materials used in Baking Products - they were also interested in the question of insecticides.

vii) The British Boot Shoes and Allied Trades Research Association -

did no research of this type although they had complaints of dermititis.

viii) The Wool Industry Research Association - occasionally investigated factors causing dermititis.

ix) British Gelatine and Glue Research Association - had plans to investigate the elimination of arsenic and other metallic impurities from gelatine and the question of bacteriological contamination.

x) Printing Packaging and Allied Trades Research Association -

did no work in the area, although the chocolate manufacturers had laid down tolerances for arsenic and lead in packaging and for lead in pigments and inks.

xi) British Hat and Allied Feltmakers Research Association - had done an investigation into mercury poisoning in the fur cutting and hat manufacturing industry. As there was no evidence of this among the workers they assumed there was no danger to consumers.[45]

The research establishments run by the D.S.I.R. were not particularly concerned with questions of the toxicity of chemicals. Research that had been done was on specific substances of interest to the

institution concerned, and there was no laboratory that was interested in investigating the more general implications of toxicological research.

d) The Medical Research Council (M.R.C.)

The Medical Research Council had taken responsibility for most of the toxicological work that had been done, which was directed by their Toxicology Research Committee. The function of this committee was to investigate all kinds of toxicological problems. In addition, a new committee had been formed with the specific brief of investigating chemicals intended for use as food improvers. During the war, the nutritional laboratory at Cambridge was directed to solving problems arising out of the processing of food with regard to essential food constituents, including vitamins. This work was done for the services, for the Ministry of Food and for the Food Investigation Board of the D.S.I.R.[46] The Toxicology Committee had been established in October 1947, and had obtained requests for information from a variety of institutions which are summarised in Table 5.2 The chemicals and their uses were very wide ranging showing the breadth of interest in the toxic effects of substances. The methods for carrying out the investigations ranged from completing a literature review, to the instigation of research work, and finally giving recommendations to the body requesting information. The literature review was undertaken by members of the committee, and on the basis of this either recommendations were made, or a request for further research at a research laboratory. Laboratories which had accepted work included the Department for Research in Industrial Medicine at the London Hospital, the Toxicology Laboratory at I.C.I., and the M.R.C. Toxicology Unit. The latter was located at the Chemical Defence establishment at Porton, and equipped to undertake both experiments on human volunteers and on animals. In certain cases inspection of manufacturing processes was also undertaken to see if this needed

TABLE 5.2. Information Required by Institutions from the M.R.C. Toxicology Committee (1947-1949)

INSTITUTION REQUESTING INFORMATION	CHEMICAL OF INTEREST	USE
A.R.C.	Dinitro-orthocresol Selenium: DDT, BHC. Various Organo-phosphorous Compounds.	Insecticide
	Alpha-naphthyl thiorea Sodium fluoacetate	Rat poison
British Leather Manufacturers Research Association	Toxicity of fungicides	Leather making
Department of Atomic Energy, Ministry of Supply	Dibutyl Carbitol	Solvent
Home Office Technical Committee on Fumigation	Ethylene Oxide	Fumigant
M.R.C. BAL Committee	Nickel Carbonyl	Possible therapeutic use
Standard Telephones and Cables	Selenium	Manufacture of electrical apparatus
Garner Manufacturing Co.	Duchloro-difluoro-methane	Proposed as a fire extinguisher in aircraft
Ministry of Supply Flux Committee	"Panogen"	Fungicidal Seed dressing
High Commissioner, East African Office	Piperonyl butrocide	Insecticide for stored grain
J.M.Steele & Co. Paint Manufacturer	Methylene chloride Ethylene chloride	Paint remover
Pyrethrum Board, Kenya (Commercial firm)	Pyrethrum	Insecticide for stored grain.

improving. The action taken on the results of the investigations included informing trade associations of the information recommending that chemicals should be controlled by the Poisons Board and also suggesting to manufacturers which chemicals should be avoided.

The evidence obtained from the M.R.C. showed that the Council was well aware of the problems that existed, as it ran the only research laboratory specifically oriented towards toxicology, and had links with other institutions working in the area. The M.R.C. however, did not carry out any routine testing of new chemicals to evaluate their safety, and did not intend to develop this, although they were involved in collating information on the toxicity of various materials from various sources.

f) The Agricultural Research Council (A.R.C.)

The A.R.C. had the special responsibility of looking at the growing area of chemicals used in agriculture. Besides requesting research and information from the Toxicology Committee of the M.R.C., they also had access to information on toxicology from the Toxicology Sub-Committee of the Research and Development Co-ordinating Committee on Insecticides. The major concern had been the chronic toxicity of ingestion of DDT and BHC, and investigations on large animals, such as cows, pigs and sheep had started at the A.R.C. Veterinary laboratory at Weybridge, while the Ministry of Supply were sponsoring work on rats at Porton. In addition the A.R.C. had attached one worker to the M.R.C. Unit to be involved with the work on the organo phosphorous insecticides, which was specifically concerned with sub-acute and chronic tests. A leaflet outlining the dangers of these chemicals to farmers was in preparation, as well as discussions with other departments on the possibilities for control.[47] The A.R.C. was aware of the potential problem of toxicity arising from the use of chemical substances in agriculture, and had taken some steps

to assess the hazards that these presented. The other responsibility of the Council was to inform agricultural workers of any danger to health that existed and how to control them.

g) The Food and Drug Administration (F.D.A.)

The general question of substance in consumer products was not specific to Britain, so it was natural that the committee would consider the ways in which other countries had found a solution to the problem, and they were aware of the interest in the matter by the F.D.A. in America, and their efforts to develop a system of control. Subsequently there was considerable communication between the committee and the F.D.A. including a number of visits made by members of the committee and others to gather information about the role of the F.D.A. in implementing American laws relating to the control of chemical substances.

The F.D.A. was organised around a number of administrative and technical divisions, business operations, cosmetics, field operators, food litigation, medicines, microbiology, penicillin control, immunology, pharmacology, program research, vitamins and state co-operation. The central organisation consisted of officers of the commissioner, deputy commissioners and associate commissioners. Total staff was 900, with 600 in field service and the remainder in the headquarters in Washington. Personnel included chemists, bacteriologists, physicians, veterinarians, microscopists, pharmacologists, inspectors and administrative officers. There were three inspection districts, Eastern, Western and Central, each with headquarters in strategic cities, equipped with extensive laboratory facilities for analysis, and for developing new analytical methods, often to deal with specific cases.

The Food Division acted as a repository for existing technical knowledge, it was concerned with developing methods of analysis for establishing definite proof of violations and other scientific methods

for food law enforcement. It provided expert witnesses for court cases and undertook investigational work. The Drug Division acted as a source of technical information on questions of medicine, physiology, therapeutics and pathology, particularly for practical questions like food, drugs, cosmetics and therapeutic devices, while the Cosmetic Division concentrated on cosmetic analysis, with particular emphasis on the possible toxicity of coal tar colours. The Vitamin Division had to determine the validity of claims of products for vitamin content, which included developing methods of vitamin determination. The Bacteriology Division looked at the dangers to health through the transfer of germs, decomposition of food, filth, sewerage and pollution, while the Division of Pharmacology undertook biological assays of drugs and toxicity studies. Finally, the Division of Microbiology did microscopical identification of ingredients of mixtures, detection of decomposition, and of filth in food, drugs and cosmetics.[48]

The main concern of the Food and Drug Divisions was to enforce the 1938 Food Drug and Cosmetic Act, by which their authority was restricted to interstate commerce only, although they would help manufacturers in interpreting the law, and F.D.A. inspectors could do spot checks to see if violations of the law had occurred or were likely to occur. Three courses of action could be undertaken, immediate seizure of consignment, criminal prosecution of shipment maker, serving an injunction against the manufacturer. Laboratory analyses were reviewed by F.D.A. staff, the litigation department prepared evidence for the U.S. attorney. Pharmacologists of the F.D.A. were concerned with the toxicity of substances in food that were not impurities such as insecticides and of the toxicity of new drugs for licencing.[49]

One advantage of the American legislation was seen to be the ability to ban the addition of specific ingredients to food if they were shown to

be harmful, whereas the British legislation required that a food product should be shown to be harmful.[50] The committee was concerned to discover whether the F.D.A. kept central files of information on various substances, and whether this information would be accessible to other groups interested in the same questions. The chairman visited the Deputy Commissioner of Food and Drugs, Mr. Crawford, to obtain access to information on specific drugs requested by the Ministry of Health. A number of ideas were exchanged such as the possibility of a joint British and American Pharmacopia, and the possibility that, if the British government established some central laboratory for toxicology, exchange of information and collaboration would be possible.[51] Further enquiries by C.A.Adams from the Ministry of Food, showed that in the Division of Pharmacology where most of the work on toxicology was done, no abstracts of enquiries or results were kept, but information was filed under specific manufacturers. The Division did not carry out tests on every chemical that was sent to it, but obtained information on non-toxicity from the manufacturer, the Division then satisfied themselves there was a real use for the chemical and that its use would reach serious proportions. If the information on toxicity was not adequate, research would start on the chemical and traders warned not to deal with the substance until its safety had been proved. The staff of the Division totalled 60 half of whom had a scientific qualification to deal with an average of 20 enquiries each month.[52]

Other institutions in the United States, that were interested in these questions included the National Research Council, whose Food and Nutrition Board proposed to establish a committee on Food Protection to assemble information on the problem of toxic substances in Food and to find a solution that would be acceptable to food producers and processors, government agencies and consumers. The American Public Health Association passed a resolution that, noting the increasing use of chemical

substances in food, they should recommend to congress that they introduce legislation to prevent the incorporation into foods of chemicals or other new ingredients before they have been reviewed and approved by the Food and Drug Administration,[53] and since the existing legislation referred only to interstate commerce, to recommend the enactment of similar legislation by states. The American Medical Association was concerned about the toxicity of agricultural chemicals and their residue in food, especially on the contamination of baby food by DDT, and the American Institute of Baking had been looking at chemicals in bakery products.

The existing law in the U.S.A. although in principle allowed the prohibition of harmful substances from food, drugs and cosmetics, failed in that the F.D.A. had to develop evidence against a specific substance, and there was no protection against the introduction of new substances. The fact that evidence against a substance had to be produced by the governmental body, however, meant that the F.D.A had laboratory facilities which were devoted to the safety evaluation of chemicals. It was this fact that particularly interested the committee, and the question as to whether a similar situation was desirable in Britain, by funding a government laboratory for the testing of substances. This issue was discussed with the recommendations of the committee.

h) Recommendations of the Committee on Toxic Substances in Consumer Goods

Between the time of their first meeting on 4th November 1948, and the final report published in the Third Annual Report of the A.C.S.P, in 1950[54] the committee took evidence from the Ministry of Food, Ministry of Health, Department of the Government Chemist, the Medical and Agricultural Research Council, the Department of Health for Scotland and the Board of Trade. They had covered all existing departmental arrangements for the control of ingredients in foods, drugs, cosmetics

detergents, fertilizers and insecticides. The three main points of inquiry were whether the departments had sufficient powers to obtain information about new substances being used in preparation or processing of consumer goods and to protect the public against substances proven to be harmful, whether there was in existence a corpus of knowledge of the toxic or potentially toxic effects of a substance in consumer goods and whether the existing facilities were adequate for testing suspect products.

The answers to these points turned out to be generally negative. Departments did not possess the legal powers that would require industry to notify their intentions over using new ingredients. In particular the Food and Drugs Act 1938 put the onus of safety for ingredients on the manufacturer, but as 'the toxicity of many of the substances now being used is not immediately apparent and may be revealed only by testing the cumulative effect of ingestion of small quantities taken regularly over a long period,[55] harmful effects could not be traced to particular foods. The committee thought that these problems should be solved individually by different departments, the Ministry of Health wanted new legal powers, while the Ministry of Food preferred to rely on a voluntary system. The committee recommended however that there was a possibility that there may be many small firms who are not members of trade organisations and who would not consider themselves bound by a voluntary agreement between the Ministry of Food and the Food Manufacturing Industries, 'we are not entirely satisfied that a voluntary method would prove effective over the whole range of food manufacture,'[56] and that a reliable method should depend on the powers of inspection and sampling. The Ministry of Food estimated that even a statutory requirement to disclose ingredients used in food would only reach 90% of manufacturers. The existing legislation was considered to be adequate where a substance had been shown to be harmful due to the weight of scientific evidence against it. This area was seen to cover solvents, metals and mineral oils, on which there was

much literature, although it would take several years to collect, classify and centralise. A new group of synthetic chemicals were identified as becoming increasingly more used after 1947. In such a short time no evidence of harm had been collected, and this was seen as a problem even in countries which already had extensive laboratory facilities. In Britain even this was absent. Because of the lack of any independent centralised equipped laboratory large enough to undertake the responsibility for the question of the biological effects of novel substances, the committee recommended the need for resources to be put in that area,

> we are therefore convinced that there is an urgent and vital need for a central scientific advisory organisation, independent of any executive department of government, which could serve as the focus for scientific advice tendered to department - (To be) responsible for the direction and co-ordination of schemes of research, handing out fundamental research problems to the Universities and other agencies for research, and supervising and co-ordinating routine testing in the Department of the Government Chemist.[57]

It would take several years to achieve the goal of a complete and comprehensive library of knowledge, with laboratories for testing, so as an interim measure the committee suggested 'that the existing structure of the Medical Research Council might well provide the nucleus .... the M.R.C. consider that it is their responsibility to promote research in the field .... they would be interested to examine any proposals that might be made.'[58] There should be a co-ordinating committee made up of representatives from various departments to channel requests for information, on the facilities for research in the universities and the Toxicology Unit at Porton should be utilized. Facilities for collecting a central body of knowledge should begin as soon as possible, and arrangements should be made with the F.D.A. to exchange information. In a later draft the committee decided that the type of research institution that they had in mind would place an unacceptable burden on governmental

finance and scientific manpower, unless manufacturers also contributed. It was recommended that industry also contributed information on different substances due to limitations of personnel and research facilities, and that industry should also bear the financial cost, with the government, of the new organisation.[59]

The Board of Trade, it turned out, had no control over the manufacturers of goods over which it supervised. These included toilet preparations and cosmetics, detergents, clothing fabrics, dyed fur, floor coverings, foor and shoe polishes. On the assumption that the risk to public health was quite small the Board of Trade had no plans to improve the situation. The committee criticised this position on the grounds that substances prohibited from use in drugs could be used in cosmetics without limitation. There were also a large number of agricultural chemicals to be considered, such as insecticides, fungicides, herbicides and fumigants. The committee favoured that all proposed uses for new chemicals or change in use for known substances should be submitted to the government departments concerned,

> before introducing new substances or processes, or applying old substances to new uses, manufacturers should submit their proposals together with evidence of non toxicity to the appropriate department and that the evidence should be reviewed by the central advisory organisation .... the only other alternative to this method is for government to accept full responsibility for protecting the consumer and to bear the vast expense and use of scientific manpower which this would entail.[60]

In summary the main conclusions of the committee were that the Departments of government were not in a sufficiently well informed position to be able to control the situation where many novel substances were being used in consumer goods,

> The Committee reached complete agreement on three main conclusions first that while it is the responsibility of Departments to protect the public against hazards arising from the

> use of potentially toxic substances and processes in the manufacture of food drugs and other consumer goods, they are not in a position to discharge the responsibility effectively, owing to present deficiences in departmental powers, and to lack of arrangements by which Departments may obtain authoritative scientific advice: second that the first responsibility for showing that a new ingredient or new process is not actually harmful should fall on the firm proposing the innovation; and third, that there is a need for a research organisation to investigate the toxicity of doubtful substances and processes, and that the Medical Research Council is the appropriate body to advise upon the form and size the organisation which would be required.[61]

The Medical Research Council had appointed a committee to consider the recommendation,

> The report had raised a number of issues which the committee thought were important. The question of the toxicity of compounds they identified as two - they were concerned both with acute and chronic effects. They especially felt that as a result of recent developments, however, we have reached the conclusion, after considering the evidence received from Government Departments that the public is exposed to the danger of chronic effects.[62]

Furthermore, while the onus was on the manufacturer to show that his products were not acutely harmful, the possibility of chronic toxicity meant that a particular food would rarely be blamed, some of the substances now being used may have toxic effects which are not immediately apparent and which may only be revealed by the cumulative effects of ingestion of small quantities taken regularly over a long period,[63] and the superiority of the American system was that it required the testing of the toxicity of the substance itself, not of the food to which it had been added.[64]

As far as the Ministeries were concerned, the Board of Trade did not consider the risk sufficient enough to warrant legal powers for manufacturers to declare the ingredients used. The Ministry of Food

was also happy with the existing legislation. The Ministry of Agriculture was itself in control of infestation of stored food owned by the Ministry of Food, and they felt fairly certain that the larger farmers at least, accepted the Ministry's recommendations.

The committee exposed the lack of facilities in existence in the country for assessing the potential public harm that may occur from allowing manufacturers uncontrolled licence to add new substance, to goods which would come into extensive contact with people, through ingestion, or from contact with the skin. A number of organisations had seen this as a problem in an ad hoc way but there was no co-ordinating body in existence to show that this was a problem of more general concern. In addition the Ministry of Food were also particularly worried over what they saw as an increasingly important problem, although this attitude was not shared by all - the Government Departments with responsibility over consumer goods were not convinced of the seriousness of the question, a fact that made any thought of introducing universal legislation to cover the whole area quite impossible. Neither could they agree whether such a change in the law would be beneficial or not.

The major recommendation of the committee was that there should be a massive extension in available facilities, both for collecting information and carrying out its own research. The function of this organisation was primarily to give advice to Government Departments on policy recommendations with regard to specific substances. This idea seems to have been modelled on the American Food and Drug Administration, as there was no other country with such a well developed governmental infrastructure, although some of the responsibilities of the F.D.A. were already under the jurisdiction of other structures in Britain.

The committee identified the basis of the problem as that being chronic, rather than acute, toxicity, and pointed out weaknesses in the

law to deal with this. They also recognised that the problem they were confronting required routine testing rather than fundamental research and suggested that manufacturers needed to become involved in the production of information. The Medical Research Council were reluctant to become involved in the analysis of routine tests, although they planned to extend their own Toxicology Unit which would remain interested in problems of basic research. They recognised the lack of trained manpower, but did not suggest ways in which this could be ameliorated, especially regarding the lack of institutional places primarily concerned with toxicology. It seems as if the committee may have ultimately been constrained by the demarcated structure of Governmental Departments, and lack of access to decision making over funding priorities for science.

5.4. Conclusion

In the immediate post-war years the question of toxic chemicals began to be seriously examined. The laboratory established by the M.R.C. depended on the support of well established scientists from other disciplines who were in a position to develop the idea of a toxicological laboratory. This institutional development occurred within the only existing establishment that had a particular interest in toxicology. The establishment of an advisory committee staffed with highly qualified scientists with multidisciplinary backgrounds to advise the laboratory on research problems is another example of the commitment of the M.R.C. in this area. The M.R.C. Toxicology Research Unit was essentially a laboratory established by academic scientists with the determination that questions of toxicity, would have a social component in their research programme, and the first candidates for research were industrial hazards and pesticides. The investigation of these substances was, however, to be an academic one, rather than routine testing. The first industrial laboratory was established, and the Committee on Toxic Substances

in Consumer Goods recommended that industrial responsibility for testing should be encouraged. They also favoured an institutional development for toxicology in the form of an establishment which would combine both the applied research aspect of toxicology with exploration of basic problems. This would, in the long term, have been an innovation beneficial to government, industry and the developing science itself, being a 'problem solving' establishment that would also foster the development of a professional identity for the scientist. The work of the committee forms a period of review of British policy towards the inclusion of chemicals in consumer goods. This is however, defined entirely as a discussion internal to the governmental system. The committee members were all civil servants and governmental scientists. Evidence was taken solely from governmental organisations, and there was no question of widening the deliberations to explore the issues of the social need for the products which were seen as inevitable. In part this was because the committee was reviewing an area in which some governmental responsibility had been acknowledged, particularly in issues of public health, and was thus just part of an ongoing process. The committee did, however, identify novel aspects of this question in the increasing utilization of synthetic chemicals in consumer products, and following increasing need for these new substances to be tested in some way before they were marketed. The committee made the first clear public distinction between single dose toxicity, and chronic toxicity, while legislation had concentrated on the former. The developments within the F.D.A. on animal testing was known, and limited work had been commissioned by the Ministry of Health on animal tests. A comprehensive view such as that of the Division of Pharmacology did not develop in Britain, although central facilities for analysis were available in the form of the Government Chemist. This department had started limited animal tests but its expertise was in analytical chemistry and it had to answer a wide range

of queries for many different sources which precluded the development of a similar series of pre-market animal tests for toxicity.

The committee also identified considerable differences of attitude to these questions between departments. The Ministry of Food was well aware of the problem having a duty to administer the Food and Drug Act and having been involved in wartime questions of food substitutes. The Ministry was in fact determined not to lose its powers for extracting information from the industry, voluntarily if possible, but if not, with legislation. Concern for toxicity of drugs, however, did not seem to be identifiable at a ministerial level, nor was concern for other common products, beyond the newly developed agricultural chemicals.

This was an important factor in the changing attitude to British policy towards the use of novel substances in consumer goods. The post-war trends were to insist on pre-market testing of all new chemicals, and the committee on Toxic Substances crystallised the particular form this was to take. They had identified a shortage of laboratory facilities for such routine toxicological testing that would be required, and had developed a proposal for a specific institutional innovation to circumvent the problem. This recommendation was rejected in favour of a policy which would ensure that industry itself carried out the toxicological work on the new substances that it developed.

CHAPTER SIX

SETTING THE POST WAR TRENDS

(1950-1959)

The Committee on Toxic Substances in Consumer Goods had exposed the relative failure of the existing governmental policies to provide adequate controls to ensure the non-toxicity of novel chemicals. During the fifties that situation began to change, as the first initiatives requiring the pre-market testing of new substances were taken. These were orientated around the question of the assessment of pesticides and food additives, although the actual controls that developed for these two types of substances emerged in an ad hoc, specific manner, resulting in completely different forms of policy. There was also much discussion over the establishment of tests for the assessment of the safety of a substance, and some criticism of this approach from basic scientists. In the commercial field there was evidence that the recommendations of the Zuckerman committee concerning the responsibility of industry to undertake testing, were being taken seriously. Industrial firms started to formalise their toxicological research, two contract laboratories were established, and collaboration between certain companies and the Department of Scientific and Industrial Research (DSIR) brought a toxicological research association to fruition. The developments in these three areas showed a decisive break with the pre-war attitude to the problem, and set the framework for subsequent controls that were to develop.

6.1. Institutional Innovations in Toxicology

There were a number of institutional developments during the fifties. Increasingly, industrial firms developed small research groups to investigate toxicity. The first contract research organisations were established, although they did not at first specialise in toxicological research, they were to become an important characteristic of the science. The question

of a government funded laboratory was still open, but this finally matured into a research association funded by both industry and government.

In 1951 Alastair Worden established the Nutrition Research Unit to undertake contract research for industry.[1] He had previously held a chair at the University College of Wales, where he had received requests from the chemical industry to do research. As universities were not equipped at that time to do contract work, he set up the company with financial assistance from his father, and a staff of two. The concept of this company was entirely novel. The first work was some limited analyses for the food industry to demonstrate that antibodies had a growth effect on pigs, but toxicological work started in 1954 with a long term study of a food colour. Work on organo-phosphorous pesticides and insecticides helped to develop expertise in toxicology, while contracts from the pharmaceutical industry were soon forthcoming. The Unit moved into a house, (once owned by Cromwell's father) in Huntingdon, Cambridgeshire, with 2½ acres of land. In the first year the income was £7,000 but this had risen to approximately £80,000 by the end of the decade, when the number of employees was twelve. A few years after the establishment of the unit, Zuckerman, as a cabinet adviser, went to discuss the possibility of its nationalisation, but concluded that it should remain independent. By 1960 work had been done for a number of firms including Reckitt and Coleman, British Cod Liver Oil Company, Bob Martins (Vitamins), Unilever, Shell, Albright and Wilson, and the Coalite Chemical Company. There was some collaboration with the M.R.C. Toxicology Research Unit over the question of organo-phosphorous pesticides on contract from Albright and Wilson and the Coalite Chemical Company. Towards the end of the decade the attitude to regulation was tightening up both in the U.S.A. and in Britain, although there were no set tests, and the atmosphere was very free and flexible. It was possible for Worden to meet

the head of toxicology at the F.D.A., A.J.Lehman, to discuss and devise protocol for tests, and to return if there were problems encountered during testing. Much the same approach was evident in the Pesticides Safety Precaution Scheme in Britain.[2] There was much discussion about methodology in both countries. In Britain both Worden and Leon Goldberg (first Director of BIBRA) gave evidence to the Preservatives sub-committee on the necessity of such tests.

A number of industrial firms had started small research groups. In 1953 Burroughs Wellcome Pharmacology Department had one qualified pathologist, Dr. Vernon Udall and a technician doing limited dosing tests and some histology.[3] Udall qualified in medicine at University College hospital and worked as a pathologist in the pathology department under Roy Cameron. He was interested in the safety of drugs, especially in the safety of poliomyelitis vaccine.[4] By the end of the fifties the group had grown to about 20-25 in size, and had started doing independent experiments mainly on rodents, rabbits and guinea pigs, occasionally using a second species such as dogs or primates. The first in house experiments on reproductive toxicity was started in 1959 with a group from the pharmacology and pathology departments, as this work had previously been contracted out.

Other industrial companies who formulated their interest in toxicology during the fifties included the multinational Unilever, who specialise in various chemical and food products. Their Environmental Safety Division was set up in 1954 at the Colworth research laboratories in Bedfordshire. Initially ten staff were employed on toxicology, two of whom were graduates.[5] In the same year the Shell Tunstall Laboratory was opened in Sittingbourne, Kent, to carry out toxicological work with six scientists, who were to investigate the full range of toxicological experimentation. Work done at Tunstall, however, was only a small

part of the toxicological work carried out by the Royal Dutch Shell Group.[6] Finally Boots, the retail chemists with research interests in pharmaceuticals, cosmetics and toiletries established departments of Toxicology and Pathology at their research laboratories in Nottingham in 1956, employing six scientists. Their research task was to carry out safety evaluation tests on interesting chemicals.[7] In 1957 another contract research organisation was opened near Edinburgh in Scotland. Inveresk Research International, a subsidiary of the Arthur D.Little Institute, a large American contract house, was designed to discover areas in which applied scientists could work fruitfully in the biomedical research field. Research into toxicology did not begin until 1964, when five scientists began to work in this area.[8]

Another industrial initiative that was made during this period was the attempts to establish a toxicological research association funded by government and industry.[9] By 1955 the D.S.I.R. had to inform the industry that neither the Ministry of Food nor the M.R.C. could fund a testing laboratory, but Department was prepared to fund a research association on a pound for pound basis. The industry itself was divided over the question. The Chocolate and Confectionary industries and the Chemical industry were prepared to put up the funds, but the Food industry was undecided. There were real divisions within that industry with some sections advocating that the government should take the responsibility of testing as the risks were high. Furthermore, the idea of co-operative research would mean that a few firms would pay for research that would benefit the whole industry, and they were not convinced that enough work could be found for the laboratory to keep it going. The Food industry eventually withdrew as such divergent interests could not be reconciled. The Confectionary and Chemical industries determined on seeing the plan through, but raising the funds proved to

be a difficult task, and the association was not finally established until 1960.

These developments illustrate that, throughout this period, the question of the toxic nature of new chemicals was becoming regarded as increasingly important by the industries concerned. It was also becoming evident that there was a reluctance on the part of the government departments concerned to accept the responsibility to fund the testing of chemicals, as this was regarded as the responsibility of industry. A number of different institutional laboratories emerged in response to this situation. Larger companies could afford to devote resources to the area of safety testing, and support the development of in house expertise. The novel development was the emergence of contract research laboratories, which, because they could specify a fixed price for tests, while ensuring confidentiality, could aid smaller firms less able to face the cost of an in house laboratory. Finally, the establishment of a research association jointly funded by government and industry posed another, more co-operatively based, solution to the question of testing, and toxicological research. This institutional base, established during the fifties was to remain the most important location for research into toxicology in the post war period.

6.2. Developments in Toxicology : Basic Research

The institution most concerned with developing a research programme in basic research during this period was the M.R.C. Toxicology Research Unit. As it was intent on defining its role as an independent laboratory, more effort was put in defining the nature of toxicology,

> From the earliest days of experimental physiology and biochemistry toxic substances have played an important role as tools in the study of mechanisms of normal biological processes. Toxicology as a practical problem involves the effect of poisonous materials on the whole

> animal .... Toxicology is not a discipline in itself; it is or should be, the application of recent advances in the basic sciences to the study of practical problems.[10]

This position drew on a demonstrable tradition in the biological sciences, and was taken up by contemporary scientists. In particular R.A.Peters emphasised the use of toxicology as a research tool for other biological sciences, and believed,

> Dissection by the use of poisons has been employed in the past by physiologists.... Toxic substances are now being employed by biochemists with equal success to map the course of metabolic events in vivo.[11]

There were problems in attempting the study of substances rendered toxic by the metabolic processes of an animal which were acknowledged by the scientists at the Unit,

> The possibility that any compound may only become toxic after it has been attacked and changed by the metabolic processes of the animal further complicates the study of the toxic action of any compound and may make it difficult or impossible to correlate the behaviour of a compound against a biological system set up in vitro and its behaviour in the intact animal.[12]

The work of the Toxicology Research Unit was defined as the study of physiological and biochemical processes by investigation of the disturbances produced by physical and chemical injury. Substances were to be chosen because of their interest to industry or agriculture or because they exhibited particular toxicity.[13] Some testing would be done on new materials or those for which new uses were proposed to keep the Unit in touch with current problems in the area, and observations of interest may spring from such work and provide a stimulus to research on new lines.[14] The main interest of the Unit was to examine the mechanism of toxic of action of substances on physiological processes. The prime motive of any routine experiment would be an attempt to design better

methods for assessing chronic toxic effects.[15]

Some of the research problems taken up included the study of demyelination lesions of the Central Nervous System produced by organophosphorous compounds after accidental poisoning in a factory.[16] The chlorinated hydrocarbons were added because of the exposure of the public to chronic dosing over many years due to their stability in the environment.[17] The liver was identified as an important organ in the metabolism of substances, and a frequent site of toxic injury, so techniques to measure blood flow and internal temperature were developed.[18]

The unit, then, was attempting to develop the tradition in toxicology which used poisons as a tool in elucidating biological mechanisms, rather than becoming a laboratory oriented towards industrial research. Despite this, however, they were sensitive to the social aspects of toxicology, and realised that their research programme could be oriented both towards those substances that were likely to pose a problem for human health. In addition, they took an interest in improving and assessing the safety testing systems that were being suggested.

6.3. Safety Assessment

While this basic research programme was developing there was much debate over the use of animal tests for predicting the safety of substances for use in consumer products. The development of these tests had a champion in Alastair Frazer, Professor of Medical Biochemistry and Pharmacology at Birmingham University. Worried about the increasing use of chemicals in food he believed,

> It is the duty of all who have knowledge of food, whether they be nutritional experts or industrialists, to advise and help less informed sections of the population if synthetic chemicals are to be introduced into foods for purposes of improvement, or for other legitimate reasons, full responsibility lies with those concerned with the use and distribution of the materials, and adequate safeguards for the health of the public must be taken before any responsible body can agree to the use of such materials.[19]

So the policy of waiting for a substance to be shown to be toxic after it had been used in food and then ban it was no longer credible. Frazer thought,

> such an attitude is at variance with present experience in this field of toxicology and in related nutritional problems. It is often difficult to demonstrate the causative factors in a toxic condition derived from food, especially if the article of diet is widely distributed and consumed by a large number of people .... The controversy that raged over now well recognised vitamin deficiencies clearly indicates the difficulties of establishing scientific facts in nutrition.[20]

The addition of chemicals to food he felt, was justified for technological reasons and to avoid food shortages, as public safety could be ensured providing adequate pre-market testing was done. So,

> There is no need to suggest that the use of all chemicals in food manufacture should be forbidden, even if such extremist action were a practical solution, since the problems raised by the use of chemicals in food can be solved along more rational lines.[21]

The effects of a food additive could be inferred from biochemical and pharmacological assessment of the chemical with an appreciation of its nutritional effect, chemical structure and purity, a publication similar to the British Pharmacopia for tested chemicals would be useful.[22]

Frazer suggested short and long term feeding tests through several generations, tests in more than one species and in human volunteers. A second investigation should be undertaken to assess possible indirect effects of two types, one due to interaction of the chemical with some other food constituent, producing a toxic agent, and the other due to interference with the nutritional properties of the food.[23] Such a proposed plan could not ensure complete safety, but, Frazer thought, it would keep the risks to a minimum,

> There are those who say that these investigations do not provide a 100% guarantee of safety. Of course, this is true - there is practically nothing we do in our lives that carries a 100% guarantee of safety. It is contrary to the whole basis of biological research to expect such absolute results.[24]

The uncertainty attached to such evaluations could only be reduced by increasing the extent of basic understanding in biological science, so that, 'the greater and more accurate this basic knowledge, the more complete and more reliable is the safeguard derived from its application.'[25] Important systems for study were gastro-enterological research, visceral function, and special aspects of toxicity such as effects on tissue structure, growth, carcinogenesis and haemolysis.[26] There was no doubt, according to Frazer, that,

> The essentials will become clearer as knowledge in this field accumulates. For this reason the first important step from the point of view of the food industry is to encourage and promote fundamental research on the nutritional and gastro-intestinal aspects of these problems .... University laboratories, which are primarily concerned with fundamental work must lead the way, they must be given every opportunity to provide the essential foundation upon which the more applied studies of the industrial or the toxicology laboratory can be based.[27]

While such attempts at devising a reliable set of tests was in progress, a critical review of the experimental methods used in chronic toxicity testing was published by two members of the M.R.C. Toxicology Unit, J.M.Barnes and F.A.Denz.[28] They stated that the recognition of the possibility of long term toxicity arose from the experience of industrial hygiene in estimating safe doses:

> Those responsible for the health of either the general population or the group of industrial employees exposed to chemicals have to decide what, if any, would be the largest quantity that could be absorbed with safety for a more or less indefinite period.[29]

The most common way to set safety limits, they held, was on the basis of past experience with people exposed to chemicals, but there were so many novel chemicals entering the human environment that biologists had been charged with the responsibility of assessing their potential harm, although 'absolute proof of the safety of a chemical for man will not be demonstrated by experimentation on animals, but equally it is clear that

some observations on animals must be made.'[30] The basic criticism of the tests was that they were not standardised and were a poor substitute for more basic knowledge of the metabolism of a chemical. Generally, the aim was 'to find a 'safe' or 'harmless' dose that might be fed to animals over long period',[31] rather than investigating any specific effect. It was thought to be necessary to define conditions of safety that would cover all age groups with different nutritional states. Most of the test designs did not take these factors into consideration, so that such tests should, the authors felt, be looked on as temporary, as

> always a makeshift affair to be replaced as soon as possible by a more permanent structure of knowledge built on the foundations of physiology, biochemistry and other fundamental sciences.[32]

The review criticised all the techniques suggested for use in chronic toxicity tests, and the factors that may affect its outcome. On the choice of test animals they noted, that besides the rat, which was commonly used because it was 'cheap', fertile omnivorous and hardy, is well standardised and studied and has a short life span',[33] other animals that were used included mice, hamsters, guinea pigs and rabbits, with pig, dog or monkey as a second species. But the use of a few dogs in an experiment where three other species were investigated were very difficult to interpret, and there was little evidence to show that more species differences would show up. There was rarely enough evidence to compare animal results with those in the human, although many chronic responses were specifically found in humans. With rats it was also necessary to decide which strain to use, as there was a desire to attain greater uniformity between animals by eliminating genetic variations, although there was no evidence that this was an important factor. The evidence on which the sexes were treated differently was unclear, and it was recommended that 'unless reproductive studies are to be included, it may be better to use a larger group of one sex in a given experiment.'[34]

One problem, long recognised in industrial toxicology, was the presence of impurities in the test substance arising from its manufacture. The experimenter must then decide whether to use the purified material, or that arising from one manufacturer, both of which could be meaningless in terms of human exposure. Once the material had been selected, however, the choice of dose levels was difficult, as

> A large dose range means many small groups or unmanageable numbers of animals. A small range calls for skill and luck in reaching a correct decision with the chance of much wasted time and effort.[35]

The method of administration was also fraught with problems. Most commonly, the substance would be mixed with the feed, sometimes in the presence of a solvent which could alter its toxicity. If the food intake was reduced due to the unpalatability of the food, then the actual dosage was not known. Food intake also differed with the sex and age of the rat.

The actual composition of the diet was known to affect such factors as food intake, absorption of the material, its nutritional basis animal growth and resistance to disease. Administration through the drinking water had the problem of measuring dosage, and the possibility of dehydration, while inhalation studies, most often used for industrial chemicals, had the additional problem of the distribution of particles of differing sizes.

