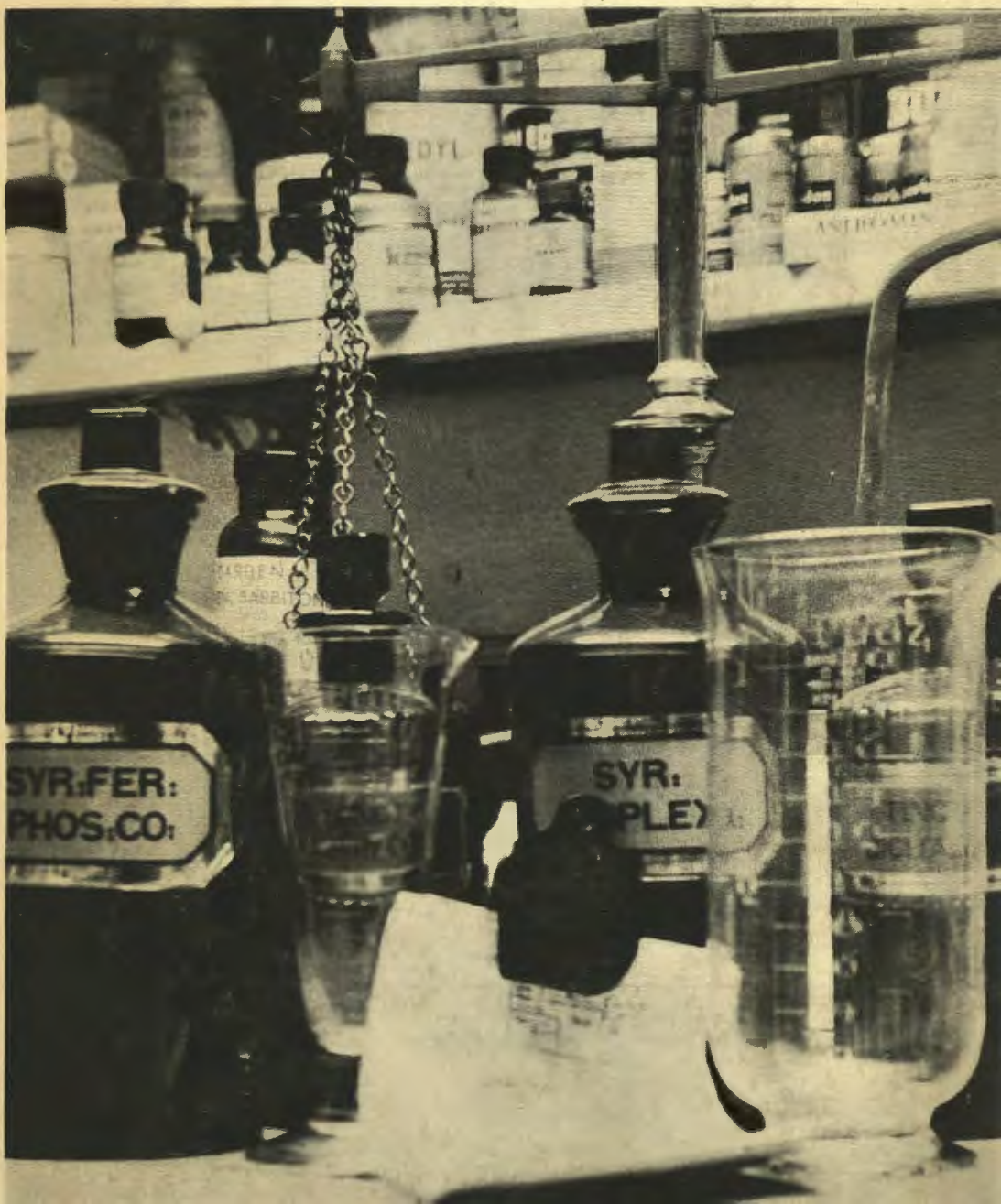
Office of Health Economics
Symposium held at Royal Society of Health, Buckingham Palace Road, London

Edited by G.Teeling-Smith

Science, Industry and the State



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Based on a series of six lectures discussing some of the special considerations which arise when a science-based industry has the government as a major customer in its home market, with particular reference to the relationship between the pharmaceutical industry and the National Health Service. The book challenges conventional attitudes to costing, pricing and marketing which in the past have been applied to science-based industry. The first paper discusses the influence of patents on the pattern of progress. The second paper challenges conventional economic concepts, and discusses new criteria on which the economic performance of science-based industries could be judged. The third paper describes the role of marketing in scientific progress, emphasizing that scientific advances are not adopted into practice until they have been successfully sold, and the fourth is devoted specifically to a description of the international pattern of pharmaceutical research, discussing the way in which it is organized and financed. The fifth paper describes government relations with a research-based industry, drawing attention to difficulties which have arisen with electronics, aircraft, etc. This book will be welcomed by all those with an interest in science-based industry, its economics, and its relationship with government; by civil servants, administrators and members of committees; and by all students of this important subject.

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Edited by

G. TEELING-SMITH

Introduction by

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Introduction

THE title of this symposium of papers, as well as indicating their coverage, admirably epitomises the most far-reaching tripartite industrial relationship of the twentieth century. Indeed, of all the factors which have influenced the pace and pattern of U.K. industrial growth in the last fifty years, probably none has been more significant than the widespread acceptance and application of the fruits of scientific discovery on the one hand, and the increased participation of the State on the other. Inasmuch, too, as these two developments have been, and are, themselves closely inter-related —the State, for example, has been both one of the major initiators of scientific education and research, and the institution most affected by the economic and social repercussions of such education and research—the triangular relationship between Science, Industry and the State is often an all-pervading one.

Moreover, the ordering of the words in the title is not without its significance, certainly when considered in the light of the pharmaceutical industry, with which most of these papers are primarily concerned. For perhaps the chief reason for the State's increasing involvement in industrial affairs is that the impact of scientific advance directly on conditions of production and marketing, and indirectly on education and social attitudes, has shattered the nineteenth-century belief in *laissez faire* and its philosophy that the interests of the private sector of the economy and the community must necessarily coincide. Industry, up to the turn of the present century, was largely free from State intervention; there was little, if any, organised research and development, and the application of scientific techniques was in its infancy. The impact of the new technology of the internal combustion engine and electrical power had scarcely made itself felt, and the rapid expansion of industrial output in the second half of the nineteenth century was as much a reflection of the growth of markets as of the innovation of new products, materials and processes. Because of the basic simplicity of most production methods, which were labour rather than capital intensive, the typical firm at this time was still the family-owned business or small private company, and unregulated competition was the rule rather than the exception. While it is true that monopolistic arrangements were increasing and economic power was becoming more concentrated, these forces, as they operated in the electrical equipment, public utilities and chemical industries were, as much as anything, a product of the scientific innovations of the later nineteenth century.

Within such an industrial environment many of the economic and social problems with which we are familiar today, and which are dealt with in this book, did not exist. There was, for example, comparatively little large-scale advertising as there was, as yet, neither standardisation nor branding of products: in the pharmaceutical industry, for example, the majority of goods sold were prepared by pharmacists on the premises and sold locally; there was no true division of labour between the production and marketing functions of economic activity. The registration of patents dates back only to 1879 and until the first decade of the twentieth century there was little organised research as we know it today: there was no question of a full international exchange of knowledge as few firms had any foreign connections and the channels of scientific communications were limited; all these factors circumscribed by Government intervention, are essentially features of the present day and age. Such papers as are presented in this series could not have been given simply because the problems they deal with did not then exist. Even the criticism, expressed by Mr. Lee, of the irrelevance of much of contemporary economics to the problems of the business man, could hardly have been voiced in the time of Alfred Marshall.

The situation is now quite different and it is particularly commendable that the authors of these papers have appreciated not only the scale of the changes which have occurred, but their far-reaching impact on both industry and commerce and the welfare of society. This is a time of general criticism and self-examination in Britain. Events, again largely sparked off by scientific innovation and education on the one hand and the revolution in social attitudes on the other, have moved so quickly in recent years that there has been little time to examine their implications for traditional explanations of behaviour or on institutional arrangements. Instead, one has had to make do with re-interpreting existing theories and taking *ad hoc* institutional action to ensure that the effects of the new events are kept in line with (what is conceived to be) the public interest.

To take an example from a totally different sphere, nowhere is the spirit of change in thought more obviously seen than in the theological writings of Paul Van Buren, John Robinson, Alec Vidler, John Wren Lewis and others.[1] Here, more than elsewhere, traditional explanations and values do not easily fit in with modern scientific thought. The "wind of change" is no less apparent, though in a different way, in the realm of literature, art and the theatre and it is also penetrating the social sciences where a brave attempt is being made to look anew at long-established *a priori* theories. All this is an indication of the widespread acceptance of scientific empiricism and the merit of testing hypotheses by facts rather than by intuition or introspection.

Until very recently this new methodology of enquiry and outlook, previously confined to the experimental sciences, had not penetrated to the

sphere of industrial affairs, which is strange since it is here that the impact of scientific progress has been the greatest. For example, little attempt has been made to extend or remould the principles of economic analysis to help us understand either the workings of science-based industry or of the role of the State in industry. It is only in the last decade that work has been done by John Jewkes, Charles Carter, Bruce Williams and others on evaluating the economic significance of research and development.[2] Of even more recent origin is the interest shown by economists in quantifying the costs and benefits of various kinds of economic decision taking in the public sector, including the nationalised industries.[3] Both fields of research are now commanding increasing attention, but so far little effort has been made to study the wider implications of the relationship between science, industry and the state as it is at present developing. Occasionally, of course, attention is drawn to certain repercussions of this relationship—such as the recent troubles in the aircraft industry and the current problem of drug prices. But nowhere, to my knowledge, has a systematic attempt been made to look into the basic economic and institutional issues which such a relationship involves.

To say that the papers contained in this volume do this would be claiming more than their writers intended. But there is a certain parallel to a volume of essays entitled *Soundings*, published in 1962, which caused such a ferment in theological circles. In that volume a number of modern practitioners of theology sought to examine some of the major implications of modern lines of thought and methods of enquiry for traditional theology and its institutional framework. To quote from the introduction:

> The authors of this volume of essays cannot persuade themselves that the time is ripe for major works of theological construction or reconstruction. It is a time for ploughing, not reaping, or to use the metaphor we have chosen for our title, it is time to make soundings not charts or maps.[4]

In these essays, I sense a similar dissatisfaction with the ability of traditional theory to explain, and existing institutional arrangements to deal with, some of the major economic problems now facing science-based industry, being voiced again by practitioners intimately involved. As in *Soundings*, more questions are asked than answered—to clarify "where our perplexities lie, not by making claims which cannot be justified".[4] But the freshness of the approach and the ready desire to re-think old problems in their new setting make this contribution an important and timely one.

Admittedly, the contributions in this book are mainly about the problem as currently being faced by the pharmaceutical industry. But if it recognised that this industry is, in some sense, the prototype of a wide section of U.K. industry as it is evolving in the latter part of the twentieth century, and that the major problems facing this industry are likely to be faced by other science-based industries in the near future, the subjects raised are of

wider import. That this is, in fact, the case I think may best be illustrated by referring to some of the features which characterise any science-based industry and which are given particular attention in this study.

First, the pharmaceutical industry is *par excellence* a science-based industry. In proportion to its turnover, it spends more on research and development than any other industry, except the aircraft and electronics industries, and no other industry employs a higher proportion of qualified staff.[5] In part, at least, this may account for the rapid expansion of the pharmaceutical industry in the post-war period as there would appear to be a generally close correlation between the amount spent on research and development and industrial growth:[6] certainly it would explain why the U.S. dominates international advances in this particular industry at the present time. Nevertheless, the question may be asked at a micro-level as at a macro-level: what is the optimum rate of growth that a particular industry can achieve, or again, how much of an industry's resources ought to be allocated to research and in which directions should these resources be used? Are there indeed any generalised principles which can be applied in answering these questions—questions which would have been less important even ten years ago than they are today. Since, too, research tends to be concentrated in the hands of larger firms,[7] it also means that there is a built-in tendency for industrial concentration to increase in the science-based industries. What does this increased power imply for the public interest? Some of these issues are tackled in this volume by Dr. Fryers who is particularly interested in ways and means of stimulating a more efficient use of research resources in the pharmaceutical industry and by Mr. Lee who is concerned with developing a model which will enable a better managerial evaluation to be made of the research contribution.

Second, as in many of the other newer industries, pre-manufacturing and post-manufacturing costs in the pharmaceutical industry are a considerable and growing proportion of total production costs. But in this particular industry, as Mr. Lee points out, the combination of a substantial research budget and a very considerable advertising outlay makes it an unusual case study. It is not easy to obtain up-to-date statistics on this point but in 1958 compared to an average proportion of non-operative to operative labour in all manufacturing industry of 27·1 per cent the average for the five main science-based industries mentioned by Mr. Jones in his paper* was 48·3 per cent and that for the pharmaceutical industry 64·3 per cent. This comparatively high ratio is a fairly modern phenomenon: in 1935 for example, the ratio in respect of all industry was only 13·6 per cent. While the size of this ratio may not always be closely correlated to industrial

* Aircraft, chemicals, electronics, scientific instruments and the electrical industry.

growth or efficiency it does have vital implications on the product pricing and investment policy of firms involved. Indeed, in his contribution, Mr. Lee goes as far as to say that the growing significance of non-manufacturing activities in science-based industry is forcing us to make a re-appraisal of economic analysis, as the traditional theory of the firm in its concentration on the production side of the economic activities explains little about "the complex economic relationship between research, development and production".* I believe his paper to be an important one as it raises issues of very general interest to science-based industry.