An important question in the design of a chronic toxicity test was its duration. The F.D.A. favoured two years as adequate time for all toxic effects to be manifest, but after this time Barnes and Denz felt there could be too few animals remaining to determine whether the disease is due to age or the material under test. The most unambigious response is the death of the test animal and they considered that death of an animal to be as sensitive an indicator of toxicity as the chronic test,

which implies 'a damaging conclusion indicating that the chronic toxicity test is often crude and insensitive',[36] Other indices of chronic harm included reduction in the growth rate, usually taken as changes in body weight or organ weight. There were problems in its measurement, as growth is affected by environmental conditions and so a group of animals exactly the same age was necessary. The problem of differential organ growth weights had rarely been studied in chronic tests. The weights of organs were often within the normal range, and increase in liver and kidney weights had often been given as evidence of toxicity, but

> It is doubtful if increased organ weights alone can be accepted as evidence of disease .... it is clear that many organs, including the kidney and the liver, rapidly hypertrophy when given more work to do .... The toxic material requiring metabolism or excretion supplied the stimulus of work.[37]

So there should also be evidence of functional inefficiency for indications of abnormality.

One of the most vulnerable results of a chronic test was a negative one, open to the criticism that the material may be shown to be toxic with a different test, which 'shows the difficult of finding acceptable criteria of poisoning or abnormality attributable to the toxic agent.'[38] As there are always some reactions too small to be detected, and the limits with a group of animals in normal laboratory housing is a detection rate of 1 in 100, Barnes and Denz felt it was necessary to decide the rate of abnormality which could be disregarded. There were special tests such as fertility studies, but this needed a considerable knowledge of rat breeding, and those substances shown to be toxic with this study, were also toxic in more conventional studies. At best a negative result could strengthen confidence in the material. Investigation of the metabolism of the substance, often ignored by scientists, could give a more useful result, and 'work along these lines might well lead to the

acquisition of a more satisfactory understanding of 'toxicity' than will ever be learnt from conventional studies of histological or haematological changes in an aging population of experimental animals'.[39] The possibility of carcinogenicity was also frequently ignored in studies, for there the investigator needed standardised reproducible experiments, while the toxicologist wanted evidence of safety under all conditions of exposure. The conventional chronic test was not thought to be the best means of obtaining information. Barnes and Denz favoured exploring the mode of action of the material under test.

> The assessment of a toxic hazard can be properly based only on some knowledge of the fate or behaviour of a compound after its introduction into the body. A study of the absorption distribution and elimination of a compound might take longer and prove more exacting than a routine feeding test. But such work would lead logically to biochemical and physiological studies. This approach would be scientific in contrast to the empirical method of chronic toxicity tests .... The value of routine long term feeding tests as measures of administrative expediency is not a question for discussion here. The use of such an experimental approach should not be confused with a scientific attack on a difficult problem.[40]

The limitations of chronic toxicity tests were widely acknowledged, although the assessment of their value was contested by Frazer, who wrote, 'I do not consider, however, that one can altogether dispense with acute, sub-acute, and chronic tests that are intended to pick up unpredicted effects.'[41] Indirect effects, such as alteration in nutrition could be investigated with multigeneration test, stringent testing being used to decrease uncertainty, measuring fertility, birth weight, and lactation, as 'it is usually found that the most important indices are weight gain and reproduction in multigeneration tests',[42]

The use of such tests could enable the use of chemicals in food, according to Frazer,

> it seems unreasonable that food technologists should be denied the proper use of advances in chemical industry .... there is a need for two types of control of the use of chemicals in food - one might be termed 'technological' and the other 'toxicological.'[43]

Toxicological control means the chemicals should not be harmful to health, although 'practically all of the food additives in common use are non-toxic .... a theoretical risk does attend the use of chemicals in food'.[44] Frazer highlighted two possibilities of harm, one from the direct effect of a substance on the organism, and one from its indirect effect on the nutritional value of the food, or the formation of a toxic substance. The type of knowledge required covered many disciplines. The chemical and physical properties of the material, known pharmaceutical knowledge to predict possible action. The nature of impurities should be known, and the proposed use of the chemical, its action on food, an estimate of the standard dietary dose. The biochemical data that was necessary included information on whether the chemical was modified by enzymes in the body, the absorption from the intestinal tract and the metabolism of the additive, for the route and rate of elimination so that evidence of injury to the liver or kidney could be obtained with information on the culmination of successive doses. An acute test should be done, and 'as a rough guide it may be said that the LD50 of a potential food additive should be at least 1000 times the standard dietary dose and preferably of the order of 10,000 times.'[45]

Other tests which should be done included a long term study in an animal which had not been shown to be particularly resistant to the toxic effects of the chemical, and 'to examine this we need a group of forty animals; ten males and thirty females. These are fed control and test materials over several generations .... three generations are sufficient'.[46] Two dose levels were suggested, one 100 x the standard dietary dose, and a control should be included. Measurements of body weight taken weekly,

and fertility and related measurements. At the end of the experiment a number of organ weights should be taken, the most common ones being heart, liver, spleen, kidneys, adrenals, small intestine, large intestine, uterus and testes. The question of species specificity must be tackled, and controlled tests in humans were considered better than multispecies testing. Some assessment of nutritional damage should be done but such tests should be carefully interpreted as 'reduction in nutritional value may be more than counterbalanced by improved palatability or availability'[47] of the food.

There was, then, considerable debate about the scientific nature of the safety testing of chemicals which had been stated in such a pragmatic way. Although the limitations of animal tests were exposed, the main debate was concerned with the relative emphasis that should be put on basic research versus safety testing. Thus it was acknowledged, that, to a greater or lesser extent commercial requirements meant that some testing was necessary. The differences arose with the question of uncertainty about the results of these tests, and the necessity to improve their predictive value through support of basic research. These considerations had been developed principally by academic scientists, rather than those located within the other laboratories which had been established to carry out safety testing. Their concern was less to consider the scientific justification for testing, but to be practically engaged in utilizing tests which were accepted as adequate. Thus pragmatism was to win over science, as pressure from commercially based scientists required that some accepted guidelines were developed which indicated the extent of tests needed to give an acceptable indication of safety. As an example, the use of safety factors can be seen as the acceptance of practicality over scientific problems.

6.4. The 100 Fold Safety Factor

This had been suggested by the Division of Pharmacology, as an ad hoc way to minimise the uncertainty attached to the results of safety tests. Frazer accepted the use of a safety factor in combination with a range of tests, despite the lack of an established scientific basis, as 'it is common practice to use some arbitary multiple of the standard dietary dose of the substance under test. A reasonable margin of safety would seem to be provided by using 100 x the standard dietary dose'.[48] He felt that the 100 fold safety factor could be used as a safe dose, one hundred times smaller than the known coverage effective doses (ED 50);

> With most common drugs, the general ratio of uneffective, effective, toxic, and lethal dosage in man is not greater than 1: 10: 100: 1000 .... Dosage has a direct relationship to body weight.[49]

The aim with a food additive would be to find one that is biologically inactive up to 100 times the standard dietary dose, although there was not consensus over how these experiments should be interpreted.

This lack of consensus was of more concern to Barnes and Denz, who felt that although there were problems in the interpretation of test results, particularly with the need to extrapolate to a safe dose, the common solution, the adoption of the 100 fold safety factor, 'should not obscure the fact that it has no experimental or theoretical base'.[50] This was especially important as a very weak area of knowledge was in the extrapolation of animal data to the human environment. In addition to this, the difficulties with administering the test substance in the feed made experiments using 100 times the normal dietary dose difficult to interpret, so paired feeding tests were necessary.

Despite these reservations the use of a safety factor was suggested in some of the test guidelines put forward during this period. In an article on the proposed investigation of a food additive Frazer included

dosage levels of 50 and 100 times the standard dietary dose to be administered during the chronic test. An advisory committee to the M.R.C. - the Toxicology Committee also favoured the use of a safety factor, because of the difficulty of extrapolating from animal experiments to the human population,

> The magnitude of this safety factor must depend on the seriousness of the toxic reaction when it occurs. In general a factor of 100 has come to be accepted as generally reasonable. The possibility of unpredictable reactions in man and the enormous size of the population at risk means that such a factor may not be excessive.[51]

This then, illustrates the developments that were taking place in the establishment of tests that were considered suitable for testing new commercial chemicals. Despite the fact that scientists widely accepted the lack of scientific base to the 100 fold safety factor, it was accepted pragmatically as its use was felt to decrease the intrinsic uncertainty about the assessment of safety using animal tests.

On the policy side, two major questions arose, over the control of agricultural chemicals and of food additives. These problems arose independently of each other, and illustrate the ad hoc nature of the development of government controls in this area. Both voluntary and statutory controls were developed and these changes brought the scientific debate over the uncertainties involved in assessing safety into the political arena, forcing an official position to evolve around the question.

6.5. The Evolution of the Control of Pesticides

The Second World War marked a turning point in pesticide technology. The nineteenth century had seen the introduction of highly poisonous chemicals such as lead, arsenic and hydrogen cyanide into agriculture. These, coupled with naturally occurring poisons such as derris, nicotine,

and pyrethrum formed the basis of pest control until the 1930s. The use of acute poisons was prohibited under the 1933 Pharmacy and Poisons Act. By this time the development in oil refining had opened the way for the synthesis of a large number of synthetic organic chemicals and the large chemical firms were looking for new chemicals that showed pesticide activity. A Swiss firm, Geigy, which discovered DDT, had shown an interest in pest control in 1927, this was broadened in 1935, and by 1944 DDT had shown its effectiveness by successfully supressing a typhus epidemic in Naples. Research at IG Farben on organo fluorine compounds began in 1934 to look for a more effective insecticide than those already available. This proved to be a fruitful line of research which gave rise to a number of potentially useful organo phosphorous insecticides and also equipped the German army with a lethal nerve gas.[52] Gillespie stated that,

> By 1947 five distinct groups of insecticides (which dominated these early developments) had been developed with different principles governing their synthesis : DDT, Benzene hexachloride (BMC), cyclodienes, organo phosphorous compounds and carbonates.[53]

These novel compounds produced during the war subsequently gave rise to much concern over their safety. The chlorinated hydrocarbons were shown to be extremely persistent in the environment, and by 1954 the concentration of DDT in the food chain was recognised.[54] The subsequent developments of the organo phosphorous compounds led to their substitution for the older, more toxic pesticides.[55] The use of pesticides had also expanded since the end of the war. Few of the natural and inorganic agents had acted as specific agents against particular pests, and were mainly used on high value crops such as market gardens or greenhouse crops. By the 1960s systematic organo phosphorous and organo chlorine compounds had increased the number of approved pesticides from 27 in 1955 to 98 in 1965.[56] New products such as specific acting herbicides

growth regulants and systematic fungicides were introduced, increased the number of approved products to 200 in 1975.[57] Overall a decreasing use of organo chlorine products gave way to the organo phosphates and carbonates. Increasing pest resistance to chemicals stimulated the introduction of new types of insecticides.[58]

The first major safety problem to be acknowledged regarding agricultural chemicals was their potentially lethal effects on the health of agricultural workers. There were seven deaths between 1946 and 1950, which resulted in the establishment of a Working Party to investigate precautionary measures against toxic chemicals used in agriculture, by the Minister of Agriculture and Fisheries.[59] The committee was chaired by Professor Zuckerman and members were scientists in governmental employment (see Table6.1). The Working Party was required,

> To make recommendations for the promotions of the safety of workers in the agricultural use of substances which are toxic or harmful to human beings [60]

by collecting evidence from interested parties. They found that the deaths of the agricultural workers was due to their regular employment on spraying dinitro-ortho-cresol (DNOC) without protection in hot weather, so the prolonged exposure had allowed a lethal dose to accumulate. There were other workers who had shown non lethal symptoms of DNOC poisoning.

This report gave rise to a Parliamentary Bill for the compulsory medical supervision of agricultural workers.[61] The Zuckerman Working Party took the view that the manufacturers should study the acute and chronic effects of any new compound, and should issue information about the prevention of accidents. In addition, they urged that,

> In view of the need to inquire into such precautionary measures as might be necessary, the Agricultural Departments should satisfy themselves that their arrangements with industry are adequate to obtain prior information about chemical compounds which the manufacturers propose to market as insecticides and weed killers.[62]

TABLE 6.1 : Members of the Working Party on Precautionary Measures against Toxic Chemicals Used in Agriculture 1951.

Chairman	:	Professor S. Zuckerman	Office of the Lord President of the Council
Members	:	A.B.Bartlett	Ministry of Agriculture and Fisheries
		R.A.E.Galley	Agricultural Research Council
		C.J.Gimingham	Plant Pathology Laboratory, Ministry of Agriculture and Fisheries
		A.Holness	National Agricultural Advisory Service, Ministry of Agriculture and Fisheries
		J.M.Roger	Medical Research Council
		W.H.Senior	Department of Agriculture for Scotland
		H.Cole Tinsley	Agricultural Improvement Council
Secretaries	:	K.R.Allen	Office of the Lord President of the Council
		J.T.Martin	Plant Pathology Laboratory, Ministry of Agriculture and Fisheries

Source Report of the Working Party, HMSO, 1951.

This view was reinforced in the House of Lords by Lord Carrington, that it was the manufacturers duty to carry out tests rather than that of the Ministry of Agriculture.[63] The Agriculture (Poisonous Substances) Act was passed in 1952, and gave statutory authority to the recommendations of the Working Party.[64] In effect it gave the minister power to make regulations concerning the safe use of any approved pesticide.[65] Following the passage of the act the incidence of fatal poisonings in British agriculture improved. None were reported in 1953,[66] while there were two in 1955,[67] and the British Medical Journal reported,

> As a result of a co-operative effort by many people, including manufacturers, distributors and officials of the Ministry of Agriculture, Great Britain has had in more recent years a good record in the safe use of the more dangerous pesticides.[68]

The Working Party was reconvened by the Ministers of Agriculture and Fisheries Health and the Secretary of State for Scotland in May 1951 to examine potential hazards from residues in food, with Professor Zuckerman acting as chairman, but with an extended membership (see Table 6.2). There was a general lack of information on the mode of action of new agricultural chemicals, and the lack of a notification scheme meant that official bodies were dependant on the goodwill of manufacturers for information about new preparations.[69] The Working Party discovered that a few manufacturers had the facilities for investigating the toxic properties of their compounds, but food manufacturers had no means of finding out which chemical substances they bought, and only carried out analysis for established poisons such as arsenic.[70] The report recommended that

> New administrative precautions are required of a reasonable check on the introduction of new toxic compounds is to be maintained, so that only those about which sufficient toxicological and analytical data are available could enter the market. In view of the industry's willingness to co-operate in any reasonable measures to

TABLE 6.2 : Working Party on Precautionary Measures against Toxic Chemicals Used in Agriculture, 1951-3.

Chairman	:	Professor S.Zuckerman	Office of the Lord President
Members	:	J.M.Barnes	Medical Research Council
		R.M.Barrett	Ministry of Health
		A.B.Bartlett	Ministry of Agriculture and Fisheries (May-September 1951)
		P.N.R.Butcher	Ministry of Health
		W.Moreley Davis	National Agricultural Advisory Service, Ministry of Agriculture and Fisheries
		F.A.Denz	Medical Research Council
		N.R.C.Dockeray	Ministry of Food
		R.A.E.Galley	Office of the Lord President of the Council
		R.F.Giles	Ministry of Agriculture and Fisheries (May-September 1951)
		W.McAuley Gracie	Ministry of Agriculture and Fisheries (From September 1951)
		A.Holness	Agricultural Improvement Council
		D.G.Inch	Ministry of Agriculture and Fisheries (From January 1951)
		B.S.Lush	Medical Research Council
		J.R.McCallum	Department of Agriculture for Scotland
		R.J.Peters	Department of Health for Scotland
		H.W.Taylor	Agricultural Improvement Council
		H.Cole Tinsley	Agricultural Improvement Council
		E.E.Turtle	Ministry of Agriculture and Fisheries (From January 1951)
		H.M.White	Ministry of Agriculture and Fisheries
Secretaries	:	K.R.Allen	Office of the Lord President of the Council
		W.H.Melrose	Ministry of Food
Assistant Secretaries	:	Mrs. E.D.Cookson	Ministry of Food
		Miss D.M.M.Kenyon	Ministry of Food
Assessors who attended meetings with Trade and Professional Organisations			
		Professor F.Bergel	Chester Beaty Research Institute
		B.A.Ellis	Department of the Government Chemist
		G.G.Taylor	Agricultural Research Council
		Mrs. J.Taylor	Public Health Laboratory Service

Source, Report of the Working Party : Residues in Food HMSO 1953.

> prevent danger to the public it should be relatively simple to arrive at a satisfactory solution to this problem.[71]

The report highlighted the lack of facilities either public or private for routine pesticide testing in Britain, and the insufficient knowledge about toxicity which resulted. It urged that,

> some central body is needed whose main function would be to direct or co-ordinate the collection of information about the use of toxic substances in the protection of growing crops and stored food, and to advise the Ministry concerned about administrative measures which may be required to obviate such risks to the eventual consumer as may arise from the use of such substances.[72]

This body would have an independent chairman and permanent secretariat which would ensure that the official departments collected the information about the effects of various chemicals and would be available to Departments for consultation about new chemicals proposed by industry. Manufacturers would also notify the Departments concerned when new products were developed.[73]

The report was favourably received, although medical opinion was not wholly convinced. The British Medical Journal wrote, 'the risks of consuming very small quantities that could find their way into food are difficult, if not impossible to measure',[74] and that there was a better case for banning the use of bacterial cultures as rodenticides where other methods were available. As there was no evidence of illness from eating treated food, the case was not one of immediate danger, and a more pressing problem was to establish the chemical residues in food imports by some agreed means.[75] There was some feeling that the medical profession should make the decision over which chemicals could be added to food, as

> several experts have suggested that decisions about the permissable chemical additions to food should be within the province of the medical profession, which they think is losing control of the situation.[76]

Other people worried about the lack of toxicological information

available to the profession to make this type of decision, supported more animal testing,

> But it is difficult to interpret the findings of animal tests. Some would allow a large safety factor and expect a substance to be harmless to animals in doses exceeding by 10 or 100 fold those likely to be consumed by man.[77]

This would, however, lead to the banning of sodium chloride as a flavouring agent. In effect the argument boiled down to one of risk versus benefit,

> We must know the facts be they political, economic, chemical, or biological - before we can assess what advantages will accrue from accepting an uncertain risk entailed by eating food containing foreign chemicals .... When an advisory committee such as the one suggested by the Working Party has collected enough facts it may eventually frame a policy in which the use of chemicals in agriculture and food storage will come to represent a balance between productivity, cost, quality, keeping properties, nutritional value (for example, vitamin content) of the food and any possible risk of injury to health from chemicals persisting in the food.[78]

The government accepted the recommendation of the Working Party that an interdepartmental advisory committee should be set up to review all risks that might arise from the use of toxic substances in agriculture with an independent chairman and assisted by expert sub committees. Negotiations were to take place with the Association of British Insecticide Manufacturers so their members would notify relevant government departments of new toxic substances or new uses for existing products. It was expected 'that these and similar voluntary arrangements would obviate the need for any statutory requirement of notification'.[79] The primary function of the precautionary measures was to keep under review any possible risks, as it was emphasised that there was no specific incidence of disease directly attributable to chemical residues in foods.[80] The terms of reference of the committee were wider than those suggested by the Working Party, and were to keep under review all the

risks that may arise from the use of toxic substances on agricultural products and in food storage and to make recommendations to the ministers involved. The manufacturers supported these developments as long as it was possible to arrange notification of new substances in such a way that would provide safeguards against premature disclosure.[81]

The voluntary notification scheme was finalised in 1957 after negotiations between the A.B.I.M. and the Ministers of Health and Agriculture Fisheries and Food. Manufacturers and distributors of new pesticides or new formulations of known pesticides would voluntarily give notice of their intention to market the product with full details of its proper use so that government could advise on measures to protect both workers and consumers.[82] The advisory committee would consider the data available and make recommendations as to whether or not the substance should be included in the Agriculture (Poisonous Substances) Regulations, or whether to encourage manufacturers to include precautions in handling on their labels, and to decide what dosage level is safe as a residue in food.[83]

From the beginning the notification scheme expected that the toxicological data received from industry would be curtailed by the amount of funds available to devote to testing. In the view of the pesticides regulation department,

> It should be pointed out that the toxicity requirements of the 1957 Notification Scheme and the 1966 Pesticides Safety Precaution Scheme were the result of negotiations between Government Departments and the Pesticides Industry. They represent what was felt to be reasonable but not what would be nice to know if money was no object.[84]

The object of a pesticide is to be inherently toxic to some form of life, it was necessary to establish their potential toxicity to man at an early stage to submit with notification procedures. The Notification Scheme urged,

> All pesticides are toxic to some form of life or they would have no commercial value. It is therefore essential that their potential toxicity to man should be studied at an early stage by suitable experiments on animals. No practicable pattern of tests can be suggested that would make it possible to provide adequate data on all existing or likely future compounds.[85]

The tests were designed to protect agricultural workers, the public as consumers of treated crops, domestic animals and wild life.[86]

A range of investigations were suggested. The acute toxicity with an approximately LD50 value for rats, mice and a number of other species, (one non rodent), for the largest non fatal and smallest fatal dose. Full studies on the characteristics of poisoning were required, with behavioural and pathological changes, with the apparent mode of action of the substance. The oral and percutaneous routes with the purest available active ingredient and the standard commercial formulation. A guide to the toxicity for pesticidal chemicals not likely to be present in food was given as

> those requiring a dose of 500mg/kg or more to poison an animal may require little further study. For those killing animals in dose range 50-500 mg/kg some knowledge of their mode of action as poisons must be established, e.g. by cumulative toxicity tests etc. The results of these additional tests will point to the necessity or otherwise of further study. For substances with an LD50 of 80mg/kg or less the toxicological properties must be studied in much greater detail.[87]

Other suggested tests included cumulative toxicity, where multiples of the threshold toxic dose would be given daily, 5 days a week for 2-4 weeks. This gives information on risks to workers exposed intensively for short periods of time. This test can be extended into a chronic toxicity test involving repeated daily administration of small doses for six months, and longer if unexpected reactions occur. If carcinogenic action is expected, this would be extended for two years. The general condition and rate of growth should be studied, with all animals subject

to a post-mortem study.[88]

Other recommended studies were on delayed toxic effects, metabolic studies, the possibility of potentiation of the chemical, skin penetration and absorption, physiochemical properties including persistence and information relating to early signs of poisoning with anticlotal measures. The risks to users in the field should be assessed during the field trials of a new product, and the possible risks to consumers estimated from information about the scale of use, the crops to be treated and the toxicologically active residues at the time of harvest for a comparison of the likely human intake with the highest harmless dose for animals. Special attention was required for residues which are found in staple dietary factors and infant and invalid food. This information was necessary, however,

> It will thus be seen in some circumstances a quite elaborate and time consuming investigation must be carried out in order to provide adequate evidence for the safety of a chemical's proposed use on food crops. In other circumstances adequate data may be obtained with comparatively little expense and effort. The better the data the more certain is the safety of the user and the public.[89]

In order to facilitate the assessment of the scientific data an advisory committee was formed in 1954, following a recommendation of the Working Party, called the Advisory Committee on Poisonous Substances used in Agriculture and Food Storage. This committee, with the aid of a scientific sub-committee gave technical advice to all the departments concerned with the scheme. Although neither committee has industrial representatives on it when a particular product is being considered an industrial representative may be co-opted to ensure that commercial secrecy is maintained, and the company is represented throughout the negotiations.[90]

The question of the toxicity of chemicals used as pesticides was

raised, initially as a response to the deaths of agricultural workers, which was the traditional regulatory attitude of the British government. Once the problem had been identified, however, the solution was more innovative and far reaching than controls of toxic substances had been in the past. The Ministry of Agriculture and Fisheries, having established an expert committee compiled of governmental scientists to report on the question of safety, accepted the recommendations of the Working Party. It is notable that these recommendations were compatible with the expressed governmental policy, that industry should be responsible for listing new substances. The ministry also accepted the advice that adequate controls for pesticides could be established on a voluntary basis through negotiations between industry and the government. They then ensured their own access to scientific opinion by setting up an advisory body containing academic scientists. This policy was established in an ad hoc manner, with no reference either to controls that existed in other countries, or the developing questions of the assessment of food additives safety which was being considered by the Ministry of Food.

6.6. Food Legislation

The problem of the intentional addition of chemicals to food for specific technological reasons, is different to the question of pesticide residues in foodstuffs, and is controlled by different legislation, that is the Food and Drugs Act 1955. This, however, was a development in a longer history of the legislative control of food adulteration.[91]

The increased use of novel food ingredients which had been noted by the Ministry of Food, and documented by the Committee on Toxic Substances in Consumer Goods showed no sign of abating, and it was soon giving concern to both scientists and politicians that these may involve unknown long term hazards for the health of the population. In 1951 a leader in

the British Medical Journal pronounced that 'there is .... still great anxiety about the quality and purity of the food sold to the public',[92] and that the use of chemicals as food ingredients,

> should be under the control of the government so that there is full information about the extent to which substitution is taking place .... Similar considerations apply to the use of synthetic dyes.[93]

The wartime advisory committee was renamed the Food Standards Committee in 1948. In 1951 it set up a sub-committee to review the Public Health (Preservatives etc.) in Food Regulations and make recommendations for their amendment. The sub-committee was to consider the technical and scientific data relating to the use of various chemicals used in food, and wanted to collect the views of research associations, food processing firms and medical and technical associations on the existing regulations.[94] The sub-committee was chaired by Professor E.C.Dodds, a well known biochemist, and included both governmental and academic scientists. They set up a pharmacology panel to further give advice on the medical aspects of chemicals in food. The members of the preservatives sub-committee during the fifties are shown in Table 6.3.

In the same year the question of chemicals in food was raised in the House of Lords by Lord Douglas of Barloch, who drew attention to the increasing use of chemicals in the growing and preparation of foodstuffs, so that it was difficult to find any food that had not been treated in some way. In particular he drew attention to the fact that the F.D.A. in America had a list of 842 chemicals used or proposed for use in food, while there was no scientific evidence on the safety of many of them.[95] Similar concern was shown in the House of Commons when Dr. Barnett Stross asked the Minister of Food whether the powers contained within the 1938 Food and Drug Act were sufficient to protect the public and to enforce the testing of new chemicals before use, or whether the government should help the trade to set up research facilities. The attitude of the

TABLE 6.3 : Members of the Preservative Sub-Committee 1951-1959

Chairman	:	Sir E.C.Dodds
Members	:	C.A.Adams
		Professor S.J.Cowell
		M.Crompton
		A.Glover
		E.B.Hughes
		J.M.Johnson
		H.E.Magee
		J.R.Nichols
		Professor B.S.Platt
		A.Propper
		G.Roche Lynch
		M.G.Smith
		R.F.Tyas
Secretaries	:	W.A.Godby
		M.O.M.Franklin
		B.W.Smith

Additional Members of the Pharmacology panel :

Professor E.Boyland
Professor G.A.H.Buttle

Source: Food Standards Committee Reports.

government on this occasion was that the biggest threat to public health was the risk of contamination by bacterial infections. Mr. Frederick Willey, Parliamentary Secretary to the Ministry of Food emphasised that most food poisoning was bacterial in origin and that the use of chemicals in food was indispensable. In effect there was no need to be unnecessarily alarmed, as there was no record of deaths by poisoning from these chemicals, and the Ministry was in consultation with scientific officers of the Ministry of Health, the M.R.C. and the trade. More research was required to create a field of precise scientific knowledge which would avoid such difficulties. The need for the powers under the Defense Regulations had shown that the 1938 Act was not altogether satisfactory.[96] Dr. A.D.Broughton added that there were at least 400 chemicals in use in food manufacturing in Britain about which there was no information on their long term effect on the human body.[97]

There was some speculation as to how the scientific objectives of policy could be achieved. The lack of knowledge on the biological effects of chemicals weakened the power to control them as 'the dangers to health that may result from the chemical manipulation of food cannot yet be exactly defined.'[98] The B.M.J. reported, however, that some people felt it a waste of scientific training to spend time in deciding whether a chemical substance was safe in use, even though Sir Edward Mellanby had suggested that some of the increasing incidence of disorders of the alimentary tract could be related to food processing, and there was also an increasing use of hormones and chemicals in the manipulation of live animals.[99] Methods of testing and the design of tests were not universally accepted, particularly when the amount of the substance used in the test was much larger than that intended for human consumption,

> Much of the work consists of long feeding tests on the experimental animals, but the results can be strictly applied only to those animals - usually rats and rarely is time devoted to the study of the mode of action of any of

> those substances .... Had similar experiments and reasoning been applied to the study of vitamins some would be considered too toxic for inclusion in human food.[100]

In 1952 the British Association for the Advancement of Science held a meeting to discuss the extent of food adulteration, and in 1954 a meeting of the International Union of Nutritional Sciences in Amsterdam looked at the question of additives in food.[101] An important influence in Britain was the establishment of a U.S. congressional committee in June 1950. The 'Delaney committee', was to investigate the use of chemicals in food, and it was discovered that, of the 704 substances considered by the committee 204 were open to doubt about their safety, a fact which the B.M.J. predicted would call for administrative action in Britain.[102] Attention was paid in Britain to the activities of the F.D.A., but it was felt that progress was slow, 'tremendous efforts have been made there .... but the real scientific knowledge that has resulted from all this work is meagre.'[103]

In 1950, Mr. C.A.Adams, head of the food standards and labelling division of the Ministry of Food, gave an address before the division of Food, Drug and Cosmetic Law of the American Bar Association, in which he expressed the hope that legislation of food and drugs could be standardised between countries to establish a free flow of world trade, as legislation contemplated in the U.K. would bring it more into line with U.S. law.[104] The B.M.J. had another opinion on legislation, however,

> Few would recommend applying compulsion in order to ensure the public is offered only what acknowledged experts on nutrition consider to be a more wholesome article than that which the consumer appears to want.[105]

The actual mode of controlling chemicals was also under question, particularly with respect to the banning of nitrogen trichloride for use as a bread improver;

> But the substitution of one chemical for another is not necessarily the best answer and a search is in progress in this country for other agents, physical or chemical, that may have a similar effect as improvers without the risk of producing drastic chemical changes in the composition of the wheat protein.[106]

In general, the British Medical Journal felt that there seemed to be a place for a national laboratory to be established,

> There have been repeated calls for the establishment of some national institute where toxicological problems associated with the increasing use of chemicals in food industry and other fields, including food production, can be studied.[107]

The question was raised again in the House of Commons on February 11th 1952, when Mr. D.W.Wade asked the Minister of Food what investigations he was undertaking on the nature of food chemicals. This led to a reiteration of the governmental policy by the Minister, Major G.Lloyd George, that food chemicals had not yet shown themselves to be dangerous, and that research into their safety was being carried out.[108] A Food and Drugs Amendment Bill was introduced into the House of Lords on November 10th 1953. Its primary purpose was to improve the quality of hygiene applied to food, and to prohibit the sale of food made injurious to health by the addition or obstruction of chemicals during manufacture. The Bill gave powers to the Minister of Food to obtain full information from manufacturers about any new substance intended for use in the preparation of food. In addition it gave ministers the power to prohibit the use of certain substances in food if they had reason to believe it injurious to health, and powers to regulate labelling and advertising to control false claims about its nutritional value, thus putting wartime regulations on a permanent footing. The Bill went further than the 1938 Act on the sanitary condition of premises used in the preparation of food, giving the Ministers of Food and Health the power to make regulations covering the whole field of food hygiene. The Bill served to

centralise power in the hands of the Ministers of Food and Health, and the B.M.J. saw the proposal as continuing,

> a trend of rule by regulation which is deservedly unpopular but it may be welcomed as showing the government intention of coming to grips with a serious health problem.[109]

When the intention of updating the Food and Drugs legislation was announced there was some feeling that the question of drugs should be removed from the Bill. There were very few prosecutions related to drugs under the existing Act. The need for a new consolidating act was deemed 'urgent', due to the large number of amendments passed after the end of the war.[110] The Act was also needed because of the changing responsibilities of the Food and Drug analysists since the 1938 Act was passed. The Pharmaceutical Journal had the opinion that,

> Before 1938 they were concerned mainly with offences which related to adulteration or mis-description on sale of foodstuffs and drugs. Today they are concerned also with offences relating to the exposure for sale, advertise-ment and labelling.[111]

The journal supported legislation which would remove the supervision of the sale of drugs from the Ministry of Food to an authority with greater technical knowledge, such as the Pharmaceutical Society or the Ministry of Health.[112] They were, however, wary of the proposed regulation-making power that the new Bill gave to Ministers,

> Government control by regulation may have been a necessity in wartime, but it should not be needed as a means for controlling the sale of food and drugs in peacetime.[113]

Some rationalisation was needed as 'the present system with its dupli-cation of legislation and duplication of enforcing and administering authorities is cumbersome in the extreme'.[114] The Bill conferred extensive powers on the Ministers of Food and Health to make regulations concerning food and drugs especially to discover whether they contained harmful ingredients. There was, then, a contradiction in the fact that there was no similar control over the marketing of cosmetics, according to

the Pharmaceutical Journal,

> The growing practice of marketing beauty creams alleged to contain hormones or assimilate vitamins is one which needs to be watched, for so long as this development in the cosmetic trade is ignored by the legislature, pharmacists will have good reasons for arguing that the sales are unduly tipped against vendors of really useful medicaments.[115]

The Bill had a second reading in the House of Lords on November 24th, when the applicability of the Bill to controlling cumulative toxicity was emphasised.[116] Viscount Woolton moved that the regulations were necessary because of the increasing popularity of 'eating out', and the increasing use of food processed in factories.[117] He also reported that during the war the Ministry of Food had sent a group of experts, including Sir Jack Drummond, to the U.S.A. to study the labelling of food, and the Bill was a direct result of conversations going on between the Ministries of Food and Health during that time.[118] During the second reading of the Bill in the House of Commons (July 1954), Broughton (Batley and Morely) said that the Labour government had started to prepare legislation in 1951, when the local authorities and other parties had been consulted. Since the 1951 election the Conservative government had carried on the work, but had 'put the Bill into cold storage', as they had been faced with the difficulty of resistance to the Bill from irresponsible quarters in the catering industry.[119] The Parliamentary Secretary to the Ministery of Food, Dr. Charles Hill said that a consideration of the Bill was the effect of regular consumption of small amounts of chemical substances arising from the developments in food technology over the past fifteen years which entailed a move from dealing with proved injury to a need for more experimental work.[120] Dr. Barnet Stoss outlined the problem with regard to additives,

> We have to be careful not to fall between the one stool of excessive enthusiasm for the protection of the public health .... and the other stool of making light of the whole subject and assuming that there is no danger.[121]

The Ministry of Food was, however, prepared to defend the use of chemical additives. Hill warned, 'do not let us develop around the word 'chemical' a kind of hoodoo',[122] while Mr. Richard Fort (Clitheroe), in a reply to Mr. John Eden (Bournemouth West), held that

> He has allowed his imagination to run riot in suggesting that diseases like poliomyelitis and the more complex cancer might be connected with the chemicals which are used in the food industry.[123]

The Bill received the Royal Assent on November 22nd, 1955, and now forms the basis of the U.K. approach to the control of food additives. That is that the manufacturer must examine any new chemical intended for use in food products for toxicity particularly with regard to possible chronic effects, before it is put onto the market. It was possible to enforce these regulations, as the Ministers had access to technical advice from the Food Standards Committee, its preservatives sub-committee and the pharmacology committee. In fact, 'the development of the use of the permitted list was closely accompanied by the consolidation of an advisory mechanism'.[124] Responsibility for the implementation of the Act is shared by the Ministry of Agriculture Fisheries and Food, the D.H.S.S., the Scottish Home and Health Department and the Department of Health and Social Services (Northern Ireland).[125]

The United Nations were interested in the question of the evaluation of food additives. The Fourth Session of the Joint FAO/WHO Expert Committee on Nutrition suggested that a conference on food additives should be convened by the WHO and FAO, with the intention of convening an expert committee to lay down general principles on the use of food additives. This meeting took place in September 1955, where the Joint FAO/WHO Expert Committee on Food Additives was formed. The first report was published in 1957.[126] This report listed the technical purposes for which the use of a food additive was justified, and was an advantage to the consumer. These included the maintenance of the food, enhancement

of its keeping quality or stability, with the resulting reduction of wastage, making food attractive to the consumer, and providing essential aids in food processing.[127] The use of chemicals was not felt to be permissable when used to disguise the use of faulty processing and handling techniques, to deceive the consumer when this results in reduction of the nutritive value of the food, and when the desired effect could be obtained by good manufacturing practices which were economically feasible.[128] Other factors which should be taken into consideration were whether there was evidence available to show that there was a benefit to the consumer either because of qualities not shown by any other chemical or because it produced a product which was cheaper. Their use should be reduced in food intended for infants and young children.[129] In order to ensure safety, the chemical and physical properties of the additive should be known and limits in use set by restricting its use to specific foods. Legal control of food additives should be based on the principle of permitted lists, which 'effectively prevents the addition of any new substance to food until an adequate basis for judgement of their freedom from health hazard has been established'.[130] The committee also favoured the principle that consumers should be warned of the addition of chemicals to their food by a declaration on the label, and that food legislation should be enforced by adequate staff, laboratory, and technical provision.[131]

Guidelines for safety evaluation were published in a second report, in 1958.[132] Its intention was

> to give those engaged in this field, in either a scientific or administrative capacity, a general picture of the type of data that should be available about any additive before its use in food is officially approved.[133]

The fear of chronic effects was paramount,

> The fact that additives may be taken over the greater part of a lifetime gives rise to concern lest such prolonged intake may produce reactions hitherto unsuspected.[134]

but they would not recommend a system of tests.

> No single pattern of tests could cover adequately but not wastefully the testing of substances so diverse in structure and function as food additives. The committee considers that the establishment of a uniform set of experimental procedures that would be standardised and obligatory is therefore undesirable. Furthermore, it would not necessarily resolve the difficulties that have sometimes been encountered in reaching decisions on the safe use of food additives. For this reason the committee concluded that it was only possible to formulate general recommendations with regard to testing procedures.[135]

The recommendations included acute toxicity in at least three species, short term tests on two species, rodent and non rodent, with groups of 10-20 rodents of each sex, and at least two non rodents of each sex. A range of dosages in feeding tests was desirable with a control group on an untreated diet. A chronic (long term) study should be carried out on rats of both sexes with groups large enough for adequate statistical analysis. Other recommended investigations included biochemical tests, pharmacological techniques to learn about the mode of action, and chromatography and radioactive tracer methods could be used to separate unknown compounds from highly complex mixtures, useful for identifying metabolites. During the long term tests weight gain and possible nutritional effects should be established, and studies of different organs and of carcinogenic action are necessary. The Committee also recommended a safety factor of 100 fold to be adequate.

The establishment of a British policy towards food additives drew on a different tradition from that of agricultural chemicals. There had been a long history of food control in Britain, and the Ministry of Food had taken an interest in the use of chemicals in food ingredients

since the increase in their use during the war. In addition there was an initiative in America, with the establishment of the Delaney Committee, which was significant enough to take the question of food additive control in Britain beyond the concern of the Ministry of Food. The question was raised in parliament, due to the need to update the 1938 Food and Drug Act. The Ministry of Food had a standing expert advisory committee which could offer information on the best controls which could be adopted. In this case, however, expert advice was not the only imput to policy making, which involved statutory legislation passed in parliament. The recommended guidelines, also, were those developed by the World Health Organisation, rather than a British source, so there was no standardisation of tests between the pesticide and food additive scheme.

6.7. Other Aspects of Policy

In 1957 two articles on toxicity were published in the Monthly Bulletin of the Ministry of Health. The first, prepared by the M.R.C. Toxicology Committee, gave an outline of the information required in the assessment of toxicity.[136] The role of the committee was strictly defined,

> The role of the Toxicology Committee .... is to discover and interpret the available information about the safety of harmfulness of chemical compounds to which the general population or a particular group of it may be exposed, and to make suggestions for further research work where this is deemed to be necessary. Such tasks as those of defining the conditions of safe use or the setting of permitted concentrations in foods or other consumer goods depend so largely on factors outside the purview of the Committee that the Committee cannot in general undertake the formulation of practical advice.[137]

The emphasis was on the difficulties of prescribing a series of toxicity tests for every compound, and the need for the examination of a compound to be carried out after the preliminary examination of the compound. The general information required was the acute toxicity and LD50, the

signs of poisoning elicited by a non fatal dose, the cumulative effects, the maximum dose that could be consumed by rats during the period of their most rapid growth without impairing growth, or affecting their general condition, the metabolic fate of the material, and where necessary special tests, such as skin penetration or inhalation. The Committee favoured the use of a safety factor, as has already been indicated. The Committee felt that as general rule human exposure to foreign chemicals should be minimised as far as possible, particularly with regard to chemicals in food products, and occupational exposure to chemicals.

The second article, written by J.M.Barnes, was on the question of the interpretation of toxicity tests.[138] A major problem he pointed out, was the biological complexity of such tests, which were not easily reducible to mathematical techniques. The LD50 test was developed under special circumstances, as 'it was the need to assay insulin and other powerful pharmacological preparations as efficiently and economically as possible that led the late Dr. J.W.Trevan in 1927 to publish his suggestion for using the LD50 as a method for expressing the toxicity of a drug.'[139] This technique, however, demanded a laboratory where all variables were under control, which implied it had a limited use for the majority of uses that chemicals have. In many cases testing would show how toxic materials could be safely used, although 'in some fields toxicological work may be directed towards establishing a case that a given substance is not toxic and therefore permissible as an additive to food or other consumer goods'.[140] Barnes distinguished two interrelated properties, toxicity and hazard,

> Under the general terms toxicity which is the ability of a material to produce poisoning we need to know something of its properties - physical, chemical and biological. In order to assess the hazard or the probability that the substance will produce poisoning, we need to know in addition something about the manner and circumstances under which it is used and the dose to which the operator or consumer is exposed.[141]

Different data should be required from a toxic and a non toxic compound. For the latter (e.g. a food additive) certain minimum requirements could be laid down, but a toxic compound, such as a pesticide should be investigated by a trained scientist, as the problem was deciding on a safe dose. An idea about the mode of action of a compound was desirable, as it would 'help us to devise suitable laboratory tests to measure or detect the early effects of such poisons'.[142] The cumulative effects of a poison, such as cancer might take years to develop, and there would always be a danger that a new form of poisoning might appear. There were difficulties in extrapolating results from animal tests, but some work in America indicated the versatility of the liver in dealing with foreign chemicals, and studies on behavioural danger could become important. The best indications of toxicity were 'well tried formulae of growth, longevity and perhaps fertility'.[143] The absence of knowledge in the area tended to make recommendations on the subject of safety conservative.

> This lack of any absolute standard of safety in such matters as toxicity probably accounts for the inconsistencies which commercial interests usually have no difficulty in detecting among administrative and scientific recommendations.[144]

The toxicity tests could never be an appropriate substitute for knowledge, and caution was therefore necessary,

> The toxicity test by itself is not a satisfactory basis for decisions on safe use. Everything else must be taken into consideration and the more this is done the greater are the opportunities for individual's opinion - prejudices if you like - to sway the balance of judgement of the problem as a whole.[145]

Thus, it can be seen that it was in the policy arena that pragmatism obtained its supremity over basic research, as Barnes, the principal defender of basic science admitted that some compromise in the assessment of safety could be reached.

6.8. Comparison of the Suggested Test Procedures

The major testing schemes that were suggested during the fifties have been summarised in Table 6.4. These include one suggested to cover the addition of chemicals in food, suggested by Professor A.C.Frazer and published openly in the trade press, and guidelines suggested by those responsible for implementing the pesticide notification scheme. In addition there is the scheme suggested by the M.R.C. toxicology advisory committee for general purposes and the WHO/FAO suggested tests for food additives.

It can be seen that, there is a great deal of agreement over the necessity of certain tests, while with others there is very little. The area of concurrence is with the tests for acute toxicity and the administration of the LD50 test to at least three species of animal. It can be said, however, that the agreement is over the need to examine the lethal effect of the substance - and this had long been the concern of those wishing to control poisonous materials. The area of the lack of consensus was with longer term toxicity, a concept that has been scientifically accepted for a much shorter time. Not only is there disagreement over the need for a cumulative (or sub-acute, as the F.D.A. had termed it) toxicity test, but also on the method by which it should be carried out. This applies also to the investigation of chronic toxicity, as both the recommended duration and the suggested dose levels vary widely.

There are also a number of extra tests which were suggested, and the variation here is also large. In particular the pesticide scheme required a number of tests which could be related to the safety in use of pesticides. The recommendation by Frazer for human trials, both small groups under observation, and larger ones with a statistical survey, were not popular, and not taken up elsewhere. The M.R.C. Toxicology

TABLE 6.4 : Comparison of Suggested Test Procedures

TEST	SCHEMES			
	(a) A.C.Frazer	(b) Pesticide Notification	(c) M.R.C. Tox. Committee	(d) W.H.O. Food Additive
Chemical and Physical Examination	√	√		√
Acute Toxicity Test (LD50)				
oral	√	√	√	√
parenteral	√	√		√
mice	√	√	√	3 species
rats	√	√	√	1 non
other	√	non rodent	√	rodent
Biochemical studies	√	√	√	√
Cumulative toxicity				
Dose:- Largest non toxic		√		
Range				√
2 species 10-20 animals				√
2-4 weeks		√		
Chronic toxicity				
Duration - 6 months		√		
12-24 months		√		√
Life span	√			
Dose : 2 dose levels & control	√			√
Largest non toxic		√	√	
Several generations	√			
Rats, both sexes				√
Skin Toxicity		√	√	
Potentiation		√		
Delayed effects		√		
Diagnostic Information		√		
Human Trials	√			
Investigate for signs of poisoning with non-fatal dose			√	
Maximum concentration consumed during period of most rapid growth			√	
Inhalation			√	
Opinion on general mode of action			√	√

Source :

(a) A.C.Frazer (1952) 'Problems Arising from the Use of Chemicals in Food'. Chemistry and Industry May 24 p.457

(b) The Scope of Toxicological Studies in Relation to the Safe Use of Pesticides. Pesticide Notification Scheme 24th March 1958. Plant Pathology Laboratory, Harpenden Laboratory, Harpenden, Herts.

(c) M.R.C. Toxicology Committee (1957) Assessment of Toxicity Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service 16 January p.2.

(d) Joint FAO/WHO Expert Committee on Food Additives (1958). Procedures for the testing of Intentional Food Additives to Establish their Safety for Use. Rome.

Committee also suggested some observations of a more general nature that were not taken up elsewhere. As far as governmental policy went, the Ministry of Agriculture and Fisheries was officially recommending the pesticide studies while the Ministry of Food suggested industry should follow the WHO/FAO guidelines. Thus because official responsibility was divided, and the scientists responsible for carrying out the tests isolated within industry, the question of standardising the test procedures and methods did not arise as a problem.

6.9. Conclusion

The decade 1950-1959 was important in establishing the new relationship between the scientific and policy arenas. In the scientific field there was a major assessment and reassessment of the issues surrounding the question of the evaluation of chemical safety. Two major approaches can be identified one stressing fundamental research, the other, routine testing. All the major laboratories that, in Britain, are specifically concerned with toxicology were established by 1960, and the diversity of institutional settings in which toxicology is found, was established during this decade. On the policy side, two major efforts - to control pesticides and food additives - were made, both policies emphasising the ad hoc nature of British effort in this area. Each problem was confronted individually, even though the Committee on Toxic Substances in Consumer Goods had illustrated the common threat that the addition of chemicals under different circumstances showed. This decade consolidated the former trend, that scientific development and legislative control were interacting factors. Consultations between scientists from government, academic and industry defined the problem of safety as a technical one which could be solved by ensuring new substances were subject to certain tests before they were put into use.

The M.R.C. Toxicology Research Unit continued to define its

attitude to research. Toxicology was conceived primarily in terms of its practical orientation - the objective of research was to reveal answers to problems of social or industrial interest. This orientation, however, was not to interfere with research into the basic mechanisms of toxicity. Toxic substances were a tool for investigating biological processes. Their metabolism would throw light on biochemical questions, and investigation of their mechanism would illuminate basic physiological processes. Where routine testing was necessary it was to be regarded as a temporary substitute for basic research, which at best would present problems for more research. At worst it was a time consuming effort which was impossible to interpret due to the uncertainty involved. The philosophy of the Toxicology Unit saw the development of a specialty organised around questions external to the science, which would lead to an increase in fundamental understanding of chemical and biological interaction.

For those who supported the development of testing programmes, there was a slightly different starting point. Frazer stressed the uncertainty in fundamental research, and the length of time for new knowledge to become accepted. He was critical of the backward looking approach which would allow the use of a chemical until evidence accumulated against it. In particular the food industry provided a social function in feeding the population, but had a responsibility to ensure the safety of its chemical additives through the rational application of scientific knowledge, biological investigations with an adequate safety factor. There should be an ongoing programme of basic research, but this was not the primary aim, and would be physically removed from the day to day testing in industry. The criticisms of chronic tests, that they ignored variations in age and nutrition, the presence of impurities in the test substance and the difficulty in measuring dosages, he felt could adequately be overcome by good test design, the use of a statistically significant number of test animals and controls and the use of a safety factor.

These two approaches differ more in emphasis than scientific analysis, and to a certain extent are as much related to the institutional setting where the protagonists envisage the work being carried out as to differences in scientific opinion. Both agree on the importance of basic research, and under particular conditions the necessity for testing substances to make an evaluation of safety. The philosophy of the M.R.C. Toxicology Unit is, however, one that could be developed by a research laboratory with its own direction and no external or commercial constraints. The conception of a testing programme is for an industrial laboratory which requires an evaluation of a specific substance for its own use but has little interest in funding basic research which is undertaken in universities.

The major policy initiatives during this period were in the control of agricultural chemicals and food additives. Both had been identified by the Committee on Toxic Substances in Consumer Goods as problems requiring attention. In the traditional way, however, the control of pesticides was highlighted as a reaction to the deaths of agricultural workers applying toxic chemicals. The subsequent policy was based on the recommendations of a Working Party consisting of governmental scientists. These embodied the concept, already stated by the government, that industry should bear the cost of testing their novel substances. They also recommended voluntary collaboration between government and industry, whereby the results of such tests could be independently scrutinised by a governmental expert advisory committee. This was a completely new procedure in policy administration, and depended on the co-operation of the industry through its trade association, while the Ministry of Agriculture and Fisheries had the ability to prescribe the use of any indescribable substance under the Agriculture (Poisonous Substances) Act 1952. Such factors as flexibility and co-operation in the setting of tests was emphasised by industry in the operation of this

scheme.

The question of chemical substances in food was of more topical concern. There was in existence a series of legislation relating to injurious substances in food, and the establishment of the Delaney Committee in the United States highlighted the problem. The Ministry of Food had already made its concern known to the committee on Toxic Substances, and was anxious to retain the power to elicit from manufacturers the ingredients of their products. The question was raised a number of times in both Houses of Parliament, and although the official position emphasised the problem as being one of bacterial infection, the numbers of chemicals involved caused much alarm, so the Food and Drugs Bill that was introduced included powers to control the safety of food chemicals used. An advisory committee structure for food was already in existence, so a philosophy of permitted lists for food additives did not entail a radical new innovation in administration. A statutory law was the traditional way that food ingredients had been controlled. The manufacturers responded to the fact that they would bear the cost of testing by endeavouring to establish a research association for that purpose.

The interaction between science and policy was firmly established during this decade. The science was in many different institutions oriented around practical problems, and the developments in policy ensure that a good part of the research done would be to satisfy the governmental committees that new substances are safe. The first schemes of information required to ensure safety are put forward, by scientists both to act as a guide for industry and through the publications of the Ministry of Health. The Pesticide Notification Scheme also suggested its own programme of research. These suggested guidelines, however, differed quite considerably in tests suggested, and different programmes became officially recommended for different situations. As this established its own programme of research. At this stage however, the negotiations were

on a voluntary level, flexibility and discussion between government, industry and scientists was stressed with suggested tests acting as a guide, and specific schemes for each chemical set up. Scientists were brought into the centre of the policy making stage in pesticides, in suggesting controls and setting test programmes, although they were not so important in the control of food additives. The decade 1950-1959 had finally established the post-war trends for both science and policy.

CHAPTER SEVEN

THE 'SAFETY EXPLOSION' (1960-1974).

The 'Safety Explosion'

The developments of the fifties ensured that the views of the Committee on Toxic Substances in Consumer Goods, that there should be some centralised co-ordinating base for toxicology in Britain had given way to an ad hoc approach to the control of toxic substances. The main development during the next decade was to add the question of the safety of new pharmaceuticals to the list of substances to be tested. This episode itself highlighted misgivings that were developing over the question of safety testing as it stood with regard to the question of detecting completely new and unforseen forms of toxicity in humans. Not only were statistical tests for carcinogenicity added to the test guidelines produced by government departments, but the experience with thalidomide raised the question of testing chemicals for teratogenicity, which had previously been completely unsuspected.

The publicity given to thalidomide ensured a quick political response to the problem of testing drugs, and brought more toxicological departments into pharmaceutical firms. In addition, the general increase in the number of chemicals that were to be tested brought more contract research organisations into existence during this period. In the area of basic research, however, the M.R.C. Toxicology Research Laboratory continued to develop their research programme, which remained the most coherent articulation of research problems in toxicology.

7.1. Basic Research

As the M.R.C. Toxicology Research Unit continued investigating the basic mechanisms by which chemicals exert their toxic effects, they continued to emphasise the particular biological basis for interest in this area, and the reasons why certain chemicals should be adopted as research problems. All the substances studies were potentially

dangerous because of occupational exposure except the two naturally occurring poisons aflatoxin and pyrrolizidene alkaloids for which there was evidence of wider human exposure.[1] The two strands of toxicological activity were well identified, by the director, Dr. J.M.Barnes,

> Experimental toxicology comprises of two rather different activities. In one, tests for toxicity by accepted methods are performed to provide information for some regulatory body which in turn may recommend the extent of use of a compound as a drug, pesticide, food additive or for other purposes. The responsibility for this work rests on industry and industry also now provides the basic information on the toxicity of the starting materials and intermediates to which industrial workers may be exposed. The second aspect of research in toxicology centres around the elucidation of mechanisms by which poisonous substances exert their effects. Knowledge of mechanisms is essential if the possible effects of exposure are to be realistically assessed. The work of the Unit has largely been oriented in this direction ....[2]

The emphasis of the type of work done by the Unit was of the disordered metabolism produced by some types of chemical and physical injuries.[3] The function of such work and its relationship to safety testing was also seen,

> The work on mechanisms of toxicity will be continued in the belief that the information so derived will influence the climate of thought in toxicology and make it possible to interpret more usefully results of arbitrary tests which are often all that can be suggested for the rapid assessment of likely hazards.[4]

Although this was an ultimate aim, progress was hindered by lack of knowledge of basic biological factors,

> However, the effects of the substances studied cannot yet be fully explained because of limitations of existing knowledge in biochemistry and physiology. Indeed it is often studies of mechanisms of toxicity which lead to a better understanding of the molecular basis for cellular organisation and function.[5]

The main interest was substances which produce unexpected toxicity.

In the early part of the 1970s the work was reorganised from

specific programmes to more general groupings. Some of the work undertaken was specifically commissioned by the Department of Employment 'so that more information on toxic hazards can be generated'.[6] The effects of substances on the nervous system was an area of interest relating to work on pesticides as some substances produced well defined lesions, and behavioural changes.[7] Work was done on carbon disulphide as it is an occupational hazard resulting in a raised mortality from coronary heart disease.[8] Interest in the liver centred on disturbances in porphyium metabolism and haemo synthesis as evidence of toxicity. There was a programme of investigation into toxic heavy metals and their metabolism, particularly cadmium, mercury, cobalt and beryllium. A programme of investigating chemical carcinogenesis was also started. It was argued that the work of the Unit should be seen as an investment, 'to some extent the Council's investment in this kind of work must be regarded as an insurance policy, for it seems inevitable that new toxic hazards will continue to be recognised or suspected'.[9]

While the unit was involved in investigating occupational hazards, it did not wish to restrict its work to this, which should be free from restriction,

> The Unit should continue to have the opportunity to study a problem in some depth and its work should appear as papers in the learned journals. It is therefore essential that a careful selection of problems suitable for examination by those experimental procedures it can undertake should continue to be made.[10]

Reliable information was needed therefore to identify toxic risks about which more knowledge was required. Good epidemiological procedures and clinical facilities were also necessary. But the study of toxic abnormality could also be restricted by lack of knowledge of normal physiological processes,

> The extent to which the Council continues to support the Unit for research into the mode of action of toxic substances must in part be a

> matter of assessing the probabilities of learning more about the function of an organ in health and disease by studying the action of toxic substances that disturb it.[11]

An emphasis was put on the fact that the Unit must derive its own criteria for deciding which substances to adopt as research problems. A number of criteria were developed to aid such choices :

1. The compound(s) are known to present a real or potential hazard to people
2. The pattern of use. as far as can be forseen, implies a continued exposure of some people
3. There is inadequate information to enable an acceptable level of exposure to be proposed
4. The nature of the toxic effects produced have some relevance to natural disease
5. The potential value of understanding the mechanism of toxicity for the possible development of safer alternative compounds
6. Interest of the proposed work in advancing biological knowledge and/or developing expertise within the Unit.[12]

As for the multidisciplinary dimension, the Unit had been successful in attracting biochemical expertise, with some support from pathology, but unsuccessful in attracting physiologists or pharmacologists. It was hoped that immunologists would take more interest in toxic mechanisms.[13] The work of the Toxicology Research Unit was expected to help evaluate the balance between risks and benefits of using particular chemicals, a question that was becoming increasingly important with regard to toxic chemicals.

> This situation frequently arises with the use of drugs but here the risks to the individual from an exposure to the drug

> can be balanced against the risks of not receiving the drug. In other situations, particularly an occupational exposure to a toxic substance there is no such simple cost benefit equation for the individual though there may well be one for the community.[14]

Such work must be located in an appropriate institution,

> Success in elucidating mechanisms of toxicity to the increasing degrees of refinement needed for the ever higher standards of safety demanded will only come if the work takes place in an institute where research on a broad front is being carried out.[15]

By 1960 the population was exposed to many different chemicals. Barnes felt that two few resources were invested 'for the experimental study and proper analysis of the properties and mode of action of toxic substances'.[16] Most of the concern had been over the indecision of relatively non toxic chemicals to foodstuff, so that increasingly greater laboratory facilities are being devoted to carrying out set procedures, to show that substances almost biologically inert can be tolerated by rats and dogs for years on end.[17] He felt this detracted from the assessment of real potential hazards, and common sense should be applied 'to ensure that scientific research in the field of toxicology is applied to situations where real hazards are known to exist'.[18]

The M.R.C. Toxicology Research Unit, then, had developed its particular orientation around the question of toxicological research, with a clear view of investigating the mechanisms of toxic action. Many of the substances chosen for research were occupational chemicals, reflecting the original reasons behind the establishment of the Unit. The toxicity of pesticides had also been taken up early in the research programme, and was continued during this period. To aid the choice of research problems, a number of criteria were developed, which drew both on scientific and social concern about toxic substances. Finally there was still criticism from the Unit on the type of data obtained from safety testing which

added little to the understanding of toxic mechanisms.

Further indication of the type of problems that were investigated as basic research was given in a symposium on Mechanisms of Toxicity held by the British Medical Bulletin in 1969.[19] This was a tribute to Sir Randolph Peters, acknowledged as an intellectual leader in the field of molecular biology.

> The reaction of arsenic with thiols is now classic and his work with fluoroacetate indicates an interference with metabolic pathways which incidently provided the ultimate proof that Sir Hans Krebs elegant studies in vitro of the tricarb-oxcylic acid cycle applied equally to the intact animal.[20]

Sir Roy Cameron was also acknowledged as an intellectual leader, who 20 years previously had recognised that the biochemical approach was a way in which understanding of toxic lesions was going to advance.[21] The assessment of the basic knowledge of toxicology was that there were no principles from which it was possible to predict the behaviour of compounds. For example the drug metabolising enzymes detoxify some compounds, but transfrom others into more poisonous ones.[22] Other means of investigating mechanisms beyond the biochemical are the effect on the CNS* and associated physiological and behavioural disturbances, and pathological investigation to define sites of damage and types of injury produced.[23] Contributions were drawn from the academic community and from industry, indicating that even within basic research the scientists from a range of institutional bases were involved in toxicological research.

Finally there was a growing concern to generate more generalised knowledge from basic research as the more unspecialised the relevant knowledge developed the general understanding becomes applicable to many specialised problems. A biochemical explanation of responses to chemicals was desired, but this was seen to be limited by biological complexity. The need to conduct this research was, however,

* central nervous system

emphasised by the growing problems with the tests used to assess the safety of chemicals during this period. Not only were the results of these tests questioned, but new types of potential harm became recognised.

7.2. Safety Testing

The conviction that chemicals could be safely screened for toxicity lost some of its certainty during the sixties. As popular concern for environmental matters grew, a number of shortcomings in the testing system were revealed. During 1963 Rachel Carson's 'Silent Spring' was published.[24] This book had a wide impact on popularising some of the scientific uncertainties in the general use of pesticides in the environment. In Britain the episode which excited public horror was the birth of malformed babies caused by the drug, thalidomide. It seemed that here the worst possible case had happened, and a completely unsuspected form of toxicity had been released.on to the public, although Worden suggests 'the manufacturers were not guilty, by the standards of the day, of any glaring errors in the pre clinical or pre marketing investigation of this compound'.[25]

After this episode the list of suspected chemicals increased. There were controversies over pesticides, particularly aldrin and dieldrin, food additives such as the emulsifier ME-18 implicated in Dutch Margarine sickness, and the sweetners cyclamate and saccharin. Other considerations related to the quality of the environment, related to industrial polution and the effect on wild life.[26]

These trends formed the background to various changing factors within safety testing itself. On the one hand there developed an increasing desire to strengthen the answers gained from these tests, as Worden states,

> with current legislation, widespread public and parliamentary attention and a genuine

> desire on the part of almost all manufacturers to avoid real grounds for incrimination, the testing of products or candidate products for safety purposes has increased greatly during the past decade.[27] (1963-73)

With this emphasis on tighter control through safety evaluation, requirements for testing for carcinogenic effects was growing,[28] and after thalidomide teratogenicity could no longer be ignored.

It was also discovered that the safety evaluation tests suffered from a number of shortcomings as toxicity seemed to be influenced by almost every possible variable environmental factor, rendering the experimental results neither absolute nor repeatable. A confirmation of the problems identified by Barnes and Denz in 1954. Improvements in techniques meant that substances could be detected at doses so small that their toxic effect was unknown. This gave cause for concern particularly with respect to potential cancer causing agents.

The major controversy was developing over the concept of zero tolerance. As analytical techniques improved it became possible to quantitatively detect smaller and smaller traces of chemicals in the environment and in foods. It also became apparent that an arbitrary figure for a safe level would still affect a large number of people if it was allowed to contaminate consumer products. Lack of knowledge on the action of the reversibility of the damage, exogonous factors, or co-carcinogens also blurred the question of a safe dose of a proven carcinogen. The major problem of interpretation at the lower end of the dose response curve was identified.[29].

Frazer put the case for testing food additives for carcinogenic potential,

> We want to be well assured that any food additive when consumed throughout the life span does not significantly increase the likelihood of the consumer developing cancer.[30]

There was little knowledge on the relationship between chemical structures and carcinogenicity, and although there were problems with the dose response curve, most experiments were thought to imply that a substance that is administered at a high dosage level over the life span of an animal and fail to cause any measurable change in tumour incidence is not a total carcinogen.[31] There were problems with the mode of administration, but all food additives and food packaging materials should be tested. Frazer suggested that an innovation in administrative control was needed to evaluate safety and suggested a scheme where four groups of experts would have a voice.[32] Group 1 would compile information on the specifications of the material, and should be composed of analytical chemists, physicists and those involved in chemical manufacturing practice to advise on the exclusion of potentially dangerous impurities. A description of methods of quantitative analysis would be given. This stage required co-operation between manufacturing industry and government analysts as complete confidentiality would be required, until the substance was adequately protected. The second stage in control would be to assess the technological benefit of the substance, so the second group should contain people competent in food science and technology with people from the food industry concerned with the needs of the consumer. This group decides on the necessity and efficacy of the food additive, and should be in contact with the Research Associations working in the field. When the food additive has passed these two stages then it is ready for biological evaluation. All toxicological data should be published as the material would be adequately protected by this stage. A third group was thought to be needed to evaluate this data and decide whether the highest no effect dose could be determined, or whether extra data was required. This group should include people with experience in biochemistry, nutrition, food science, pharmacology, toxicology and pathology. A final group would then decide whether or not the additive should be used, a decision to be made by food

scientists and technologists, people from food consumption surveys, nutrition, medicine, law and governmental administration. They should set permitted lists which are reviewed every seven years. The actual committee structure for evaluating the safety and necessity of food additives fell far short of this ambitious plan.

The assessment of maximum allowable concentrations (MAC) for industrial chemicals by the American Industrial Hygiene Association (AIHA) also came under some criticism.[33] Barnes held that the limits were not made after in depth studies of the toxicity of the material, in fact, 'in some cases the MAC is based solely on human comfort and bears no relation to the systematic toxicity of the material.'[34] Some limits were based on animal tests, but a systematic safety factor was not used. In fact new techniques of exposure of animals to concentrations in air had been developed, which should be used with two control groups, one in the apparatus breathing air, and one kept in cages, while a range of possible toxic effects should be investigated. There should be an acute test, and one of a two to three month duration using observations of mortality, growth or body weight change and the relative weight of liver and kidney, long and respiractory tract lesions. Damage to the CNS needed to be observed, although behavioural studies were not popular in Britain or America. Industrial exposure to chemicals is usually larger than the exposure of the general public, so, 'it is worth bearing in mind the general epidemiological principle that the larger the dose the more likely is an effect to be seen'.[35] The fundamental concept in industrial toxicology was that there are permissable levels of exposure and these are achieved by monitoring the environment and the workers. The latter were monitored by analysis of biological samples, commonly blood and urine. The breathalyser method had been adopted by some firms to identify inhaled substances and estimate the amount absorbed.

Other advances in techniques occurred during this period, which aided the identification of small amounts of chemical in biological tissue. Thin layer chromatography was as more rapid and more sensitive technique than paper chromatography. Even more sensitive a method of analysis is gas chromatography, but the last method, mass spectrometry, was found in few laboratories. Other techniques in use were polarographic analysis and bioassay. These techniques were introduced to evaluate pesticides, as every year about half the published papers in the pesticide field deal with methods of analysis on the occurrance of residues,[36] although this could be due to an imbalance in research in the area. 'it is important that studies of the biological significance of pesticide residues should keep pace with their detection and measurement'.[37]

It was in the safety evaluation of pharmaceuticals where the testing was left to firms that some of the conflicts between scientific interest and commercial expediency were located, according to Paget,

> the future of many pharmaceutical firms to mount investigation of problems of toxicity employing techniques new to the field is that, should they obtain information of which the significance cannot be evaluated, they anticipate severe difficulties with the regulating agency.[38]

This was given as the reason why many firms required test guidelines from the government to ensure that data on new chemicals would be acceptable.

During this decade there was increasing criticism over the whole subject of the medium lethal dose, and what, if anything, it measured. Studies on interlaboratory differences in absolute values were undertaken, as 'an oral LD50 is a function of the test procedures as well as of the substance tested'.[39] That as the value obtained is related to the conditions of the experiment, and is not an absolute value,

> there is a tendency to use the LD50 as if it were a fundamental property of the material .... This attitude is reflected in the wide scale reporting of LD50 data in the scientific literature with limited or inadequate specification of the test procedure .... recent trends to categorise substances by legislative and regulatory action introduce classes of acute hazard on the basis of numerical LD50 values.[40]

A more rigid study undertaken in 1967 was more ambiguous in its results. It attempted to determine the degree of variability of the single dose oral LD50 values obtained on a group of reference chemicals when different laboratories used their methods and animals and when the same laboratory used standardised methods and animals.[41] The outcome showed fairly stable results with all procedures, and concluded, that 'the results of this study would not provide justification for outlining rigid procedures to be used for determination of acute oral LD50'.[42] The evaluation of some British researchers was that the value of LD50 bore no relation to the maximum dose used in any chronic test, 'In the past the death of the test animals had the merit of being an unambiguous and apparently objective index of drug effect. In the light of modern physics chemical and biological techniques, however, such a gross effect is unnecessarily crude'.[43] They emphasise the factors influencing variations in result, such as changes in environment, and differences between strain, sex and species of the animal tested. They say that the LD50 gives excessive attention to accurate figures but not to causes and effects and 'is not only useless from a scientific point of view, but also uneconomical'.[44]

Discussion over the applicability of tests was constantly under review.

> Recently discussion has centred on the current applicability of the method used to determine toxicity, hazard and safety. These methods and principles have been used for many decades for chemicals known to produce injury to organs to alter various functions in animals. However the application of these same principles to

> reproduction, teratogenesis, mutatenesis or carcinogenesis has sometimes been questioned.[45]

With techniques to detect small amounts of chemical, there is the uncertainty of the validity of the dose response curve at this level, particularly where the response might be cancer.

The problems facing toxicology were cited by Aldridge as the large volume of work done to satisfy regulatory bodies. Lack of communication between scientists in the field and little contact with those working on industrial disease. There were organisational reasons for this separation, although the questions of exposure to chemicals were the same. Toxicology should investigate selective toxicity to expand knowledge of organised cellular systems while a whole animal multidisciplinary approach needed to be encouraged.[46] Other problems were identified as the reluctance of the establishment to update their scientific thinking by twenty years and accept there are no black and white answers to toxicity. Too little time and money was spent by industry while there is a lack of expertise, and too much of it concerned with hepatocarcinogenesis. Development of short term bioassays to place potentially hazardous chemicals in some sort of order of priority was needed.[47]

Another new problem that arose for toxicology during this period was the discovery of poisons that 'hit and run', that is that kill the organism after all traces of poisoning have left. Examples of 'hit and run' poisons include the work done, mainly at the M.R.C. research unit on nitrosamines and nitrosamides, which act as 'single dose' chemical carcinogens. This has also shown to be a property of organophosphorous compounds.[48] The concern was to elucidating mechanisms of selective toxicity with the aim of eventually finding a predictive structure-activity relationship, to explain these new problems. The main drawback to this work seems to be a general lack of both 'academic' research and funding.[49]

The predictive value of animal experiments came under scrutiny, and three general guidelines were suggested, 'first one must know how to look; secondly what to look for; thirdly one must look under the appropriate circumstances'.[50] Although experience is important in this, young technicians are often left to do the observations. Experience helps in giving some due of what to look for, from the chemical structure, physiochemical and pharmacological properties, 'but the greatest handicap in the effective application of existing knowledge is the scattered nature of the published information. It is easy to miss a toxic response unless there are definite lesions associated with it'.[51] It is necessary to start with an assessment of the pharmaco-dynamics and the metabolism of the compound. In improving predictability and reproducibility of experiments and standardising the health of the animals, Paget thought,

> A positive advance has been made through an elegant compromise, combining the advantages of both germ free and conventional animals, i.e.the absence of infectious diseases and normal physiological reactions, the so called Specific Pathogen Free (SPF) animals.[52]

It was not obvious whether the interests of standardising and reproducing experiments had removed such animal studies even further from the conditions of health found in the human population they were supposed to protect.

During the mid sixties a change in the orientation of education was taking place, emphasis was starting to be placed on the patent rather than the product. Clinical pharmacy was born during the late sixties, and by the early seventies had caught the attention of all colleges of pharmacy.[53] In this atmosphere more emphasis was being put on the toxic effects of drugs, highlighted by the thalidomide tragedy in 1962. More colleges started to run courses on toxicology in the U.S. There is no reason to believe that the trend in Britain differed significantly from this. This lack of specific training led to the situation where most toxicologists who are working for industry were obtaining only 'on the job' training,

which tended to be routine and a "recipe book" application of specific tests, with little room for more creative thought, even in the design of tests which may be 'conducted by technicians who might be inadequately qualified to observe and interpret the unexpected or to modify protocols as might be indicated by findings along the way'.[54]

In this period, then, the practical problems associated with the approach of safety testing were recognised. This was particularly true where novel forms of toxicity appeared, as they could not be predicted from tests that were designed to demonstrate known types of harm. A number of controversies over the safety of specific chemicals that had been through conventional tests emerged, for which the lack of generalised basic knowledge was blamed. In the case of chemical carcinogenesis there were two competing theories, which had different regulatory implications.[55] One way that was suggested to improve the situation focused on changing the administrative structure rather than the tests, but this was not generally taken up. General improvements in techniques complicated the situation, as traces of chemicals could now be observed which were much smaller than those used in toxicological evaluation. There was then, a general lack of confidence that tests would pick up all forms of toxicity, which was compensated for by the development of new tests for the newly discovered toxicological possibilities.

The institutional structure of the science in Britain was also a development of what had been established during the previous decade. In this period, however, the first innovations of a university course took place.