This leads us on to our third point. Following the development of science-based industry the main direction and focus of decision-taking has changed. Indeed, even the questions asked of the decision-takers are different from those once asked. Price formation is no longer of the crucial importance it once was in determining the pattern of supply and demand. In most of the newer industries the supply of both existing and new products is increasingly related to the fruits of research and development while consumer demand tends to be price-inelastic while taste-elastic. Dr. Fryers makes this point in his paper and argues with Mr. Teeling-Smith that competition is based largely on product innovation and hence advertising must play an important role. Nevertheless, decisions on the size of the research and advertising budget have to be taken but on what criteria? How does one calculate the cost of production of a new drug when the contributions to research and marketing are spread over such a wide range of products and the expected life of the product is so uncertain? Several contributors, directly or indirectly, tackle these questions from the pharmaceutical industry's viewpoint; Dr. Beesley in the final chapter asks the same question but from the viewpoint of the community as a whole.

Fourth, each of the newer industries is supplying some products under patent protection; each therefore is operating under quasi-monopolistic conditions although the fruits of such patent protection may be quite short-lived. In the pharmaceutical industry it is recognised that the knowledge patented is primarily contained in the materials' formulae and, once a product is marketed, it is easy enough to analyse it in order to find its constituents. But the initial research might have cost millions of pounds. What incentive is there to undertake such research without the assurance of some protection? This point, which again has vital implications for pricing, investment and research policy, is dealt with in some detail by Dr. Fryers in the first paper as he re-examines the existing patent system in the light of the industry's needs. Taking as his starting point the view that the best pattern of innovation is the one which stimulates the safest, fastest and most economical progress, he examines alternatives to the

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* See p. 24.

present system to see whether this aim could be achieved more effectively.

Fifth, there is the problem, faced by most manufacturers of packaged consumer-goods today, of marketing a standardised, mass-produced product. Again, the modern pharmaceutical industry illustrates some of the challenges faced by all new industries selling a branded product under conditions of international competition. As Mr. Teeling-Smith reminds us in his paper, effective marketing is an indispensable adjunct to scientific progress for the simple reason that (at least in the pharmaceutical industry) "proven advances are not adopted in practice unless they are sold".* But, he argues, as product style or content increase in complexity, consumer resistance to buying them is also enhanced—particularly if there is any kind of risk involved, e.g. in the case of pharmaceutical products, to the user's health. The barrier of imperfect knowledge has to be broken down and this is the function of selling—the "lubricant of change". Though the Director of the Office of Health Economics is primarily concerned with the role of marketing as it affects the pharmaceutical industry the points may apply equally well to other industries.

Lastly, mention might be made of the relationship between Government and Industry. Many are the reasons why the State should participate in industrial affairs and many the forms such intervention may take. Up until now, the State's main influence on the pharmaceutical industry has been in its role as purchaser of branded prescribed medicines for the National Health Service. Since, however, it has a virtual monopoly of such sales (apart from those exported) and the profits earned thereby substantially finance the industry's research effort, the State, by its purchasing policies, is able to influence the extent of pharmaceutical research and thus the growth of the industry. Indirectly, too, by its policy towards patents and foreign investment in this country, the State's influence on this and other science-based industries is far from negligible. Mr. Jones, in his paper, after surveying the developing role of the State in fostering industrial research takes a long look at the way in which the country's research effort is being directed today.

These are then some of the features of the pharmaceutical industry dealt with in this book which are common, in a greater or lesser degree, to most other science-based industries and, indeed, to some of the more traditional industries as well. The pharmaceutical industry may, however, be in some sense unique in that it not only possesses them all but that it possesses a number of additional distinctive characteristics of its own. And it is this which makes it such a fascinating study for economic analysis. Three of these distinctive features may be briefly mentioned.

First, the pharmaceutical industry supplies a range of products which

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* See p. 42.

literally are of life and death importance: indeed, as Mr. Lee puts it, the first function of the industry is the discovery and development of new drugs and biologicals to alleviate pain and to control or to cure disease.* It is difficult to think of an objective more likely to advance the public interest (and hence be of vital concern to the State, which is (or should be) the main guardian of such an interest) and it is understandable that the industry is sometimes impatient of anything which adversely affects the pace and effectiveness of its research programme and its ability to communicate its findings promptly. But everything—even life itself—has its cost. Dr. Yule Bogue and Dr. Beesley are particularly concerned with two aspects of this cost. Dr. Bogue emphasises the need for a proper system of safety control in the testing of new drug preparations and urges that more work ought to be done on drug toxicity. This is another field in which the State must act on behalf of its subjects to protect them against insufficiently tested drugs without "legislating discovery out of existence".† Dr. Beesley, as an economist, attempts to grapple with the even more difficult problem of evaluating research in the pharmaceutical industry in terms of the alternative uses to which the resources could have been put. To measure the value of people's health and lives in this way may seem an unduly cold and calculating procedure but in a society whose demands for goods and services far outstrip the resources to satisfy them a choice of this kind has constantly to be made. Or, to take an example from two possible courses of action, each having the same ultimate object—on which basis should it be decided to devote £1m. to additional cancer research or to finding out ways and means to reduce road accidents?

The second unusual feature of the pharmaceutical industry lies in its almost complete dependence on patent protection. Dr. Fryers takes up this point more fully in his paper, but the fact that, once discovered, a new chemical substance can often be quickly copied using no more than general chemical skill‡—quite a different situation from that in the aircraft industry, for example, where it might take years to reproduce a particular aeroplane design—does pose particularly interesting and difficult problems in devising a system that rewards efficient research without stultifying competition. And, thirdly, the pharmaceutical industry is the only one of the major science-based industries which is not directly dependent on the Government for research finance and where almost all the research is undertaken either in academic or industrial institutions. Mr. Jones and Mr. Lee touch upon the implications of this last feature in their papers.

Most of the attributes of the pharmaceutical industry are, of course,

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* See p. 17.
† See p. 63.
‡ See p. 6.

shared by the pharmaceutical industry in other countries, as are the problems associated with them. The problem of the size and distribution of the research budget, what price to charge for a new life-saving drug which has a very low elasticity of demand, and how to secure the right balance between speedy product innovation and the public safety—these are issues experienced equally by U.S. and Swiss producers. At the same time, the very special relationship which exists between the State and the pharmaceutical industry in this country and the social and economic implications of this relationship, poses its own particular problems, some of which are dealt with by the authors of these papers.

If the reader is seeking easy answers to the type of questions raised by this short introduction he will probably be disappointed. If, on the other hand, he wishes to be enlightened as to the problems currently facing the U.K. pharmaceutical industry, problems which, to a certain extent, are being faced by all science-based industries; if he wishes to know why traditional explanations of economic and social behaviour and institutional arrangements are inadequate to deal with these problems; if he wishes to share in a tentative exploration of how these problems might be tackled—then this series of essays will both interest and stimulate him.

Although it is not for me to summarise the main conclusions of this book, I cannot, however, refrain from one general comment. It is this. The scientific evolvement of modern industry has produced a series of economic and social repercussions, the implications of which have not, as yet, been fully appreciated or seriously studied. At the same time, the role of the State in public affairs has widened to such a degree that the particular industry studied in this book (as a supplier of one of the main social services) is directly or indirectly very largely dependent on its patronage and goodwill.

Under a free enterprise system in an industrial structure comprising a large number of competing firms undertaking little research and with reasonable freedom of entry into and exit from the industry, it might be reasonably argued that the profit motive is a sufficiently adequate impetus to ensure a pattern of resource allocation largely consistent with consumer wants. This is no longer true and some would argue that in so far as the branded prescription medicine side of the pharmaceutical industry is concerned, since the demand for health ought not to be limited by price, it never was. Certainly this latter viewpoint is the dominant principle determining the pattern of the pharmaceutical market in this country where, in the words of Mr. Lee, "the doctor prescribes, the patient consumes and the Government pays".* This fact, together with the changes in industrial structure wrought by scientific advance has meant the old motives and the old institutions are no longer able, as once they were, to ensure that public

* See p. 21.

welfare is maximised. Indeed, one is not even sure what *are* the right ends for the industry to pursue or what will best advance the public welfare. At the moment, as we have seen, the maximisation of research is the popular answer but Dr. Beesley has questioned whether this aim is in fact the right one. Or to take another field of controversy, neither is it clear how far the State should control the amount of advertising undertaken by the industry.

These are the kind of issues which are dealt with at some length in these essays. If the answers are not always clear cut, at least the authors are asking the right questions. And this, after all, is the first step to progress in any field.

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REFERENCES

1. See, for example, P. VAN BUREN, *The Secular Meaning of the Gospel* (1963); J. ROBINSON, *Honest to God* (1964) and *The New Reformation* (1965) (all published by S.C.M. Press Ltd.); A. VIDLER ed., *Objections to Christian Belief*, Constable, 1963; and C. F. D. MOULE, J. WREN LEWIS, P. R. BAELZ and D. A. POND, *Faith, Fact and Fantasy*, Fontana, 1964.
2. See, for example, J. JEWKES *et al.*, *The Sources of Invention*, Macmillan, 1958; C. F. CARTER and B. WILLIAMS, *Industry and Technical Progress* (1957) and *Investment in Innovation* (1958), O.U.P.; J. R. MINASION, "The Economics of Research and Development" in *The Rate and Direction of Inventive Activity*, Special Conference Series, No. 13 (Princeton, National Bureau of Economic Research, 1962), pp. 93–142; B. R. WILLIAMS, "Research and Economic Growth—What should we expect", *Minerva*, Autumn 1964.
3. For a useful summary of the main research undertaken in this field see M. FELDSTEIN, Cost benefit analysis and investment in the public sector, *Public Administration*, Vol. 42, Winter 1964, and B. WILLIAMS, Economics in unwanted places, *Economic Journal*, Vol. LXXV, March 1965.
4. *Soundings*, ed. A. R. VIDLER, Cambridge University Press, 1962, p. lx.
5. F.B.I. Survey, 1959–60.
6. Research and Development: a comparison between British and American Industry, *Nat. Institute Economic Review*, No. 20, May 1962.
7. J. H. DUNNING and C. J. THOMAS, *British Industry*, Hutchinson University Library, 1963, p. 124.

The Influence of Patents on the Pattern of Progress

GORDON R. FRYERS, *Nicholas Laboratories*

THE complex pattern of innovation in the pharmaceutical industry, which probably offers many parallels in other industries, can be compared with the effects of ecology and evolution on natural history. In general there are few major, or by themselves revolutionary, single advances. Occasionally, as when the tip of a coral reef breaks the surface of the sea and becomes the first point of a new island, an isolated step forward may start a new era. Thus, also, a single invention may prove epoch-making; but as Jewkes has pointed out, this is a much rarer event than is commonly supposed.[1] In any science-based industry the usual pattern of progress is by a series of small steps, each by itself constituting only a minor advance.

Britain as a nation has long been dependent on international trade, and now in the twentieth century international trade depends also on innovation. Increasingly, in order to succeed in the world markets one must have the most advanced goods to sell. It is necessary to concentrate much effort on the stimulation of inventors, and the efficient use of inventions. Therefore, if it is true that innovation comes most frequently in small steps, it is important to ensure that each of the steps succeeds its predecessor as quickly as possible. Although there are means by which we believe the process of discovery can be advanced in this way, so far very little is known about the other theoretical way in which progress could be hastened. That is, we know little about how to make each single inventive step greater, and on its own more important.

To increase the speed with which each small step follows the last, the simplest method is merely to increase the number of designers, or inventors. However, if these larger numbers of inventors are not to indulge in wasteful duplication there must be early publication of their results. Besides this, early publication is even more important for a second reason. Like coral, new ideas tend to be built upon preceding ideas. There is no particular reason why two successive ideas should come from the same scientist or innovator, instead of from two men of equal competence working in the same field. Therefore, the speed of making one new step on top of the previous one may depend almost directly on how quickly the earlier discovery was published.

For example, it is possible to imagine the case of an inventor who has a "one-in-a-thousand" idea. That is, during the period in which he conceived this one idea, he rejected probably subconsciously nine hundred and ninety-nine lesser ideas as being of no particular value. Whilst the idea is unpublished, it is another thousand-to-one chance that the same inventor will develop a further, better idea. As soon as the idea is published, however, it can form the basis for other improvements by all who read it. One could envisage a thousand other inventors reading about the first idea, and each allowing it to stimulate some further idea. In this case the probability is that amongst the one thousand ideas thus stimulated there will be one which is equivalent to the next one-in-a-thousand idea of the original inventor. In this simple case, the cycle between inventions will be the length of time between the first inventor making his discovery and its publication being read by others—unless this period is so long that the same original inventor has had a further one-in-a-thousand idea before his first was ever published.

Delayed publication can also slow up progress in another way. Unless the new invention or design is translated into goods the check of experience in use will not be provided to evaluate the direction and degree of advance. Apart from the commercial implications of this delay, which will be more fully discussed in the paper on marketing, there is no chance to measure the success or desirability of the innovation.

The need for early publication is only one aspect of the philosophy which should underlie the patent system. Its broad objective should be to obtain for society the maximum benefit from innovation. To do this it must not only hasten disclosure, but it must also provide a motive and stimulus to the inventor, and encourage the rapid exploitation of invention.

The present system of pharmaceutical product patents in Britain is almost 15 years old. During that period, Britain, along with other countries, has steadily increased her research expenditure, and the pharmaceutical industry in Britain has produced a share of the world-wide total of new medicines roughly proportional to its share of the total expenditure on research. More recently Britain's proportion of the total research expenditure has fallen, and this fact needs explanation. Is it merely a coincidence that this fall in Britain's research has occurred at the same time as an erosion of the patent system in Britain by compulsory licensing and a strengthening of the system in some other countries?