7.3. Institutional Developments

Due to the public concern over the thalidomide disaster, it is not surprising that more commercial pharmaceutical firms established toxicology departments during this period. In addition, a European society on drug

toxicity was set up. An important event in Britain, however, was the opening of the British Industrial Biological Research Association (BIBRA). BIBRA was officially established in 1960 and in December 1961, Dr. Leon Goldberg was appointed as director. He was qualified in both chemistry and medicine, and had been senior lecturer in Medical Pathology at Manchester University. In 1956 he became Medical Research Director of Benger Laboratories where he remained until taking up the position of Director of BIBRA.[56] He felt the aim of the research association was 'to provide a rapid preliminary assessment of toxicological acceptability, as the first step needed to facilitate successful commercial development of a new product or process'.[57] In the light of thalidomide, toxicological thinking was being re-developed. 'What is needed is a completely fresh approach which seeks to establish the biological potentialities of a compound as the essential first step needed to facilitate successful commercial development of a new product or process'.[58] BIBRA was to carry out both basic research and safety evaluation,

> By carrying out basic research on testing methods and by performing tests to ensure the acceptability of existing or new food additives BIBRA seeks to help the manufacturer and to protect the consumer .... The work of BIBRA, both in its choice of projects for basic research, and in the selection of substances for testing, is intended to eliminate the scientific obstacles to international uniformity in food additive legislation.[59]

The first European society concerned with toxicology was formed in 1962. A meeting was held in Zurich on the 20th September, attended by twenty six scientists from nineteen of the major pharmaceutical companies from six European countries, who formed the "European Society for the Study of Drug Toxicity."[60] The need for this forum had been developing, according to Liljestrand,

> the growing complexity of toxicity problems and the ever present fear of unforseen reactions to drugs in man indicated the need for a forum in which opportunities would be

> provided for frank discussion of these questions with the objectives of developing better methods for the study of drug toxicity or drug safety.[61]

The society was established under the guidance of Professor Tansk with three objectives:

> 1. to encourage and extend research in the field of drug toxicity;
> 2. to establish working groups with a view to scientific study of the various aspects of drug toxicity;
> 3. to ensure, by means of meetings, symposia, working groups and bulletins a regular exchange of all information bearing on drug toxicity and its evaluation.[62]

Scientific meetings were held twice a year until 1967 and once a year after that.

> These scientific meetings have provided excellent opportunities for discussion and exchange of information between scientists in industry, in academic professions and in the control authorities.[63]

In 1962 four working groups were established. The three that published reports were 'Duration of Chronic Toxicity', 'Effects of Drugs on the Foetus' and the 'Effects of Strains and Species of Animals on the Toxicity of Drugs'.[64] The president, until 1965, Dr. D.G.Davey, had an interest in defining the basic principles for the study of toxicity,

> The importance of establishing such principles, which have a scientific basis and consider all reasonable dangers without being excessively cautious, cannot be overemphasised. The basic principles presented by the society have had a great influence on current regulations in Europe.[65]

The membership of the society rose from 285 members at the first scientific meeting in 1963 to 774 members in 1971.[66]

The sixties was also a period when a number of pharmaceutical firms began to institutionalise their toxicology research. Among the laboratories set up included Smith Kline and French whose interest in toxicology started in 1960 with 40 research staff, only two of which were

employed full time on toxicology, with a budget in the region of tens of thousands of pounds.[67] In 1964 Ciba Geigy opened a toxicology unit in their British subsidiary, with four graduate staff and nine technicians.[68] In the same year Pfizer started investigating drug toxicity with one graduate pharmacologist reporting to a medically qualified pharmacologist and by 1974 they had 40 staff, ten of which were graduates.[69] Reckitt and Coleman established an interest in drug safety in 1961, employing fifteen staff by 1965, and a maximum expenditure of £400,000.[70] In 1966 Wyeth Laboratories established a Department of Drug Safety Evaluation which employed approximately six to eight scientists.[71] Bionex Laboratories, research and manufacturing chemists founded a toxicology laboratory in 1963 with four staff.[72]

This expansion in toxicological activity encouraged the establishment of some contract research associations. In 1970 Wickham Research Laboratories opened with two graduates to do safety evaluation.[73] In 1971 Toxicol Laboratories opened in London but moved to Ledbury in 1978 with about ten staff and an annual expenditure in 1974 of £300,000; mainly from the pharmaceutical, agrochemical and chemical industry.[74]

As demand grew for safety evaluation, particularly after the passage of the Medicines Act, it became obvious that there was a lack of facilities for training toxicologists at a national level. Professor R.J.Williams was interested in this, and when the chair of Biochemistry at the new University of Surrey was created in 1966, a former student of his from St. Mary Hospital Medical School, Dennis V.Parke , was appointed on the understanding that he would be allowed to develop toxicology as a subject. In 1967 the first undergraduate degree variant in Biochemistry and Toxicology was initiated with the first graduate in 1971 - the first undergraduate toxicology degree in the world. The chancellor of Surrey at this time was Lord Robens, chairman of the committee on Health and Safety at Work

with a special interest in developing occupational health, and well aware of the lack of expertise in the area. The undergraduate course gave training in fundamental sciences, but early in the seventies they started to plan a masters course in Toxicology intended as a broad technical training in all aspects of toxicology, with the idea that it trains people to go straight into laboratories. The course lasts for a year, but can be taken part time by people seconded from industry. There are a wide range of lecturers from government, industry and academic, especially from the M.R.C. Toxicology Unit and BIBRA who were involved in the original discussions about the course. The first course began in October 1973.[75]

After studying with Professor R.Cameron at University College Hospital Medical School, A.E.M.McLean went to Professor J.D.Judah at the Chicago Medical School, then to the M.R.C. Toxicological Research Unit for two years. In 1967 he was appointed senior lecturer in the Division of Experimental Pathology at U.C.H. Medical School where he retained his interest in toxicology.[76]

Changes in the social organisation of toxicology during this period, then, were essentially a development of the structure established during the previous decade. In particular, however, there was more interest in toxicology from pharmaceutical firms due to the increase in concern over the safety of drugs, and a general increase in the number of chemicals to be tested, which led to the establishment of smaller contract houses. BIBRA also started research attempting to get a programme of safety testing that was funded by the collaboration of industrial firms, and balancing this with an appropriate basic research programme. The first academic post graduate course also began during this period, due to the fact that there were a number of people at Surrey University who were concerned enough to get such a venture off the ground. Finally, the

international concern over these problems was demonstrated by the establishment of the European Society for the Study of Drug Toxicity which provided a forum for scientists concerned with this problem to meet.

In the legislative arena, during this period, two major pieces of statutory regulation were passed, the Medicines Act and the Health and Safety at Work Act, both of which required the testing of chemicals before human exposure. They both followed the trend that had been set during the fifties, as specific new committees were set up to analyse data submitted from industry. They also followed the cases of pesticides and food additives, in that both these problem areas were tackled in an ad hoc manner, were responses to different pressures, and scientists themselves were involved in the legislative process to different degrees.

7.4. The Regulation of Pharmaceuticals

The spectre that haunted the decade of the sixties was the unsuspected teratogenic effect of the drug, thalidomide. Both public and governmental concern over the safety of medicines dates from that time. Although novel pharmaceutical substances had shown toxic effects,[77] the question of drug safety did not seem to be recognised at a ministerial level. This was shown by the evidence given to the Committee on Toxic Substances in Consumer Goods by the Ministry of Health in 1949. The ministry had been concerned with the labelling and standards of medicines but the question of toxicity was not raised. The question had not been totally ignored by the medical profession. The British Medical Journal published a suggestion that the introduction of new drugs needed some sort of monitoring for safety by George Discombe in 1952.[78] He noted that some drugs showed toxic effects when used on humans and that the existing poison regulations had no facilities for notification of newly observed idiosyncratic effects. He suggested a small standing committee could be established composed of clinical and forensic pathologists,

> to collect evidence on the production of injurious effects by drugs administered for therapeutic purposes; to deduce from this and any other evidence available whether the therapeutic value of any such drug is great enough to warrant its continued use; and to submit representations and recommendations to the Poisons Board on the regulations for the manufacture, sale, advertising, packaging, labelling or prescription of drugs which have been shown to produce injurious effects.[79]

He suggested the Association of Clinical Pathologists should set up a small committee to collect the evidence.

The official attitude towards drugs remained one of complacency, faith in the manufacturers and reluctance to interfere with the right of the medical profession to treat patients as they wished.[80] When the association between thalidomide and congenital malformations of the limbs was recognised in 1961, it had a major impact on this laissez-faire mentality which had been dominating the question of pre-clinical drug control.[81] The Association of the British Pharmaceutical Industry (ABPI) set up a committee to consider testing procedures for new drugs,[82] while the B.M.A. were also worried about the media representation of the affair, and set up a committee to review the subject of drug testing.[83]

The publicity given to the question of drug safety after thalidomide was discovered exposed an area over which there was a lack of control and ensured it would be taken up in the political arena. On the 5th March 1962, the Minister for Health, Mr. Enoch Powell, in an oral answer in the House of Commons had to admit that the government had no powers to ensure that all new drugs were submitted to independent and reliable scrutiny before their use in the N.H.S.[84] The responsibility of the manufacturers was acknowledged in the House, with the acceptance that there had been no case of negligence in testing thalidomide, according to the current standards, that much time and money was spent on research, and 'it is the manufacturers responsibility to decide on the extent of safety testing

needed before the introduction of any drug is justified'.[85]

A number of suggestions were put forward in the House of Commons on the ways in which evidence of toxicity could be collected. Dr. J. Dickson Mabon proposed a centre to collect facts on effects and side effects of drugs.[86] Mr. Edleman asked the Minister of Health if he would set up a statutory authority comparable to the F.D.A. in America to supervise clinical trials, while Kenneth Robinson asked if the Minister of Health would set up a committee to consider the avoidable risks attendant on the introduction of new drugs and establishing standards for an independent assessment or control of clinical tests. Powell replied that he was seeking advice on the questions from the interdepartmental Standing Medical Advisory Committee.[87] This Committee set up a joint sub-committee to the Standing Medical Advisory Committee in August 1962, chaired by Lord Cohen of Birkenhead to advise on the testing of new drugs.[88] The M.R.C. appointed a committee to study the methodology of toxicity testing, with Sir Charles Harrington as chairman, but the Council did not want to undertake any routine testing. The government however, did not want to create a situation in which it appeared it was giving certain drugs a clean bill of health.[89]

A suggestion was made by Pfizer Ltd., for a controlling authority independent of industry or the consumer, to be set up under the Home Office to assess the evidence for the safety of new drugs, and 'the manufacturers would carry out their own testing procedures and submit their results to the proposed authority comprising experts capable of interpreting that type of data'.[90] The manufacturer would pay a fee when the data was submitted to provide revenue to finance an expert research group, to examine existing test procedures and develop latest methods for testing new drugs.

The ABPI released details of its proposals on drug testing on

22nd November 1962. The association had discussions with the joint sub-committee and their proposals were in line with the thinking of the committee. They wanted an advisory centre on drug safety, independent of government and commercial control, set up as a trust with permanent staff and director to review all data necessary to assess safety of a drug. No new drug should be released until it had gone through this procedure, and an 'early warning system' could be set up with the help of G.Ps.[91]

The B.M.A. also favoured the establishment of an independent body representative of all branches of medicine and ancillary services. It would assess the claims made by the sponsors of a drug, assess animal toxicity tests, encourage and assess clinical trials, publish information concerning limitations and hazards of the drug and approve all literature relating to it, including assessment report on the chemistry of the drug, assessment of therapeutic trials, supervision of drugs in use. They also recommended that drugs should have an approved name, included on the label, and all the scientific literature distributed to doctors with the drugs should be approved.[92]

The joint sub-committee of the Standing Medical Advisory Committee produced an interim report in November 1962 for the Minister of Health, after preliminary talks with the industry and the M.R.C. They recommended that responsibility for testing new pharmaceutical preparations should remain within industry because 'the industry as a whole, discharges that responsibility effectively within the limits of contemporary knowledge of methods of testing'.[93] The M.R.C. should give advice and guidance on the extension of knowledge through research. It was acknowledged that safety in animals did not necessarily mean safety in humans, and that a drug may be toxic in some species but still be of some value in the treatment of disease where there were no other options or a 'safe'drug may

produce adverse reactions in a few people. In effect the safety of a drug was seen as relative and not absolute. Finally, the sub-committee recommended 'there should be an expert body to review the evidence and offer advice on the toxicity of new drugs, whether manufactured in Britain or abroad, before they are used in clinical trials'.[94]

Further support for control over the safety of drugs came from the TUC Conference on 4th September, where a resolution was carried unanimously urging the government to ensure that all new drugs were subject to clinical trials. They favoured a statutory committee,

> It must not be another nominal committee without power like the committee for the classification of proprietary medicines under the chairmanship of Lord Cohen, nor in our opinion, an independent professional body, as suggested by the British Medical Association. It should be a top committee answerable through the appropriate minister.[95]

This committee should have a medical secretary comparable to the status of the secretary of the M.R.C., with the onus on the manufacturers to provide enough information to satisfy the committee of the safety of new drugs.

A Private Members Bill was introduced on 23rd November by Mr. Peter Emery,[96] but it was talked out at the second reading. Mr. Bernard Braine, Parliamentary Secretary to the Ministry of Health felt that the Bill did no more to control the introduction of new drugs than the recommendations of the joint sub-committee, as legislation would have to be very detailed and was not suitable for a Private Members Bill.[97]

The joint sub-committee had published their final recommendations on 4th April 1963.[98] The major philosophy behind the report was that voluntary rather than statutory control should be employed. It advocated (and the Health ministers accepted) that a Committee on the Safety of Drugs (CSD) should be appointed, with advisory sub-committees on toxicity, clinical trials and adverse reactions. Two members of the committee

dissented from this view. Mr. J.B.Grisset and Sir Hugh Linstead favoured early legislation, as they deemed a voluntary scheme to be too weak to be effective. The three sub-committees would monitor the three stages in demonstrating the safety or otherwise of a new drug while the CSD would gather and co-ordinate the activities of the sub-committees which would have the power to consult outside experts where they saw fit. Manufacturers would submit information on animal toxicity for the assessment by the toxicity sub-committee, while the manufacturer be responsible for organising clinical trials. There should also be some machinery set up by the CSD to monitor any adverse reactions caused by the drug when in general use.

The ABPI had earlier put forward a proposal for an advisory centre on drug testing as a trust independent of government and industry, supervised by an executive committee of seven members.[99] The joint sub-committee, however, did not feel that this would be a satisfactory solution as public opinion would be unlikely to be content with anything short of ministerial responsibility for verifying that adequate precautions, in the light of current medical and scientific knowledge, had been taken to secure the safety of drugs.[100]

The Ministry report listed the major defects of the voluntary scheme proposed. That it depended on the co-operation of the whole of the pharmaceutical industry, which could be difficult in the case of smaller firms with inadequate research facilities. The sanctions available to a voluntary scheme would be few, and would therefore give an advantage to unscrupulous manufacturers over their more conscientious rivals. Other important factors which were missing in the voluntary scheme were the restriction of all new drugs to prescription at least until their safety had been proved, and specific labelling requirements such as the last date that the drug could be used and a warning about its dangers. There should also be controls over manufacture and packaging so as to prevent

deterioration.[101]

Despite these reservations the recommendations of the sub-committee were accepted by the Minister of Health as an interim measure before a review of the legislation relating to drugs could be carried out. The Pharmaceutical Society supported the minority report, urging comprehensive legislation at an early date, as it had favoured since 1954.[102] The ABPI, however, had the view that the industry was doing an adequate job in testing new drugs and the association had established its own committee on clinical trials. It did not favour hasty legislation and felt a voluntary scheme would be effective as over 95% of prescribed products were manufactured by members of the association.[103]

In the House of Commons, the Labour Party also supported the view that statutory legislation was necessary, and a voluntary scheme would serve only as a cosmetic exercise to stop public and professional anxiety with no real sanctions. Enoch Powell defended his decision by the fact that collecting data would depend anyway on the voluntary co-operation of the industry, and it was unlikely that a drug not cleared by the CSD would be prescribed by doctors. It was felt that responsibility for harm caused by a drug should lie with the pharmaceutical companies and doctors, not the government. Sir Hugh Linstead asserted that manufacturers would prefer legislation co-ordinated with other countries so that their drugs could be sold without the complications of international legislation. He asserted,

> The present machinery for the provision of the manufacture and distribution of drugs in Britain is in complete chaos. As secretary of the Pharmaceutical Society I have lived with this for 30 years of my professional life. I am appalled at the way in which six or seven authorities acting under six or seven Acts, are inefficiently trying to handle the problem. If ever there was a jungle of administration which needed clearing up it is this.[104]

In a further article in the Pharmaceutical Journal Sir Hugh Linstead

outlined the proposals he would like to see. Legislation was needed to protect the public against the worst 5 or 10% of manufacturers. Some form of early warning system was necessary as animal experiments cannot discover delayed sensitivity, so after the drug has been tested on animals it should be available on prescription only. The State should aim to provide doctors with enough information to make an informed choice over medicaments, and should also aim to protect the public against long term toxicity, deterioration, fraud and exploitation by advertising campaigns. Drug legislation therefore, should be separated from food and poisons legislation, and the system whereby drug legislation is the responsibility of six ministers should be changed to being the responsibility of the Minister for Health and the Secretary of State for Scotland, while the freedom of the industry should be guaranteed.[105]

The TUC also objected to the proposed solution. At their meeting in Brighton in 1963, Mr. Bob Edwards, General Secretary of the Chemical Workers Union and M.P. for Bilston denounced the government's policy as miserable and makeshift, the government had no intention of establishing an independent testing organisation for new drugs. In 1961 only 25 of 169 new drugs had been tested, although the industry claimed 60% contain old drugs, new formulations may themselves be dangerous.[106]

The Committee on Safety of Drugs (CSD) was formed and began operating on 1st January 1964. It was independent from the ministry, papers were kept separate from official documents. There was a small full time staff of six doctors and two pharmacists and twelve part time physicians and scientists paid as civil servants and not regarded as members of the committee. The committee laid down standards for tests and evaluated scientific data. There were no legal sanctions against an untested drug but unofficially the medical profession could be warned according to the chairman, Sir Derrick Dunlop,

> The Minister of Health for instance, has promised that should a drug be marketed without the committees approval he will report the fact to all practising doctors in the United Kingdom who would draw their own conclusions; further, if a drug which had not been cleared by the committee gave rise to toxic reactions neither the manufacturer nor the prescriber would stand in a very favourable position in a court of law.[107]

In addition the ABPI and the Proprietary Association of Great Britian agreed to co-operate with the committee before it began to function. They agreed that none of their members would put a new medicine to clinical trial or market a new medicine without the approval of the committee. The manufacturers undertook the animal tests and clinical trials while the CSD evaluated the manufacturers submissions on the tests and lay down certain standards for them. The terms of reference of the committee included obtaining from the manufacturer or prospective marketeer of a drug 'any reports which they may think fit on the toxicity tests carried out on it',[108] and to give advice as to whether the drug should be submitted for clinical trial, or whether more animal trials are necessary. They were to assess the information on the clinical trials of each drug, and to consider whether it may be released for marketing.[109] The committee were also to give general advice to manufacturers, assemble reports on adverse effects of drugs in use and prepare information for doctors and others concerned. Finally, they were to advise Ministers on these matters. However, clearance of a medicine for marketing did not necessarily imply the committee's approval of it as a therapeutic agent. The three sub-committees that were proposed were established although the two concerned with animal tests and clinical trials eventually merged into one. The CSD was not responsible for any drugs marketed before 1964 unless it could be shown that they were producing unexpected adverse reactions. The CSD developed informal communication with the industry.

In 1967 the Government published a White Paper on forthcoming legislation on the safety quality and description of drugs and medicines.[110] The CSD had recommended in 1965 that legislation in the field was needed, and that the voluntary system should only be regarded as an interim measure, especially considering Britain's wish to join the E.E.C. The White Paper outlined a proposal whereby responsibility for the control of drugs would be separated from that of poisons and would lie with the Health and Agriculture Ministers rather than the Home Office. A commission known as the Medicines Commission would be appointed by ministers after consultation with professional bodies representing medicine, dentistry, and veterinary surgery. The commission would advise ministers on matters of policy and make recommendations on the terms of reference of expert committees. It would assume responsibility for producing the British Pharmacopia and would be concerned with drugs used in diagnosis and treatment, but not with non-medical aspects of drugs.

> The controls will not automatically apply to substances marketed for non-medical use such as cosmetics or disinfectants, but the ministers will have the power to list substances of this kind as subject to control.[111]

A licence will be required for the marketing, importation, manufacture or wholesale dealing of drugs, as well as for clinical or field trial, to prove toxicological testing has taken place. There will be a fee for the procurement of a licence which can be refused, revoked or suspended as the Medicines Commission directs. Retail sales will be limited to pharmacies, advertisements should not be misleading, doctors should receive information from manufacturers and ministers are obliged to consult organisations before making regulations.[112]

The Medicines Bill had its first reading on the 2nd February 1968, and received the Royal Assent later in the year. The aim of the legislation was to consolidate the diverse aspects of legislation on medicines. It provided an inspecting and licencing system for drugs, it also gave

the successor to the CSD, the Committee on the Safety of Medicines legal power. The Act also included veterinary products and animal feeding stuffs. The Secretary of State for Health and the Minister of Agriculture are required to act as a licencing authority for the marketing, importation and manufacture of medicines for human and veterinary use taking advice from the CSM, and committee on veterinary products. The responsibilities of the medicines commission are to act as an advisory body to the ministers on broad aspects of policy regarding medicines, to direct preparation of the B.P.,* and to advise ministers on numbers, functions, and personnel of expert committees required to give advice - although they are not subject to the control of the commission once established, but it can act as an appeal tribunal against an adverse decision by the authority taken on the advice of the committees. Of the fourteen members of the commission, there are four medically qualified, two veterinary surgeons, an expert on animal nutrition, two pharmacists, two members of the pharmaceutical industry and a stipendiary magistrate. The Act does not cover restriction on price of efficacy, but provides an inspecting system by qualified civil servants for sound manufacturing practice, also that all medicines must be sold from pharmacies, some restriction on the number of mild analgesics to be included in a pack and restrictions on sale of vitamin D. There is a list of prescription medicines only, although small amounts of some such as insulin are obtainable.[113]

The reasons for legislation were primarily to stop unscrupulous manufacturers buying licenced premises, and to control the introduction of substances as 16 year patents began to run out on products of the 50s, and also to control imports and potentially hazardous substances, but with the desire to maintain the flexibility and the exercise of professional responsibility which the Safety of Drugs Committee has shown to be necessary.[114]

* British Pharmacopœia

The other major influence on British drug legislation is the desire to harmonise legislation throughout the E.E.C. member states. In 1973 a report was completed on the effects of harmonising legislation. This would decrease the price of drugs to the consumer as it would decrease the cost of developing the drugs. It also noted that there had been no progress in harmonisation for eleven years although the development of drugs had been similar in all countries. The major differences in requirements were in the number of animal and species required, duration of the tests and the point at which clinical testing could be done. Each country regards its own system superior to the others, and there is to some extent an element of protection of the domestic industry. A new drug will have to pass through different requirements in nine different countries which may be monitored by scientific experts or civil servants, so there is also a bureaucratic resistance to change. The report suggested, therefore, that a new preparation should be tested to the standards required for the domestic market, and when it has achieved a licence and been marketed there for a certain length of time the information on safety could be submitted to a specially appointed transnational body on the safety of drugs to be considered and if approved, recommended for acceptance by the other member states.[115]

In the case of pharmaceuticals, although the problem of teratogenicity was discovered by the scientific profession, the publicity it raised ensured that the question of the control of drugs was commented on by many groups in society. Even though the question was raised in the House of Commons, as had happened with food additives, the eventual controls that were brought in were suggested by a committee appointed by ministers, as were the pesticide controls. This implies a limited number of ways in which policy recommendations can be presented to the British Government. It was the regard for the benefits that new drugs offered society which resulted in the original, voluntary controls similar

to the Pesticide Safety Precaution Scheme. At the time this was arranged, however, there was dissatisfaction with it as a solution, but legislation was eventually passed due to the fear that many new formulae for drugs would enter the market as patents began to expire.

These various reforms, then, took place in an ad hoc manner in response to the various concerns as they were raised. There is a picture, then, of piecemeal changes, unco-ordinated with each other. The case of occupational chemicals also reinforces this picture.

7.5. The Health and Safety at Work Act

The recognition of poisoning from industrial chemicals was as old as toxicology itself. Despite this the control of potential hazards to health from chemicals in the workplace had to wait until 1974, when these substances became the next on the list to undergo predictive animal toxicity tests. During the period under consideration there was increasing concern over health hazards which had a long inception rate and did not become manifest until the employee had retired from work. Surveys by the Factory Inspectorate showed that the existing system fell short in protecting against these types of hazard. In 1964 the Industrial Health Advisory Committee was set up to review the appointed doctor service. This Committee recommended increased worker participation and government involvement in occupational medicine.[116] In April 1970 an Employed Persons Health and Safety Bill was published, which provided the means for joint consultation on safety in industry and the establishment of an Employment Medical Advisory Service. In organisations with ten or more employees Unions would have the right to appoint a safety representative with whom the employer would have to consult. This seemed to be an attempt to please the unions as 'the TUC had for many years pressed for legislation on the setting up of safety committees whereas the CBI had taken the view that the voluntary principle should be persevered with.'[117]

The Secretary of State for Employment and Productivity, Mrs. Barbara Castle, introduced the Bill also announced her intention to set up a committee to enquire into the question of safety across industry.

> I have become convinced that .... we ought to be asking some far reaching questions about our safety legislation .... I have therefore decided to set up a small, high powered body to conduct a general inquiry across the whole field.[118]

The committee was established in May 1970 with Lord Robens chairman of the National Coal Board acting as chairman. The committee intended to make a number of industrial visits meeting CBI officials and TUC representatives, as well as receiving written evidence from a number of sources.[119] The terms of reference of the committee were,

> To review the provision made for the safety and health of persons in the course of their employment (other than transport workers while directly engaged on transport operations and who are covered by other provisions) and to consider whether any changes are needed in:
>
> 1. the scope and nature of the major relevant enactments, or
> 2. the nature and extent of voluntary action concerned with these matters, and
>
> to consider whether any further steps are required to safeguard members of the public, from hazards, other than general environmental pollution arising in connection with activities in industrial and commercial premises and construction sites and to make recommendations.[120]

In the report toxic substances were addressed as a particular hazard. The 1970 Annual Report of the Chief Inspector of Factories had warned that 'the proliferation of more subtle hazards and particularly potential carcinogens, must also be the subject of continuous vigilence'.[121] This was seen as an area of control for engineers and chemists, although 'the profession of industrial hygiene which sees environmental control as a new and distinct scientific discipline, independent of medicine, has now gained widespread acceptance'.[122] The development of the Factory Inspectorates Industrial Hygiene Unit since 1966 served to strengthen the

field, so that 'the emphasis in this field is now placed heavily on prevention through scientific assessment of the risks and precise quantification of preventative standards in the form of agreed maximal levels of exposure'.[123] In evidence to the committee the M.R.C. stressed the need that medical records needed to be improved for epidemiological reasons.

As far as statutory control was concerned the Factories Act covered atmospheric pollution within factories, but beyond this and the regulations made about agricultural pesticides under the Agriculture (Poisonous Substances) Act 1952, toxic substances in industry were not regulated by any statutory provision, nor was there any mechanism by which new hazards could be spotted:

> there is no adequate mechanism for co-ordinating relevant information from industry, the universities and bodies such as the Medical Research Council and for linking this with the regulatory work of governmental departments.[124]

The M.R.C. favoured an approach which was comparable to the compulsory screening of new medicines, but other ideas favoured the use of in house research and testing facilities, fearing that official screening was not feasible. The British Chemical Industry Safety Council felt that there were too many new chemicals arising within industry to keep track of them all, but up to 30 may be accepted into an industrial process. At this stage it may be possible to have an early warning system here, by the notification of an official body, although new legislation and administrative arrangements will be necessary to deal with this arrangement. This legislation should provide powers for the introduction of regulations to specify those substances which should not be used without prior approval, or to prohibit the manufacture, use or import of particular substances. It should also impose a requirement on employers to undertake periodical atmosphere testing and sampling. This would be achieved by the early

creation of an independent, and advisory expert committee on toxic substances,

> we believe that the creation of an authoritative body of this nature, responsible for giving expert advice on specific problems, on the establishment of authoritative threshold limit values, and on the methods of measuring and control would fill a vacuum in the present arrangements and would help to ensure that new toxic hazards are more likely to be picked up and intensively examined at an early stage before they have been able to do harm.[125]

There should be some thought given as to how new substances would be notified to the committee, so they could follow up those which seem doubtful, and the relationship of this body with similar bodies in the field should be identified. If this plan was to succeed the research facilities for occupational medicine would have to be strengthened. The committee noted that the Medical Branch of the Factory Inspectorate had been incorporated into the Medical Services Division of the Department of Employment, but had set up an Accident Prevention Studies Unit and an Industrial Hygiene Unit. The committee also pointed out that ICI had a very advanced occupational hygiene unit for studying toxic hazards, but in general this research was fragmented not clearly defined, split along more rigid, specialised lines of established disciplines. A more multidisciplinary approach to integrate these strands is required, and this could be one responsibility of the proposed authority.

The report was published in 1972 in two volumes, one containing selected written evidence presented to the committee. The reactions to the report by the director of the TUC Centenary Institute for Occupational Health, Professor R.Schilling, felt that a new authority would make the situation tidier, although independent assessment of work to be done is needed as the situation was of an advisory committee under the Department of the Environment.[126] Professor Gordon Atherly of the Safety and Hygiene Group at Aston University felt that safety and health at work was

seen as an identifiable discipline in its own right, but the desire of the Robens committee to see safety designed into the system would be difficult due to the fact that safety is not easy to predict.[127]

In January 1974 the Health and Safety at Work Bill was presented to Parliament by the Secretary of State for Employment, William Whitelaw. Its main function was to set up a Health and Safety Commission with representatives from the CBI and the TUC. It would appoint an independent executive with the approval of the Secretary of State for Employment. There was some criticism of vague terms in the Bill, 'safety' was not defined, but could cover the plant and systems of work, handling and storage of articles and substances, the provision of instruction training and supervision and safe travel to and from the workplace, although some statutory provision already covered the maintenance of safe and healthy working environment. There were also vague requirements for consultation with relevant parties, and calls to ensure that people who were not directly employed were not exposed to risk.[128]

As far as toxic substances were concerned, a consultative document on their control was produced, due to the importance placed on this by Lord Robens. This document followed one published in 1967, by the D.O.E. as a first consultative document which suggested compiling an authoritative list of potentially harmful substances. The new proposals covered manufacture, production, and handling, and suggested that measures were needed to ensure the pre-testing of chemicals before their use in industry, and the best way to ensure this is if an advisory committee on safety and health was set up.[129]

During the committee stages of the Bill the words 'so far as reasonably practicable' entered the discussion. The Secretary of State was to retain power to make regulations on specific cases.[130] There was still some doubt as to the necessity for more legislation especially from

employers organisations although it was acknowledged that it had been trade union pressure which had 'led to changes in those clauses in the Health and Safety at Work Bill which deal with consultation and self inspection requirements'.[131] The Health and Safety at Work Act was passed in 1974.

The question of health and safety at work had been raised by the unions and the Factory Inspectorate rather than the scientific community in response to fear of long term poisoning. This had been given to a committee by a minister, as with the question of pharmaceuticals. The recommendations of the Committee on Safety at Work, however, were completely different from those which covered other toxic substances, as they required consultation with all the parties affected - government, industry and the unions. A representative committee, rather than the expert committees that had been set up before. Furthermore, the committee which would consider the question of toxic substances would be responsible to the Health and Safety Commission, which itself was to be independent from any direct ministerial control. This then formed yet another ad hoc solution to the control of another class of toxic substances.

The other policy question to arise in this period was, of course, the publication of recommended test guidelines for the various compounds that had to be evaluated for safety. These can again be compared to elucidate whether the differences in approach to the control of toxic substances also gave rise to different requirements for the toxicity data to be established about each compound.

7.6. Test Guidelines

It has already been noted that a completely unforseen type of toxicity was recognised during this period - that of teratogenicity. This could not be ignored in the recommendations for toxicity tests that were made for the different types of substances. A number of test

recommendations were published, both by governmental departments and other organisations. In particular the World Health Organisation published guidelines on the evaluation of the carcinogenic hazards of food additives,[132] and on testing drugs for teratogenicity.[133] The British Ministry of Health appointed an expert panel on carcinogenesis, which reported in 1960[134] and in 1968[135]. This was set up by the Committee on Medical and Nutritional Aspects of Food Policy to advise the Food Standards Committee and the Advisory Committee on Poisonous Substances Used in Agriculture and Food Storage.[136] There were three sets of guidelines covering the general toxicity of substances. The Pesticide Safety Precaution Scheme was reissued in 1967,[137] and the Ministry of Agriculture, Fisheries and Food issued a memorandum on testing food additives.[138] Finally the Association of the British Pharmaceutical Industry (ABPI) published their report on the evaluation of drugs for toxicity.[139]

The recommendations of these three committees are compared in Table 7.1. Each set of guidelines was set by a different committee. The Pesticide Safety Precaution Scheme was set by the Advisory Committee on Pesticides and other toxic chemicals (formerly the Advisory Committee on Poisonous Substances Used in Agriculture), in consultation with industry, while the memorandum on the testing of food additives was compiled by the Food Additives and Containments Committee and its Pharmacology Sub Committee. The recommendations on drug toxicity, however, were suggested by a committee of industrial scientists established by the trade association, the Association of British Pharmaceutical Industry. As the members of the committees are now drawn from an established community of toxicologists it is not surprising that the tests suggested differ quite considerably. The core tests that they all recommend however, are the acute toxicity, short term and chronic toxicity, including the investigation of carcinogenic hazards, and the metabolic fate of the compound under study. Further to that, the extra tests that are suggested

TABLE 7.1. Comparison of Test Guidelines (1960-1974)

Tests Suggested	(a) MAFF	(b) PSPS	(c) ABPI
Physio-chemical properties, composition	√	√	√
Acute Toxicity	√	√	√
Apparent mode of action		√	
Skin penetration and absorption		√	
Percutaneous toxicity		√	
Cumulative toxicity (Short Term)	√	√	√
Chronic toxicity	√	√	√
Delayed effects		√	
Potentiation of or by other toxic chemicals		√	
Diagnostic and therapeutic possibilities		√	
Carcinogenicity	√	√	√
Metabolism	√	√	√
Effect on humans	√		
Pharmacodynamic activity			√
Toxicity of local application			√
Effects on reproduction			√
Synergism			√

Source:

(a) MAFF (1965) Memorandum on Procedures for Submissions on Food Additives and on Methods of Toxicity Testing (HMSO, London).

(b) Pesticide Safety Precaution Scheme agreed Between Government and Industry (1966) (MAFF, Plant Pathology Laboratory, Hatching Green, Haryenden, Herts.)

(c) ABPI (1968) First Report of the Expert Committee on Drug Toxicity together with Recommendations on Toxicity Evaluation (Association of British Pharmaceutical Industry, 162 Regent St., London, W.1.)

especially for drugs and pesticides, arise from the particular use that is intended for those substances. Thus there is concern over the effect of pesticides on the skin due to their mode of application. For drugs concern is directed towards their pharmacodynamic activity and their effects on reproduction.

7.7. Conclusion

Developments during this period continued the trends set during the 1950s. The M.R.C. Toxicology Research Unit continued to develop its basic research programme, while setting down the criteria for choice of a valid toxicological problem, which included both social and scientific criteria. The major problem in toxicological research was the lack of basic biological knowledge in the surrounding disciplines, and this had to be taken into account when planning research. In the field of safety evaluation the basic tests suggested remained the same for twenty years, but new test requirements were added to this during the sixties in the form of guidelines for carcinogenicity and teratogenicity tests. The influence of environmental factors on the final toxicity of the compound became more accepted, as did the limitations and difficulty with the interpretation of test results. Improvements in the sensitivity of techniques led to a situation where very small amounts of a chemical could be detected in biological material, but the harmful effect of very low doses of a chemical could not be adequately assessed. Such developments, however, were thought to indicate the crudity of the LD50 test as a measurement of toxicity.

The British Medical Bulletin Symposium on toxicology included a number of papers from institutions interested in toxicology - the M.R.C. Unit, ICI, UCH Medical School and St.Marys College, but also from other academic institutions. Even so there was no focus for a community of scientists, and there was evidence of a shortage of adequately trained

scientists and technicians, particularly for industrial training. Publications were lacking in the area, laboratory developments in the commercial sector continued the trends of the previous decade. The establishment of an MSc Course at Surrey University was an important development. It is also interesting that the Chancellor, Lord Robens, had an interest in the toxicity of chemicals, and the staff of the biochemistry department, were brought in from St.Marys Hospital had worked with Professor R.T.Williams, with interests in developing toxicology. Progress during the sixties was summed up by Dunne and Mansel Jones,

> Toxicology has made considerable advances over the past decade but its development is beset by some funadmental problems. Its origin as an applied science has denied it a strong academic tradition and even now few centres offer facilities for formal training.[140]

Legislation during this period continued the ad hoc control of hazards that had been established. The question of the pre-market testing of drugs arose in response to public concern. There was, therefore, much discussion around the question of drug control, and a number of organisations suggested types of solutions. The government, however, responded to the advice from the sub committee, set up to report on the question of legislation, despite the fact that it was divided over the recommendations to make. The resulting voluntary control, depended on the surveillence of the Committee on Safety of Drugs, whose own Toxicology sub committee did not make its own recommendations for tests, but assessed the data submitted to it. The trade association, the ABPI, who established a committee comprising entirely of industrial scientists was left to produce a system of recommended tests for drugs. A lobby still existed for the establishment of statutory controls for drugs which was effected with the change to a Labour Government. The Committee on Safety of Drugs and its successor the Committee on Safety of Medicines, with their sub committees were comprised of academic scientists from a

variety of medical and biological disciplines.