A fall in expenditure on research by the pharmaceutical industry is no more than one pointer to the need for reappraisal of the present patent system. Another indication of the effectiveness of the system is the extent to which inventors feel that they will get a greater return by keeping their invention secret. The codes of ethics of the medical profession and the pharmaceutical industry preclude the use of "secret remedies". It is therefore only on production techniques rather than on the products themselves

that manufacturers can rely on secrecy instead of on patents, and it is difficult to assess how widely "secret processes" are employed in practice. However, the recent illicit sales of pharmaceutical production secrets to companies who do little or no research are evidence that companies do now, to some extent, rely on secrecy either instead of, or in addition to, patent protection.

Against this background, the question must be asked as to whether the present patent system is really the best that can be devised. Are the higher prices permitted by a system of patents justified by the incentives which they provide for innovation, and is the innovation of the right sort? The task of balancing all the factors is extremely difficult, but this very difficulty is surely a further good reason for questioning the present compromise.

Before considering these questions it is necessary to make two assumptions. The first is that an economic motive is necessary to encourage innovation. In industry this is certainly so. If a company derives no economic advantage from discovering new products, it has no incentive to spend money on research. It will be at an intolerable disadvantage compared with its competitors if it does attempt to pay for a substantial research programme. This is true whether the industry is privately owned or State owned, although in the latter case it has been suggested—as with British Railways—that the State should be prepared to stand the loss if it is in the public interest. A commercially viable industry must, however, get some economic reward for its discoveries.

A theoretical alternative would be to have pharmaceutical research provided and financed by the State, in the same way as the State finances other aspects of medical research. If such a system could be accepted internationally, patents could cease to be granted on pharmaceutical products in the same way as there are no patents for new surgical techniques. All valuable findings would automatically be published and available for free exploitation by manufacturers in all countries. Apart from the difficulty of getting international agreement—and under a unilateral arrangement Britain would get the worst of both worlds—it is doubtful whether this alternative would be very successful. The present system is essentially product-oriented: a company is rewarded by the degree of success its researchers have in developing new products. It therefore directs its research department so that it is likely to yield products of value in practice, rather than to extend its fundamental knowledge. The economic motive to undertake this type of research would be lacking in a non-commercial laboratory which might concentrate on the more interesting theoretical problems, as academic scientists do at present. Such academic research is of more fundamental value, but is essentially complementary to product-oriented research, rather than an alternative to it. The lack of incentive to develop new products could perhaps be overcome by a system of honours

or prizes, but certainly State research in other countries has so far contributed little to major pharmaceutical progress. No one can say definitely that commercial research financed by the pharmaceutical industry must give better results than any other method; but at present it seems fair to assume that a system embodying economic incentives to discover new medicines and severe sanctions for failure to do so is more successful than the alternative of State financed research, separate from pharmaceutical production.

The second assumption is that Britain wishes to remain amongst those countries engaged in pharmaceutical research. Some smaller or industrially backward countries, with no indigenous research-based pharmaceutical industry, have chosen to rely on pharmaceutical products discovered abroad. Having made the decision to opt out of pharmaceutical research, they have also decided that they have nothing to lose by abolishing pharmaceutical patents and manufacturing other people's discoveries without giving any reward to the inventors. They contribute nothing to world-wide pharmaceutical progress. They tend to export scientists rather than the fruits of scientific research; they have little or no opportunity to build up pharmaceutical exports; but in compensation they obtain cheap medicines. It is assumed that Britain would not wish to be amongst these countries, and intends to continue making its traditional contribution to the discovery of new medicines.

Next it is necessary to examine in more detail the pattern of pharmaceutical innovation, so as to know what types of research and progress one should be trying to stimulate. There are three broad ways in which pharmaceutical discoveries are made. The first is by chance, and there is no doubt that serendipity has played a significant part in pharmaceutical progress. Fleming's observation of the anti-bacterial action of the penicillin mould is a good example. More recently, the search for better antihistamines led to the discovery of related compounds acting as tranquillizers. All such discoveries require trained and imaginative observation, scientific method and the most up to date knowledge; but nevertheless, in essence they result from chance.

The second, and in the past the most productive, type of research depends on the systematic screening of chemical compounds which might be expected to have a pharmacological action. Most often these are related to medicinal chemicals already in use, and have been produced by altering one or more of their chemical groupings—"molecular manipulation". It is a characteristic of this type of research in particular that it leads to small steps forward. Amongst new products discovered in this way, it is not always easy to distinguish between those which show a marginally different pattern of activity and are also better than the medicines already in use, and others which are different but no better.

Thirdly, new products may arise through the synthesis of a chemical which has been tailor-made to achieve a particular therapeutic purpose. Its success in doing so will have been forecast from knowledge of the mechanism of the particular disease process. For example, the action of the antitubercular chemical PAS was predictable, because it was expected to compete with the chemically similar para-amino benzoic acid which the tubercle bacillus required for its survival. The value of penicillamine in the treatment of Wilson's disease was another theoretical prediction, and the chemical was specially synthesized for this purpose.

Progress of this sort depends on advances in fundamental understanding of disease processes. This greater understanding will itself often come in small steps. Nevertheless the therapeutic results which eventually come from such progress are likely to constitute more dramatic improvements than those which result from modifications of known medicinal chemicals. The former may be based on an entirely new line of thought, whilst the latter are more usually improvements on an established pattern of therapy. On the other hand, however, the chances of practical success from this type of research are very much less, because instead of starting from a known point, one is searching for clues into the unknown causes of diseases or disease processes.

These three aspects of pharmaceutical innovation are interrelated, and all three often contribute to the discovery of a single new product. Nor can the distinction between them always be as sharply defined as this simple description may have suggested. Even for the scientist involved it is not always clear in retrospect whether a discovery resulted from chance, from systematic examination of likely products, or from new theoretical knowledge suggesting which *were* the likely ones.

Superimposed on this already complex pattern of innovation is the need for the further practical development of the new discoveries. Once the theoretical value of a new compound has been established, it is still necessary to develop manufacturing processes for it, to formulate preparations of it which will be safe and active in man, and to investigate further its action by extensive clinical and pharmacological testing. Penicillin is one classic example where the theoretical discovery was made and recorded, but the necessary work to develop it into a practical therapeutic substance was delayed for many years.

Against this background, what pattern of innovation should be encouraged? The aim must be to stimulate the safest, fastest and most economical progress. That is, to find compounds which prevent and cure as many diseases as possible, as quickly as possible, at the same time avoiding therapeutic "accidents" and avoiding "waste". With these general objectives in view it is not really important that it usually tends to be easier to hasten the process of innovation by making small steps more frequently, rather than attempting to make each step greater.

Dealing first with the two issues of safety and economy; there was formerly a risk that a system which provided a strong incentive to market products quickly would militate against safety. This risk has always been to some extent offset by the brand name system, whereby the manufacturer stakes his reputation, coupled with that of his product, on its safety and efficacy. Now, in addition, there is the additional safeguard provided by the Committee on Safety of Drugs, under Sir Derrick Dunlop, without whose approval products are neither subjected to clinical trials nor marketed.

The question of economy is more difficult, because there must to some extent always be a conflict between the desire to make progress fast and to make it cheaply. It is, however, certainly desirable to avoid the proliferation of new products which have no advantage over existing ones. They result in waste through the marketing and handling costs inherent in an extra product being added to a company's range. They are also wasteful because of the confusion they cause. Reverting to the subject of safety, therapeutic accidents may occur more frequently if doctors have to comprehend the possible dangers of a large number of different medicines; on the other hand, a wider range of medicines allows personal differences to be catered for more effectively.

It would certainly be wrong to dismiss or discourage the whole approach of producing variations of existing compounds. This method of research should be carried out alongside the investigation of the fundamental causes and theoretical methods of controlling disease. Both are desirable, and there should be an appropriate proportion of each. One problem in assessing the success of different systems of patent protection arises because there is no formula to establish what *is* the appropriate proportion of each of these different types of research. It is possible, however, to consider the ways in which variations in patent protection or other incentives to innovation will make possible or stimulate these two types of research.

First of all, patent protection could be withdrawn altogether. In some industries patents have proved more or less unnecessary, because other factors ensure that there is a long delay between innovation and imitation. Those who innovate can therefore command premium prices for their more advanced products for long periods without the fear that their improvements will be quickly imitated. In aircraft design, for example, it is many years before a rival manufacturer can imitate a new structural configuration after it has been introduced and proved successful. Nor is there any question of postponing disclosure of new designs, and thus delaying progress. In this case the benefits which would derive from patents are generally achieved automatically simply by the nature of the progress and the industry.

In pharmaceuticals, however, the chemical substance itself can often be copied, using no more than general chemical skill and standard chemical

equipment. By the time there is an established demand for a new medicinal chemical, many other manufacturers would be able to produce it—and, in fact, do so in countries which have no pharmaceutical patents. Without patents, therefore, the innovator of new pharmaceuticals would be faced with competition from companies who had spent nothing on research and nothing on spreading knowledge on the use of their discoveries, as soon as these imitators felt it worth while to enter the market. There would be little economic incentive to discover new products, and it would be difficult to support the research needed to do so.

Second, patent protection could be confined, as it was in Britain, until 1949, to production processes rather than to products themselves. This led to quite wasteful research in which competitors tried to find different chemical syntheses for existing products. They would be prepared to employ these processes whether they were more or less efficient than that of the original patent holder. Equally, the patent holder had an incentive to investigate alternative production processes, in order to obtain patents on these to keep out competitors. This type of research is unlikely to lead to therapeutic progress; and only in some cases will it lead to more efficient production.

Third, there is the grant of compulsory licences to other manufacturers who wish to exploit the discoveries of the innovators. These must tend to reduce the net return to the inventor, but their effect depends on three factors—the length of period which must elapse after the invention before a licence may be granted; how easy it is to obtain such a licence; and the rate of royalty which is awarded to the original patent holder.

In considering the rate of royalty, it is often misleading to look at percentages, and it is better to examine in absolute terms the extent to which they bridge the gap between the original patent holder's chosen selling prices and his marginal production cost. This is the extent of the loss to the patent holder unless the competition also forces him to bring down his prices. In the latter case his revenue is reduced not only by his loss of sales: it is further reduced as a result of the lower profit margin on his remaining sales.

Clearly, a royalty fixed so as to bridge this gap—which could be termed a "fully compensating" royalty for the original patent holder—would provide no incentive for anyone to obtain a compulsory licence, except in the unlikely event of his production process being substantially more efficient. Nor would it cause any price reduction.

The highest royalty which would give some profit to a competitor would exactly equal the difference between the purely competitive price and the innovator's chosen price. This would allow the licensee a competitive marginal profit, but it could be termed a "price maintaining" royalty in that it would have no effect on reducing prices. The loss to the innovator would be small, the licensee—who generally relies on a lower selling price

to get a share of the market—would get little benefit and the advantages for the community would be negligible.

In practice, substantially lower royalties are granted, which establish a price level somewhere between the originator's chosen price and the price which—royalties apart—would satisfy his imitator. Royalties fixed at a level near to a "price maintaining" royalty will give compulsory licences little effect; those fixed at very low levels could create a situation almost indistinguishable from the total abolition of patents.

However, the effect of compulsory licences can be further mitigated by refusing to grant them until a certain number of years has elapsed since the invention. If the period of initial exclusivity runs for almost as long as the patent, compulsory licences will have little effect, and the reverse will be true if they can be granted immediately. The impact of compulsory licences can also be varied by the extent to which "abuse" of the original patent must be proved before they are granted. Their adverse effect will be greatest if no abuse need be proved. If abuse must be proved, and is narrowly defined, their effect may well be beneficial.

It would seem that in the future, compulsory licensing might be used as a flexible weapon to achieve a good balance between too much and too little patent protection. In the pharmaceutical field in the past, the opportunity to obtain compulsory licences has for many years been neglected, and when it has been exploited recently it has become apparent that under the present legislation it may be too blunt an instrument. For patents covering food or medicines in Britain there is no period of exclusivity before a licence can be granted; there need have been no abuse or misuse of any sort by the original patent holder; and royalties have certainly fallen far short of the "price maintaining" royalty defined above.

In any overall system it is possible that some inventors get an inadequate reward whilst others do better than society intended. But the balance of incentives for all is disturbed if the most successful few are penalized. Taking the patent system as a whole, no one has ever advanced good reasons for a discriminatory reduction in incentives to inventors in the food and medicine field. Yet the use of compulsory licences to ensure wider use of inventions than would result from their being worked by the inventor alone does, in effect, amount to discrimination. The compromise, which must be involved in any system of rewarding inventors, seems in this case to be put out of balance by the present system of compulsory licences.

Fourth, it might be possible to devise a method of distinguishing between different types of invention, so that they were awarded different degrees of protection. For medicines, this could depend either on their therapeutic value, or on their degree of originality. Greater protection for more original or more valuable discoveries would certainly encourage the most useful type of research and there might be a case for simply refusing to grant a

patent on a compound which has no demonstrable therapeutic advantage over those already in use. However, such a policy would probably have very little effect, because it is unlikely in any case that another manufacturer would wish to copy a new product which had no demonstrable advantages over those already in use. Certainly, in practice, it would be difficult to assess either originality or therapeutic superiority, and the patent office at present would be unable to do so.

In addition, market factors undoubtedly make less important innovations commercially unattractive. Not only do they generally have to be lower priced, but it also costs more to achieve sales of less original products because they tend to be more difficult to sell. To some extent, therefore, it can be argued that research expenditure and marketing expenditure could be substitutes. However, in any progressive science-based company there must in fact be a balance between research and marketing costs, and the more critical the consumer, the higher the research to marketing costs ratio tends to become. Understandably, therefore, the prescription medicine industry is characterized by relatively high spending on research in relation to its marketing expenditure.

The question also arises of the degree to which originality could be stimulated by varying the extent to which the other related compounds should be protected by a patent on one single compound. At present the practice for an inventor is to attempt to cover as wide a range of related compounds as possible with his patent or patents. This prevents the related compounds being marketed by a competitor. However, even this practice does not prevent other companies from developing further similar chemicals outside the area of patent protection which they are able to market as improvements over the original compound. Also, under the present system the extent of cover afforded to related chemical compounds probably depends more on the skill of the patent agent, rather than on any fundamental logic. In borderline cases, where a related compound has only a weak protection under the originator's patent, he will often concede the rights for it rather than become involved in costly and possibly fruitless litigation.

Total protection for all related compounds is undesirable because it inhibits chemically very similar, but therapeutically very superior, discoveries. Lack of protection is perhaps even less desirable because it may encourage too much research by the inventor on minor chemical variations. One solution might be to include very widespread cover on related chemical compounds in the patent on the original product, provided that any such related compound should be subject to immediate compulsory licensing on request. The rate of royalties would have to be delicately balanced if anything useful were to come from the scheme. The aim would be to discourage too much effort being spent on investigating chemical variants of

established products, whilst at the same time giving an incentive to do so if such compounds apparently included ones which had significant therapeutic advantages.

Also included under this heading are the problems which arise at present when a new compound is for some reason unpatentable. Simple natural compounds, found to have valuable therapeutic properties which had been unrecognized in the past, are examples. Several such products have played an important part in therapy recently. There is, however, only a limited incentive to investigate or develop such products since the inability to patent them restricts their originator's advantage over his imitators. It can be argued that some form of protection should be extended to cover these products, so as to avoid a bias towards the search for complex synthetic compounds at the expense of simpler natural products. There are, however, difficulties in cases, for example, where the product is derived from a commonplace herb which grows wild in the countryside. These difficulties could be overcome by the system, similar to that recently adopted in some countries, which allows patent protection for preparations which are made up specifically for an original therapeutic purpose, even if their principal ingredient or formulation is not itself original.

Fifth, there is the question of the right length for patents to run. The present 16 years has an historical significance, related to the length of time it took to train two generations of apprentices; but it does not necessarily have any special significance currently. (The increased time now taken in testing products before they are sold and the speed with which competitive advances supersede most inventions have in any case considerably shortened the nominal 16 years.) On theoretical grounds, an innovator should have the opportunity to earn a sum equivalent to his research investment, plus a reasonable return on it, which he can reinvest in further research during the life of the patent. Once the patent has expired, the product will have to face competition from non-researching companies, who can sell at prices which need contribute nothing to research overheads, and at that stage the innovator can no longer rely on such products to finance his research either. On this theoretical basis, it is possible to construct a simple mathematical model to demonstrate the effect which might be anticipated if the normal life of a patent were varied.

Assuming a return of only 8 per cent on research investment, Fig. 1 shows how the monthly revenue must vary according to the length of time in which it is expected to provide further finance equivalent to the original investment. Roughly speaking, this is an indication of how much profit a product must earn to make the original research investment worth while.

Several facts emerge from this model. First, there is indeed still an obvious logic in the present duration of patents. Their effective life (after a period of development and initial marketing) is usually about 12 years.

The model indicates that lengthening this present period of patent protection would have very little effect, and would allow for very little reduction in price to compensate for a longer period of exclusivity—even assuming that the product had not been superseded by a therapeutic improvement

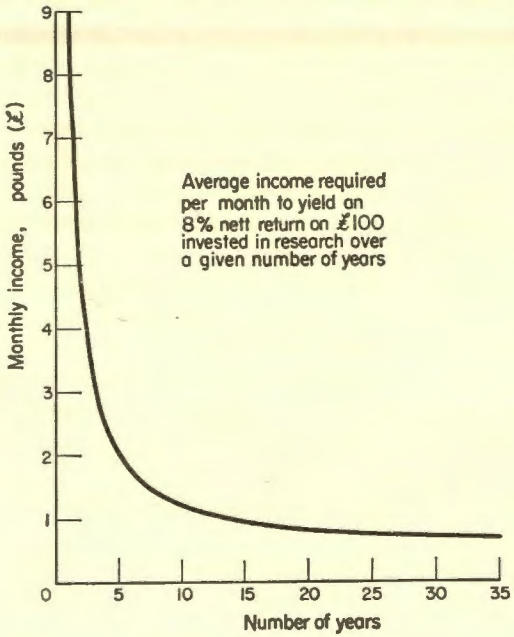

FIG. 1

within 12 years. Shortening the patent life, however, would have a considerable impact. If it were cut to an *effective* four years—one-third of the present period—it would, on this model, have to earn rather over twice as much profit each year during its shorter life. For a research-based product this would mean initial prices approaching double those indicated by this model under the present circumstances. If it is assumed that the price of a product falls away sharply to a commodity price once it is out of the period of patent protection this higher price would be obtained for a period only one-third as long as that during which a higher price can be obtained at present. Other things being equal, the total cost to the community would therefore be lower with shorter patents and higher initial prices. The innovator would be just as well off because, roughly speaking, he would have less money tied up in his product "know-how". His higher initial prices would give him a more rapid return on his research successes. However, the assumption that one could charge higher prices ignores the effect of definite price barriers which operate in practice even in the case of prescription medicines. New products in an established therapeutic

class are most likely to succeed if they are priced quite close to the most widely used similar preparations.

Shortening the patent life would also be expected to have other effects. It would encourage more rapid introduction of new products, as manufacturers would probably strive to find replacements for their products as they emerged from their short period of patent protection. This might encourage manufacturers to introduce replacement products, for which some advantage could be claimed, shortly before the patents on the original products were due to expire. Unless total research expenditure and the rate of true successes were increased it seems likely that manufacturers would be tempted to market marginal advances which they reject under the present circumstances, because it is usually more profitable to continue concentrating on established products as long as they have patent protection. If, on the other hand, total research expenditure were increased, there would no doubt be more rapid progress. In either of these cases the theoretical saving to the community inherent in shorter patents would be offset by the larger number of new products being marketed more frequently at higher prices. If they were unnecessary variations, waste would be involved; if they represented true progress, the community would be benefitting from the higher price they were paying. Shortening patents would therefore undoubtedly have some effects; it might, however, be a double-edged weapon.

Finally, it has been suggested that innovation might be rewarded by a grant or grants to those who were responsible for valuable progress. This would enable those making the grant to reward what they considered the most desirable type of advance, and reject "unnecessary" innovation. This would, in effect, be replacing the individual decisions of prescribing doctors (who cumulatively determine the reward to pharmaceutical innovators at present) by the opinion of the central committee making the grants. Such a scheme would be fraught with the difficulties which are inevitably associated with central decisions on the relative values of different medicines. It is even difficult to reach the right central decisions on safety and efficacy—as the American F.D.A. experiences, in particular, have shown. Such grants might, however, play a special part in encouraging the development of valuable products which, for some reason, are difficult to reward adequately under a normal system of patents.

A variation of this proposal would be for the innovator to receive an agreed State subsidy on his sales, whilst all others would be free to market it without this subsidy. This would have a similar effect on the automatic grant of licences to other manufacturers—the subsidy corresponding to the royalties in the latter case. However, this system would have severe disadvantages when it came to getting a return on British inventions from other countries.

Having speculated on the ways that some individual changes in the patent law might alter the patterns of innovation, it is also useful to look at the way that other factors influence research decisions, and how the position in Britain is affected by the international situation.

First, commercial and marketing policy will considerably affect the pattern of innovation. It has already been pointed out that from both the commercial and the marketing points of view, a fundamentally new product is much more attractive than a variant on an existing medicine. Those who make the commercial decisions and those who have to market the new products will therefore influence the research teams to seek major rather than minor advances. In practice, the decision whether to market a new product, or to reject it as having insufficient advantages to make it worth while, will depend largely on the company's existing product range. If they have many good products, still with many years of patent life to run, and still with therapeutic advantages over other prescribed preparations, it would be to their advantage to extend the use of these, rather than to add a new product of doubtful value to their range. If, however, many of their existing products cannot for much longer be expected to contribute substantially to the company's revenue, there is a temptation to market a marginal improvement to replace one of their "dying" products. This is an oversimplification, but it reinforces the suggestion that shortening the life of patents might encourage the marketing of marginal improvements. If each product, however successful, has only a short commercial life, research must be aimed at more frequent successes, and it may be more difficult to support long-term fundamental research.

Second, there is the part which could be played by statutory or other central machinery in diverting research into the most fruitful lines. This would include the possibility—already discussed—of restricting the introduction of new medicines with no demonstrable advantages over those already available. However, authoritative evaluation of well-established medicines has proved peculiarly difficult and it would be much more difficult to evaluate the very much larger number of possible products. It does not appear appropriate to use a sanction of this sort to discourage "molecular manipulation".

Central direction of research itself, and the use of tax incentives to encourage longer-term research projects, might also be considered. However, on the whole the Medical Research Council, faced with similar problems, has found it better to allow individual research units a maximum of freedom. Similarly, a number of the larger companies in the pharmaceutical industry have also deliberately split their research into units. They believe this increases its success because there is a limit to the size of unit that can be efficiently controlled.

Nevertheless, there is reason to believe that this diverse many-centred pattern of research may leave loopholes. Perhaps information on the areas being covered by individual research could be centralized. Based on such information, incentives could be offered for work in the neglected areas. However, there would always remain the great difficulties involved in the central selection of the most worthy research projects. A single misguided central judgement could do immeasurably more harm than the inevitable individual errors of judgement which must in any case occur in research. Those most closely concerned with the type of research employed in discovering new medicines seem convinced that the main part of such work is most effective when responsibility for it is widely spread.

Next, there are the international considerations. Britain, although an important pharmaceutical innovator and producer, conducts less than one-tenth of the total world-wide pharmaceutical research. Correspondingly, some nine-tenths of the recent major pharmaceutical discoveries have originated oversea. Most of these oversea discoveries are now manufactured by subsidiaries or associated companies in Britain, and many are exported to other territories. However, it is from the 10 per cent or so of locally discovered products that the greatest benefit to Britain's economy can be expected. There is, therefore, a temptation to discriminate in favour of indigenous discoveries, at the expense of those from oversea. There is a temptation to be more ready, for example, to grant compulsory licences on patents owned by American or Swiss companies than on those owned by British companies. However, this is a dangerous policy, because it tends to lead to reprisals in other countries, gradually eroding the whole international patent system. The law in Britain should therefore apply to British and foreign owned patents alike.

Nevertheless, it is only reasonable that the British patent law should be framed so as to give the maximum benefit to research by British companies. In effect, this will be achieved by ignoring international considerations. British-based companies will naturally tend to be more affected than oversea companies by British patents, because a larger proportion of their business tends to be in Britain. Therefore, British-based companies should automatically be the ones to benefit most from the most favourable system of British patents—the system which most successfully encourages and rewards worthwhile innovations. If the British patent system encourages the wrong sort of innovation, or does not encourage it at all, it is British companies who will suffer most both in Britain and abroad.

REFERENCE

1. JEWKES, J., SAWERS, D., and STILLERMAN, R. *The Sources of Invention*. Macmillan, 1958.

The Economics of Research-based Industry

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THE subject of this paper, the Economics of Research-based Industry, is all-embracing. It should not mislead anyone into false hopes that this contribution to the symposium will contain a brief, clear and concise set of economic principles explaining the operations of science-based industry which provide guide lines for future policy. The contents are the very opposite. Against the background of the pharmaceutical industry's growth and function, it describes the situation which arises when conventional methods of economic analysis are used to explore such basic economic problems as pricing and profits in science-based industry. These questions are not unique to the pharmaceutical industry; the problems are shared by other industries whose character has been shaped by the scientific revolution of recent decades. The conclusion drawn from the discussion is largely negative. The conventional economic model of the firm, derived from the theory of price competition and investment which is static, provides an inadequate framework for the explanation and understanding of problems encountered in research-based industry, where the keynote is growth and change. This contribution, therefore, is perhaps not the most appropriate in a discussion of the pharmaceutical industry; it is a diagnosis without a prescription. However, given a healthy environment, the prognosis for science in industry is undoubtedly good.

The potential of science-based industry is great and its importance for the future growth of the economy has been generally accepted without question. This consensus and uncritical acceptance of the place of science in industry has its disadvantages. The problem has not been the subject of critical public discussion. The impression has gained ground that scientific industrial progress—like a 4 per cent growth rate—is inevitable; that it is merely a question of time before the community reaps the economic benefits of modern scientific technology. There are, however, many obstacles to be overcome. There are many problems which are far from understood about science in its industrial setting and its impact on firms and enterprises. Over half the nation's scientific research expenditure is on research in an industrial context.[1] What are the effects of this on an

industrial organization's operations and growth? What means should be used to judge efficiency? Are the conventional methods of considering prices and profits adequate?

It is strange that the relevance of these subjects to industrial scientific innovation has been neglected for so long. The Government, the nationalized industries and other public services are important customers of most science-based industries. Public authorities have, therefore, been directly involved in questions of prices, profits, efficiency and quality. To make a list of science-based industries, however, is virtually to list the major problems which have faced a string of Cabinet Ministers in the past few years.