Toxic hazards in the workplace had been controlled by engineering standards, but the Robens committee recommended testing on animals for new industrial chemicals. The tripartite system suggested by Robens was the most innovative factor in the proposed Health and Safety Legislation, which went much further than the question of controlling toxic substances, although it dealt with this. The Robens report was the first to suggest that a group affected by a chemical hazard should be involved in the consultation state of the evaluation of its safety. In addition the location of this system within the HSC was independent of any one department within government, another solution proposed by the committee and accepted by the government. Toxicology was seen as a part of industrial health, itself an ill-defined multidisciplinary science which had depended on an engineering approach but was changing to a more medically based one.

CHAPTER EIGHT

MOVEMENT TOWARDS PROFESSIONALISATION

(1974-1981)

Movement Towards Professionalisation

The events of the sixties ensured that the concern over the question of toxic chemicals that had emerged in the international policy sphere would not disappear. In Britain, most of the substances of concern had been covered by legislation although the question of controlling substances in cosmetics and industrial chemicals came under directives from the E.E.C. during this period. There was also a number of developments in the social organisation of the science during this time, particularly in the number of new courses that were established, and in the membership of the Royal College of Pathologists. Another movement towards the professionalisation of the science was the establishment of a professional society which covered both industrial and academic scientists. In the cognitive sphere a number of key problems central to toxicology were identified, and two international conferences highlighted the emergence of a community of scientists in agreement over the basic area of research which the science would cover.

8.1. The Social Structure of Toxicology

During the seventies there were some changes in the social structure of toxicology. Two new postgraduate degrees were started, and the British Toxicology Society was established in an attempt to raise the standard of toxicological work generally, the Royal College of Pathologists began a diploma scheme in 1981. Even so in 1980 Aldridge and Schlatter noted,

> The number of professorships and departments of toxicology in academic institutions in Europe are quite inadequate for a balanced development of education in the subject[1]

although they acknowledged some expertise, toxicologists as such are lacking.

> Many scientists both in routine testing of chemicals and in research on mechanisms of

> toxicity will be classified by their primary disciplines and may or may not be called toxicologists. The kind of toxicologists in short supply are those scientists who by their research and by their experience are able to link the many disciplines involved in a coherent concept of toxicity and to assess the risk of exposure to man.[2]

In 1977 the Royal Postgraduate Medical School started an M.Sc. in Experimental Pathology which trains six students a year in pathology with some pharmacology and biochemistry. The course is run by the departments of Histopathology and Clinical Pharmacology with some visiting lecturers.[3] The course was designed to meet the demand for scientists trained to study the biological responses from chemicals in the environment. The aims of the course are,

> i) To acquire a background in General Pathology and to integrate experimental pathology, pharmacology and biochemistry into a course oriented towards toxicology.
> ii) To use these disciplines to derive and teach a mechanistic approach to the overall problem of toxicity and its pathogenesis.
> iii)To instruct students in an investigative as well as an empirical approach to practical problems and human toxicology.[4]

In the same year, Dr. Andre McLean, reader in Toxicology at University College Hospital Medical School, established an undergraduate course in Toxicology, to train toxicologists for industry,

> If industry wants a better supply of people who understand toxicology, it will have to support university departments prepared to teach the subject .... There should be a two way interchange between industry and the universities. Industry should get people who have advanced training in the universities, which, in turn, should be able to go to industry for some skill and information.[5]

Especially in toxicology as most of the information is in industry. The course was established as part of the clinical pharmacology department, although there was a lack of funds for detailing staff, support was forthcoming from the Cancer Research Council, Nuffield Foundation

and the Shell Research Laboratory which was concerned with the national shortage of toxicologists. In McLean's view the country needs a central data bank to collect information usually concealed by industry, even old information is useful. An academic body could sort out information to put it on a general basis.[6]

The third postgraduate course, in the Department of Biochemistry at Birmingham University began in 1979 after two years of preparation.[7] The university careers service had suggested that it would be a good course to develop as there seemed to be career opportunities in the area. As there was a drug metabolism group in the department, with whom R.T.Williams once worked, they took responsibility for designing the course, and sought advice from people in other institutions working in the area.[8] The pathology course is taught by scientists from ICI, and there are other external lecturers. The type of graduates that apply are from a range of disciplines including pharmacology, and some are from contract organisations wishing to broaden their knowledge. When A.C.Frazer left Birmingham his toxicology group split up, but two former members remained and are now senior lecturers involved in the teaching.[9] Twelve to fifteen students were accepted in 1980.[10]

An alternative qualification is membership of a professional society. The first one to recognise toxicology has been the Royal College of Pathologists who have started an examination system in Toxicology at Diploma and Membership levels and have set up a Standing Advisory Committee on Toxicology composed mainly from their own members shown in Table 8.1. There was an international reason for such developments. Pressure from the E.E.C. to produce a list of recognised toxicologists was an important factor in initiating these procedures.[11] There is also a view on the social and institutional background of toxicology held by the Royal College of Pathologists,

TABLE 8.1. Membership of the Specialist Advisory Committee established by The Royal College of Pathologists.

Professor J.R.Anderson
Professor D.N.Baron
Dr. R.W.Brimblecombe
Professor R.C.Curran
Dr. A.S.Curry
Dr. A.D.Dayan
Professor G.W.A.Dick
Dr. M.S.Dunnill
Professor F.A.Fairweather
Professor F.V.Flynn
Professor A.E.M.McLean
Professor W.H.Spector
Professor J.R.Tighe
Sir Robert Williams
Professor A.N.Worden
Dr. Joan F.Zilva.

Source: Private Communication M.G.Rinsler, Registrar.

> Toxicology is a subject that has greatly developed over the past few years, especially in relation to the possible ill-effects of drugs on patients and of environmental chemicals on the community. Toxicologists may have had their primary training in medicine, pharmacology, veterinary science, biochemistry or other related subjects. They work in university departments, government laboratories, industrial companies or elsewhere.[12]

The Diploma in Toxicology is intended for those engaged in responsible work in toxicology or in teaching and research in the subject . To enter for the diploma a medical, dental or veterinary qualification is necessary, or at least a 2nd class honours degree in an appropriate subject with two years training in an approved laboratory,

> The Diploma examination will cover all major aspects of toxicology, and will require a knowledge of related subjects such as histopathy and pharmacology. It will include a written paper, a practical examination, and an oral examination.[13]

The first examinations for the Diploma were held in Spring 1981. The first Membership examination took place in Autumn of that year,

> This qualification is of equal status to the other Membership examinations of the College, being taken at the completion of specialist training and marking full professional competence or eligibility for a Consultant or equivalent appointment. It is therefore, at a distinctly more senior level than the Diploma in Toxicology ....
> Entrants to the Membership examination must have passed either the Diploma examination in Toxicology, or the Primary M.R.C. Path. examination (in any subject) or have been granted exemption from the latter. At least five years approved training will be required ....
> The Membership examination consists of two written papers, one on general toxicology and one on a choice of special subjects selected by the candidate, a practical examination, a dissertation, and an oral examination.[14]

In 1978 the British Toxicology Society was formed.[15] This had its roots in an informal group set up in 1971 called the British

Toxicology Club, whose main function was to provide a forum for the discussion of toxicological problems, and they held a number of meetings at different British Universities. The emphasis of these meetings was predominently educational aimed at bringing together scientists from different disciplines related to toxicology to discuss a common theme.[16] Membership was open to anyone interested in toxicology, and the numbership rose from 45 in 1971 to over 200 by 1974, 'reflecting the increasing importance given to toxicology in the Legislative Authorities, the Pharmaceutical, Chemical and Food industries and the Universities.[17]

In 1977 it was agreed that the Club should be reformed with a two tier membership - 'Full' and 'Associate'. The reasons behind this were that;

> .... the balance of interests and experience of members and the increasing impact of legislation produced a general feeling that toxicology must become a recognised profession in its own right and that an essential requisite for this to occur must be the formation of a professional society with high scientific standards.[18]

The following year the Toxicology Club transferred its assets to the British Toxicology Society. A steering committee was appointed under Dr. Andrew Swan, and all former members of the Toxicology Club were made full members of the Society for one year, while their qualifications for full membership were reviewed. Working Parties were established to review the areas of interest of the Society. The constitution was drawn up and first election of the committee took place in 1979. The Society runs scientific meetings - typically three a year, one usually a joint meeting with another professional society. Every two years a John Barnes Prize Lectureship is awarded. The Society is also committed to 'encouraging the development of training courses in toxicology'.[19] A Representative sits on the Royal College of Pathologists Standing Committee on Toxicology, and it has given evidence to the Home Office

Committee of Enquiry on the LD50 test and 'to comment on the DHSS Medicines Commission 'Guidelines on preclinical trials' '[20] The Membership total for 1980 was 406.[21]

Other institutions which were set up at this time included the B.P. Group Occupational Health Centre. This gradually came into existence over a number of years, and has been operational in its present form since 1976, but prior to that the Company did some work on toxicology and obtained outside help, for example from BIBRA. The Toxicology Unit was established in 1979, but is still small, designed mainly for pilot studies, urgent work, basic research studies and teaching. The majority of the testing is done in contract research organisations (CROs). Scientists are organised around toxicological 'problems' rather than tests, so that toxicologists are concerned with everything to do with that problem. In 1982 10 such 'problem solvers' were employed. Such an organisation also means that studies for basic research are often identified in the course of carrying out an assessment. Dr. P.Grasso who heads the centre worked at BIBRA, while the chief toxicologist, Dr. M.Sharratt, took his PhD at Birmingham University under Professor A.C. Frazer, and also worked for BIBRA and the DHSS on toxicological matters.[22]

Estimating the national expenditure on toxicology is not an easy matter as so much testing is done in industrial firms who may either define toxicological studies in different ways, have much of their work carried out overseas, or include toxicological expenditure in the total research and development budget. In 1978 a Royal Society Study Group gave an estimate of £50-60 Million which appears to be a reasonable order of magnitude still.[23] The vast majority of this budget is, of course, spent by commercial institutions on the routine testing of new chemicals. Little more than 4% of this figure can be spent on basic research. A list of the institutions in Britain which are currently interested in toxicology appears in Appendix 1.

During the latter part of the seventies, then, there have been real developments in attempts both to professionalise toxicologists, and to train new scientists to enter industry due to the manpower shortage that the country is facing. The British Toxicology Society has a wide ranging membership both from academia and industry, which endeavours to encourage scientists from both camps to talk to each other. The membership examinations of the Royal College of Pathologists aims to bring commercial scientists of differing standards up to one acceptable level, which they hope will also give the science a greater status and visibility, and also start to provide a well marked career path to attract some of the new young graduates. An important aspect of the training courses is that they also require speakers from industry to form part of the teaching that students obtain. Toxicology is, then, widely accepted as being an industrial science before anything else. But, although industrial scientists enter universities, it is also possible for basic research to form part of an industrial research programme. This can best be illustrated by the complexity and diversity of the research done at the ICI Central Toxicology Laboratory.

8.2. ICI Central Toxicology Laboratory

The Industrial Hygiene Research Laboratories was established in 1948, 'with the main objective of providing a service of information and advice to production divisions of the company on the toxic properties of chemicals, to help ensure the safe operation of manufacturing processes and the safe use of the company's products by other industries and by the general public.'[24] In 1974 the name was changed to the Central Toxicology Laboratory. Throughout this period 'the range of the laboratory's activities has changed, of necessity, to meet the needs of changes in the pattern of the company's business and to fulfil the greatly increased official requirements for toxicological information prior to product

registration in most developed countries',[25] but activity has also changed with the use of new powerful analytical tools, although 'toxicology is still a very heterogeneous collection of experimental data, assembled for many different practical purposes'.[26]

Toxicology can both provide the basis for advance in fundamental knowledge, and generate vast amounts of empirical test data. Thus an important aspect is research into methodology. Some sustained lines of research are necessary which can be subject to scientific criticism, according to Dr.A.A.B.Swan,

> Co-operation between laboratories in related fields of work, whether independently supported by the research councils or in industry, universities or departments of government, is becoming of increasing importance not only because of the complexity of the problems and scarcity of skills to tackle them but because there is so much public concern over some types of danger (e.g. carcinogenic hazards) that only information from several independent sources will carry conviction.[27]

The laboratory has 50 graduates with wide range of expertise, and two units - Biochemical Mechanisms and Experimental Pathology - conduct research relatively free from service work with increased interest in animal feed supplements from single cell protein, new smoking material, and development of new materials for prosthetic implants, the distribution of laboratory effort has changed so that now almost half is devoted to meeting official requirements for product clearance and just under one third to industrial toxicology.[28] They have a computer based data system. The company's policy is far sighted in that it 'believes its immediate and long term interests are likely to be served best by a laboratory that does not merely respond to official demands, but is seen to be continuously active in contributing to the development of thought and methods of investigation in fields of toxicology related to the company's business.'[29] The research function takes up to a quarter of

its effort. In 1973 a Toxicology committee was established chaired by Dr.A.Spinks to review all process intermediates and products for compounds suspected on structural grounds of being potential hazards, or carcinogens, so 'it is vital that CTL should be seen not just as a toxicity testing laboratory for the company but is an important resource centre able to offer both information and ideas.'[30]

The CTL is organised between different units, each one concerned with a different aspect of work with a different balance between routine and research work, but all units interact over specific projects.[31] The analytical biochemistry unit is concerned with occupational hygiene and clinical biochemistry, and is mainly concerned with dealing with toxic effects on humans.[32] The Metabolism Unit is concerned with discovering how substances cause cancer, with interests in single cell protein, and pesticides.[33] The Biochemical Mechanisms Unit 'was formed in order to investigate the mechanisms of toxicity of compounds which are of importance to ICI',[34] and one of the major projects has been concerned with paraquat. The unit is headed by Dr. Michael Rose who left the M.R.C. Toxicology Unit for that purpose.[35] The Acute Toxicity Unit is interested, besides lethality, in questions of whether a substance penetrates the skin and so cause toxic effects and whether it has a sensitising potential to cause allergies. There has been some collaboration with other laboratories here, with Shell Tunstall Laboratory and Unilever Colworth/Welwyn Laboratory on a test for skin sensitisation. The basic research programme is concerned with factors influencing the rates of dermal absorption of chemicals. The former leader of the Unit, Dr. David Ferguson regarded the positive aspects of such commercial research as,

> I like to know why I'm doing something, and that the reason is a practical one. You can see your contribution to the solution of a problem far more clearly than you can in a university.[36]

The other units are the long term toxicity units concerned with testing chemicals for regulatory procedures.

> At any one time there are 25-30 long term studies under way on about a dozen different compounds. The number of animals involved is in the order of 5,000 rats, 3,000 to 5,000 mice, 150 dogs and a variable number of rabbits according to the substance under test.[37]

Teratology and reproduction tests are done here. With inhalation toxicity there are problems in setting satisfactory experimental procedures but much of the work is short term and routine, although there has been work done on tobacco substitutes.[38]

A more recent development, a spin off from long term toxicity, has been in bio-engineering. In collaboration with the Pharmaceuticals Division and Liverpool University work on Biochemicals has started for materials intended for use in medical, surgical and dental applications.[39] The work of the Experimental Pathology Unit is in trying to develop a reliable screen for carcinogens, which 'should give an estimate of the likelihood that a particular substance is carcinogenic'.[40] The Behavioural Unit is concerned with subclinical effects of substances at low concentrations, but this work is still very speculative.[41] Ancillary Units include an extensive library and information service. The Pharmaceutical Division have an animal breeding unit, while within CTL there is an Animal Health Unit responsible for health and welfare which do routine autopsies.[42] There is also a small Management Group of high level scientists with the responsibility of overseeing the laboratory, co-ordinating and budgeting the projects, and co-ordinating an outside divisions request.[43]

The work of the Central Toxicology Laboratory illustrates the nature of toxicology as an industrially based science. The research goals are, necessarily, commercial, but the nature of the work includes a component of basic research. This is felt to be particularly important

where the existing knowledge in the field is so limited that existing tests are long and cumbersome, as in the field of carcinogenesis. Here, there is an obvious economic benefit for the firm if a reliable short test for carcinogens can be developed, but this is not possible without some further development of the basic knowledge in the area. The CTL, however, encourages collaboration with other research institutes on questions of basic research, and on questions which have generated public concern. The emphasis, then, is on how the laboratory can make a positive imput to the problem of the evaluation of chemicals, rather than just responding to public policy that already exists in the area. This they feel can best be done by original research, and improvement in test methodology, so that both the pure and applied functions of toxicology feed each other. This demonstrates how science can develop a basic research programme even when it is undertaken to fulfil goals external to the scientific field.

During the seventies an international community of toxicologists began to emerge, identified by two international conferences on toxicology. In addition much more began to be published in books, and, in general it was a time when the basic core problems facing toxicology were identified and elucidated.

8.3. Defining the Nature and Scope of Modern Toxicology

This was a period when much effort was put into identifying the particular issues that are of concern to the science and toxicology. These are, of course very wide ranging due to the number of approaches and concerns that toxicology encompases, so that numerous definitions of the science can be found. In 1977 a book edited by the senior medical officer of the Chemical Defense Research Establishment was published. It carried a succint definition of the orientation of toxicology, by the editor, B.Ballantyne,

> Modern toxicology involves a multi-disciplinary approach to the study of the interaction between chemical and biological systems in an attempt to define the likelihood of producing adverse effects in the intact organism; and if potentially harmful changes do occur, to investigate their nature, incidence, detection, mechanism of production and reversibility.[44]

An arbitrary classification of toxicology was suggested, covering three overlapping areas. The medicolegal aspects and clinical diagnosis in man, aspects of the environment which come into contact with toxic materials, such as plants, animals and chemicals in the atmosphere or in water. Finally, where chemicals influence economic factors, that is chemicals that are introduced for specific purposes, which has given rise to the proliferation of legislation in the area, and generated some unsatisfactory trends, according to Balantyne,

> Already there is an attitude in some minds of the 'check list' type of toxicity testing, a tendency to official dogmatism, and even more a cause for concern, a lack of informal communication between assessor and notifier.[45]

Of the topics picked out for review, a new area, temporal variations in toxicology was highlighted, because 'many compounds have been shown to exert different degrees of activity at different times of the day and there is a need for further awareness of this phenomenon in toxicology.'[46]

The Commission of the European Communities called a conference to review testing methods and procedures for their application to public health including methods to reduce pollution. In 1973 the E.E.C. members adopted a common environmental policy, underpinned by the dose response relationship based on scientific research, Recht states,

> We are living in a fascinating age, characterised by the discrepancy - not to say opposition - between, on the one hand progress in the form of extraordinary inventions and imagination applied to devising and meeting new needs for man and on the other a society which is becoming aware that this progress is not always beneficial and is trying to limit the resulting damage to health or to the environment.[47]

It was recognised that 'ideally toxicological studies should aim at elucidating both the toxicity of a compound and the mechanism of its toxic action',[48] but for economic and reasons of capacity, short term tests in two species give good enough results. The hazards from single exposure are necessary knowledge from the point of view of handling and transportation, although many factors can influence the experimental results.

In 1978 the first International Congress on Toxicology was arranged by some of the leading societies of toxicology. There was a feeling here of the emergence of toxicology as Grice noted,

> Narrow professional attachments and pigeon holing are being submerged and replaced by a spirit of team work and co-operation .... The profession of toxicology has reached that stage of maturity where its practitioners willingly acknowledge toxicology as their vocation, proclaim their loyalty to it, take pride in it, and find their confidence and a sense of community that has formerly eluded them.[49]

But the pursuit of toxicology was legitimated in terms of its important social function, in protecting the health of the population, Grice again,

> Society has a right to know the level of risk involved in the use of substances on the market, substances that turn up in the food they eat, the air they breathe, and the water they drink.... Toxicology is not a science in a glass box, recording and analysing observations for academic purposes. Today it forms the basis of predictions that affect everybody's lives, on the safety of air, food, water and drugs. With its guidance we can use chemicals more safely and effectively and make rational choices between them. It helps us manage the chemical environment to get the most benefit at the least risk.[50]

He, however, did not consider toxicology to have developed into a predictive science, so that,

> the problem of the assessment of hazard is one of the interaction of a chemical with a biological system. That we resort to lengthy

> empirical tests and use such devices as a hundredfold safety factor underlies our basic ignorance .... We must generate a more basic understanding of the underlying biology so that we may be more accurately predictive.[51]

The current toxicological tests, with long term exposure of many species is a gesture of defeat, brought about because current understanding of biology is not good enough for predicting effects such as cancer or mutagenesis. What is needed is a unified approach at defining early responses and improvement in short term tests for measuring toxic potential.

One view of the development of toxicology, that ' a dilemma for modern toxicology is the fact that the demand for regulatory control has far outpaced the development of toxicology as a quantitative and predictive science'.[52] The trend in research appears to be for an increasing amount of 'applied' toxicology. This covers carcinogenicity, including screening tests, improvement in the reliability and sensitivity of methods used for detecting toxic materials (although the precise meaning of finding small amounts is still in question). Other factors in the current state of toxicology are the recognition of the importance of metabollic transformation of drugs and carcinogens, the emergence of the interaction of academic toxicology with other biological disciplines, work on the epidemiological analysis of lung carcinogens and tests with cell cultures as predictors of toxicity. There was concern with the difficulty of obtaining objective opinions, according to Allison,

> Commercial interests tend to minimise risks while representatives of labour unions tend to magnify risks .... Applied toxicological research should, as far as is practicable be undertaken by independent and uncommitted organisations.[53]

The first International Conference was demed to be a stage in the development of a wider perspective for toxicology, Grice again,

> we are at the crossroads in the development and growth of our profession. The problems that face us today are of such magnitude and complexity that we can no longer restrict our practices to parochial concerns. There must be a commitment by toxicologists to seek answers for these problems through greater international co-operation.[54]

The factor that is agreed in these conceptions of toxicology as a science is that it is concerned with and influenced by non-scientific factors. These are social, economic or political, and they are accepted as being a basic part of a science whose main concern is the evaluation of the safety of chemicals. The emphasis is, however, that toxicology should not become so captured by external factors to the detriment of the development of new scientific knowledge.

One particular result of this orientation of toxicology is the role that commercial laboratories play. In an unusual position are the Contract Research Organisations (CROs), which have been an important feature of the science since the early fifties. One British CRO, Inveresk Research International held a conference in 1977, on the question of quality control in toxicology. The director, G.E.Paget, saw a positive contribution that the CROs could offer,

> Toxicology is a science that stands at the intersection of several interests and disciplines. These intersecting forces are by no means all scientific since some are legal and some are commercial.... Toxicology is also a field in which contract research particularly flourishes and a number of major contract research companies have established over the years a reputation for contributing usefully to the practice of this skill.[55]

As CROs serve many companies, they are aware of a wider diversity of problems than scientists in industry. There is a lack of fora for toxicological discussion, which means 'issues of current importance cannot be dealt with while they are still live'.[56] but there is a role for CROs to organise meetings as 'there is a need for small, highly

specialised and specific meetings arranged at relatively short notice to cover important current issues in toxicology.[57] One of the major problems identified in toxicology is that it generates a large amount of data, 'a releatively small experiment in safety evaluation may readily generate in excess of quarter of a million separate items of data'.[58] These are fed into decision making about a particular chemical, so the data must be valid, reproducible, and in the hands of those properly trained to collect it. It is also necessary to protect the public image of the science, as 'the science of toxicology has been made to look either inefficient or foolish by failures to predict catastrophies and by apparently absurd inconsistencies.[59] One result of this is the increased concern that has been given to evaluating the relative risks and benefits posed by new chemicals in the environment.[60]

It was not until 1970 that the rapid expansion of toxicology in the post war period was acknowledged, Paget noted,

> Until the 1930s such toxicology as was done on new medicines and on environmental chemicals was carried out, on what would be regarded today as a very small scale by scientists whose primary interests lay elsewhere. It was only in the late 1940s and early 1950s, with the so called 'therapeutic explosion' that the toxicology of drugs became of considerable importance and as a consequence pharmaceutical companies developed advanced facilities and staff for studying the dangerous properties of potentially useful medicines.[61]

Now, all new chemicals undergo extensive toxicological investigation, either inhouse or contracted to a research organisation. This development has because of its nature been beset with problems over defining the scientific validity of toxicology,

> This rapid growth has not been based upon fundamental new discoveries about the nature of toxic action, but has for the most part been based upon the widespread application of empirical rule of thumb methods. Similarly, until recently formal training of toxicologists did not exist and even now there is by no means general agreement as

> to what such training should comprise. In these circumstances, it is not surprising that a number of areas of particular debate or of intrinsic scientific interest have developed.[62]

This illustrates the fragmented way in which a science develops under conditions of commercial secrecy where accepted standards are not openly set. A scientific area, however can be identified by its core research problems and in toxicology these are seen as covering both the questions of basic biological research and those of safety testing. The second international congress, held in 1980 illustrated this. The theme of the congress was on the subject of mechanisms of toxicity and hazard evaluation. The topics considered included developments in the mechanisms of neurotoxicity, short term tests for assaying mutagenic potential, and early changes in chemical carcinogenesis. Long term exposure to occupational intoxicants, clinical toxicology and the legislative, scientific and socio-economic considerations underlying the testing of new chemicals. The final sessions were concerned with metabolism of chemicals, hepatotoxicity, and the toxicology of metals.[63] This illustrates the range of issues considered under the toxicological umbrella.

The trend in toxicological research is, then, to acknowledge the scientific limitations in both the elucidation of toxic mechanism and the safety evaluation of chemicals. The former involves identifying the important chemical reactions and their biological or biochemical consequences. The whole process involves penetration, absorption, excretion, secretion, distribution and metabolism, but chemical reactions involve looking at enzymes, nucleic acids and receptors. The different steps in the toxic process and their relative importance should be elucidated, as therapy can be designed to enter the process at many stages. Although, the view of Aldridge at the M.R.C. Toxicology

Laboratory is that,

> it is found that our basic knowledge of biology is inadequate to explain the development of toxicity, and it is then that the elucidation of mechanism of toxicity is the same as the use of toxic chemicals as tools to study biological processes.[64]

The M.R.C. Toxicology Research Unit continued to develop their research programme on toxicology. As far as defining the scope of basic work in the area, this provides the best guide, in Britain, to the type of problems that are sufficiently developed to become research projects. It also gives an indication of how social factors can influence the choice of research programmes. The Unit reaffirmed their role in assessing the mechanisms of potential or known hazards, as Connors states,

> knowledge gained from fundamental studies can often be used to devise methods to monitor exposure and safe ways of handling dangerous but useful substances. For people exposed to toxic levels of a chemical, effective therapy is sometimes available based on understandings of the compounds mechanism of action. Most important of all, once the mechanism has been elucidated, generalisations can often be made which are useful in the consideration of the toxicity of other chemicals.[65]

The definition of toxic response is open ended, as 'a change from the normal in the structure and/or function of a living organism'.[66] The Unit, however, defined its areas of interest through four terms of reference, Connors again,

> 1) To study mechanisms of toxicity in order to expand knowledge of sensitive biological systems and their interaction with chemicals of actual or potential hazards to humans.
> 2) To apply knowledge gained from fundamental and other studies to problems of toxicity in humans and to undertake where necessary appropriate clinical and epidemiological studies.
> 3) To provide technical and scientific training in toxicology.
> 4) To undertake work at the request of the Council on toxicological problems.[67]

In particular, compounds of low molecular weight are chosen as the aim is to throw light on mechanisms of toxicity in mammals. The main current research interests of the Unit are summarised in Table 8.2. Toxicity is not taken as a parameter of a compound but must be qualified by route of administration and other environmental factors. The two components of toxicity are acute and chronic, the former 'results in signs of poisoning appearing quickly after absorption of the chemical and recovery from sub-lethal doses is complete',[68] while chronic effects, Aldridge notes as,

> can result from accumulation of a toxin until sufficient is present to cause damage (e.g. kidney damage by cadmium) or from rapid chemical reaction which indicates a cascade of biological biochemical responses leading to the final clinical condition.[69]

In effect, the approach of understanding mechanisms is to give a biochemical explanation of selective responses to chemicals, so the reaction at the site of action must be correlated with the biological effects. Increasing biological complexity increases the difficulties with interpretation, but the aim is to acquire generalisable knowledge, as 'the more unspecialised the relevant knowledge becomes, and the general understanding one develops as applicable to many special problems'.[70]

The T.R.U. is involved only indirectly in the safety evaluation of chemicals. Part of the function of the M.R.C. is to provide a scientific basis for the governmental hygienic standards,

> In order to facilitate and co-ordinate this research, a small group has been formed of the directors and other senior scientists of the Council Units engaged in relevant research - this is the Environmental Directors Group (EDG) .... Environmental problems identified by members of the group or brought to their attention, which require the expertise of more than one of the above units, are discussed by the EDG who will then consider whether research is required and whether more than one Unit would be involved.[71]

Problems in environmental research require background information for

TABLE 8.2. Research Projects at M.R.C. Laboratory. 1979

PESTICIDES	Organophosphates, Acute Toxicity Chronic Toxicity - delayed neuropathy
	Organotin compounds Pyrethroids : Distribution and Metabolism Neurophysiological actions Neurochemical actions.
	W.H.O. Collaborating Centre.
HAZARDS OF INDUSTRIAL ORIGIN	Mercury : Methyl mercury intoxication Mercury distribution after exposure to atomic Hg Mercury-selenium interaction
	Cadmium : Chronic cadmium toxicity Acute toxicity of cadmium in the pregnant rat. Renotoxicity of isolated metallothioneins
	Turnover of cadmium-induced metallothioneins in relation to dose, age, sex and species
	Cadmium - heavy metal interactions Beryllium Carbon Disulphide: and catecholamine metabolism and fuel utilization in the whole animal.
	Pharmacological effects of carbon disulphide in the rat myocardium.
	Carcinogenicity of nitrosocompounds : Molecular mechanisms involved in carcinogenesis induced by alkylating agents.
	Potential carcinogenicity of a nitrosated ethoxyquin in BALB/c mice.
	2,3,7,8 - Tetrachlorodibenzo - p - dioxin (TCDD)
NATURALLY OCCURRING TOXINS	Aflatoxin : Whole animal experiments Metabolism of aflatoxin Cellular aspects Effect of ethoxyquin on the carcinogenic activity of aflatoxin B_1 Endemic (Balkan) nephropathy Toxin from the palmyra palm Pyrrolizidine alkaloids : Comparison of the toxic and antiritotic effects of pyrrolizidine metabolites in cultured cells.
DISTURBANCES IN HAEM METABOLISM	Degradation of the haem of cytachrome P 450 caused by alkyl-containing chemicals etc.
	Disturbance of the central nervous system Alternatives to animal experimental models Advanced analytical techniques Clinical Toxicology.

Source : M.R.C. Toxicology Research Unit Research Booklet 1979

decisions to be made on their priority and feasibility, so 'in 1977 an Information Assessment Group, based at the Toxicology Unit was set up to provide background material'.[72] This is gathered from a number of sources including computerised data bases, industry, government departments and experts in the field. From this information gaps in the knowledge can be identified. The M.R.C. Toxicology Unit provides the best example in Britain of a co-ordinated basic research programme, with objectives related to investigating the biochemical mechanisms of toxicity.

In trying to define the nature and scope of toxicology as a science, then, it is important to realise that it comprises both work done on safety testing of chemicals, and fundamental research. It is this former concern that is responsible both for the majority of the funding in the area, and has made a significant impact on attempts to professionalise the scientists involved. It has contributed to fears that toxicology has become a routine science, carrying out research in a 'recipe book' manner and is fragmented and disorganised within commercial institutions, lacking any generalised theories, and of a low scientific standard. It is, however, accepted that society has reason to expect results from toxicologists, and the commercial activity in the field is inevitable, due to the costs involved.

In response to this the unique role of the CROs has been pointed out. They are in a position to link commercial testing, with a more general view of the results they achieve, and can act as disseminators of knowledge throughout industry. They are, however, constrained by economic objectives and the need to cater to industrial needs for safety testing. On the other hand, those engaged in basic research are still arguing that it is from improvements in biological knowledge that real improvements in safety evaluation develop and steps have been taken to promote this. This complexity in the cognitive structure of the science,

then, cannot be divorced from its social and institutional base. It is of interest, then, to investigate some of the problems with the evaluation of long term toxicity in greater depth.

8.4. Current Issues in Toxicology

It has been noted, that the largest proportion of the total expenditure on toxicology is used on testing chemicals. On this question, Paget has identified five areas of importance to the continued development of toxicology :

1. Good Laboratory Practice (GLP)
2. Acute toxicity (the LD50 test)
3. Environmental toxicology
4. Alternatives to animal testing
5. Legislation.[73]

The FDA introduced the GLP regulations in order to tackle the problems with reproducing experimental results in toxicology, due to the discovery that some data submitted for approval had been falsified. GLP involves the inspection of data collection, places controls on the way experiments are carried out and ensures data is collected in an accurate and reproducible form. GLP recommends that a Quality Assurance Unit is set up within the organisation. The uncertainties with assessing the toxicity of a compound affect the reproducibility of any experiment, but this is often made worse by poorly constructed experiments, carelessly executed, inaccurately analysed and poorly recorded. Reports records and data were often unavailable to refer to after the experiment had been completed. Thus the main thrust of GLP is to standardise experimental procedures in toxicology and to improve the standard of record keeping.[74]

Although most reputable organisations have accepted GLP, in general it is thought to add 20-30% on to the cost of testing, and badly run

laboratories could go out of business. Inevitably it is thoughtthat it will be applied as a world wide standard due to the importance of the American market. Industrial scientists claim, however, that some level of error is unavoidable in experiments of such magnitude. The basic requirements for quality assurance in safety evaluation include a supply of healthy animals of known age, pedigree, and spontaneous disease. ICI did some of the pioneering work on developing SPF colonies of rats and mice. As a carcinogenic study will involve up to 1400 animals, this is a condition no university department could provide. Good animal accommodation is needed as is the recruitment and training of adequate staff with time to become involved in their own research into methods of assessing toxicity. Good information storage, quality control systems and experienced pathologists are also necessary. It is felt that GLP requirements should not be allowed to turn safety testing into a 'cookery book' occupation, as it is important to keep highly trained scientists interested. Methodologies advanced during the 1960s, and Leonard states that,

> most responsible labs have changed their technique according to the best available knowledge at the time .... The science of toxicity testing is a gradually developing science and the science can only be practised according to the scientific information and recommendations which are available at the time of testing.[75]

In Britain, Contract Research Organisations have the status of consultancies in that they have expertise and independence, and to survive they 'must make themselves particularly attractive to sponsors through the maintenance of high standards of quality'.[76]

The necessity of obtaining a number for the acute toxicity (LD50) of a new chemical has often been questioned.[77] It was developed as part of a complete investigation of the biological properties of drugs during the 1920s, but has become a convenient number to quote as an index of toxicity. Both the U.K. and E.E.C. have had committees reviewing the

test, but such a piece of knowledge about a compound has not been abandoned.[78]

A growing area of interest is environmental toxicology. This covers chemical pollution of the natural environment and indiscriminate chemical dumping. Paget holds that a form of 'disaster toxicology' needs to be developed before large parts of the globe are rendered unfit for human habitation. The benefit here is that substances can be studied directly on the biological system at risk, unlike the need to extrapolate to humans from animal experiments.[79] Also at a European conference, a new approach of ecotoxicology was identified, composed of related parts of mutagenesis, teratogenesis, carcinogenesis and the symbiotic action of chemicals. It involves investigating the total effect of the chemical concerned on the environment, for example it is necessary to investigate under what conditions they are naturally produced in the environment. It is possible to detect over 400 organic chemicals in various waters, but techniques for detection have developed before adequate explanation, and could give rise to unnecessary alarm.[80]

The fourth priority identified by Paget was the development of alternatives to animal testing. There are many reasons for interest in this, particularly the cost of a full scale animal experiment, public criticism of the use of animals and scientific dissatisfaction with such an unsatisfactory trial and error method. The most promising of non-animal test systems are those for bacterial mutagenesis which detect genetic changes in the material. There has been some success with the Ames test in detecting known carcinogens as positives, although some false results are obtained. These tests are cheap, do not use animals and can be done by relatively unskilled staff. The problems occur in the difficulties with the interpretation of the test for which expertise is in short supply, and there is a danger of obtaining false positive or

negative results, so these tests may only be regarded as one step in determining priorities for full scale studies.[81] Thousands of animals are sacrificed in a normal safety test, and the aim of tissue culture techniques is to reduce this number. Organ culture was first developed during the 1920s to investigate limb buds cultivated in vitro. Tissue cultures have been used in toxicology since 1954, but the results of such tests cannot be accepted without confirmation in the whole animal. There are three basic categories for techniques to culture cells, and recently there have been many modifications added to these techniques.[82] During the 1970s, alternatives to animal testing were firmly on the toxicological agenda. The advantages of these systems is that they are isolated from homeostatic and hormonal control, and there is accurate dosing and quantitation of results. The major uses of tissue culture methods are to examine a particular aspect of the toxicity in vivo, and to form a rapid screening test to compare the toxicity of a group of compounds, but they cannot replace whole animal studies.[83] There is a definite economic incentive for the development of short term tests for carcinogenicity, which has its origins in the 1940s, but started experimentally in the 1960s, although, at the moment none of these tests 'provide clear evidence of carcinogenic activity'.[84] The question of the use of animals in experiments is so sensitive that many scientists are concerned to see them replaced. This is the objective of the Fund for the Replacement of Animals in Medical Experiments (FRAME). They use the term 'alternatives' 'to describe any technique or system which could replace or reduce the demand for laboratory animals while at the same time providing information or results of a comparable quality'.[85] The shortcomings of in vitro models could be overcome by in vivo tests, and the numbers of animals could be reduced by better statistical design of experiments. It is the aim of FRAME to have a complete review of toxicity testing procedures and to explore the concept of a battery of tests for their predictive value.