In electronics, an industry which has one of the highest ratios of employment of scientific staff,[2] the repercussions of the Ferranti story had scarcely time to die down before they were replaced by doubts and rumours over the whole future of the industry's research programme. The once high hopes for the aircraft industry, which spends more on research than any other, have vanished with difficulties and doubts over the Super VC 10, TSR 2, P 1154 and HS 681, together with the most inappropriately named scientific project, the Concord. Barely noticed eighteen months ago was the resignation of the chairman of an atomic energy consortium as a protest against official tendering and contracting policies. The single-minded pursuit by the Central Electricity Generating Board to provide as cheaply as possible an electrical supply is now adversely affecting the exports, research and development programmes of the electrical plant industry.[3] In pharmaceuticals, where in the research oriented firms the ratio of scientific staff employed is as high as in electronics, the long drawn out cold war over prices, patents, promotion and profits is a dreary regular feature of discussions on the National Health Service. What is the background to this situation?

The popular impression of the pharmaceutical industry is of a largely anonymous, monolithic, homogeneous group of manufacturers. They are largely anonymous because their prescription products, though consumed by nearly everybody, are not promoted to the general public and are usually dispensed in the chemist's own pack. As supplies are obtained under the National Health Service, the impression is given of large-scale and national organization. Reality is, however, different. The pharmaceutical industry comprises a large number of firms with many and diverse characters, methods of operation and interests. There are few among the suppliers of branded medicines to the National Health Service whose interests are confined solely to prescription goods. Through subsidiaries or parent companies, the product range is diverse and overlaps into many fields including industrial chemicals, plastics, paint, fertilizers, cosmetics, food and drink. Industry is not a clearly distinct commercial entity. Its cohesion comes from its function and its scientific discipline.

The industry has three major functions: first, discovery and development of new medicinals to alleviate pain and to control or to cure diseases; second, the translation of these developments as quickly and as safely as possible into useful tools of medicine in the hands of the practising physicians; and finally, the production and the distribution of existing medicinal products.[4] The first two of these functions raise the economic questions of research and development, while the third concerns the more straightforward and conventional issues of supply, demand and prices.

The production and the distribution of existing medicinals is the traditional role of the industry. Through this, it is the direct lineal descendant of the herbalists and the apothecaries of medieval times. From the end of the eighteenth century, many individual chemists and druggists extended their back-shop manufacturing and compounding by supplying other chemists. This was the origin of many long-established pharmaceutical firms, such as Allen and Hanbury, Thomas Kerfoot and Co., Duncan, Flockhart and Co., Wright Layman and Umney, and Smith and Nephew Ltd. The discoveries in organic chemistry during the first half of the nineteenth century, particularly the abstraction of pure chemical compounds from natural sources and technological advances in processing, such as the introduction of tableting machines, gave impetus to the shift from retail to industrial production.[5]

The discovery and the development of new medicines is a more recently acquired function of the industry. Its range of activities was extended to include pharmacology, the science of chemical actions in the body, as an addition to pharmacy, the extraction, purification, standardization and presentation of medicinals.

A fortuitous result of an experiment in pharmacy indirectly provided the stimulus to this development. Perkin at the age of eighteen in 1856 attempted to synthesize quinine at his home in Southwark. He experimented with coal tar and obtained a substance with excellent dyeing properties—aniline purple, the original synthetic dye. He patented his discovery and started manufacture at Greenford in 1857. In 1874, he abandoned manufacture to devote himself to full-time research.

The full scientific and commercial development of synthetic dyes took place in Germany—the home of much of the original work in organic chemistry. The search for a use of a by-product of synthetic dye production in Duisberg in Bayer's industrial laboratory resulted in the development of phenacetin, and research by Hoffman in the same firm resulted in the development of aspirin. These two products became the financial pillars for the nineteenth-century German pharmaceutical industry.

The First World War led to an international diversification of the chemical industry, and concurrently to industrial pharmaceutical research development in most western European countries. The Second World

War brought a great stimulus to industrial pharmaceutical research, particularly as it coincided with major advances in bacterial chemotherapy. Ehrlich had discovered that some of the aniline dyes he used to stain histological specimens had strong antibacterial properties. He clothed arsenic with these dyes to produce Salvarsan, the first specific treatment for syphilis, in 1909. His observations on the antibacterial properties of dyes led to a systematic search by industrial laboratories for a dye effective in systemic bacterial infections. Although the search produced a number of useful local antiseptics, it proved unsuccessful for many years. At the time medical opinion generally placed a greater hope in the development of serum treatment rather than in the search for antibacterial drugs. In 1935 came the break through when Domagk at Bayer's industrial laboratory discovered that prontosil had the properties foreseen by Ehrlich and could cure bacterial infections. Within a few months, scientists at the Pasteur Institute in Paris showed that the activity of prontosil was due to sulphanilamide—a simple molecule that could readily be modified chemically. Industrial laboratories in Britain, the U.S.A., Switzerland, Germany and Sweden started the search for and the development of derivatives. The best known result is probably May and Baker's famous M. & B. 693. The discovery of the sulpha drugs was a major triumph of chemotherapy, yet it had a disastrous effect on that section of the industry concerned with the production of anti-sera against bacterial infection. One of the firms, Lederle in the United States, was particularly hard hit; it had invested large sums in a vast complex of animal houses for the accommodation of horses and rabbits for the production of sera.

In the same way as anti-sera were replaced by the sulpha drugs, they in turn were rapidly largely superseded by the antibiotics, antibacterial substances produced by micro-organisms. In 1939, Florey and Chain at Oxford decided to investigate Fleming's observations on the properties of penicillin. In 1941, its curative power in man was demonstrated but as Fleming's original mould produced only a minute quantity of penicillin, its practical value was doubtful. There was a chance that synthetic production might solve the difficulty and industrial chemists attempted to achieve this for five years but without success.

The pharmaceutical manufacturers at that time had little experience of micro-biological production. Fortunately, there were firms then outside the industry, among them Chas. Pfizer & Co., who had many years' experience in the micro-biological production of citric acid. They developed the biological production of penicillin by deep fermentation and so entered the pharmaceutical industry.

The industrial contribution in the field of antibiotics was not limited to the development of production methods. In 1944 Waksman isolated the antibiotic streptomycin. A vast screening effort for new antibiotics was

begun following the discovery of the curative power of penicillin and streptomycin. The result was the discovery of a whole range of new and important antibiotics: particularly chloramphenicol, the tetracyclines and the others in the present broad range of antibiotics.

It is not suggested that industrial research was the most important or dominant factor in the discovery of new medicines. Both industrial and university laboratories have made equally important contributions each in their own specific manner and the best results have often been obtained in the past and are likely to be obtained in the future by the closest collaboration between academic and industrial research laboratories.[6]

The development of antibacterial drugs has done more than any other factor to shape the present pharmaceutical industry. They extended the range of firms engaged in pharmaceutical production and established that the basis of success is extensive research. Also, antibacterial drugs, unlike many earlier discoveries such as insulin, opened a large market, so that their sales produced a flow of funds sufficient to sustain and increase the research effort.

The impact of this research effort in chemotherapy is illustrated by the fact that thirty years ago seven in ten of today's prescriptions could not have been written—the drugs did not exist.[7] Figure 1 plots cumulatively

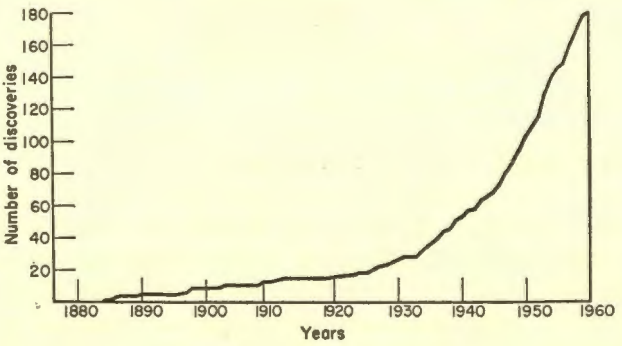


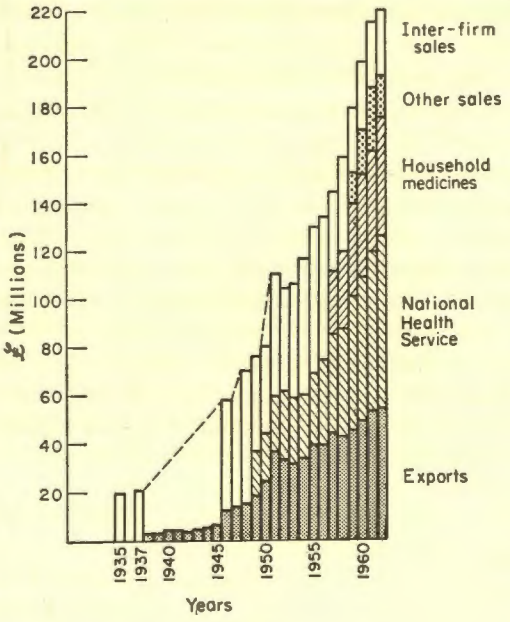
FIG. 1

Source: Ref. 14.

180 basic drug discoveries, which constituted a substantial advance in the healing arts, against the year of discovery for the period between 1875 and 1960. Not all of these rapidly achieved the status of products. Penicillin, for example, is listed among the discoveries of 1929. Nearly nine out of ten of the basic discoveries were made during the twenty-five years after 1935, and over half since 1948—the year which saw the introduction of the National Health Service. The period also saw a shifting geographical centre of pharmaceutical advance. What progress was made before the 1930's

came largely from Germany. Britain was the most prolific for a short period towards the end of the 1930's, but thereafter the United States became overwhelmingly dominant.

The impact of these scientific advances on the industry are summarized in Fig. 2. In 1935 U.K. production of pharmaceuticals amounted to



Source: Ref. 8. FIG. 2

approximately £19 million. By 1950, this had risen to nearly £100 million, reaching an estimated £193 million by 1962.[8] Production increased ten-fold by value in twenty-five years. The export record of the pharmaceutical industry provides an apt illustration of the general economic advantages a nation derives from the development of science-based industry. Typically, when a new technology or group of products emerges, there are good opportunities for export growth. Towards the end of the 1930's pharmaceutical exports from Britain amounted to £3·3 million, compared with imports of £1·7 million. Exports have increased over sixteen times pre-war levels; in 1963 they amounted to £54 million compared with imports of £6·3 million. In 1962, sales to the National Health Service accounted for approximately 37 per cent, exports for 29 per cent and sales of household or non-prescribed medicinals for 25 per cent of the industry's output. The balance comprised the small but growing market of veterinary products, feed additives and so on.

Figures for research expenditure by the industry in Britain are available for the period 1953 to 1961. In 1953, expenditure amounted to £2·8 million. By 1962 it had increased three-fold, to £8·3 million. The industry's research in the U.K. represents about one-third of the total amount spent on all medical research. The industry, however, is international. Expenditure on research by the industry in this country—as indeed is all expenditure on medical research—is small compared with that in the United States. The annual research effort of the United States' pharmaceutical industry reaches approximately £100 million a year.[9]

Correlative with the scientific advances in the past thirty years, the pharmaceutical industry has witnessed rapid growth, increased sales both at home and overseas and heavy investment in scientific research. Two broad groups of firms, which operate under basically different economic circumstances, have also emerged in the industry. There are, firstly, the research oriented firms who fulfil the industry's function in the discovery and development of new medicinals. Secondly, there are the smaller and usually longer established manufacturers of existing medicines. The groups are not wholly mutually exclusive nor even fully inclusive. Among the members of the A.B.P.I. are firms such as William Ransom and Sons Ltd., whose herb farm, since its foundation in 1846, continues to play a highly specialized function. Given this growth and character of the industry, what can be learned from economic analysis?

In an economy governed by the price mechanism, the enquiry centres upon the effectiveness with which the market forces of supply and demand operate. It discusses marginal returns and costs and prices derived from these vectors. Using the economist's traditional assumption of *ceteris paribus*—all other things being equal—prices should respond flexibly to changes in conditions of supply and demand and should generally settle at levels to cover all costs, including the competitive return on capital. Should profits be excessive, it is expected that through competition, prices will tend to fall to levels which yield competitive rates of return. All other things being equal, it can be shown with a high degree of precision that an industry in this competitive equilibrium transforms scarce resources into goods and services more efficiently than one where price levels are affected by imperfections in price competition.

Applying this analytical framework to the pharmaceutical industry, there are obvious and outstanding imperfections. On the demand side, the industry in this country is faced with a market where the doctor prescribes, the patient consumes and the Government pays.[10] The National Health Service apart, with prescription goods it is the doctor who makes the choice of products and not the ultimate consumer, the patient. Even if this complication in demand were set aside, in the nature of things the demand for life-saving medicines is highly inelastic as requirements do not vary

sensitively with price. Profits, resulting from market imperfections, are greater where demand is inelastic, as the quantity sold is relatively unaffected by price.

The barriers to competition in the supply of existing medicinals are firstly the formal safeguards afforded by patent protection. The strength of this varies from country to country according to the state of legislation. Equally important are the less formal barriers erected by product differentiation through trade-marks, brand names and product promotion which makes a product unique and not susceptible to substitution.

There is much evidence to show that prices of certain ranges of pharmaceutical products are substantially higher where these features are present than they would be if they were absent. In this country, the Ministry of Health was able to import certain antibiotics at a substantially lower price from countries where no patent protection for medicines exists.[11] The Public Accounts Committee has frequently called attention to the price differential between branded medicinals and the substantially similar items supplied as anonymous generic products.[12] The most detailed evidence comes from the United States.[13,14] There, as in this country, the main controversy concerns the prices of antibiotics. Price competition in antibiotics is intense in unpatented drugs such as the earlier penicillins and streptomycin, but is considerably less in evidence with later patented antibiotics. Figure 3 shows the prices of penicillin, streptomycin and certain patented broad spectrum antibiotics over the period 1947 to 1960. The difference in the decline between penicillin prices and the lesser proportionate falls in prices of patented antibiotics measures the effect of restriction in entry to this market.[15]

The question of prices leads directly to consideration of profits. In looking at profits, the economist borrows from the accountant and expresses annual profits as a ratio of real capital employed. Where this ratio is substantially above that for industry as a whole, all other things being equal, the industry is not in competitive equilibrium. Here too there is evidence of market imperfections. The Committee of Public Accounts examined a schedule of the published accounts of forty-three firms engaged in the production of pharmaceuticals.[16] Figures of capital and profits are available for the years from 1955, and are summarized in Fig. 4. The schedule showed that average profits as a ratio of real capital employed for these pharmaceutical firms were substantially higher than for industry as a whole. It may be noted that the Committee of Public Accounts concentrated on eight subsidiaries of United States drug houses. In the schedule, their profits as a ratio of capital employed averaged over 70 per cent. However, a subsidiary may receive a substantial amount of aid from its parent firm at little or no direct cost. These benefits include the services of research and development departments, central administration, promotion and so on.

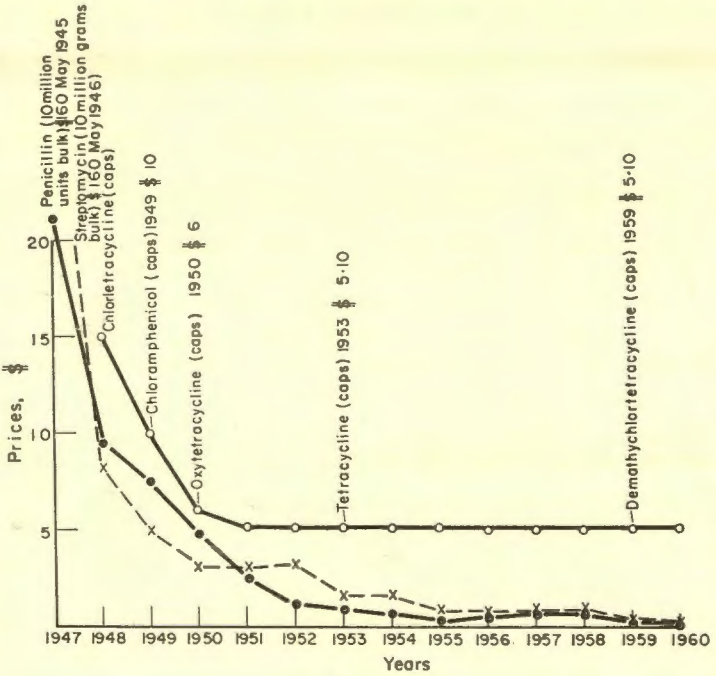


FIG. 3

Source: Ref. 15.

When the schedule was adjusted for these costs, the average profit ratio dropped to 33 per cent—less than half the amount first put forward to the Committee of Public Accounts, but still substantially above the average for industry as a whole.

It is this analysis, derived from the economist's traditional theory of price competition and investment, which lies behind the general and popular impression of the pharmaceutical industry. The argument follows highly predictable lines. Through patent protection and product promotion, the industry is charging high prices for products that could be made cheaply available in standard form. The medical profession is persuaded into prescribing branded products instead of standard preparations by commercial pressure. The price difference between a branded and a standard product is used to finance this massive selling programme. Thus all the public is getting for much of the amount spent on pharmaceuticals is a wholly unnecessary and wasteful advertising campaign.[17]

On the more sophisticated levels of economic analysis, the discussion of the industry in terms of the conventional theory of price competition leads to two simple but radical recommendations: the abolition of patent protection as it applies to pharmaceuticals and the introduction of restrictive

FIG. 4. PROFIT RATIOS

(a) P.A.C. Sample

Year	Units	1955	1956	1957	1958	1959	Average
Firms	No.	43	43	40	43	33	—
Capital	£000	70,091	77,609	79,977	90,240	88,819	—
Profits	£000	16,770	19,462	22,023	24,536	29,436	—
Rate	%	23·9	25·1	27·6	27·2	33·1	27·6
Profit Rates—British Industry							
Year	Units	1955	1956	1957	1958	1959	Average
Rate	%	18·4	17·9	16·5	14·8	16·0	16·7

Source: Committee of Public Accounts, Special Report, First and Second Reports, Session 1959–60, pp. 217–40 (Unpublished Appendix).

Note: The average for the P.A.C. sample is weighted, while the average for British industry is unweighted. The unweighted average for the P.A.C. sample is 27·3 per cent.

controls over pharmaceutical advertising. When the question of research is raised it is normally suggested, often as an afterthought, that this function should be delegated to some non-industrial or state institution.[12]

It is a measure of its grave defects that, when applied to the problems of research-based industry, the traditional theory of price competition inevitably concludes that science and industry should be divorced. The paucity of results from situations where science and industry are divorced and the general economic gains which have flowed from situations where they are closely linked provide empirical warnings against basing any policy on the results of this analysis. The traditional theory of the firm touches on only the third and perhaps the least important of the pharmaceutical industry's three functions: the production and supply of existing medicinals. It treats it out of context. It assumes that research oriented firms operate under the same conditions as firms concerned only with production. It explains nothing about the first and the second functions of the industry, the discovery and the development of new medicinals, or about what is the most interesting question of them all—the complex economic relationship between research, development and production.

In face of these conclusions, there have been attempts to modify the competitive model and to discuss the industry's operations in terms of product rather than of price competition. There is evidence to support a general conclusion that the principal means of competition in the industry is by products rather than by price. Clearly, the stress on product rather than on price competition is one key to the understanding of science-based

industry. One object of scientific advance, particularly in its industrial setting, is the creation of new products and services, of doing things which could not be done before.

Following on this, a strong case might be made for the pharmaceutical industry's mode of operations through considerations of the broad social gains the community has derived from new medicinals. There are perhaps few fields where the public's welfare is best served by the highest feasible rate of scientific progress. The social costs of a delay of ten years in the discovery of the automatic gear shift, the electric lamp, or the household refrigerator could be measured in terms of discomfort and inconvenience. A similar delay in discovering the various antibiotics or a cure for cancer involves costs which must be measured in terms of human lives.[18]

The contribution to social welfare of the chemotherapeutic revolution is substantial. The original sulphonamides were first widely available in 1939. In that year deaths of young adults from pneumonia were more than halved.[19] Between 1940 and 1943, nearly five million children were immunized against diphtheria. Three thousand child and infant deaths from diphtheria occurred annually in the 1930's: in 1962 the number was two.[20] Tuberculosis mortality was slowly declining at about 3 per cent a year up to the late 1940's. With the introduction of anti-tuberculosis drugs, the decline accelerated to 15 per cent a year. An estimated total of 100,000 persons are alive today directly as a result of these new compounds.[21] Poliomyelitis became a serious epidemic in 1947, when almost 8000 cases were notified. Vaccination started in 1956, and the campaign became intensive from 1958. The number of cases fell away rapidly to reach a new record low figure of fifty-one in 1963. It is estimated that up to the end of 1963 2000 persons had been saved from permanent disability.[22] Tranquillizers and anti-depressants have given hope to long-stay patients in mental institutes. A large number of persons can keep at work and maintain a reasonable state of health through treatment with psychotropic medicines.[23]

These great gains in the health of the nation have major economic implications, which might offer a basis for judging the operations of the industry. It is estimated, for example, that 170,000 persons are alive today as a result of the more effective treatment of pneumonia brought about by antibacterial drugs. Assuming this group enjoys the same employment conditions as the rest of the population, their annual earnings amount to £43 million a year.[19] This is nearly ten times greater than the total amount spent by the National Health Service on the treatment of pneumonia, only a small part of which is accounted for by expenditure on antibacterial drugs.[24] Although these calculations are attractive, and although they help bring some perspective on the amount spent by the Health Services on pharmaceutical products, they are hardly a satisfactory substitute for the

traditional economic analysis of industrial problems. Their methodology involves difficult conceptual and computational problems, which are far from solved, and the results, though striking, cannot even at their best give any indication of the effectiveness with which resources are being used or provide a suitable basis on which a choice of investments can be made.[25] They fail to provide specific guidance on problems such as pricing or patents except to underline the unexceptional presumption that advances in medicine are desirable. They also isolate the industry from the general run of science industries, and imply that specific economic considerations should be suppressed. The pharmaceutical industry provides the finest example the community derives from industrial scientific research, but this does not set the industry apart from economic analysis. Such a step would in effect relegate the industry to an economic limbo which the dictionary defines as a place or condition of neglect or oblivion.

In the complex relations between research and production and their interaction and dependence on profits and pricing the pharmaceutical industry shares problems common to other science-based industries. The relevant question is why the conventional economic model of the firm built around price competition throws so little light upon the workings of science-based industry. An examination of these defects might lead to a more satisfactory and informative analytical tool. What is needed is an explanation of the inter-relation between all three functions of a science industry, how research and development may revolutionize production and sales; how sales and production may in turn provide a feed-back which recoups and extends investment in research.*

In recent years, economists have been devoting greater attention to the importance and the impact of knowledge on the economy. This has led to considerations of both its production, research, and its distribution, education. Discussion has concentrated on the general economic impact of advances in knowledge, particularly in relation to economic growth and rises in national income. The Keynesian revolution focused attention on short-term variations on the supply and demand for goods and services in a market economy. It provided government with tools for maintaining full employment and economic stability. But this theory was static in the sense that the technological and social framework within which these short-term fluctuations take place is taken for granted or treated as a constant. Their influence had been eliminated from the theoretical model by

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* It is not suggested that problems of technological changes have been ignored in the discussion of the competitive equilibrium. It was much in vogue among professional economists at the turn of the century (see particularly J. B. Clark, *The Distribution of Wealth*, 1900, and *Essentials of Economic Theory* in 1907). The discussion, however, tended to treat technological invention and change as exogenous, occurring at little or no cost. This was generally appropriate at the time.

the economist's traditional assumption of *ceteris paribus*—other things being equal.

This screening off of "other things" was to a large extent maintained when economists turned their attention to growth problems. Though changes in "other things" were sometimes assumed to have taken place, they were mostly left unexplained, and unrelated to the variables of economic models. However, these changes left out as a "residual" could explain a large, if not the greater, part of economic growth. Consequently, economists working on the problems of economic growth increasingly felt the need to penetrate the facade of *ceteris paribus* and to investigate the mechanisms of technological and scientific progress.[26]

A number of attempts have been made, particularly in the United States, to measure the contribution to economic growth of changes in the input of the principal factors of production. Generally, the conclusions are that increases in the input of the traditional factors of production, labour and capital can explain only a small part of the long-term increase in labour productivity while the factors grouped under the general heading "technical progress" traditionally left out as a residue account for a substantial part in the rise of real income per person employed. A study, for example, of the United States economy between 1889 and 1957 found that the combined inputs of real capital and labour increased at a rate of 1·9 per cent a year, while the output index increased at about 3·5 per cent a year, leaving nearly half the growth rate (about 1·6 per cent a year) to be explained by "residual factors".[27] The general conclusion rather than the precise figures is important since the computational and conceptual problems these studies encounter are formidable.[28]

Scientific knowledge, research and innovation have yet to find a firm place in the traditional static economic model. So far as this is true of the wider field of economic analysis, it is equally true of the discussion of the firm. The traditional economic model of the firm in competitive equilibrium—*ceteris paribus*—based on the framework of marginal returns and costs and prices derived from these vectors fails to explain the central issues of science-based industry. The analysis draws attention, for example, to the difference in price behaviour between patented and unpatented antibiotics once they are on the market, but it in no way explains the far more important and relevant problem of how they came to be there in the first place, nor of their relation to the later discoveries in other therapeutic fields.

The difficulty is that the marginal analysis ignores the implications of significant or "productive" overhead expenditure. Costs already incurred have no bearing on prices in a perfectly competitive market. Research investment, the factor behind the creation and the growth of science-based industry, is not, except where the definition is broadened to be virtually

meaningless, a marginal cost of production. It has more in common with overhead expenditure. On the whole, overheads are conventionally treated as an unavoidable necessity, and the efficiency of a company is normally measured by their smallness. However, in science industry, such an overhead is the key to the items produced and their marginal costs.

It is, therefore, hardly surprising that difficulties arise where the reasonableness of prices of products of science-based industry are judged mainly against their costs of production. The best that can be done with research expenditure in the traditional economic model of the firm is to treat it on par as investment in real capital, such as the purchase of production plant. The amount spent on research may, therefore, be assessed against the present value of the future stream of income the investment is likely to create. Given the normal workings of the price mechanism, the returns to research or the profitability of science-based industry should tend to reflect competitive returns set by other forms of investment after allowing for the differences in risk.

There are, however, three formidable objections to this analysis which are worth examining in detail as they throw light on the nature of the economic problems within science-based industry.