In the view of one scientist, 'we are not far from the point where a large shift in emphasis from the whole animal testing of bioactivity of organic compounds to a much simpler system is likely to occur.[86] It may be possible to improve the predictive power of the Ames test by the use of mammalian cells, and some improvement in the understanding of structure-activity relationships is necessary. Most toxic chemicals fall in one of two groups, they act directly or require metabolic activation.. The M.R.C. group has been using the Ameoba Proteus as a single cell model. The use of tissue culture methods requires an increasing understanding of toxic mechanisms.

Governmental policy in this area has increased its influence on the testing of chemicals for safety. The haphazard legislation in the area often means the repetition of experiments for different legislative bodies. Thus, this is an area which requires simplification on an international basis.[87] New legislation in the area, particularly in the field of ecotoxicity needs to be based on adequate toxicological data. In the evaluation of toxicological data, according to Aldridge,

> For the solution of these problems we require the help of all disciplines not only for experimental studies but also for the development of unified philosophies for the assessment of hazard.[88]

Other types of toxicity that are recognised include drug allergies, blood dyscrasis, hepatotoxicity and renal damage, damage to the gastro-intestinal tract, cardiotoxicity, interference to hormones and toxic effects to the nervous system.[89] Opthalmic toxicity covers three areas, assessment of any acute systematic effect produced by a material absorbed through the vessels of the eye and measurement of local sensory irritant effects produced by a chemical which is typically applied to the eye. It also includes determination whether a chemical or a formulation of a chemical produces any adverse structural or functional effects on the eye

and to define the onset duration, nature and mechanism of any effects produced. Opthalmic toxicity is a growing area for investigation with its own developments in methodology. A similar situation exists with regard to ototoxicity.[90]

Industrial toxicology is becoming an important area, with the estimation that 25,000 chemicals used in industry have never been tested, and there are on average another 500 chemicals introduced every year.[91] Inhalation toxicity is not easy to assess by animal tests, although there is plenty of epidemiological evidence that lung diseases are an important source of illness.[92] In this field, 'the trend is now away from concentration on the environment to more intensive examination of the individual, or away from engineering towards medicine.'[93] Biochemical screening is becoming more popular, especially in America. The fact that no two individuals are biochemically alike has been generally accepted, although the majority fall within the normal range for concentration of blood constituents. Chemical enzymology, developed from biochemistry and cytology are useful in assessing specific organ damage. The estimation of threshold limit values (TLV) are not intended to cover those who may be hypersusceptible to the chemical, but now there are four tests to detect the hyper reactor. The behaviour of metals in the body may give insight to the mechanism of action of some toxic substances. Behavioural studies are now more often used to lower the TLV. Other techniques include electroneuronyography (to detect signs of impaired nerve muscle), electroencepliciliograph, and renal injury indexing.[94]

Despite the recognition of totally new forms of long term harm, the chronic toxicity test is still the cornerstone of safety testing, now supplemented by specialist tests. Worden regards this scheme as working as well as possible, as,

> Within the limitations of present day predictive evaluation, methodology and interpretation however the public seems well protected from the intentional or proper use of medicinal and food products.[95]

These supplementary tests included concern over teratogenicity, carcinogenicity and mutagenicity. In the former case the animal is a crude tool for analysing potential fatal hazards, as there may be species specific effects, or the chemical may require metabolism before it is active, but this is still the most scientific way assessing the hazards involved and specific guidelines have been drawn up by experts from industry and university.[96]

Knowledge of the mutagenic capability of chemicals arose during the 1950s, as a consequence of the development of atomic energy, although, 'concern over problems arising from chemical mutagenesis is ascribed to the discovery of supermutagens in the mid sixties',[97] which could be missed by accepted testing procedure. This resulted in an explosive development of the fields of genetic toxicology or environmental mutagenesis, but it has taken over twenty years for the hazards to be properly realised.[98] Knowledge is needed in genetic activity, but advances have been made in mutagenic screening, although it is not clear,

1. Which tests produce results that are applicable to man
2. Which decisions can be made on the basis of available tests
3. To what extent can the damages be quantified and
4. Is extrapolation to predictable genetic damage in man possible[99]

The safety evaluation of a chemical is essentially a risk/benefit evaluation. In the evaluation of toxicological data for the protection of public health four types of value judgement can be identified, what type of effect should be considered, or what quantity of an effect should be considered relevant, how probable must an effect be <u>not</u> to occur, and what tolerance to irritation is acceptable. These problems of interpretation are related to the presentation of numerical data.

Statistics are useful, but not as a substitute for biological knowledge. The LD50 is usually reported as a number when much more information is needed if it is to give useful information on the substance. It is impossible to obtain knowledge regarding the absolute safety of a chemical, so an arbitrary safety factor is still used, influenced by the normal factors which influence toxicity. An emphasis is now being placed on the maximum acceptable daily intake, similar to the concept of threshold limit values in industrial hygiene.[100] One of the major problems facing toxicological evaluation is the need for 'downward extrapolation for the estimation of risks at low levels of exposure',[101] as there is no proof of linearity at this level, the curve form is often unknown, so we are left with safety factors and the ADI, in safety legislation, concepts which may not be universally applicable to all effects, such as carcinogenicity. The most recent trend is that which requires some quantification of biological risk assessment. There are examples of both high and low risk chemicals from which society has derived some benefit. There are about 1000 new chemicals marketed every year, ten thousand are sold in quantities greater than 500 tonnes, and a quarter of a million natural substances of low molecular mass are known.[102] Information from the DHSS suggests that the health of the population of all social classes has improved over the last 50 years which implies that 'there is no evidence of mass harm to the population from new chemicals'.[103] Information from working populations can be interpreted to show a close response relationship with chemical carcinogens, and this implies that by cutting exposure to very low levels the risk of tumour incidence can be reduced to levels of 1 in 10^6 or 10^7.[104] It is possible to predict the number of tumours expected within the population from epidemiological data. In medicine the risks and benefits accrue to the same person so the equation is easy to balance. It is more difficult when the risks and benefits fall to different sectors of the population as do industrial

hazards. Safety margins are the traditional way of defining safe doses but the size of the margin 'can be answered only in the context of who will use the substance, for what purpose, to what benefit, with what precautions, and with what information and consent'.[105] In effect it is necessary to have epidemiological data to supplement the toxicological data that is produced. Toxicology must also develop if it is to be practically useful, particularly theory and practice must develop together if the subject is to develop as an exciting and useful branch of science.[106]

In 1978 a report was published by the Royal Society Study Group on Long Term Toxic Effects.[107] They reported that public health in the U.K. improved between 1900 and 1950 but in 1974, 30% of men died before the age of 65, and some diseases were increasing in prevalence. The R.S. Study Group were to investigate whether chemicals played a part in these diseases, and if so how these adverse effects could be prevented. This was interpreted as how to 'define the means by which it would be possible to detect, predict and quantify the risks and benefits associated with the introduction of new and existing substances or processes'.[108] A series of meetings reviewed various points about the safety evaluation of chemicals, but gaps in knowledge were seen to be a problem, either due to ignorance or commercial secrets. The study group reached a number of general conclusions after they had held a number of meetings. The major factor was the amount of effort that goes into safety evaluation rather than into the investigation of mechanisms of toxicity, they conclude that 'only if mechanisms are understood is it possible to extrapolate toxicity measurements across species and from the large doses used in experimental animals to the exposures experienced by man, commonly a thousand fold smaller'.[109] Variables such as nutrition which alter toxic effects are poorly understood. The difficulties in assessing the risk of carcinogenesis to man were noted, and the lack of statistical information about human disease, but it would be hard to improve this without first

improving the biological basis for extrapolation from animals to men, and by making provision 'for the linking of the records of exposure to industrial and other hazards with hospital discharge and mortality data'.[110]

These problems that have been highlighted with regard to the assessment of long term toxicity have arisen, in particular, due to the nature of the science outlined above. If there was greater understanding of the biological processes at work in the mechanism of toxicity, these issues would not be problematic. For example, the G.L.P. regulations have been implemented strictly because the scientific standards between testing laboratories varied greatly. This is essentially an administrative move to standardise tests, and attempt to ensure that experimental results are reproducible.

The criticisms of the LD50 test also depend on the fact that it is excessively used as a purely administrative measure of toxicity, having little relationship to the actual hazard presented. In this case the question of its necessity has been raised, particularly by anti vivisectionist groups. These groups have also applied the social pressure by which the question of non animal tests have become an issue. This has been taken up seriously by scientists wishing to develop such tests, despite the difficulty in obtaining funding.

The essential long term test has remained unchanged for forty years, while the criticisms by Barnes and Denz made in 1954 can still be applied.[111] A number of new concerns have been added to this, however, related to the growing concern with environmental toxicology. These are mutagenicity, carcinogenicity and teratogenicity, all areas where the basic scientific knowledge is lacking, although there are known chemicals which produce these effects both in animals and humans. The final area which appears to have increased in importance during this period is that of industrial toxicology. Here, there is a limited population exposed to the hazard, but at relatively high doses. Thus the emphasis has been on measurements

in humans, as well as tests on animals.

It is these problems with long term tests for toxicity which influence the legislation in the area. Despite the governmental position that such testing guidelines that are produced are not enforceable, but are suggestions for testing programmes, there is a real question as to how easy it is for a firm to avoid meeting all the test requirements. There is obviously a section of industry that wants such guidelines to follow, without making any advances or improvements to the programmes, while larger, more science based firms would prefer to have a larger influence on the tests which are suggested, and to see them altered as more knowledge and experience accrues. This must be seen in light of the question as to how long term harm to public health from toxic chemicals can be identified, given the general improvements to health that have taken place during the post war period.

The two major areas that came under some public scrutiny in this period were cosmetics and industrial chemicals, both because of action by the E.E.C. In the latter case the working of the Health and Safety at Works Act (1974) had to be elucidated.. In addition a number of new testing systems were published, covering pesticides, drugs, general toxicology, and the low dose effects of carcinogenicity and mutagenicity.

8.5. Cosmetics

In the latter part of the seventies one of the most important influences on regulative legislation in Britain has been its entry into the European Economic Community, and the undertaking to accept legislation designed to harmonise the differences between the member countries. In the field of toxic substances, this has had most effect on policy which had not been finalised when Britain entered the E.E.C. In particular it has had a major affect on chemicals in the workplace and cosmetics.

In the former it made an input to the deliberations of the committee who were setting the testing standards, but in the case of cosmetics a positive list was brought in although the British Government had no particular policy intentions in this direction.

In Britain the trade association, the Cosmetic, Toiletry and Perfumery Association has been mainly responsible for setting the standards of safety for cosmetics, and many manufacturers contracted out testing to commercial organisations.[112] The use of gross poisons was prevented under the 1933 and 1972 Poisons Acts, and those that made curative claims are considered under drug legislation. In the U.S. cosmetics had been regulated since 1938 under the Food Drug and Cosmetics Act, but with the exception of colour additives, 'manufacturers may use essentially any ingredient in a cosmetic until it has been determined that an ingredient or cosmetic may be hazardous to consumers under customary conditions of use'.[113] Thus, the FDA have to prove a substance is harmful, before the manufacturer is required to remove it.

The E.E.C. Directive on cosmetics published in September, 1976 requires that governments enact legislation to ensure product safety ,[114] but it was urged that in Britain 'commensense will prevail, and that the safety evaluation testing required by these countries will be relevant to the product'.[115]

The E.E.C. Directive hoped to eliminate technical barriers to trade.[116] A positive list was given for general substances, and colours, which laid down packaging and labelling regulations. In addition a "Committee on the Adaption to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Cosmetic Products Sector" was set up.[117] Member countries were given three years to comply. Britain passed its Cosmetic Product regulations in 1979. The Directive listed the type of chemicals that should be controlled,

Annex III: List of substances which cosmetic products must not contain
Annex 3 : Part 1 : List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down
Part 2 : List of Colouring Agents which can be contained in cosmetic products intended to come into contact with the mucous membranes
Annex IV : Part 1 : List of substances provisionally allowed
Part 2 : List of Colouring Agents provisionally allowed which may be contained in cosmetic products intended to come into contact with the mucous membranes
Part 3 : List of Colouring Agents provisionally allowed for in cosmetic products which do not come into contact with the mucous membranes. [118]

Despite these moves to improve the situation the inclusion of chemical substances in cosmetics remains relatively uncontrolled in the policy arena. They are not covered by either voluntary or statutory requirements for safety testing by government, this is left up to the manufacturer, and test results are not independently scrutinized by an expert committee. This situation exists despite the fact that there is a large consumer market for cosmetics and is reminiscent of the attitude taken by the Board of Trade in its evidence to the Zuckerman Committee in 1949, when no problem had been identified. Other areas where the problem is weakly defined include household chemicals, pollutants, toxic waste and toys.

The Health and Safety at Work Act (HSWA) however, is an example of an area where weak controls have been considerably strengthened due to the passage of this legislation. The Act came into effect on the 1st April 1975, and the question of the safety of chemicals immediately became an important issue, especially with the E.E.C. Directive being published.

8.6. The Health and Safety at Work Act

After the passage of the Act, the T.U.C. made representations to the Secretary of State for Employment, Mr. Michael Foot, to ensure that the

Health and Safety Commission (HSC) was given the resources it needed to function effectively.[119] The first regulations to be considered under the new Act were to prescribe the wearing of protective clothing for agricultural workers using certain types of chemicals on farms. These regulations went further than those made under the 1952 Poisonous Substances in Agriculture Act as they now applied to the self employed.[120]

The Act did not replace existing legislation, relevant enactments continued, but committed the employer to take reasonably practicable measures to ensure the safety of the employees, while the latter were required to take reasonable care while at work.[121] Section 6 covers the safety of toxic substances. Any person who designs, manufactures, imports or supplies any article for use at work must ensure so far as reasonably practicable its safety, a substance being 'any natural or artificial substance whether solid, liquid, gas or vapour'.[122]

By December 1975 the HSC had issued a consultative document on its proposed advisory committee structure. It proposed two committees to advise on general hazards, one for medical matters with eighteen industry boards. The general hazards committees were to deal with toxic and dangerous substances, and in addition a third committee was to be established in January 1976 to advise the commission on major hazards. The committees would take their secretariat from the Health and Safety Executive (HSE),[123] and have a tripartite membership drawn from industry, government, the unions in accordance with the Health and Safety at Work Act 1974. The medical advisory committee was appointed by the Health and Safety Commission (HSC) in January 1977 to advise on medical aspects of occupational health.[124] The membership of the Toxic Substances Advisory Committee and the Dangerous Substances Advisory Committee had not been announced, although two advisory committees - on major hazards and asbestos, had already been set up, each chaired by a senior member of the HSC.[125]

The need to control the risks of new chemicals used by industry was soon tackled. Large cost had been undertaken in order to ensure the safety of food additives and agricultural chemicals, but there had been little expenditure on testing industrial chemicals. The HSC proposed to issue in a discussion document a scheme for the notification of all new chemicals before their introduction into industrial use, because 'it is quite clear that a much greater expenditure is going to be required in future in all industrialised countries in checking that chemicals are not carcinogenic or toxic over long periods of use'.[126]

The Toxic Substances Advisory Committee was set up in March 1977 with Miss Audrey Pittom as chairperson, director of the Hazardous Substances Division of the HSE, as 'part of a new general structure of advisory committees being established by the commission, in order to help more effectively all the expertise available in its task of raising the standards of Health and Safety at Work'.[127] The Membership is listed in Table 8.3. The committee was to advise the commission 'on means of controlling health hazards to workpeople and related hazards to members of the public which may arise from the manufacture, import, storage, and use of toxic substances.'[128] They also had the power to appoint specialised sub committees . Its special responsibility was to draw up a scheme for the notification of new chemicals, based on the Department of Employment's scheme proposed in 1973. The director of the Executive, John Locke, assured industry that the aim of the proposals would be to 'minimise the effect on useful innovation',[129] particularly by concentrating on chemicals to be manufactured if a substantial quantity is to be manufactured. He continued,

> We see it as our function in HSE to hold a careful balance between the interests of those who will benefit from innovation and those who must take the risks of damage from innovation. On the one hand we have the interests from industry (including the livelihood of those who work in it) and, perhaps more important,

TABLE 8.3. Advisory Committee on Toxic Substances (1976-1981)

Chairperson	:	Miss L.A.Pittom
Members	:	Dr. T.A.Connors, Director, M.R.C. Toxicology Unit
		Mr. R.N.Bottini, TUC General Council, NUAAW
		Professor R.S.F.Scilling, University of London School of Hygiene and Tropical Medicine
		Dr. N.Sharratt, B.P.Occupational Health Unit
		Dr. K.S.Williamson, Principal Medical Officer, ICI.
		Mr, D.J.Barnet, Chief Environmental Health Officer, Bristol County Council
		T.Baynham
		F.Dyson, General Secretary, National Union of Dyers, Bleachers and Textile Workers
		J.F.Eccles, National Union of General and Municipal Workers
		J.P.Hamilton, Social Insurance and Industrial Welfare Department, TUC
		R.M.Knowles, West Midlands County Council, Councillor
		D.A.Morgan, General Manager and Chief Executive, Commonwealth Smelting, Ltd.
		D.G.Travis, Personnel Director, Reed Building Products Ltd.
		Dr. G.M.Davies, Occupational Health Unit, British Steel Corporation
		Dr. I.Laing, Production Director, Clayton Aniline Co.
Secretary	:	Mr. A.W.Durham, Senior Principal, Hazardous Substances Division, HSE.

> the advantages to the community springing from advances in technology. On the other hand we have demands for assurances that they will not be hurt from workers in industry and from the general public .... Every major mistake also creates demands for more and more rigorous controls over all new developments. It seems to me therefore that it is in all our interests to place the emphasis on preventing disaster.[130]

The control of the production of toxic substances could be legally covered under the Act. This required that no new substance be made available for industrial use until its safety in use had been established, also the employer has a statutory duty to ensure the safety and health of his employees. The Act also provides for regulations to be made covering any particular toxic substance. On receipt of notification data the HSE would decide priorities for the Toxic Substances Advisory Committee.[131] A Discussion Document was published in May 1977 with guidelines on submissions of notifications.[132]

One factor which would influence the acceptance of the draft documents was the impending requirements of the European Council. On 27th June 1967 the Council passed a directive on the approximation of the laws of the member states relating to the classification, packaging and labelling of dangerous substances. The 'sixth amendment' to this directive dealt with the pre-market testing of new chemicals was submitted to the council for discussion in 1976.[133] Other considerations of an increased requirement for testing included the cost, and the availability of laboratory facilities. The HSE estimated that between 200 and 400 substances would be subject to the proposed notification scheme, while world wide it is estimated that 1000 new chemical substances are introduced world wide per annum. This latter estimate means that the chemical industry would incur an extra annual cost of £10m to £40m, without taking into consideration the investment in products which fail to reach the market, the costs of examining intermediaries and impurities, the duplication of

costs or the 'hidden' associated costs.[134] As for laboratory facilities, Christopher warned,

> The projected testing requirements for general industrial chemicals would require an increase in the capacity of these facilities of not less than 20 per cent and possibly in excess of 100 per cent.[135]

In July 1981 the HSC published their second document, a consultative document on the notification of new substances - Draft regulations and approved Codes of Practice,[136] which was in line with the E.E.C. directive, but also dealing with additional requirements concerned with intermediate substances produced during manufacture, and covering pharmaceuticals, pesticides, food additives and tobacco substitutes although these substances are already under scrutiny. The HSE will have powers to obtain information about substances which have already been notified to a government department under another scheme, so as to avoid duplication of data. This information is required by the HSE, as all these substances have to be handled by people employed in their manufacture. The cost of obtaining the necessary information was estimated at £45,000 (October 1980 prices) for the initial notification.[137]

The notification scheme proposed in the two documents clearly involves some form of animal testing in the initial assessment of safety. The existing schemes, it was noted, 'aim principally to ensure that substances they cover will be safe when put to a specific use and normally concentrate on problems associated directly or indirectly with human ingestion'.[138] The tests suggested by the advisory committee in their consultative document included chemical and physical information of the chemical, including structural formulae and impurities. Acute toxicity is required such that it is possible to assess whether this is high, medium or low, groups of six rats under observation for 14 days were recommended, oral, dermal and inhalation figures are requested, with skin

and eye irritancy, and skin sensitation tests. It is then suggested that chemicals be screened for the need of carrying out chronic tests, to be undertaken on groups of ten animals for 30 days, rather than the more common 90 days. They recommend that it should also be considered whether both short and long term studies on carcinogenicity and mutagenicity will be required; and a test for teratogenicity is suggested on six female animals, either rats or rabbits observed through pregnancy. In short,

> for the initial notification the following minimum tests where appropriate are suggested:
>
> (a) oral toxicity
> (b) skin irritation and dermal toxicity
> (c) eye irritation
> (d) skin sensitisation
> Sub acute toxicity for 30 days.
> A 'short' test or tests for carcinogenicity, mutagenicity and teratogenicity. [139]

In addition to the human data, some indication of the environmental risk would be desirable, and primary investigations are suggested as toxicity to one or two species of fish, and susceptibility of the substance to biodegradation.

The 1981 consultative document additionally considered, not only the E.E.C. Directive, but also a draft code for good laboratory practice. Recommended tests, test methods and observations are given in much greater detail, although the basic information for notification remained the same. Fertility tests over two generations had been added with a possibility of acute and sub acute tests in additional species and toxicokinetic studies.

The HSWA differs considerably from the previous statutory controls in two major respects. The first is that it has developed a tripartite system, bringing together representatives from government, management and unions to make decisions regarding safety in the workplace. This puts into practice the principles of the Robens Report, and is demonstrated by the complexion of the membership of the Advisory Committee on Toxic Substances. The second important factor has been the influence of the

E.E.C. directive, which meant that the first set of proposals for the safety assessment of new chemicals had to be reformulated in line with the directive. It appears, however, that despite the method of operation of the Act, the stated policy is to present as little financial requirements on industry as possible. The stringency of the recommendations for testing can best be evaluated, however, in comparison to other systems that were published during this period.

8.7. Test Guidelines

During the seventies a number of the existing toxicity guidelines were updated and republished. This applied to the pesticide safety precaution scheme[140] and the Association of the British Pharmaceutical Society (ABPS)[141] In addition the Department of Health and Social Security (DHSS) published guidelines under the 1968 Medicines Act concerned with both toxicological evaluation of drugs[142] and teratogenicity studies.[143] There were two sets of test guidelines from the HSE Committee on Toxic Substances,[144] and, finally in 1981 the DHSS informally circulated draft guidelines on toxicity testing,[145] mutagenicity[146] and carcinogenicity[147] drawn up by its various committees.

The Committee on Toxicology of Chemicals in food, consumer products and the Environment (formerly the Pharmacology sub-committee) is in the process of updating the guidelines on toxicology testing, to revise the MAFF Memorandum of 1965. The range of the substances under the scrutiny of the DHSS, had been extended,

> (a) substances for use in food, including food additives, processing aids and food constituents derived from novel sources
> (b) food containments, including substances which originate from packaging material
> (c) cosmetics and toiletries
> (d) household products and other consumer products, including some industrial chemicals
> (e) environmental pollutants
> (f) chemicals used in the formulation of medicines. [148]

An inflexible list of tests for every chemical is not desirable, but tests should 'be designed to progress logically in the light of all relevant information available at each stage'.[149] A number of factors are important in evaluating the acceptability of a chemical. Knowledge of the chemical structure is important, and the specification and purity of the chemical, so that the tested substance is the same as the one put on to the market. Its proposed use and routes of human exposure, with data on human exposure and the need for human tests. The major part of the study will be comprised from animal studies.

> Although this is not an ideal situation the use of animals for toxicity testing provides the best means currently available for assessing any potential hazard to man.[150]

Other considerations when evaluating a chemical are certain in vitro tests as part of a battery of screening tests and a risk benefit analysis.

Human exposure is classified into three routes, chemicals which may be ingested, inhaled, or may come into contact with human skin. There are also sub groups, of the population which may exhibit increased susceptibility to toxic chemicals. Individuals with genetically determined or acquired abnormalities, or those on special diets, or on long term consumption of drugs. Atropics, elderly people, children, and smokers are all groups which may be more at risk than the general population. Maternal exposure may pose a threat to both fetuses and suckling infants.

The draft report contains recommendations on animal husbandry, particularly to ensure the environment of the test animals is uniform and free from contaminents. Recommended test guidelines include acute studies, metabolic studies, sub acute, (90-day) tests, carcinogenicity studies at two dose levels, embryotoxicity, teratogenicity and reproduction studies, mutagenicity, inhalation studies, skin and eye studies,

and where low toxicity is indicated, certain controlled, low dose studies on humans are suggested. The Membership of the Committee is listed in Table 8.4.

New recommendations on carcinogenicity testing were published by the Committee on Carcinogenicity of Chemicals in Food Consumer Products and the Environment in April 1979.[151] They cover the same range of goods as the guidelines on toxicology, and suggest that the chemicals that should be tested included those with a chemical structure that suggests carcinogenic potential, where some previous biological effect has suggested that it might cause problems or where large numbers of people are to be exposed to the chemical (or small numbers subject to heavy exposure). The design of the test must be consistent with statistical evaluation of the results, and the test animals suggested are the rat, mouse and hamster. The opinion of the Committee is

> Exposure to known carcinogens tends to lead to increasing incidence of the kinds of tumour that occur spontaneously in animals. Therefore when a test substance has this effect, it should be suspected of carcinogenic activity. On the other hand since non-specific factors such as calorific intake may also influence the influence of such tumours, an increase in the incidence of such tumours cannot by itself be regarded as proof of carcinogenic activity.[152]

Care must therefore be taken in the design and carrying out such tests to ensure the results can be reproduced. The current opinion is, however, that due to the lack of basic knowledge on carcinogenesis decisions must be taken on the strength of such long term tests, as there is, as yet, no reliable short term test.

There has been one report on guidelines for mutagenicity testing.[153] The reason for this was the growth of knowledge on chemical mutagenesis during the seventies. The guidelines were produced by discussions with representatives from industry, research institutes, university departments and representatives from national and international bodies in the field.

TABLE 8.4. The Committee on Toxic Substances in Food, Consumer Products and the Environment.

Chairman	:	Professor P.Turner, MD, B.Sc., FRCP, Hon MPS, Hon F.I.Biol.
Members	:	Professor F.Beck, MD, MD, Ch.B. FRCP, MRCS.
		Professor A.E.Bendler, B.Sc., Ph.D., FRSM, FIFST.
		Professor B.E.Clayton, MD, Ph.D. FRCP, FRC.Path.
		Professor D.S.Davies, B.Sc., Ph.D.
		J.Mcl.Philp, MRCVS, F.I.Biol.
		Professor D.E.Poswillo, DDSE, D.Sc. MRC.Path. F.I.Biol.
		F.J.C.Roe, DM, D.Sc., FRC.Path.
		G.R.Tudhope, B.Sc., MD, FRC.Path. FRCPE.
		G.N.Volans, B.Sc. MD, MRCP.
		Professor O.Wrong, DM, FRCP, FRCPE.
Secretaries	:	Professor F.A.Fairweather
		B.H.MacGibbon
		W.M.B.Denner
		Mrs. S.J.Hattersley
		M.A.Garley

Also served on the Committee during the course of the Preparation of the Draft Guidelines

A.G.M.McLean, BM, B.CH., Ph.D., MRC.Path.

Professor R.T.Williams (now deceased) Ph.D. D.Si.FRC.

Source Consultative Document on Guidelines on Toxicity Testing (Draft) DHSS, July 1981

The mutagenic potential of ionising radiation is well known but the importance of the influence of the chemical environment is unknown. Far more knowledge of the role of DNA in genetic processes is needed. It is known that most carcinogens are mutagens, but nothing is known about the carcinogenicity of the several thousand known mutagens. While conventional tests are able to predict potential toxic or carcinogenic hazards with some degree of certainty, the prediction of mutagenic risk is more uncertain, because there is a high background 'noise' and mutagenic damage may take many years to manifest itself. The task of the committee was, therefore, to identify test systems, internationally accepted for which there is academic backup in Britain. As there is no single test which can be used to assess mutagenic potential, a battery of four tests are suggested. This, again, is an area where test systems have to be substituted for scientific knowledge.

A comparison of the test systems suggested during this period appears in Table 8.5. This covers those arising from government sources, but those from the Association of the British Pharmaceutical Society are included as a comparison with MAL 2. It can be seen, however, that although the suggestions differ widely in the specialised tests, according to the use that each class of chemical is put to, there is a basic core of tests that they are agreed on. These are the estimation of acute toxicity via various routes, a sub acute test, a long term test for carcinogenesis, a sub acute study, a metabolic study, and evidence of skin and eye irritation. In the case of drugs the industry's specifications are more detailed than those from the DHSS. This indicates the conclusion that tests requirements are becoming longer, rather than more succinct due to developments in basic knowledge, and this will be explored in greater depth in the next chapter.

Aston University

8.8. Conclusion

During the seventies there were positive movements within toxicology to a more professional social organisation in Britain with the establishment of the British Toxicology Society and its recognition as an independent discipline by the Royal College of Pathologists. The first signs of an academic community began to develop, but with very independent origins - and in those departments which tend to have a historical link with toxicology, or where one concerned scientist acts as an innovator. Most predominant in the area are laboratories with a sole interest in toxicology with some freedom to pursue academic aspirations. Although by far the greatest amount of resources go to safety evaluation rather than basic research, the largest industrial laboratories are concerned with questions of fundamental interest to science. The evidence from ICI suggests that interest in such problems is not in conflict with commercial goals but is focused on commercially important chemicals. In addition work on some practical problems - such as short term tests for cancer, have a long term economic interest for the firm. Thus a basic research programme can be formulated, although the question of whether external goals have an impact on the structure of knowledge is not examined. In this period also, there are first moves towards international communication through two international congresses.

Can this reorganisation and professionalisation within the social structure of toxicology be seen to have an impact on the cognitive development of the science? This may be a response with a longer lead time which develops from the greater sense of a community. The major source of consensus in the field is that toxicology is a multidiciplinary activity with distinct aspects related to economic, medical and environmental aspects in the assessment of risks from chemical hazards. It is not yet a predictive science, still more basic research is needed, but

progress could be made in defining early responses, in developing short term tests, and with more international co-operation in research. The problems which have become most visible during this period are the question of quality control, of the large amount of data produced, of legislation and the requirement of acute toxicity data, the development of alternatives to animal testing, and the quantification of risk/benefit equations. Most problems seem to be identified because the requirement of regulatory demands are greater than the knowledge available. Safety evaluation has developed rules of thumb to overcome this, but the basic chronic toxicity test has still not changed. The problems of this type of testing have become more articulated, particularly that absolute safety is unobtainable by any testing means. The alternative approach to safety is that of the M.R.C. Toxicology Laboratory, starting with basic research of the substance, with clinical and epidemiological data from humans. They see a role in maintaining a scientific basis for governmental standards and in the training of scientists and technicians. In the cognitive field more problem areas are being identified, which lead to greater uncertainty of the testing methods used, although evidence of the beginning of a small academic community and more international communication tend to balance this trend. The social, economic and political aspects of toxicology are acknowledged but with fundamental research these are external constraints on problem development, while for safety evaluation, these factors are the reason for its existence.

In this period the influence of the E.E.C. can be most clearly seen for its impact on British policy. This is particularly important in bringing the question of the safety of cosmetics to the notice of the British Parliament. An E.E.C. directive has also had an influence in the field of Health and Safety where the proposals for testing industrial chemicals from the tripartite advisory committee on Toxic Substances had to be redrafted to harmonise with the requirements of the E.E.C, which

extended the tests that the committee had previously recommended, as the directive was compiled from all the existing legislation within the community. Advice from the DHSS on all aspects of toxicity is given by its three major standing committees, on toxicology, carcinogenicity and mutagenicity, and through recourse to its own toxicology laboratory, underlining the highly technical emphasis put on governmental decisions about chemical hazards. The guidelines now cover all classes of substance so the standards of testing will be the same for all chemicals in consumer goods. In the policy field, however, there is little evidence of major change from the traditional information gained from standard toxicity tests.

CHAPTER NINE

TOXICOLOGY IN BRITAIN 1945-1980

Toxicology in Britain 1945-1980.

When investigating an industrially based science such as toxicology it is very difficult to obtain any records, such as annual expenditure or staff of institutions, that can be used to build up a picture of how the science has developed over time. Either these types of records have not been kept, or they are not accessible. The question is, then, how to measure the growth of the science, in terms of the amount of resources put into it, the number of scientists employed on toxicological research and in general, the development of a scientific community. It is possible however, to obtain some indications relevant to these questions in a number of ways. An analysis of the papers submitted to conference and books can give some indications particularly of the institutions which are most active in the area. It is true that this is not a very good measure of the extent of the toxicological community as many commercial institutions do not participate in conferences or publish papers. If, however, some companies are very prominent in this analysis, this could be taken to show their particular interest in developing the subject from an industrial base. Further evidence of this might come from attempts they make to influence government policy making. This is also an important source of information about those scientists who are most keen to develop and direct the development of toxicology. Here it is possible to investigate the 'hybrid community', following Weingart, in particular the membership of advisory committees who develop the test guidelines. Further evidence of the development of the toxicological community may be gained, if the advisors have been chosen from the institutions which have been identified as high contributors to the science. Finally, as this is the area where policy goals and science meet, an analysis of how the test requirements have changed over time will give an indication of how new developments in basic research are transferred to the political

arena to improve the predictivity of the test systems.

9.1. Ranking the Institutions

In any scientific discipline one of the important facets of identity of the science, to allow transfer of knowledge between practitioners, is its textbooks. In toxicology it is during the seventies that these begin to appear. There are two characteristics of these books that are a result of the particular way that toxicology has developed. They typically are edited by a scientist, with contributions from a number of specialists on particular topics. The second point is the high number of conference proceedings which are printed. There is a lack, particularly of books published in Britain, of textbooks on toxicology for teaching purposes, containing a straightforward account of basic principles for heuristic purposes, although some American books are available.

Because the institutional base of toxicology is dominated by industrial and commercial laboratories, the criticism has often been made that much of the scientific data that exists has never been published in the scientific press. This implies that for such industrially based sciences the traditional citation and co-citation analyses of the development of these disciplines will not accurately reflect the cognitive or institutional inputs to that scientific area. While this is undoubtedly true for the journal literature, which itself is dominated by specific studies of chemicals rather than more generalised papers, some interesting insights about the laboratories themselves can be provided by a crude estimate of the number of contributers of each institution to the books and conferences. The ranking is shown in Table 9.1.

From the table it appears that the M.R.C. Toxicology Research Unit is the most prolific institution in British toxicology, but most of the other institutions that are ranked have a particular interest in toxicology. Four of these are institutions which rely on some commercial funding. The

TABLE 9.1. The Most Prolific Contributors to Books on Toxicology By Institutions.

Institutions	No. of Articles
1. M.R.C. Toxicology Unit	24
2. ICI Central Toxicology Laboratory	15
3. University of Surrey Biochemistry Department	9
DHSS	9
5. BIBRA	8
6. Middlesex Hospital Medical School	7
Huntingdon Research Centre	7
Chemical Defence Establishment	7
9. University of Oxford	6
10. University College Hospital Medical School	5
Department of the Environment	5
Health and Safety Executive	5
B.P. Occupational Health Unit	5
Guys Hospital Medical School	5

Sources:

Conference on Mechanisms of Toxicity British Medical Bulletin (1969) 25

Royal Society for the Promotion of Health Conference : Laymans Guide to Food Regulations (1969) 90, Buckingham Palace Road, London SW1.

E.Boyland, R.Goulding (eds) (1969) Modern Trends in Toxicology V.1. (Butterworths, London).

G.Patet (ed) (1970) Methods in Toxicology (Blackwell, Oxford)

W.N.Aldridge (ed) (1971) Mechanisms of Toxicity

W.J.Hunter, J.G.P.M.Smeets, (eds) (1977) The Evaluation of Toxicological Data for the Protection of Public Health. Proceedings of the International Colloquium, Luxemburg, December 1978 (Pergamon Press, London).

B.Ballantyne (ed) (1977) Current Approaches in Toxicology (John Wright and Son, Bristol)

G.E.Paget, (ed) (1977) Quality Control in Toxicology (M.T.P. Press, Lancaster).