The first difficulty is the familiar one that the asset created by research, new knowledge, is intangible. It is open to use by either the investing entrepreneur or by his competitors. While the entrepreneur has sole use of any production plant he invests in, the same is not true of the products of research investment. If there is direct price competition, competitors who undertake no research are the more strongly placed as they do not have to carry the overhead costs of research. This, of course, is the problem the patent system seeks to alleviate by giving the innovator exclusive rights in an invention. The details of the system affect the safeguards and economic advantages provided. In this country, compared with other science industries, patent protection for food and medicinal substances is weak regarding the granting of compulsory licences. The British sector of the industry suffers most both at home and abroad from this weakness in protection.[29]

The problems resulting from the intangible nature of the product of research are far broader than those covered by the patent system. Although the facts of the situation are not fully available, it would appear that in the development of atomic energy, various consortia were asked to produce designs for plant. The development of these designs required much basic research. The best features from all competing designs were incorporated into one specification on which suppliers were asked to tender. The suppliers who incurred heaviest overheads were least favourably placed in quoting competitive prices. The same practice occurs in a field not normally associated with problems of research—that of property development. Local

authorities have asked several developers to produce plans for comprehensive redevelopment of their city centres. The contract frequently goes to the developer offering the best financial advantages, and he is then asked to incorporate the best features from other developers' schemes. Low preliminary research expenditure in investigating the economic and social nature of town redevelopment gives a developer an advantage in price competition. This practice has been scarcely conducive to research and its practical application in urban renewal.[30]

The second difficulty of looking at research as a normal capital investment in the price competitive model of the firm is that research expenditure can be related specifically to products only retrospectively, not prospectively, only with knowledge of hindsight, not foresight. It is difficult to envisage how in compiling a research budget one can discount a stream of future income from products which by definition do not exist to be sold in markets whose potentialities are quite unknown. It takes an accountant of more than normal perspicacity to value potential sales of tranquillizers when assessing research expenditure on antihistamines or to consider the field of diabetes when deciding on research into a new sulphonamide. These two examples, of chlorpromazine and the sulphonylureas, are of course extreme, but they illustrate the general problem. A further aspect is that at the start of a research programme there is no guarantee that a marketable product will emerge. Some part of research expenditure is abortive. I.C.I. spent nearly £$\frac{3}{4}$ million looking for a chemical anti-viral drug without obtaining a product.[7] Lederle in the United States spent over $10 million in searching for a live polio vaccine.[31] The risks are high.

It is true that this problem can be modified to suit the conventional economic model by spreading the risks. Although it might be impossible to relate research expenditure and specific products at the time of investing, it is possible with a sufficiently large programme to work on the probability that an expenditure of £y million a year will produce x number of new marketable products. This, however, limits research only to large-scale organizations whose size must be determined by the probability of research success. In relation to resources used, there is no reason to believe that large-scale organization is the most effective environment for industrial scientific advance: indeed, considering the many communication barriers involved in large organizations, the opposite is probably true. Limiting research to large-scale organization also inhibits product competition. Furthermore, the size of an industrial organization, set by the probabilities of research results, is not necessarily the optimum for production or marketing. Finally, with the different stages of advance in knowledge the chances of success change rapidly from year to year, far more rapidly than a large organization can adapt itself.

The third difficulty of considering research as an investment as part of

the theory of price competition is that while the physical assets produced by capital investment are consumed during the process of production, the intangible asset of knowledge becomes more useful with its exploitation. The depreciation of physical assets can be dealt with in a straightforward manner by amortizing original costs over the life of the asset so that at the end of the period there is an adequate sinking fund for replacement. The costs of the initial and the replacement asset are, after allowing for inflation, usually of the same order.

The assets created by research expenditure are not subject to depreciation; they face a risk of a wholly different nature, obsolescence, of being superseded by a superior product. Product obsolescence is the direct result of advances made either by competitors or by the initial innovating firm. Product obsolescence and product competition are, therefore, different aspects of the same factor, research expenditure. The innovating firm is not faced with the simple problem of amortizing the amounts already spent in the pricing of its successful products, it must also cope with the risks of product competition and obsolescence and these risks depend largely on the amounts spent on research.

The object of amortizing capital expenditure is the preservation of the capital assets of the firm. If the major asset a firm possesses is scientific leadership in a given field, the only way an attempt can be made to preserve this asset is by further and growing research expenditure.

The most successful response to product competition is the full exploitation of one's own discoveries. The amount required for research, however, in the full exploitation of the leads a breakthrough provides usually far exceeds the initial outlay. The best example of this is in electronics and the development of transistors. In 1946, Bell Telephone Laboratories at the sole expense of American Telephone and Telegraph, who were later joined by Western Electrical, embarked on a programme of research upon semiconductors. The process of producing transistors was patented by 1950. The whole expense of research and development work prior to the filing of the patent application was about £140,000. Since then research expenditure by the firms has amounted to over £56 million, half of which was incurred since the start of 1961. Much of this was financed from the manufacturing of profits of £20 million on the sales of transistors and transistor equipment.[32] These developments would have been impossible had there been price competition or if prices had been set at levels which no more than amortized initial research outlay. Product competition is not simply a substitute for price competition: it would appear that the two are incompatible.

There are two further points which should be noted concerning the accounting conventions used in assessing the reasonableness of prices and profits when analysing science-based industries in terms of price competition.

These are the conventions of expressing research expenditure as a percentage of production costs and of evaluing profits as a ratio of real capital employed. Both conventions aggravate the problem of understanding science-based industry.

The convention of expressing overhead costs, including research as a percentage of costs of production, produces an absurd position when the object of the research expenditure is the development of more effective means of production. A successful piece of research has the simple arithmetic consequence of raising the ratio of research and development expenditure to costs of production. The greater the effort and the success attendant on research and development in reducing costs of production, the higher this ratio becomes. However, the convention tends to accept lower ratios as the correct measure of efficiency, and not the reverse. This problem of judging expenditure in terms of ratios which arises, for example, when royalties are being set is particularly acute in a field where products are inherently simple to manufacture, but very costly to discover and to develop.

The second accounting convention concerns the treatment of profits. Expressing profits as a ratio of real capital employed involves grave anomalies. Is the concept of real capital employed derived from balance sheet figures a wholly reliable guide to the profitability of research-based firms? Research expenditure for accounting purposes is treated on a par with normal running costs and is written off wholly during the year incurred. Few, however, would argue with the contention that so far as accounting definitions are concerned, research is more in the nature of a high risk capital outlay, incurred solely in the hope of future benefits and not part of normal day-to-day production costs. Therefore, when establishing capital employed, there is a strong case for arguing that research expenditure should be considered as the creation of a capital asset, and so over the years treated as cumulative income ploughed back into the firm.

The implications of this are shown by a theoretical exercise given in Fig. 5. This illustrates no more than the simple arithmetic effect of capitalizing research expenditure rather than writing it off annually. On the assumptions stated, over a ten-year period a profit ratio of 25 per cent is reduced to 16 per cent without any other changes taking place. The example, of course, ignores many sophistications.

The general point is that the convention of using real capital employed as the measuring rod of profits fails to take account of the less tangible factors which affect the prosperity and the growth of a research-based firm. It recognizes that plant and equipment are necessary for production but fails to acknowledge that know-how and technique are of equal if not of greater capital importance. If a firm which is allegedly making "unreasonable profits" as a result of its research expenditure were to spend

FIG. 5. CAPITALIZATION OF RESEARCH

Year	Capital at Start	Research Investment	Research Depreciation	Capital at End	Profits before Research	Research Write-off	Profit after Research	Profit Rate %
A	100	10	0	100	35	10	25	25·0
1	100	10	0	110	35	0	35	31·8
2	110	10	1	119	35	1	34	28·6
3	119	10	2	127	35	2	33	26·0
4	127	10	3	134	35	3	32	23·9
5	134	10	4	140	35	4	31	22·2
6	140	10	5	145	35	5	30	20·7
7	145	10	6	149	35	6	29	19·5
8	149	10	7	152	35	7	28	18·4
9	152	10	8	154	35	8	27	17·5
10	154	10	9	155	35	9	26	16·8
B	155	10	10	155	35	10	25	16·1

Notes: 1. Years A and B show the two equilibrium positions; years 1 to 10 show the step-by-step change. In year A, research is treated as an annual running cost; in year B, research has been capitalized. All other factors are held constant.

2. Different results flow from different assumptions. Here it is assumed that annual research investment is about a third of the level of balance sheet net profits and if treated as capital has a ten-year write-off life.

3. The exercise illustrates nothing more than a general principle. Many sophisticated adjustments are ignored. For example, if research were accounted as capital, a greater area of net profits would attract tax, leaving a lesser amount to be ploughed back.

the money instead on even thicker carpets in the directors' offices, or on a real swimming pool for the typists, its ratio of profits would soon show a more "reasonable" figure, merely because of the different ways these expenditures are treated in accounting. Since profits are related to real but not to the intangible capital assets, the level of profits looks high. The greater the research effort, the greater this distortion.

In summary, therefore, the pharmaceutical industry has grown during the past thirty years correlative with the scientific advances of the chemotherapeutic revolution. Conventional economic analysis of the industry in terms of price competition based on the workings of the price mechanism reveals considerable and substantial market imperfections. The analysis has, however, the grave defect in that it throws light only on the third function of the industry, the production of existing medicinals, and explains nothing about the industry's prime functions of the discovery and the development of the new medicinals. Indeed, it leads to the conclusion, quite inconsistent with the general presumption of scientific industrial advance, that research should be divorced from the industrial process.

The conventional analysis of science-based industry in terms of the traditional theory of price competition and investment is inadequate for

explaining the behaviour of firms in relation to research and innovation. In this framework expenditure on scientific research is treated on the same basis as investment in physical assets. But this has three serious defects. First, the product of research, new knowledge, is intangible and so open to exploitation by competitors. The only safeguard is the patchy protection afforded by the patent system. Second, research costs can be related to results only retrospectively, not prospectively; the risks of failure are high. Risks can be spread according to the principle of large numbers, but this involves large-scale organization of research, with size determined by the chances of research success. This size may not be the most appropriate for industrial production or distribution, nor is large-scale organization the most suitable environment for research. Third, and most important, while physical assets are subject to depreciation, the product of research, new knowledge grows more useful with exploitation. The risk facing the successful innovator is therefore obsolescence. Obsolescence results from the exploitation of scientific ideas. Competition takes the form of superior products, not lower prices, in science-based industry. An innovator can most successfully meet this competitive challenge through the full exploitation of his own discoveries. If an innovator is to maintain scientific leadership, he cannot merely recoup past expenditure on research but needs to finance from the sales of his successful research products an expanding and growing research programme. Low price levels, brought about by notions associated with the theory of price competition in science-based industry, are not compatible with a high rate of industrial scientific progress.

The difficulties of pricing in science-based industry are aggravated by the conventions of treating overheads like research as a percentage of production costs, when they may be inversely related, and of judging profit levels against real capital employed. The concept of real capital recognizes that plant and equipment are necessary for production but fails to acknowledge that know-how and technique are of equal if not greater capital importance.

This discussion has raised many questions but provided few answers. Far more economic research is needed into the place of science in industry, into the mode in which science-based firms operate, into basic economic questions such as pricing policy and its relation to innovation and into the many ramifications of these subjects.

It would appear that in looking at science in the economy, we must replace our quantitative preconceptions of costs and prices by more complex qualitative notions of a changing, not merely a rising, standard of living. In economic growth we are not concerned merely with greater efficiency leading to the accumulation of material wealth, but also with how scientific and economic progress affects the quality of life. From any point of view, the most significant change in pharmaceutical production in recent decades

is not that penicillin prices are now only one-twelfth their 1947 level or that broad spectrum antibiotics could be obtained more cheaply: it is that these products now exist.

REFERENCES

1. Advisory Council on Scientific Policy, *Report 1961–62*, Appendix C, Cmnd. 1920.
2. F.B.I. *Industrial Research in Manufacturing Industry, 1959–60*, p. 7.
3. Advisory Council on Scientific Policy, *Report 1963–64*, p. 10, Cmnd. 2538.
4. Connor, J. T. *Drugs in Our Society* (ed. Talalay, P.), p. 117. O.U.P., 1964.
5. Duckworth, A. (1959) Rise of the Pharmaceutical Industry. *Chemist and Druggist* **172**, 127.
6. Chain, E. B. (1964) Academic and Industrial Contributions to Drug Research, *Journ. R.S.A.* **CXI**, 856.
7. Yule Bogue (1962) Economics of Research in the Pharmaceutical Industry, *Pharm. J.* **188**, 5215, 27.
8. A.B.P.I. *Annual Report 1963–64*.
9. Office of Health Economics 11. *The Finance of Medical Research*, 1964.
10. Powell, J. E. (1962) Health and Wealth, *Proc. Roy. Soc. Med.* **55**, 1.
11. *Hansard*, 27 April 1964, p. 24, col. 24–7.
12. Committee of Public Accounts, *Special Report, First and Second Reports, Session 1962–63*, pp. 154–5, H.M.S.O.
13. Federal Trade Commission, *Economic Report on Antibiotics Manufacture*, Washington, 1958.
14. Sub-committee on Antitrust, United States Senate, 87th Congress, 1st Session, No. 448, 1962.
15. Steele, H. (1964) Ethical Drugs Industry, *J. Ind. Econ.* **12**, 3, 198.
16. Committee of Public Accounts, *Special Report, First and Second Reports, Session 1959–60*, p. 217, H.M.S.O.
17. O'Brien, J. (1964) *New Statesman* **68**, 198.
18. Markham, J. W. *Drugs in Our Society* (ed. Talalay, P.), p. 163. O.U.P., 1964.
19. Office of Health Economics 4. *Pneumonia in Decline*, 1963.
20. Office of Health Economics 2. *The Lives of Our Children*, 1963.
21. Office of Health Economics 1. *Progress Against Tuberculosis*, 1962.
22. Office of Health Economics 6. *The Price of Poliomyelitis*, 1963.
23. Office of Health Economics 15. *The Cost of Mental Disorders*, 1965.
24. Office of Health Economics 10. *The Costs of Medical Care*, 1964.
25. Wiseman, J. *Public Expenditure* (ed. Peacock, A.T.), p. 128. Oliver and Boyd, 1963.
26. O.E.C.D. *Science, Economic Growth and Government Policy*, Paris, 1963.
27. Kendrick, J. *Productivity Trends in the United States*, National Bureau of Economic Research, 1961.
28. Weisbrod, B. A. (1962) *Journ. Pol. Economy* **20**, 5, ii, 106.
29. Fryers, G. R. (1965) *The Influence of Patents*, Office of Health Economics.
30. Royal Institution of Chartered Surveyors, *Methods of Tendering for Comprehensive Re-development*, 1962.
31. Wilson, J. R. *The Margin of Safety*. Collins, 1963.
32. In Re Western Electrical Co. *The Times*, 12 January 1965.