R.W.Brimblecombe, A.D.Doyan (eds) (1978) Carcinogenicity Testing: Principles and Problems, Proceedings of a Symposium held at the Royal College of Physicians, London, 1977 (M.T.P.Press, Lancaster)

G.L.Plaa, W.A.M.Duncan (eds) (1978) Toxicology as a Predictive Science, Proceedings of the first International Congress on toxicology (Academic Press, New York)

Royal Society Study Group, (1978) Long Term Toxic Effects (Royal Society, London)

Toxicology M.Sc.Course Prospectus, Department of Biochemistry, University of Surrey (1979)

Oyez International Business Communications (1980) Training Course on Industrial Hygiene and Toxicology *

V.K.Brown (1980) Acute Toxicity in Theory and Practice (John Wiley & Sons, London)

B.Holmstedt, R.Lauwerys, M.Mercier, M.Roberfroid (eds) (1980), Mechanisms of Toxicity and Hazard Evaluation (Elsevier, North Holland Biomedical Press) Proceedings of the second International Congress on Toxicology.

* Oyez Scientific & Technical Servies Ltd. Bath House, 56 Holborn Viaduct, London GC1A 2EX

TABLE 9.1. continued

C.Wood (ed) (1980) Human Health and Environmental Toxicants, Proceedings of a Conference 14-16 May 1979 (Royal Society of Medicine/Academic Press, London)

Conference on Toxic Substances, Carcinogenicity and Food Contaminents (1980) Organised by Charles Simeons, Conference Department, 21 Ludlow Avenue, Bedfordshire LV1 3RW

universities and hospitals represented are those where there are scientists who have a particular interest in toxicology, or some aspect of toxicology (for example the work on chemical carcinogenesis by Professor R.Doll at Oxford). Both the commercial and non commercial laboratories are places which are committed to the study of basic research on toxic mechanisms, and the other well represented group are those government departments with special responsibility for the control of toxic substances (except MAFF).

Further illustration of the formation of a toxicological community can be gathered by investigating the scientists prominent in the establishment of the British Toxicological Society. A list of the committee members and their institutional affiliation appears in Table 9.2., with many of the same institutions being represented again. If an alternative measure is taken, that is, the institutional affiliation of those contributors to the publications in Table 9.1., with more than one paper presented, then a similar pattern develops as seen in Table 9.3. Finally an examination of the movement of scientists between institutions during this period, again shows the same laboratories favoured as in Table 9.4. The published literature implies that, in fact, there has been little movement of scientists over this period. This, however, could be a result of the selective nature of the institutions which contribute to published work.

In the absence of adequate data on the growth of resources in toxicology, it is possible to take other indices of activity in the science. The M.R.C. Toxicology Research Unit has already emerged as an important institution in the field of British Toxicology. It is possible to obtain data both on the growth of publications by the Unit and the number of scientific staff employed. Both quantities are shown plotted against time in Fig.9.1., and Fig.9.2. Both graphs indicate the increase of

TABLE 9.2. Executive Committee Membership of B.T.S. (1979-1982)

Member	Institutional Base
Dr. W.N.Aldridge (1979-1980)	M.R.C. Toxicology Unit
Professor J.W.Bridges (1979-1981)	Robens Institute of Industrial and Environmental Health and Safety, University of Surrey
Dr. F.M.B.Carpanini (1979-1980)	
Dr. D.G.Clark (1980-1982)	Shell Toxicology Laboratory
Dr. D.M.Conning (1980-1982)	BIBRA
Dr. A.D.Dayan (1979-1981)	Wellcome Research Laboratories
Dr. R. Goulding (1980-1982)	
Dr. T.L. Hardy (1979)	
Dr. L.J.King (1980-1982)	University of Surrey
Dr. A.E.M.McLean (1981-1983)	U.C.H. Medical School
Dr. J.M.Offer (1979-1981)	Huntingdon Research Centre
Professor W.P.M.Paton (1981-1983)	University of Oxford
Dr. I.F.H.Purchase (1979-1980)	ICI Central Toxicology Laboratory
Dr. M.S.Rose (1979-1980)	ICI Central Toxicology Laboratory
Dr. M.Sharrat (1979-1981)	B.P.Occupational Health Unit
Dr. G.N.Volans (1980-1981)	Guy's Hospital Poisons Unit

Source: Information supplied by Dr. L.J.King, Department of Biochemistry, University of Surrey, Secretary, B.T.S.

TABLE 9.3

a) Contributors who Published More than Two Papers

People	Institution
Dr. W.N.Aldridge	M.R.C. Toxicology Research Unit
Dr. J.M.Barnes	M.R.C. Toxicology Research Unit
Dr. T.Connors	M.R.C. Toxicology Research Unit
Dr. R.D.Verschoyle	M.R.C. Toxicology Research Unit
Dr. D.Conning	ICI/BIBRA
Dr. M.Sharrat	DHSS/BIBRA/B.P.Occupational Health Unit
Professor J.W.Bridges	Robens Institute of Industrial and Environmental Health and Safety, University of Surrey
Professor D.V.Parke	Dept.Biochemistry, University of Surrey
Professor A.N.Worden	Huntingdon Research Centre
Professor P.N.Magee	M.R.C.T.R.U./Middlesex Hospital Medical School
Dr. D.E.Stevenson	Shell Research Centre
Dr. R.W.Brimblecombe	CDE/Smith, Kline and French Ltd.
Dr. A.E.M.McLean	U.C.H. Medical School
Dr. P.Grasso	BIBRA/B.P. Occupational Health Unit

b) With Two Papers Only

Dr. P.R.B.Noel	Huntingdon Research Centre
Dr. J.P.Griffin	DHSS
Professor R.Doll	University of Oxford

Source: As for Table 9.1.

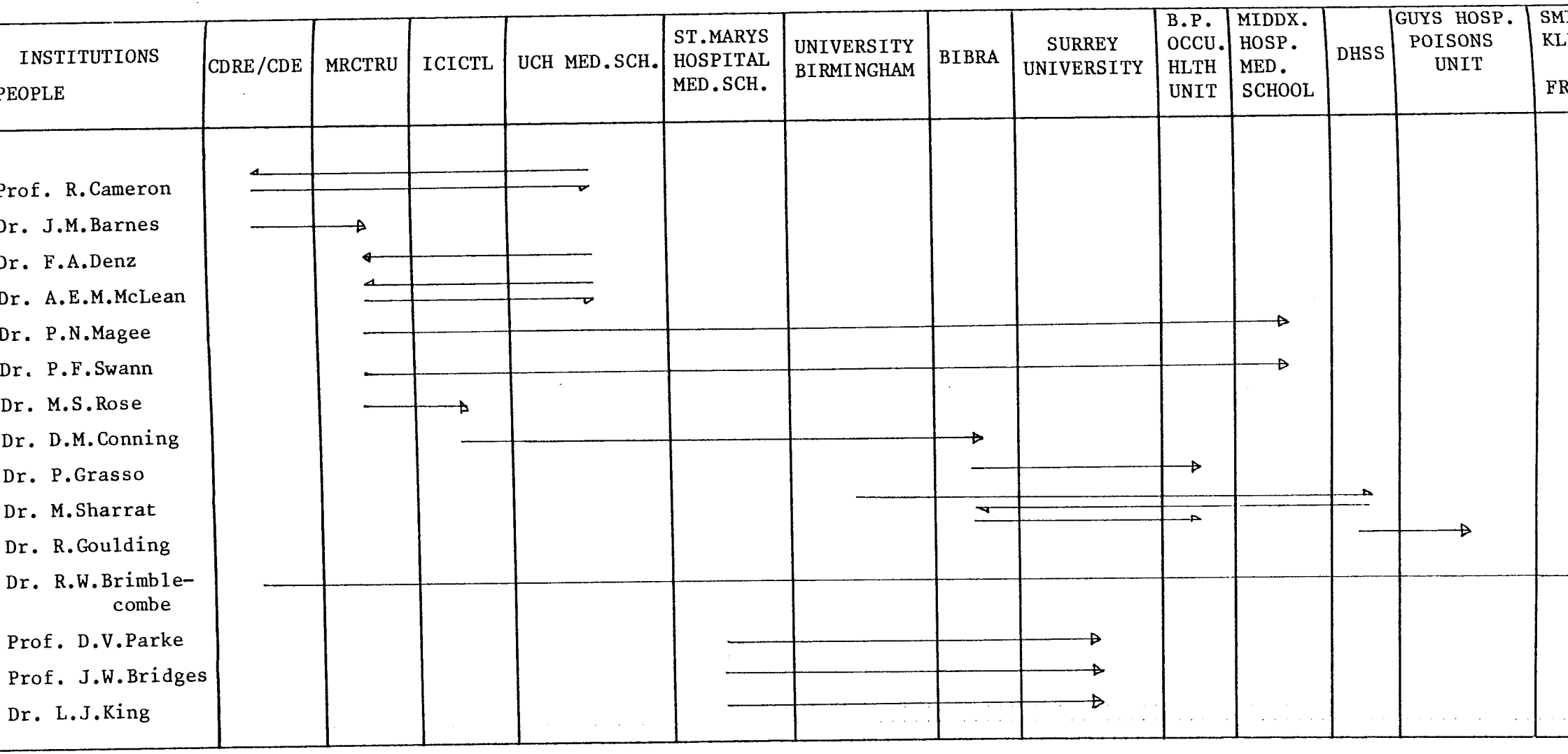
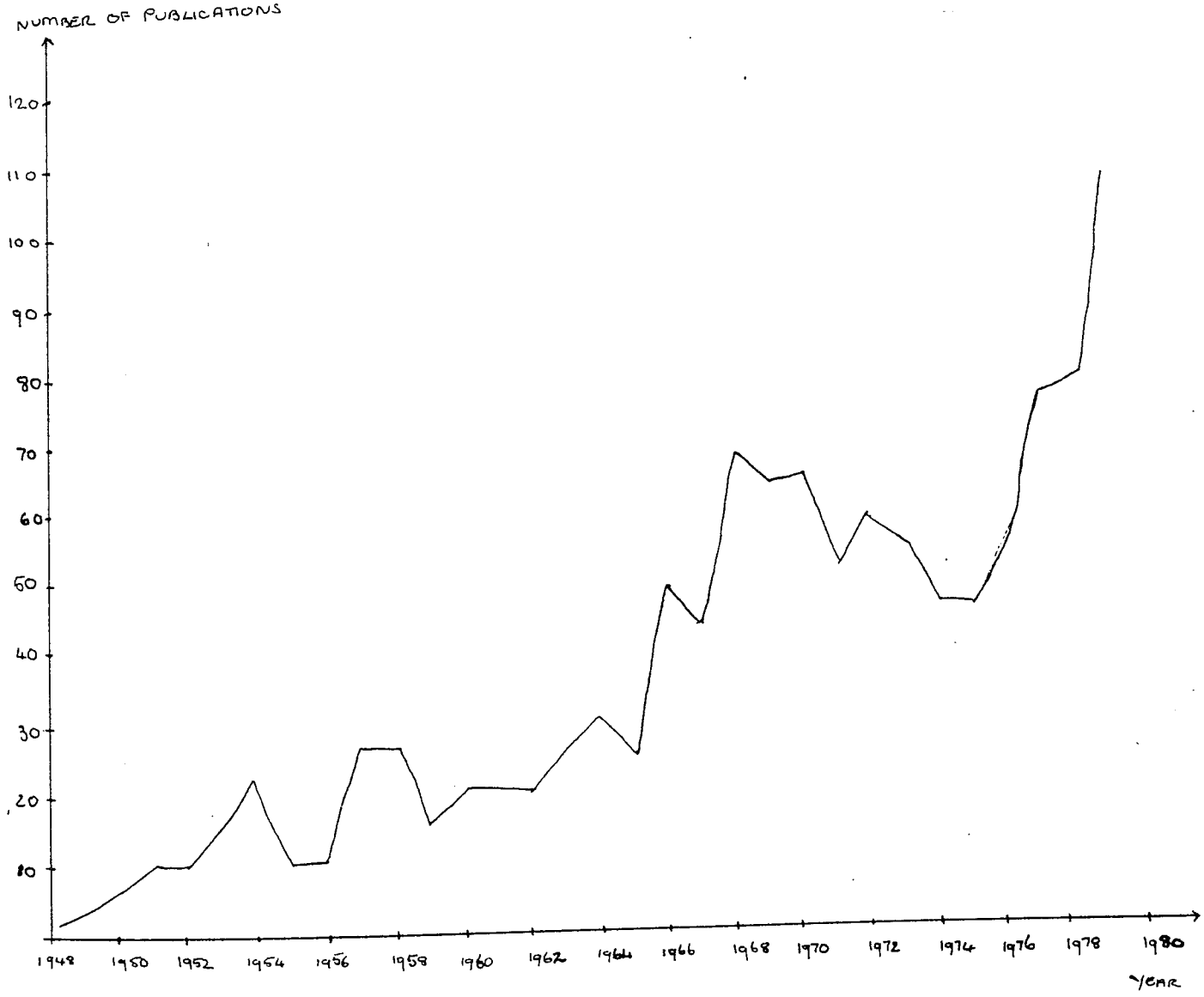


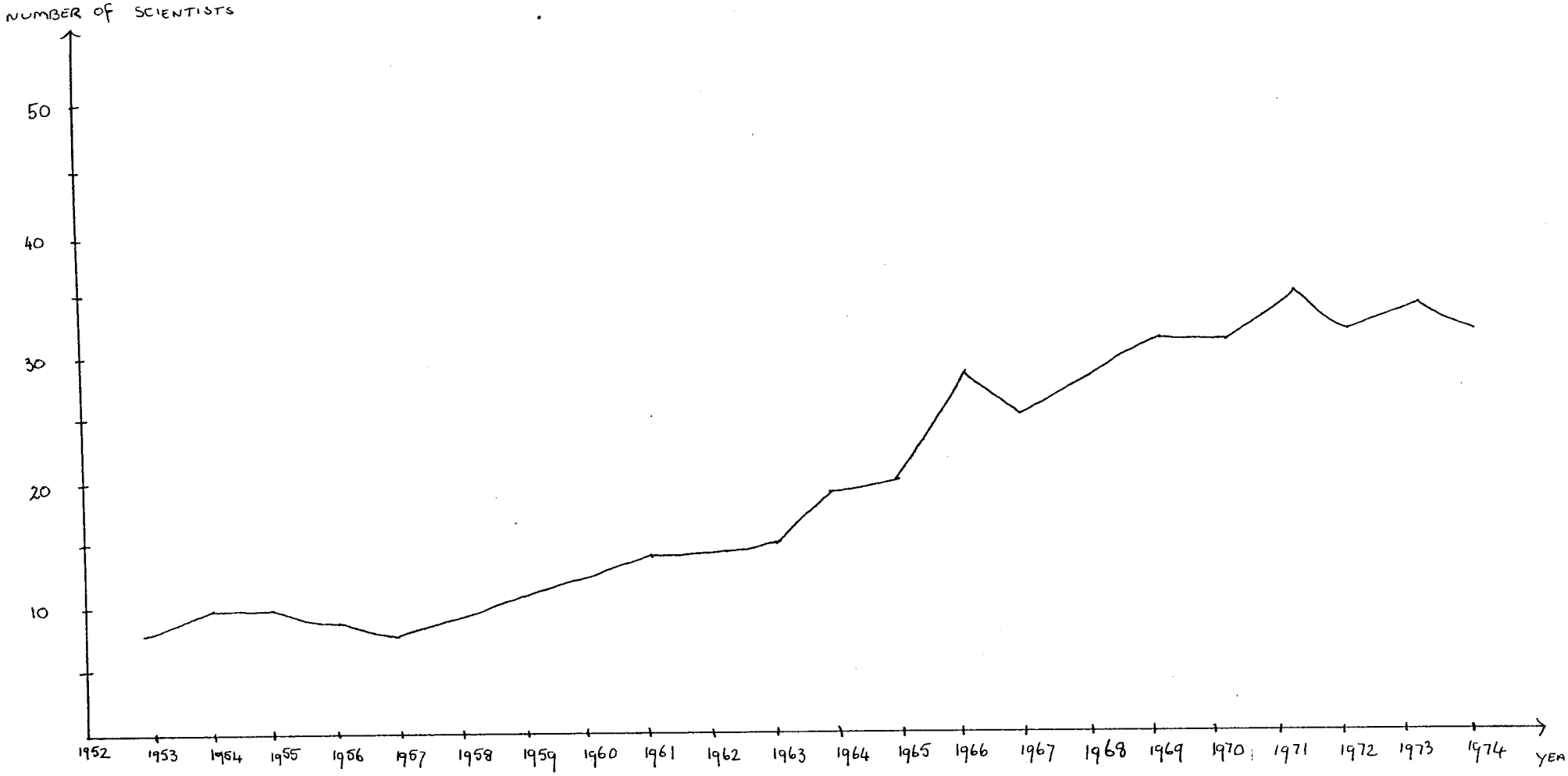
TABLE 9.4. Movement of Scientists Between Institutions, 1945-1980

Fig 9.1. Total Number of Papers Published By M.R.C. Toxicology Research Unit



Source: M.R.C. Toxicology Research Unit, Unpublished Reports.

FIG 9.2. M.R.C. TOXICOLOGY RESEARCH UNIT: NUMBER OF QUALIFIED STAFF



SOURCE : M. R. C. TOXICOLOGY RESEARCH UNIT, UNPUBLISHED REPORTS.

activity during the mid sixties, which supports the suggestion that there was an increase in concern about the safety of chemicals during that time.

There is some evidence, then, of an institutional base for toxicology in Britain in which both aspects of toxicological knowledge - basic research and safety evaluation - is located, and within this institutional structure, a few laboratories are particularly involved in the dissemination of knowledge. By examining the committees appointed by government, departments to advise on toxicological matters, it will be possible to assess how this structure of the science is perceived from the policy making arena. It is through these advisory committees that the areas of science and policy interact, so an analysis of their membership is useful to identify the source of scientific advice. Additional information about this science/policy interaction can be gained by investigating the development of suggested test guidelines, which is particularly interesting to see whether new scientific knowledge has been incorporated over time.

9.2. Government Responsibility For Toxic Substances

As it has developed, public policy in this area is divided between different departments. The Ministry of Agriculture, Fisheries and Food oversees the Pesticide Safety Precaution Scheme and has responsibility for the assessment of food additives under the Food and Drugs Act 1955. The Health and Safety commission is responsible to both the Department of Environment and the Department of Employment. The Medicines Division of the DHSS is responsible for administering the Medicines Act. These different functions all basically rely on the interpretation of similar data on the toxicology of the substances that they control, and all the advisory committees are, at certain times, in need of some expert scientific advice. The DHSS has a separate division concerned with the toxicology of chemical hazards and environmental health which serves this purpose.[1] This has three independent advisory committees on

toxicology, carcinogenicity and mutagenicity of chemicals in food consumer goods and the environment.

The DHSS has a responsibility for public health, and its concern for this, particularly in the forms of carcinogenicity and medical and nutritional aspects is not new. In 1935 the Ministry of Health (MoH) set up an Advisory Committee on Nutrition, the responsibilities of which were expanded during the war, and this committee was reformulated as the Standing Committee on Medical and Nutritional Problems. A number of sub committees were appointed to undertake its work. During the early fifties the subject of chemicals in food was prevalent, and the attitude of the Ministry of Health, was,

> Before introducing a new substance into food manufacturers satisfy themselves that it has no immediate or early toxic effects: If they did not, they would be liable to prosecution under the Food and Drugs Act or under the Common Law. The absence of such effects, however, is no guarantee against the accumulation of slight effects by continued consumption, culminating eventually in a pathological state.[2]

while the subject of toxic effects 'embraces detergents, cleansing materials, cosmetics and preservatives'.[3]

In 1957 this committee was replaced by the Committee on Medical and Nutritional Aspects of Food Policy. The Toxicology Committee of the Medical Research Council prepared a memorandum on the assessment of toxicity for the Ministry, as the M.R.C. has a duty to advise the government on progress in medical science,

> the role of the Toxicology Committee in this field is to discover and interpret the available information about the safety or harmfulness of chemical compounds to which the general population or a particular group of it may be exposed, and to make suggestions for further research work where this is deemed to be necessary.[4]

The Committee on Medical and Nutritional Aspects of Food Policy

(COMAFP) was consulted for advice by both the Food Standards Committee (FSC) and the Advisory Committee on Poisonous Substances used in Agriculture and Food storage. Their problems prompted it to establish a panel of scientists to report on the assessment of hazards from carcinogens and co-carcinogens.[5]

As the volume of work increased the committee was again reformulated as the Committee on Medical Aspects of Food Policy. This was still responsible for nutritional problems, and also for problems of toxicological, carcinogenic and bacterial hazards in food. There was a toxicology division within the MoH, which was split in 1964, into two, concerned with chemical hazards and environmental health.[6]

The COMAFP created a number of expert sub-committees. In 1951 when the FSC created its sub-committee on preservatives, this was advised by a pharmacology panel, comprised of medically qualified personnel. This sub-committee became an independent committee in 1964, the Food Additives and Contaminents Committee (FACC), and the pharmacology panel became the Pharmocology sub-committee. By 1968 it had changed allegiance and became a sub-committee of COMAFP. It also had the services of the consultative panel on carcinogenesis.

Growing pressure of work again necessitated a division and by 1972 the COMAFP had given some of its responsibility to a newly formed Committee on Medical Aspects of Chemicals in Food and the Environment. This latter committee obtained the services of the former Pharmacology sub-committee now renamed the Toxicology sub-committee. In 1978 three sub-committees became full committees, and these now form the basis of scientific advice on the question of toxic hazards. They are:

1. Committee on Toxicity of Chemicals in Food, Consumer Goods and The Environment

2. Committee of Mutagenicity of Chemicals in Food, Consumer Goods and the Environment
3. Committee on Carcinogenicity of Chemicals in Food, Consumer Goods and the Environment.

In order to facilitate advice given by these committees a DHSS toxicology laboratory was established at St. Bartholemew's Hospital in 1976, and has been operational since 1979. Its prime aim is to clear up any problems that government advisers might face in evaluating data submitted from industry, but not to carry out any independent long term testing.

The DHSS, then, has emerged as the centre in government, from which scientific advice on aspects of toxicity may be obtained. This development is summarised in Table 9.5. The total position of Ministerial responsibility for different classes of toxic substances is presented in Table 9.6. The current situation is, then, very diverse responsibility between government departments for the control of different chemical substances, with specialist scientific advice located within the DHSS. The next step is to analyse the governmental committees concerned with the toxicity of chemicals to see whether there is any evidence of a core group of scientists represented.

9.3. Governmental Committees Concerned with the Safety of Chemicals

During the period 1945 to 1980 there have been a number of committees appointed concerned with the safety of chemicals. They have mainly had members with scientific qualifications, although these have not always been strictly concerned with toxicology. In particular, there are four different types of advisory committee that can be identified:-

1) Ad hoc Committees

a) Working Party on Toxic Chemicals in Agriculture
b) Joint Sub-committee on The Safety of Drugs
c) A.C.S.P. Committee on Toxic Chemicals in Consumer Goods
d) Robens Committee on Health and Safety at Work

TABLE 9.5. Development of the Committee on Toxicity of Chemicals in Food Consumer Products and The Environment (Dates of Formation)

1942	Committee on Medical & Nutritional Problems in Food (Ministry of Health)	1942	Food Standards Committee (Ministry of Food)
1957	Committee on Medical & Nutritional Aspects of Food Policy (Ministry of Health)	1951	Preservatives Sub-Committee to FSC, with Pharmacology Panel (Ministry of Food)
1965	Committee on Medical Aspects of Food Policy with Pharmacology Sub-Committee ←	1964	Food Additives and Contaminents Committee with Pharmacology Sub-Committee
	and		
	Consultative Panel on Carcinogenesis		
1972	Committee on Medical Aspects of Chemicals in Food and the Environment (Pharmacology Sub Committee, Consultative Panel on Carcinogenesis)		
1974	Pharmacology Sub Committee	Toxicology Sub Committee	
1978	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. (Also formed - Committee On Carcinogenicity of Chemicals in Food, Consumer Products and the Environment Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment).		

TABLE 9.6. Departmental Administration of Current Legislation and Responsibility for Toxic Substances

1. Ministry of Agriculture Fisheries and Food

Agricultural Chemicals	1952 Poisonous Chemicals in Agriculture Act
	1957 Pesticide Safety Precaution Scheme
Horticultural Chemicals	
Food Additives	1955 Food and Drugs Act
	Food Standards Committee
	Food Additives and Contaminents Committee

2. Home Office

Poisons	1972 Pharmacy and Poisons Act
	Poisons Board
Household Chemicals	

3. Department of Education and Science

Schools
Advisory Committee on Pesticides

4. Department of Health and Social Security

Pharmaceuticals	1968 Medicines Act
	Committee on Safety of Medicines
Toxicology	
Carcinogenicity	
Mutagenicity	

5. Department of Trade

Cosmetics
Carriage of Toxic Substances

6. Department of Prices and Consumer Affairs

Toys
Other Consumer Goods

7. Ministry of Defence

Armed Services
Chemical Defence

8. Department of Environment

Pollution	1968 Clean Air Act 1974 Control of Pollution Act Royal Commission on Environmental Pollution
Toxic Waste	1972 Deposit of Poisonous Wastes Act.
Industrial Chemicals (with the Department of Employment)	1974 Health and Safety at Work Act Advisory Committee on Toxic Substances

Based on

M.Sharratt (1977) Evaluation of the Safety of Chemicals in B.Ballantyne (ed) Current Approaches in Toxicology (John Wright & Son, Bristol)

2) Standing Committees on Toxicity

a) Committee on Toxicity of Chemicals in Food Consumer Products and the Environment (DHSS)
b) Committee on Carcinogenicity of Chemicals in Food Consumer Products and the Environment (DHSS)
c) Committee on Mutagenicity of Chemicals in Food Consumer Products and the Environment (DHSS)
d) Advisory Committee on Toxic Substances (HSE)

3) Scientific Sub Committee to Standing Committees

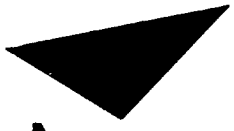
a) Scientific Sub-Committee to the Advisory Committee on Pesticides
b) Sub-committee on Toxicity, Clinical Trials and Therapeutic Efficiency to Committee on Safety of Medicines

4) Others

M.R.C. Committee on Toxicology
A.R.C. Research Committee on Toxic Chemicals.

Typically the ad hoc committees were established to investigate a problem and report on it in a short time, by collecting evidence from interested parties. They have been involved in presenting recommendations to government departments as proposals for legislation, which have been accepted. The standing committees and the scientific sub-committees remain in force over a period of time, and exist to give day to day advice over the implementation of legislation. It could be expected that, if there is a community of toxicologists, they will be represented on these advisory committees. In order to test this it is necessary to look at the disciplines represented on these committees.

Table 9.7. lists some of the people who have served on the DHSS committee on Toxicity. From this it can be seen that the DHSS has appointed advisers who are primarily drawn from disciplines which are neighbouring to toxicology. The major advisory group being drawn from the medical profession. Very few of the scientists involved belong to the British Society of Toxicology (BTS) which indicates that the people involved do not view themselves as representatives of toxicology as a profession. Thus the advisers in this case have not been drawn from



Aston University

the community of 'working' toxicologists, mainly located within industry. This can easily be explained, however, and the DHSS obviously wishes to preserve the objectivity of its advice, therefore relying on academic scientists. The question remains as to whether these scientists are toxicologists who have been absorbed into the existing disciplinary structure. Only two have worked for the M.R.C. Toxicology Unit, and the low membership of the BTS seems to discount this. On the other hand, this composition of advisers does mirror the organisation of multi-disciplinary teams working on toxicological problems found in some laboratories, due to the amorphous character of the science. It is, however, difficult to assert that an elite of the science is represented, even though the majority of the existing members are professors.

Table 9.8. analyses a second standing committee, the HSE Advisory Committee on Toxic Substances. This illustrates the novel way in which the Health and Safety at Work Act 1974 required such committees to be formulated. The ACTS has representatives from government, industry and the unions, all groups who would be involved in legislation to control toxic chemicals in the work place. As before, however, there are few members who belong to the BTS.

Continuing this analysis to the scientific sub committees with special responsibility for toxicology, Table 9.9 shows the breakdown of the Scientific Sub-committee to the Advisory Committee on Pesticides and Other Toxic Chemicals, which acts as adviser to the Pesticides Safety Precaution Scheme. This illustrates yet another approach to the appointment of advisers. They are mostly governmental scientists employed by different government run laboratories. In addition there is one academic scientist, and two from the M.R.C. Toxicology Unit, who could be regarded as toxicologists. There are here, a number of different points of view, although MAFF is content to receive advice from its own employees rather

TABLE 9.8. Members of the Advisory Committee on Toxic Substances 1977.

Government

Miss L.A.Pittom (HSE)

* Dr. T.A.Connors (M.R.C. Toxicology Research Unit)

Industry

Dr. G.M.Davis (BSC)

Dr. I.Laing (Clayton Analine Co.)

Mr. D.A.Morgan (Commonwealth Smelting)

* Dr. M.Sharrat (B.P.Occupational Health Unit)

Mr. D.G.Travis (Reed Building)

Dr. K.S.Williamson (ICI)

Union

Mr. R.N.Bottini (NUAAW)

Mr. F.Dyson (Nat. Union Dyers)

Mr. J.F.Eccles (NUGMW)

Mr. J.P.Hamilton (TUC)

Academic

Professor R.S.F.Schilling (Occupational Health, U.London)

Local Government

Mr. D.J.Barnett (Bristol District Council)

* Members British Toxicology Society

Source: Advisory Committee on Toxic Substances (1977) Proposed Scheme for the Notification of Toxic Properties of Substances (Health and Safety Commission)..

TABLE 9.9. Pesticides Scientific Sub Committee 1967-1969

MAFF Plant Pathology Laboratory

M.Cohen, M.Sc., Ph.D., F.I.Biol.

R.deB Ashworth, M.Sc., Ph.D., FRIC.

MRC Toxicology Laboratory

J.M.Barnes, CBE., M.B., B.Ch.

M.B.Stoner, M.D., B.Sc.,

MAFF Foodstuffs Division

T.J.Coomes, B.Sc.

Ministry of Defence

W.S.S.Ladell (CDRE) Sc.D., M.B., B.Ch., M.R.C.S., L.R.C.P.

Natural Environment Research Council

N.W.Moore (Nature Conservancy) M.A., Ph.D.,

East Malling Research Station

R.P.Tew, F.R.I.C.,

Department of Pathology, University of Leeds

G.M.Bonser, M.D., F.R.C.P.

National Agriculture Advisory Service

M.E.Croxall, Ph.D., F.I.Biol.,

M.C.Gough, Ph.D., D.I.C., F.I.Biol.

E.Lester, B.Sc., M.I.Biol.

MAFF Infestation Control Laboratory

E.E.Turtle, M.B.E., M.Sc., Ph.D., F.R.I.C., A.R.C.S., D.I.C.

MAFF Central Veterinary Laboratory

S.B.Kendall, B.Sc., Ph.D., M.R.C.V.S., A.R.C.S., F.I.Biol.

Department of Health & Social Security

R.Goulding, B.Sc., M.D., M.R.C.P. M.R.C.S.

Rothamsted Experiment Station

C.Potter, D.Sc., D.I.C., F.I.Biol.

A.R.C. Pest Infestation Laboratory

E.A.Parkin, M.A., Ph.D., D.Sc., D.I.B., F.I.Biol.

Department of the Government Chemist

D.C.Abbott, B.Sc., Ph.D., F.R.I.C.

Source: Department of Education and Science (1967) Review of the Present Safety Arrangements for the Use of Toxic Chemicals in Agriculture and Food Storage : Report by Advisory Committee on Pesticides and Other Toxic Chemicals (H.M.S.O.)

Department of Education and Science (1969) Further Review of Certain Organochlorine Pesticides used in Great Britain : Report by Advisory Committee on Pesticides and Other Toxic Chemicals (H.M.S.O.)

than from academic scientists.

The final Standing Committee that advises on questions of toxicology is the sub-committee on Toxicity, Clinical Trials and Efficacy to the Committee on Safety of Medicines (formerly the Sub-committee on Toxicity to the Committee on Safety of Drugs). Table 9.10 shows a breakdown of members of these committees. The result is quite similar to the Committee on Toxicology, which is also administered by the DHSS. There are, again very few members of the BTS. The majority of scientists have been drawn from pharmacology, a neighbouring discipline to toxicology, with an established university basis in Britain. This is not surprising considering the substances under consideration are pharmaceuticals. It does show, however, the influence of pharmacology from its autonomous development and strong academic position. Again, the majority of the members have been professors.

This analysis shows little evidence of an established and recognised community of scientists from which government advisers are drawn. The preceding section suggests, however, that if this community exists, it is mostly located within industry, and it is here where the elite is developing. The relatively weak institutionalisation of toxicology in the universities, explains to some extent the composition of the committees. Advisers are not all drawn from this sphere, however, some are governmental scientists. Therefore, the particular complexion of advisers on toxicology does to a certain extent reflect the fact that it is seen as an amalgam of various disciplines by many people. In addition, there begins to emerge a picture of specific departmental policies towards the appointment of scientific advisers. The DHSS committees are all staffed by scientists with high academic positions, while the one administered by MAFF has members drawn from the research laboratories of the department. The tripartite committee of the Health and Safety Executive emerges from

TABLE 9.10. Members of the Sub Committees on Toxicity of Drugs. 1970-1978

Medicine

Professor G.M.Wilson, M.D., D.Sc., F.R.C.P., F.R.C.P.E.

Professor E.F.Scowan, M.D., D.Sc., F.R.C.P., F.R.C.S., F.R.C.Ped. F.R.C.Path.

Professor A.E.A.Read, M.D., F.R.C.P.

Statistics

Sir A.Bradford Hill, C.B.E., F.R.S., Ph.D., D.Sc.

Microbiology

Professor F.W.O'Grady T.D., M.Sc., M.D., M.R.C.P., F.R.C.Path.

Obstetrics & Gynaecology

Professor J.S.Scott, M.D., F.R.C.S. Ed. F.R.C.O.G.

Professor P.J.Huntingford, M.D., F.R.C.O.G

Industrial

√ D.G.Davey, O.B.E., M.Sc. Ph.D.

Dr. W.H.Butler, M.B., B.S., M.R.C.Path.

Pharmacology

Professor C.T.Dollery, M.D. F.R.C.P.

Professor D.L.Laurence (Clinical) M.D., F.R.C.O.G.

D.F.J.Mason, B.Sc., Ph.D.

Dr. L.F.Prescott (Clinical) M.D., M.R.C.Ped.

√ Professor W.C.Bowman, B.Pharm. Ph.D., D.Sc., F.I.Biol. F.P.S.

√ Professor D.G.Grahaeme Smith, M.B., M.A., Ph.D. F.R.C.P.

Biochemistry

Professor P.N.Magee, B.A. M.B., B.Chir. M.R.C. Path.

*√ Professor D.V.W.Parke, B.Sc., Ph.D., F.R.I.C.

Psychiatry

Professor W.Linford Rees, M.D., F.R.C.P., D.P.M.

√ Dr. F.A.Jenner M.B., Ch.B., Ph.D., D.Sc., C.Chem. F.R.I.C., F.I.Biol. F.R.C. Path.

Pathology

Professor M.K. Weinbren, M.D., F.R.C. Path.

√ Dr. R.L.Carter, M.A., D.M., D.Sc. F.R.C.Path.

Unknown

Dr. K.D.Dalton, M.R.C.S., L.R.C.P.

√ Dr. J.R.Forbes, M.D., F.R.C.P.

Dr. G.Sanders, M.D., F.R.C.P., D.Phil.

Dr. I.Sutherland, D.Phil.

Dr. A.W.Asscher, B.Sc. M.D., F.R.C.P.

R.G.Shanks, M.D., D.Sc., M.R.C.P.

F.O.Wells, M.B., B.S.

* Member of British Toxicology Society

√ Members 1978

Source: Annual Reports Medicines Commission, Committee on Safety of Drugs.

the particular requirements of the Health and Safety at Work Act for such representative committees. Thus there is no standard way for advisers to be appointed. In this situation, then, it is pertinent to ask how developments in scientific knowledge are transmitted from researchers to the advisers who have the responsibility to periodically update the test guidelines. One way of investigating this is to see how these recommendations have changed over time.

9.4. Development of Test Guidelines

If new basic knowledge has been produced within the science of toxicology, it is reasonable to expect that this will become incorporated into the test guidelines recommended by advisory committees, having the effect of increasing the predictability of the tests, so decreasing the amount of data that it is necessary to collect. It is most useful to look at the test guidelines recommended by the Pesticide Safety Precaution Scheme in this context, as these have been revised twice since they were first set in 1957. Table 9.11 summarises the information suggested by the P.S.P.S in 1957, 1966 and 1979. When interpreting this Table it must be remembered that the pesticide scheme is one in which industry voluntarily complies to, and the tests suggested are those that have been agreed by the two parties as being the minimum necessary.

It can be readily seen, however, that the result shows the opposite trend to the one expected if new scientific knowledge is readily incorporated into expectations of tests. In fact, it appears that over twenty years, the discovery of new toxic properties of chemicals has far outstripped the rate that basic knowledge is developing into a predictive science. Thus in 1979 studies are required on production, teratology, mutagenicity and the toxicity of major metabolites. This is all information that was not deemed to be vital in 1966. Other factors which may have contributed to this result include the increase in the

TABLE 9.11. Test Guidelines of the Pesticide Safety Precaution Scheme.

Tests Suggested	1957	1966	1979
Pysio-chemical Properties	✓	✓	✓
Acute Toxicity			
Routes — Oral	✓	✓	✓
Percutaneous	✓	✓	✓
Inhalation			✓
Skin Irritation			✓
Eye Irritation			✓
Cumulative (28 day)	✓	✓	
90 day sub acute	✓	✓	✓
Chronic (carcinogenic)		✓	✓
Delayed effects		✓	✓
Metabolic study	✓	✓	✓
Potentiation of/by other chemicals	✓	✓	✓
Effects on humans (diagnostic & therapeutic)	✓	✓	✓
Effects on Wildlife	✓	✓	✓
Skin penetration and absorbtion	✓	✓	✓
Apparent mode of toxic action	✓	✓	✓
Allergic sensitisation			✓
Reversibility of toxicity			✓
Effects on reproduction			✓
Teratogenicity			✓
Mutagenicity			✓
Toxicity of major metabolites			✓

Source:

Pesticide Safety Precaution Scheme agreed between Government and Industry available from MAFF Harpenden Laboratory, Harpenden, Herts.

number of chemicals that are being brought on to the market, and the general tightening up of international expectations for the control of chemicals, both within the U.S.A. and the E.E.C. This is particularly true with environmental threats, but the trends seen in the pesticide field are duplicated for the other chemicals for which test guidelines are published.

9.5. Conclusion

The evidence presented in this chapter can give rise to some tentative conclusions about the interaction of science and policy during the post-war period, despite the difficulties with the available data. It appears that there has been a definite emergence of institutions over this period, that are typical of the character of toxicology. These institutions are typified by the fact that they have an identifiable interest in toxicology. Therefore they are either commercial laboratories, establishments that were specifically set up to carry out toxicological research, or they are university departments where there is a particular scientist with an interest in toxicological work.

Although this community can be identified it is clearly highly divided, and therefore does not obviously form a homogeneous scientific group. This is well illustrated by the fact that government policy advisers are not drawn on the whole from this community, although representatives may be present. In fact, there is no easily identifiable group who act as advisers on toxicology to government departments, as all committees established appear to have an idiosyncratic membership drawn from scientists who know more about the class of substance under consideration, rather than toxicological evaluation.

This situation could explain the apparent lack of uptake of new basic knowledge in toxicology, resulting in an explosion of new tests that are required in a safety evaluation. A more plausible explanation

is that new forms of toxicity have been discovered much more quickly than understanding of basic mechanisms. This, however, does not explain why the traditional chronic toxicity test has not been changed for over thirty years. A related question concerns the actual evaluation of data submitted to the advisory committees. It is not obvious whether examination of this information is critical, or whether the committees concerned accept the interpretation of the scientists who have carried out the work. Investigation of this question could form the basis for further research. The interaction between science and policy in this area is very complex, and difficult to interpret. It is to be expected that this relationship will change in the future, due to the increased professionalisation of the scientists, but as this process started only recently it is not easy to predict what effects this will have.

CHAPTER TEN

CONCLUSIONS

Conclusions

The aim of this thesis is to investigate the effect that the interaction of science and policy has had on the development of toxicology and the control of toxic substances. In Chapter 1 a number of factors were identified, considered relevant to such a study. These theoretical concepts can now be interpreted in the light of the empirical data presented. The particular issues which have been identified as important can be reviewed to facilitate this interpretation. They are:

a) the social organisation of the science and its institutional base;

b) the cognitive structure, restricted or unrestricted;

c) factors important to the emergence of the new scientific field, how social and cognitive factors are interlinked;

d) the institutional base and the factors in the professionalisation of the scientists particularly those working in a commercial situation;

e) the role of scientists in identifying policy problems;

f) their role in delineating and deciding between policy options;

g) their role in implementing the policy solution;

h) and the means by which goals external to the scientific field are translated into scientific objectives and are taken up as research problems.

These issues have been considered in the light of the long term trends which can be identified in the emergence of toxicology and the

development of concern about human exposure to toxic chemicals.

The general trend that can be identified in the legislative arena is the shift in policy from recognising the need to control substances known to be poisons to accepting that novel chemicals, intended for use in the human environment, must undergo some pre-market testing. This has been accompanied by increasing reliance on scientific advisory committees by government Departments.

Concern about controlling availability of lethal poisons arose in the nineteenth century. This was preceded by an Act to regulate the sale of arsenic, which had long been recognised as a social problem, due to its use in cases of murder. It was the Pharmaceutical Society which presented expert advice to the government on the matter. This, however, was done from a position external to the government, acting as a pressure group. An interest in the general question of the control of poisons was also related to a desire to see the professionalisation of chemists and druggists, and to prevent the medical profession gaining too much control over the distribution of poisons. The result of such attempts to influence government was that the Pharmaceutical Society was permitted to draft legislation that it felt to be workable, and to retain the responsibility of deciding which substances were to be considered poisons. The early poisons legislation was constructed with much thought given to the need to balance the availability of the substances which were in common use with the hazard that they presented.

The threat to health presented by chronic toxicity of substances was not generally accepted as a policy problem during the nineteenth century. Some specific questions were raised, however, particularly the question of pollution from alkali works. This problem was solved by the establishment of a governmental inspectorate with a scientifically qualified Alkali Inspector. Other legislation which covered

aspects of chronic toxicity related to industrial health and the adulteration of food. Neither of these cases, however, raised any general concern among the scientific community.

It was in the U.S.A. that the social goal of predicting whether a new chemical would be toxic to humans was successfully translated into specific scientific guidelines and scientists were drawn into the policy making process. This did not emerge in Britain, as the emphasis by the outbreak of the Second World War was on controlling substances which were known poisons, rather than predicting the toxicity of new chemicals. The post war philosophy towards the control of toxic substances was developed by the Committee on Toxic Substances in Consumer Goods which reviewed the controls which existed in the area. This Committee recommended the principle that industry should undertake the safety evaluation of chemicals that it wished to utilise, which was generally adopted as government policy. They also exposed Departmental differences over the question of chemical safety and its control. Their recommendation that a central government laboratory be established which would act as a central information gathering body was not accepted, however. These policy decisions ensured that subsequent developments in legislation would not give rise to a unified policy towards the regulation of chemical substances, but that it would emerge as ad hoc responses to particular problems. Two approaches, emerged; the regulation of toxic substances by voluntary agreement with industry, and through statutory control. Pesticides were the first chemicals to come under scrutiny due to the death of agricultural workers by poisoning. The Ministry of Agriculture and Fisheries established an expert Working Party whose recommendations for powers to ban the use of certain chemicals were accepted. The committee went on to recommend that new chemicals should be tested for toxicity before being put onto the market, and this suggestion was also adopted by the Ministry, which established the

voluntary pesticide Notification Scheme in 1957. Toxicological data was to be assessed by an Advisory Committee on its scientific sub-committee.

The question of the control of food additives arose in a different way. The Ministry of Food had identified an increase in new, untested chemicals being added to food during the war. The question of the safety of food additives was also raised in parliament, and incorporated into new legislation. Implementation of this legislation was left with the Food Standards Committee and its preservatives sub-committee (later the Food Additives and Contaminents Committee). Both of these controls issued independent test guidelines.

The sixties saw the addition of pharmaceuticals to the substances which were required to be tested. This was a response to the discovery of the teratogenicity of thalidomide. A government committee recommended voluntary control of drugs, similar to the pesticide scheme. This was accepted initially, until legislation was drawn up at a later date. This was implemented by expert committees, as in the other schemes. Scientists were initially involved in identifying the problem, but many other groups joined in the pressure for control. The Ministry of Health was taken by surprise with this incident as it had not been concerned about the question of drug toxicity.

The developments in the policy field that were seen during the seventies had to take into consideration the requirements of the E.E.C. This was particularly seen in the control of industrial chemicals. A Committee was established to review the legislation on health and safety at work, which made a novel recommendation for a tripartite system of consultation. This was accepted in legislation, and a representative committee was set up to make recommendations on the testing of industrial chemicals. These recommendations however, had to be reconsidered in the light of an E.E.C. directive on the matter. This development removed

some of the reasons for establishing such a committee. The seventies also saw the emergence of the DHSS as a governmental centre for expert advice on toxicology, with the establishment both of the Advisory Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, and of the toxicology laboratory at St.Bartholomew's Hosptial. The DHSS uses these resources to investigate any problems that other committees encounter when evaluating scientific data received from industry.

This review of the developments of policies towards substances required to undergo evaluation of their safety for human consumption can be made regarding the role of scientists in this process. Policy problems arise in an ad hoc responsive manner in which scientific knowledge is not necessarily involved. A common governmental response is to set up a departmental committee to review the situation and make recommendations on the policy which should be adopted. This advice has in the past, been accepted, if it involves the principle that industry should submit toxicological data to an expert committee for evaluation. This committee, which is not necessarily drawn from the toxicological community, issues guidelines on the tests required to evaluate the safety of a chemical. These test guidelines have only increased in scope over time, the central core of tests have not changed, but new tests have been added. The information required by these committees is remarkably similar considering the variation between that which is voluntarily given, and which is required by Statute.

These developments in legislative requirements have presented the external goal which has directed the programme of safety testing by commercial firms. This initial policy goal requiring industry to ensure chemical safety was set in 1950 by the Committee on Toxic Substances in Consumer Goods, and has had a profound influence on the social

institutionalisation of toxicology in its various forms, and its cognitive development. It remains, then, to consider how such external goals have been incorporated into the science. The basic conceptual development in the history of toxicology has been the distinction between substances which exert a highly poisonous or acute effect, and those which demonstrate their toxicity from continuous exposure to the substance over a number of years; that is chronic toxicity. The former case of acute toxicity has been recognised as a social problem from antiquity, giving rise to particular concern over the use of poisons in cases of murder. During the nineteenth century this concern with the criminal use of poisons provided a social reason for the emergence of forensic toxicology, which was closely linked with presenting evidence in the courts. This development was, however, closely linked with the emergence of techniques for chemical analysis during the eighteenth century. Early researches into acute poisons established the use of animal tests in experiments on poisons. Another aspect of poisoning which was practised in antiquity, and continued until the end of the nineteenth century was the use of lethal substances, in non-lethal doses, as therapeutic agents. This use was reflected in the early research into experimental pharmacology which was not seen as distinct from toxicology until the discovery of a chemical with specific therapeutic action by Paul Ehrlich in 1910. The emerging science of physiology also employed poisons as tools to investigate mechanisms at work in the body. The fragmentation which is characteristic of toxicological knowledge emerged during the nineteenth century, as poisons are studied by different sciences. Generalisations about the nature of poisoning were difficult to make due to the lack of biological knowledge available at this time.

If the action of acute poisons was well identified in the nineteenth century, the study of chronic toxicity as a social and scientific problem did not emerge until the twentieth century. There are reports of the

chronic action of substances in the development of occupational disease dating from antiquity. Unlike acute poisoning this failed to emerge as a well defined social problem, due to the difficulty in linking the substance and the effect which emerged many years later. This was exacerbated by the fact that some acutely poisonous substances were in general use amongst the population, in particular arsenic, whose lethal effect had given so much concern as well as lead. The question of the ingestion of chemical colouring matters and preservatives in foodstuffs emerged as a problem towards the end of the nineteenth century, and this gave rise to some exploratory studies on chronic toxicity. These involved dosing animals, a technique which received some criticism as not being relevant to human consumption. These tests, and those using human subjects were inconclusive, and there is evidence to show the medical profession strongly divided over the possibility of chronic harm from chemicals. The question of the chemical induction of cancer also emerged at this time, but from quite distinct origins from the investigation of chronic toxicity, and it managed to attract some government funding. Research on the chemical causation of cancer developed during the early years of the twentieth century.

By 1940, then, a number of different cognitive aspects of toxicology had emerged, but this had not generally been accompanied by the development of a community of toxicologists as such. Forensic toxicology was primarily identified with chemical analysis, while academic scientists used poisons as research tools. In the U.K. the Chemical Defence Research Establishment had been set up in 1916, but this was concerned with the use of poisons in warfare, while academic scientists who took up this problem were drawn from the field of biochemistry. The study of acute toxicity was the first to become described as a statistically significant test, and this emerged for the evaluation of new pharmaceuticals. This organisation of the science in this way meant that there was not the

common research area identified by a number of scientists, which theoretical models bearing on the emergence of a new scientific discipline identify as the early stage of such a development.

It has been pointed out that this situation changed, however, with the development of a safety testing programme for new chemicals by the Division of Pharmacology of the F.D.A. in the U.S.A. This had the aim of predicting whether a chemical would be toxic for human use, and is an example of a policy goal becoming incorporated into scientific investigation. As they were a scientific group concerned with the implementation of government policy, the Division of Pharmacology were in a good position to evaluate the potential problem posed by the increasing use of novel chemicals by industry. The scientists involved had a number of disciplinary backgrounds, necessary for developing a range of tests for screening toxic substances. What is most important, however, is that they had access to scientific resources, with which they could develop and evaluate the new test systems, and they had contact with scientists in both industry and academia, with whom they shared problems, ideas and experience. The development of a system of tests to evaluate the safety of chemicals for human use is a good example of how social, institutional and cognitive factors can interact in science. As a scientific group the job of the Division of Pharmacology was to ensure that government legislation was not violated. Thus their approach to the evaluation of chemicals followed a very pragmatic and ad hoc approach, that was designed to gather data on which decisions could be made without the necessity of extensive scientific interpretation of the significance of the results. Scientific uncertainty, then, was circumvented by the use of a suitable, estimated safety factor.

The post war concern with the safety-in-use of novel chemicals ensured the continued development of toxicology, and the emergence of a

scientific community of toxicologists. The nature of these developments, however, reflect the impact of extra scientific goals impinging on the scientific area. The MRC Toxicology Research Unit has the most well defined and coherent policy towards basic research in toxicology. Although the decision to establish the institution was based on requests from industry for information, its establishment has characteristics typical of developments in a new scientific field. It had both a social leader, in the form of Sir Edward Mellanby, who had an interest in toxicological problems, and the influence to secure resources for the field, but played no role in the actual research. Intellectual guidance was found in Professor Roy Cameron, who had an established reputation in a neighbouring biological discipline, and encouraged the development of a research philosophy for the unit which was oriented around the investigation of basic biological problems. This ensured the development of an independent basic research programme which is not found in any other British institution concerned with toxicology. Social and cognitive factors were linked here in terms of academic freedom giving rise to concentration on the mechanisms by which toxic reactions are produced in terms of the biochemical and physiological mechanisms. Despite the academic freedom of the MRC Toxicology Research Unit, however, the actual choice of research projects are directed by those chemicals which present an actual social problem, particularly in an occupational context. The social function of toxicology is accepted here.

The cognitive development of toxicology in post war Britain has oriented around two different approaches to the subject, that which emphasises the need to concentrate on basic research, and a more pragmatic approach which draws on the safety tests suggested by the FDA Division of Pharmacology. The relative benefits of these approaches were debated during the fifties. This occurred between scientists who felt that testing was a temporary substitute for basic research, which would promote

the development of toxicology as an independent scientific specialty, and those who felt that the uncertainty inherent in basic research could be overcome by the use of well designed, statistically significant tests. The pragmatic need for evaluating chemicals for safety in use ensured that the use of safety testing would become an important aspect of the science, however, as this was embodied in a number of governmental policies. This particular requirement for information soon began to expose the weaknesses in the safety testing approach. Much of the data produced in this way is for commercial purposes, and remains confidential, so much knowledge is never published in the usual scientific literature. This means that not only can this data not be subject to peer review in the usual way, but also many scarce resources can be wasted by the repetition of tests which have already been carried out. In addition, the screening tests used are designed only to demonstrate the presence or absence of known forms of toxicity. The trend has been to add new tests as new forms of toxicity are discovered, without reducing the basic information that is required. This has also led to ad hoc measures being adopted to make up for uncertainties in the results of tests, such as the 100 fold safety factor, adopted because of the uncertainty of extrapolating results from animal to people. Another example of this are the Good Laboratory Practice requirements which were introduced to impose standards on experiments which are difficult to repeat and obtain the same results.

The social organisation of toxicology in Britain is intimately related to these cognitive fields. Most of the institutions which carry out toxicological work are commercial organisations fulfilling legislative requirements. These are both research facilities of individual companies, isolated from each other, and undertaking toxicological research as part of a general research and development programme, and contract research laboratories, commercial organisation undertaking toxicological testing all the time. These latter organisations are in a potentially good

position to forward general observations on the mode of toxicity of chemicals, but are, however, limited in this as they are required to ensure confidentiality of their results.

This pattern of institutionalisation has had important effects on the social organisation of the science. There is a shortage of toxicological manpower in Britain, and many people are given on-the-job training within industry. The higher degree courses which exist depend on scientists from within industry to give lectures, and see themselves as producing manpower for industry. This situation has given rise to varying standards of training and ability, which the membership examinations for the Royal College of Pathologists has started to standardise. This situation has also meant a lack of text books in the area, and many of those which do exist are written by industrial scientists. They were also prominent in setting up the British Toxicology Society as a forum for scientists to meet and discuss scientific issues.

It appears, then, that the social and cognitive aspects of toxicology, as they are found in Britain today, are interlinked in a variety of ways. Five different aspects of this interaction can be identified. Although the development of toxicology has not been taken up at the specialty level within the universities there are scientists working in related disciplines who use toxic substances as tools in the investigation of research problems, and attend conferences with papers on this specialised work. Toxicology is also found in industrial laboratories as routine animal feeding tests carried out by technicians for submission to the relevant government committee. This is, however, often accompanied by some research into the methodology of the tests. The other extreme is the industrial laboratory with a highly qualified multidisciplinary team organised around a toxicological project with the freedom to initiate basic research if necessary. This is also true of the CROs who

are in a good position to see theoretical generalities, although they are working under particular commercial constraints, and the confidential nature of their work may preclude publication. Another form of toxicological research is in the research programme of the British Industrial Biological Research Association, which has a safety testing programme funded by industry, but has a government funded basic research programme. This takes up research into problems with test methodologies or techniques, and is in a position to communicate these results to government. In the field of basic research the MRC Toxicology Research Unit is a more traditional academic organisation concentrating on mechanisms of toxicity, and not constrained by the same need to establish safety as the other institutions. Even so, the social aspects of the science are acknowledged by choosing chemicals, as research problems which have been shown to present a hazard to society.

Within toxicology, then, the cognitive approach is related to the organisational goals of the laboratory which is carrying out the research. The question is how this can be interpreted in terms of the theoretical concepts within the sociology of science. There is, however, no conclusive evidence favouring any model of scientific development within the sociology of knowledge. The concept of functionalisation can be used to describe the routine safety testing of chemicals to satisfy government legislation, as the tests are used in order to circumvent the lack of basic knowledge. In this situation, however, some research is conducted into improving test methodology, and in some research based firms these particular requirements can be used to undertake basic research on toxicity. If safety testing is functionalised, then, this concept is not universally applicable to all institutions. Conversely, the research programme of the MRC Toxicology Research Unit may be said to be functionalised, if the only criteria is that non-scientific goals direct the

research programme, even though this laboratory is concerned with basic research. This factor, however, also fulfills the criteria that toxicology is in the early stages of development as an independent scientific specialty, as suggested by the models of emerging sciences described by Mulkay and Mullins. The case of toxicology, however, also supports Whitley's theory of unrestricted sciences with major scientists in the area being drawn from those with institutional authority, and research problems quite legitimately chosen in the way described. This can be taken further to assert that there are two particular forms of knowledge found within toxicology, both of which are quite legitimate scientific activities, safety testing which is organised around specified methods and techniques, and basic research, organised around the development of a theoretical perspective. It is difficult to decide between concepts in the sociology of science from this position. If, however, such developments in the understanding of structure/activity relationships occur so that toxicology developed a predictive, theoretical core, this would make most safety testing redundant, as predicted by the finalisation thesis, and the science would take on a more restricted character. This is not a development that can be expected in the near future, however, so must remain a more speculative development and it must be asserted that the development of a theoretical core in toxicology is not an inevitability. The external policy goals that have been set for the science have had a profound effect on both social and cognitive developments in safety testing. Test guidelines that are recommended by governmental committees are, however, established because of the need to assess the potential of all possible forms of toxicity, in the light of the lack of basic knowledge. It can be said then, that the strategic policy decisions made by the government, not to develop its own toxicological resources, but to request information on industry has had a profound effect on the subsequent development of the science. This does not

necessarily imply that a more traditional social organisation of the toxicology as a pure science would necessarily develop into a predictive science, as it cannot be automatically assumed that chemicals exert a structure activity relationship on physiological systems. In addition the mechanisms for transferring requirements for scientific knowledge for policy purposes to the policy for science are very weak. Some support for basic research is provided by the DHSS and MAFF, but general support for toxicology is through the MRC which encourages autonomous scientific developments from its Units. Conversely the influence of the science on policy is difficult to judge. There is no evidence that developments in scientific knowledge have reduced the amount of testing required on a new chemical, although research is being carried out on non-animal tests, which have the potential to influence this. There is no evidence, either, that the toxicologist supply expertise to government committees.

In conclusion, then, the case of toxicology does not support any particular approach current in the sociology of science. It does expose the limitations of these concepts, which have been developed to explain academic science, when applied to the development of a scientific field in a non-academic context. It is necessary to refine these ideas and present criteria under which they are applicable before a more profound analysis can be made of the development of scientific knowledge. In particular it appears that the response to external goals can take a number of directions, and this implies that more concentration on the development of industrial based specialties could lead to fruitful insights about the nature of scientific activity.

APPENDIX

Directory of British Institutions Concerned with Toxicology.

British Institutions Concerned With Toxicology

A) Contract Research Organisations

Consultox Laboratories Ltd.

188 Brent Crescent,
London NW10.

Hazleton Laboratories Europe Ltd.

Otley Road,
Harrogate
Yorkshire HG3 1PY

Established: 1974

Scientists Employed on Toxicology: 20 graduates, 60 animal technicians (1979)

Expenditure: £2 million (1979)

Research Interests: Smoking and health, toxicology, metabolism

Huntington Research Centre

Wolley Road,
Alconbury,
Cambridge

Established: 1951

Scientists Employed on Toxicology: 300 graduates, (50 doctorates). Over 1000 employed on toxicology (1978)

Expenditure: £2 million (1978), £500,000 (1972).

Research Interests: Animal experiments, clinical investigations, wildlife studies.

Inveresk Research International

Inveresk Gate
Musselburgh
Midlothian
Scotland

Established: 1957

Scientists Employed on Toxicology: 75 (1979)

Expenditure: £3.1 million (1981)

Research Interests: Pharmacology, toxicology, biochemistry, carbohydrate chemistry.

Life Science Research

Stock,
Essex CM4 9PE

Toxicol Laboratories Ltd.

Bromyard Road,
Ledbury,
Herefordshire HR8 1LG

Established: 1971

Scientists Employed on Toxicology: 40-45 graduates (10 in 1973)

Expenditure: £1 million (1979)

Research Interests: All apsects of safety testing.

Wickham Research Laboratories Ltd.

Winchester Road,
Wickham,
Hants PO17 5EU

Established: 1970

Scientists Employed on Toxicology: 6 graduates (1981) 2 graduates (1970)

Expenditure: £150,000 (1981)

Research Interests: Safety Evaluation.

B) Consultants

Bioscience Management Ltd.

High Entropy,
Winters Road,
Shirrell Heath,
Hants SO3 2JT

Management consultants operating in the application and implications of the biological and chemical sciences, including of the need for, and results of toxicological work. No laboratory facilities.

Lee Newman Associates Ltd.

Highbury House,
Rumsam Road,
Barnstaple,
Devon EX2 9EN

Consultancy service in the pathology of laboratory animals and related subjects.

Established: 1973

Scientists Employed on Toxicology: 3 pathologists (1982), 1 (1973)

Research Interests: Routine work for clients

C) Industrial Laboratories

Beecham Pharmaceuticals

Great West Road,
Brentford,
Middlesex

Multiproduct company including medicines, beverages, food, toiletries, home remedies, veterinary products, animal foodstuffs.

Toxicology: Confidential information.

Biorex Laboratories Ltd.

Biorex House,
Canonbury Villas,
London N1 2HB

Research and Manufacturing Chemists. Contractors to the Ministry of Health and Ministry of Defence.

Toxicology Laboratory Established: 1963

Scientists Employed on Toxicology: 8 (1982), 4 (1963)

Research Interests: Safety evaluation, some basic research.

Boots Company Ltd.

Station Street,
Nottingham NG2 3AA

Products include medical and pharmaceutical preparations, toiletries, agricultural, horticultural and veterinary products.

Toxicology and Pathology Department Established: 1956

Scientists Employed on Toxicology: 60 (1979), 6 (1956)

Research Interests: Safety Evaluation.

B.P. Group Occupational Health Centre

Chertsey Road,
Sunbury on Thames,
Middlesex TW16 7LN

Mainly concerned with petroleum products.

Established: 1976, work contracted out before that.

Expenditure: Not available. 8 major companies are involved in B.P.Ltd., total expenditure on toxicology.

Scientists Employed on Toxicology: 10-15 "problem solvers".

Research Interests: Assessment of health risks of company products, basic research studies particularly in the field of carcinogenesis. Many of the findings from toxicological 'tests' lead to the need for basic research studies and teaching. Some routine work sent to contract research organisations.

Ciba-Geigy Ltd. Pharmaceuticals Divisions

Stamford Lodge,
Altrincham Road,
Wimslow,
Cheshire SK9 4LY

U.K.unit of the multinational chemical company.

Toxicology Research Established: 1950s (internationally). U.K. (third unit) opened in 1964.

Expenditure: £1.1million in U.K.

Scientists Employed on Toxicology: 14 graduates, 23 technicians (1982)
4 graduates, 9 technicians (1964)

Research Interests: 98% safety evaluation, 2% basic research.

Cyanamid of Great Britain Ltd.

Fareham Road,
Gosport,
Hants.

Manufacture pharmaceuticals, animal feed supplements, agricultural and general chemicals. All toxicological work contracted to Huntingdom Research Centre, Life Science Research or Wickham Laboratores Ltd.

Fisons Ltd.

Fison House,
9 Grosvenor Street,
London W1X OAH

Manufactures agrochemicals, pharmaceuticals, horticultural chemicals, fertilisers.

Toxicology: Confidential information.

Gallagher Ltd.

65 Kingsway,
London WC2B 6TG

Manufacture Tobacco related products.

Toxicology: Conventional information.

Glaxo Ltd.

Clarges House,
6/12 Clarges Street,
London

Manufactures vaccines, vitamins, veterinary products, fine chemicals, foodstuffs.

Scientists Employed on Toxicology: 70 staff in the Division of Pathology.

Research Interests: Safety testing.

Hoechst U.K. Ltd.

Walton Manor,
Walton,
Milton Keynes,
Bucks. MK7 7AJ

Multinational pharmaceutical company.

Toxicology: Undertaken at parent company in Frankfurt, Germany. Only work done in U.K. related to pharmacokinetics and metabolism of new drugs in man.

I.C.I. Ltd. Central Toxicology Laboratory

Alderly Park,
Nr. Macclesfield,
Cheshire SK10 4TJ

Established: 1948

Expenditure: £8.9 million (1980) (over whole company £15-20 million.)

Scientists Employed on Toxicology: 360 (1978), 80 with doctorates.

Research Interests: Mammalian toxicology, carcinogenicity screening, behavioural and inhalation toxicoloty, basic research, project oriented work.

I.C.I. Ltd. Pharmaceuticals Division

Alderley Park,
Nr. Macclesfield,
Cheshire

Expenditure: Not available, part of the total research effort.

Scientists Employed on Toxicology: 150 on classical toxicology,
200 on metabolic and kinetic studies.

Research Interests: Safety evaluation, methodology, basic research.

Lilly Research Centre Ltd.

Erl Wood Manor,
Windlesham,
Surrey

Subsidiary of Eli Lilly & Co. Chemical company.

Toxicology: Closed in 1978, and work transferred to U.S.A. Some work on efficacy of new veterinary medicines.

Lord Rank Research Centre

Lincoln Road,
High Wycombe,
Bucks HP12 3QR

Part of Rank Hovis McDougall Ltd.

Scientists Employed on Toxicology: 1, (never more than 3)

Research Interests: Safety evaluation of new food products.

May and Baker Ltd.

Clinical Toxicology Section,
Dagenham,
Essex RM10 7XS

Manufacture pure and fine chemicals, horticulture and agricultural products, laboratory chemicals, photographic products, pharmaceuticals, industrial chemicals, semi-finished thermoplastics.

Toxicology: Confidential information.

Nicholas Institute Ltd.

225 Bath Road,
Slough,
Berks.

Part of Aspro-Nicholas Ltd. Manufacture pharmaceuticals, toiletries.

Toxicology: Department closed 1975. Now contract to Toxicol, Consultox, etc.

Pfizer Ltd.

Department of Developmental Biology
Sandwich,
Kent.

Multinational Chemical company.

Toxicology: Established in 1964 at Sandwich as a result of drug research activity during the fifties. 1976 toxicology moved to Amboise, France which now serves the entire needs of the pharmaceutical research laboratories.

Scientists Employed on Toxicology: 1964 - 1 graduate pharmacologist reporting to a medically qualified pharmacologist.
1974 - 40 staff, 10 graduates (veterinary, pharmacologists, biochemists)
1982 - (France) 20 graduates of various diciplines.
72 support staff.

Expenditure: £2.5 million in 1982

Research Interests: 10-20% of effort spent on improving methods of prediction of safety over a shorter time. Some research on mechanisms.

Proctor and Gamble

Whitley Road,
Longbenton,
Newcastle-upon-Tyne NE12 9TS

Manufacturer of foodstuffs, household chemicals.

Toxicology: All contract work. Parent company in U.S.A. undertakes safety testing and basic research. Interest in toxicology after last war when radically new product formulations were being developed.

Proprietary Perfumes (International) Ltd.

Kennington Road,
Ashford,
Kent TN24 40LT

Manufactures perfumery chemicals and fixtures.

Toxicology: No laboratories: 2 scientists concerned with safety review toxicological data in the scientific literature to ensure ingredients are not hazardous. Rely on codes of practice originating from trade associations and funded by the international perfumery industry.

Reckitt and Coleman Ltd.

Danson Lane,
Kingston-upon-Hull HV8 7DS

Manufactures food products, pharmaceuticals.

Toxicology Department Established: Interest in basic drug research and toxicology 1961.

Scientists Employed on Toxicology: 1982, none, Peak size 15 staff in 1965.

Expenditure: £150,000 in 1982. In recent years maximum has been £400,000.

Research Interests: Research needs now met by contract work to satisfy requirements of regulatory authorities around the world. When the Department of Toxicology was in existence scientists were allowed to pursue basic research for part of the time.

Roche Products Ltd.

P.O.Box 8,
Welwyn Garden City,
Hertfordshire AL7 3AY

Manufacturing chemists specialising in fine chemicals and pharmaceutical products. British subsidiary of Hollman La Roche, Basle, Switzerland.

Toxicology Department Established: 1973

Scientists Employed on Toxicology: Less than 20.

Research Interests: Rapid testing of active compounds selected from efficacy screens to enable short term clinical studies in humans. International function to carry out primate toxicology. Large scale studies contracted out. Parent company does testing on dogs. Subsidiaries in other countries also carry out safety testing.

Roussel Laboratories Ltd.

Kingfisher Drive,
Covingham,
Swindon,
Wiltshire

Manufacturer of Vitamins.

Toxicology: No in house work in U.K. All safety evaluation carried out in contract research laboratories.

Shell Toxicology Laboratory (Tunstall)

Sittingbourne Research Centre,
Sittingbourne,
Kent ME9 8AG

Part of the Shell Petroleum Company.

Established: 1954

Expenditure: Not available as toxicology is carried out at more than one centre.

Scientists Employed on Toxicology: 140 scientific and technical staff, 50 graduates (200 in total) in 1980. 6 scientists 1954.

Research Interests: Full range of toxicological experimentation, microbial mutagenesis, environmental toxicity (aquatic environment), fundamental work on mechanisms, carcinogenesis. No work on non-rodent mammals.

Smith, Kline and French Ltd.

Mundells,
Welwyn Garden City,
Hertfordshire.

Manufacture pharmaceuticals.

Toxicology Research Established: 1960

Scientists Employed on Toxicology: Of 450 staff employed on research 65 are employed on toxicology, 30 of which are senior technicians or science graduates.
1960 - 40 research staff in total and 2 were employed on toxicology.

Expenditure: Average of £2 million annually.

Research Interests: Safety evaluation of potential drugs, prediction of clinical hazards. Small amount of basic research.

Unilever Ltd.

Colworth Laboratory,
Colworth House,
Sharnbrook,
Bedfordshire MK44 1LQ

Manufactures processed foods, household chemicals.

Toxicology Established: 1954

Scientists Employed on Toxicology: Total staff 190, of which 70 are graduates (1980).
In 1954 staff consisted of 10 people, 2 of which were graduates.

Expenditure: £4 million (1982)

Research Interests: International laboratory responsible for evaluating the biological safety to the consumer of products. Increasing amount of work done for the Health and Safety at Work Legislation. Background research on methodology and increasing the accuracy of interpretation of tests results.

Vick International

250 Bath Road,
Slough,
Berks.

Division of Richardson-Merrell Ltd., pharmaceutical company.

Toxicology: Confidential information.

Wellcome Research Laboratories

Beckenham,
Kent BR3 3BS

Wellcome Foundation Ltd. manufactures pharmaceutical preparations, veterinary products.

Toxicology Established: 1953

Scientists Employed on Toxicology: 60 in pathology; 30 in drug metabolism.
1953 - 1 pathologist, 1 technician
1956 - 2-3 scientists
1960-61 - 20-25 scientists.

Expenditure on Toxicology: £2-3 million (1980).

Research Interests: Safety evaluation of drugs in line with government guidelines. Some research on methodology.

John Wyeth and Brothers Ltd.

Hunter Lane South,
Toplow,
Maidenhead,
Berks SL6 0PH

Manufacturers of pharmaceuticals, infant foodstuffs, fine chemicals.
Subsidiary of American Home Products Corporation.

D) Government Laboratories

Chemical Defence Establishment

Porton Down,
Salisbury,
Wiltshire SP4 OJD

Research on toxic chemicals for defence purposes.

Established: 1916

Research Interests: Founded to consider counter measures and retaliatory action to the use of toxic war gas. Testing, in vitro work on biochemistry, pharmacology.

M.R.C. Toxicology Research Unit

Woodmansterne Road,
Carshalton,
Surrey

Established: 1947

Number of Scientists: 39

Expenditure: £1 million

Research Interests: Basic research.

E) Research Association

BIBRA,

Woodmansterne Road,
Carshalton,
Surrey

Established: 1960

Number of Scientists Employed: 133 (1978)

Expenditure: £550,000 (1979)

Research Interests: Safety evaluation of chemicals relevant to industry. Basic research oriented towards government regulation.

Source: Based on membership of the British Toxicology Society, and personal communications with institutions.

NOTES AND REFERENCES

Chapter 1

Social and Political Aspects of Science

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Chapter 2

The Emergence of Scientific Investigation and Social Control of Poisons

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   The most famous case of state execution, with hemlock, was that of the philosopher, Socrates. An account of his death by Plato states,

   'The attendant brought it ready pounded in a cup. On asking 'what shall I do?' Socrates was directed: Nothing else than when you have drunk it, walk about until there is a heaviness in your legs. Then lie down, then it will do its purpose',
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    The 4 humours were thought to correspond with the elements, each element a temperament.

black bile	:	earth	: melancholy
blood	:	air	: sanguine
yellow bile	:	fire	: choleric
phlegm	:	water	: phlegmatic

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Sept.23 1419. Archbishop of Trebizond offers to procure death of Marselius of Canover. Offer accepted and fifty ducats paid and a horse ordered.
Jan.14 1478. Accepts offer of one, Lazarus, to poison wells from which Turkish Army takes its water.
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27. Philippus Auredus Theophrastus Bombastus Von Hohenheim lived 1493-1541.

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75. See Steward (1978), op.cit., note 71, Chapter 5.

76. Whorton (1975), op.cit., note 31, p.156.

77. Ibid., p.157.

78. The Elixier of Sulphanilamide disaster precedes the 1938 Food, Drugs and Cosmetics Act, as a number of people died from taking a poisonous solvent with the drug. This gave extra prominence to the question of safety.

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84. The legislative effects of this was that the F.D.A. were forced to raise the residue tolerance for arsenic (Whorton (1975), op.cit., note 31, p.233).
An example of the bitterness generated by these attempts at assessing safety is decribed in a letter from a fruit farmer to W.Campbell, in which it was said that F.D.A.tyranny 'is making communists out of farmers who constitute the last bulwark of that kind of conservatism which once constituted real American democracy' quoted in Whorton, p.234.

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140. Private Communication: Dr. O.Garth Fitzhugh.

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142. Private Communication: Dr. G.Woodard.

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