The Role of Marketing in Scientific Progress

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IN *The Finance of Medical Research*, the Office of Health Economics distinguished between scientific progress which resulted in new knowledge, and progress which resulted in new goods. In the main, this paper is concerned only with the latter, because it is these new goods which can be sold to finance the research programme from which they have resulted. New knowledge, being intangible, is a less easily defined and marketed commodity, and research leading to it can only rarely be self-financing. The discussion in this paper will, therefore, centre on whether the products of new scientific discoveries should appropriately be sold by commercial methods, and what special considerations arise when they are so marketed. Experience in research leading to new knowledge—much of it fundamental new knowledge—will be called upon only as supporting evidence for the arguments relating to the development of new products. None of the principles involved in the discussion appear to be materially affected by whether the particular research is undertaken by a private organization, a commercial corporation, or a public body. In each case the products of their research can be, and generally are, sold as a source of revenue.

Many of the examples in this paper are chosen from the field of pharmaceutical advertising. However, the more general comments should not be taken to apply specifically to pharmaceutical marketing in this country, except where they refer directly to such examples. Before discussing positively the role of marketing in scientific progress, I would like to discuss briefly the other ways of disseminating information about scientific innovation. These obviously have a valuable place as a source of new knowledge, but they do not fulfil the same function as the commercial marketing techniques.

Firstly, there is, of course, the theoretical possibility—which some of the extreme opponents of advertising seem to advocate—that one should simply produce new products and never make any effort to tell anyone about them at all. In this complete absence of communication there would be no awareness of the availability of the innovation, and no reason to suppose that anyone would ever benefit from it. For example, if a man qualifies,

but does not add his name to the lists of members of his profession and never tells anyone about his qualification, he is unlikely to get any clients. The same is true for the inventor. Even if Emerson's extraordinary theory about "building a better mousetrap" had been true at all, it presupposed that the mousetrap innovator had used some method of communication to make the world aware that they should make a beaten path to "his house in the heart of the woods".

Incidentally Emerson also said the same about writing a better book, and in this case there are good historical examples to contradict his theory. Arthur Koestler in *Act of Creation* recalled a striking one. He described the delay in accepting Copernicus's theory that the earth circled round the sun; "Copernicus's book *On the Revolution of the Heavenly Spheres* had been published in the year of his death, 1543, that is 50 years before Kepler first heard of him, and during that half century it had attracted very little attention. One of the reasons was its supreme unreadability, which made it an all-time worst seller; its first edition of 1000 copies was never sold out. Kepler was the first Continental astronomer to embrace the Copernican theory. His *Mysterium Cosmographicum*, published in 1597 (54 years after Copernicus's death) started the great controversy—Galileo entered the scene 15 years later." The theory of a sun-centred universe had been ignored largely because it had not been publicized; only later did it run into difficulties with the Church.

Secondly, there are the ordinary non-commercial sources of scientific information. These include publications in the journals, references in textbooks (for which it is assumed the contents are themselves derived from non-commercial sources), and reports of scientific meetings and discussions. Of course, these are invaluable and indispensable. But there is the difficulty that the commercial or other interests of apparently "independent" journals may not always be declared. Contributors may have strong biases either for or against particular products or services, and in some of the lesser journals it is possible for favourable editorial comment to be "bought" in much the same way as advertising space. The essence of the impartiality of the more reputable journals usually depends on the fact that they are paid for by the reader. The more independent they are, and the less advertising they carry, the higher is the price that the reader must pay. Over the years, experience has shown that news of inventions does not spread very fast if one relies entirely on sources of this sort, where the consumer has to take the initiative in buying the information.

This leads on to the alternative, that a third party, often the State, should pay for such publications and meetings and make them available free of charge to those interested. In the field of medicine this actually happens in Britain and in some other countries, where doctors are supplied at the taxpayer's expense with publications such as *Prescribers Journal.*

Such publications are valuable, but there are two arguments against depending too heavily on them as the main source of information about innovations. Inevitably these arguments involve the fundamental conflict between free choice as opposed to central planning or direction. One argument against a State system of providing information depends on the belief that it is better to allow the commercial innovator and producer to spend what he believes to be the right amount of his own money on telling people about his innovations and products, instead of preventing or discouraging him from doing so. This argument is strengthened by the fact that the latter involves spending the taxpayer's money to disseminate the information. This is still essentially true even in the cases with which we are particularly concerned in these lectures; i.e. those where, in a sense, the taxpayer—as the customer—"pays for" the manufacturer's marketing costs. This point should become clearer in the discussion on the commercial considerations underlying the decisions on the amount to be spent on marketing.

The other—much more important—argument is that a system of State-sponsored information must depend on central judgements about what information is to be disseminated. However eminent the experts involved in preparing this information, it is argued by those who believe in a more liberal system that the experts must sometimes make mistakes. One central error can be much more disastrous than the occasional individual errors of judgement which may occur under a system in which individual innovators each have the freedom to disseminate competing information about their own products.

In addition, there is the danger that if conventional marketing expenditures are restricted, innovators will develop other ways of "supplementing" or even "using" the official or "independent" sources of information. An enthusiastic discoverer, anxious for his new product to gain full recognition, may indulge in extensive lobbying of the experts. He may also stimulate the least desirable types of "product public relations". These suggestions do not imply unscrupulousness on the part of the inventor, but an understandable anxiety that an excessively bureaucratic system may not do justice to his discovery.

It must, of course, be acknowledged that the alternatives of "commercial" sources of information on new products and "impartial" sources are not mutually exclusive. In practice, advertising, impartial journals and directories, and information provided by the State are often all available, as they are about new medicines for doctors in Britain. The issue may not be whether one source of information should be replaced by another, but how the balance should be struck between them.

Thirdly, there are the strictly non-promotional statements of availability which come in the hinterland between unsponsored publicity (of the type

discussed so far) and normal commercial advertising. These are the brass plates on the door, paid entries in appropriate directories, and the type of restricted newspaper announcement which are permitted in some professions, such as pharmacy. Along the same lines, some producers choose to confine themselves to a straightforward list of their products in their advertising. Such manufacturers certainly cannot be accused of unjustified claims, but I sometimes wonder whether they would not be wise to show a little more enthusiasm for their wares. In any case, such announcements and advertising leave the client or customer to get in touch with one or more of the people offering the goods or services they require. The consumer may often not be very systematic in collecting adequate data on the relative qualities of the services or goods offered. Studies into the ways people in Britain actually choose their doctor have indicated the consequent limitations of this method. I am not necessarily advocating that members of the professions should be allowed to advertise; but on the other hand, it is probably wrong to assume that restricting suppliers' publicity to simple statements of availability would make it easier for the consumer to make the best choice. Fortunately, the question is largely academic in the case of scientific discoveries, because the statement of the innovation must itself constitute what the advertising men call a "unique sales proposition". There is also, of course, a different situation when professional men rather than the general public are concerned. Doctors, for example, can certainly be expected to make better use of a medical index of products than the public would make of a medical directory in choosing their doctor.

Fourthly, and as an adjunct to both commercial and non-commercial sources of information, there is the unsolicited dissemination of information by word of mouth. In this I am not including the personal salesmanship by the innovator or his staff, which is part of the normal marketing machinery. And, in parentheses, it should be remembered that this is so even in our hypothetical case of the innovator who personally tells his mouse-infested friends about his better mousetrap. He is "selling" it to them; there is a risk we may forget this in our advanced industrial society, where we generally separate the functions of innovation, production and marketing so that they are carried out by different people.

In the present context, "word of mouth" refers only to secondary discussions, in which someone who has been impressed by a particular innovation tells his colleagues about it. Very often the original source of information may have been the manufacturer's advertising. When such discussions between colleagues are on a formal basis, at a scientific congress, for example, they come under the heading of the non-commercial sources of information already discussed. However, when the discussion takes place, for example, over an informal cup of coffee, it justifies a separate heading, if only because such emphasis is put on the value of this source

of information compared with that issued directly by the manufacturer. In theory, this value rests on the fact that the information has—as it were—been through an "independent" filter. It is no longer the special pleading of the innovator and manufacturer. It is the independent assessment of a supposedly unbiased observer. In practice, of course, the extent of the value of a colleague's opinion depends on his judgement and objectivity in describing his experience with the innovation. It also depends on the extent of his experience, and his familiarity with the literature. However, even if a scientist has had quite extensive experience with the product, and has studied the literature on the subject in detail, he may still suffer from preferences and prejudices, and where many factors are involved the experts' judgements will not always agree. This explains why, in practice, "discussions with colleagues" result in a more or less random dissemination of information, covering a wide spectrum of opinions about the relative values of all the available new products. The filtering out of the special pleading by an impartial scientist does not necessarily lead to any special form of ultimate truth. It leads to a range of varied, and often strongly held, opinions about the relative advantages of different products. This is not surprising, because, in the treatment of patients, for example, the choice between different medicines must depend on multi-factorial assessments, based, *inter alia*, on effectiveness, relative safety, convenience, reliability, range of activity and cost. There can generally be no one "best buy". There is, of course, an important place for specialist opinions, but it is wrong to believe that advice from colleagues is necessarily always better than one's own independent judgement, reached on the basis of competing commercial claims from different manufacturers.

In fact, the supposed advantages of all the more or less non-commercial sources of information depend on this principle of eliminating the element of special pleading which is necessarily present in the advertising of an individual manufacturer. Each innovator states the advantages of his own discovery, and none can be expected to present a balanced review of the comparative advantages of them all. It is up to the consumer to make the choice, and, as I have already argued, I believe that any trained professional man or scientist should be well able to do this in his own field. To the extent that he is aware of his own limitations in this connection, he will consult the available independent sources of information; but it is an insult, for example, to practising doctors to suggest that they should not be exposed to rival claims for different medicines on the grounds that they are unable to reach a sound decision on the right ones to prescribe for their patients.

There must, however, be a sharp line drawn between special pleading on the one hand and misleading and unjustified claims on the other. Frankly, if a company has a world-wide business worth many millions of

pounds—and this is increasingly the pattern in the science-based industries —it seems unlikely that companies are going to jeopardize their business reputations by intentionally propagating misleading or unjustified claims for their new products. In the medical field, accusations of "misleading" advertising may often have resulted from genuine differences in medical opinion. A particular consultant—or professor—may strongly disagree with his colleagues' opinions, and will criticize a company's advertisement which is based on those opinions.

Certainly, at no time in the history of medicine or science have commercial concerns had a monopoly of misguided beliefs about their products. As a personal example, I was sent to a private school which was selected by my parents on health grounds, because of its proximity to the sea, and because it was owned by an exceedingly eminent medical man. Wisely, the physician left the day-to-day running of the school in the hands of the headmaster—except in one respect. Morning and evening each of the pupils was inflicted with a simple saline gargle and an oily nasal spray. Presumably these were intended as a prophylactic procedure against upper respiratory infections and it was probably generally accepted as a sound medical procedure at the time. The saline gargle was, in fact, probably innocuous enough, but I suspect that evaluation of the effectiveness of the oily spray in the light of subsequent knowledge might have shown that it did more harm than good. Any manufacturer who had marketed this physician's formula in all good faith would eventually have found it very difficult to justify the claim based on his sincere and authoritative belief that the treatment would prevent coughs and colds. Indeed, many preparations formerly given the official "seal of approval" by inclusion in the early pharmacopoeias have now been rejected as therapeutically inactive or unsafe.

In fact, a company jealous of its reputation has a much stronger motive than an individual to ensure that the performance of its products justifies the claims made for them. Companies are wrong to base claims for their products on the favourable reports of an isolated specialist, if the vast weight of the other evidence contradicts his opinion. However, where medical opinion is evenly divided, companies would not necessarily be acting in the best interests of anyone if they were to base their advertising claims only on the less favourable reports on their products.

This is undoubtedly an area where very real difficulties arise. In the past, companies here have sometimes erred in accepting minority advice too eagerly; but on the other hand the "establishment view" is not always right, and on other occasions when companies have fought against it they have done great service to the community. Genuinely unjustified claims which have appeared seem likely to have resulted from an error of judgement by the professional or scientific advisers to the manufacturers,

rather than from a belief that the consumer could be hoodwinked. Such errors could not necessarily be eliminated under other systems of disseminating new product information. There is, however, a strong case for independent arbitration in situations where it is particularly difficult and particularly important to evaluate possibly conflicting scientific data. One example is the Dunlop Committee on the Safety of Drugs. Such outside bodies not only help the majority of companies who sincerely want to reach the best decisions, they also prevent the few who might otherwise act irresponsibly.

Another argument put forward against allowing companies to conduct unrestricted advertising is that it prevents small organizations from getting an adequate share of the publicity for their discoveries. This is certainly a valid argument with some types of products, which depend heavily on marketing, and for which research is not a major item, such as pre-packed foods and cosmetics. However, in the research-based industries, if drowning the voice of the "small man" were to have a significant effect on the rate of progress, a considerable proportion of discoveries would have to be made in small organizations. In fact, with industries such as aircraft, pharmaceuticals and electronics this is not generally the case. The cost of fundamental or even development research is such that only very large companies or groups of companies can engage in it. The much-publicized development costs for the TSR 2 have been estimated at £750 million. Rolls-Royce have recently allocated £15 million for the research and development to produce a new jet engine over the next four years. The minimum annual pharmaceutical research budget likely to yield useful results has been put at about £200,000. In general, the equipment needed for research is becoming increasingly costly. For the price of a single nuclear magnetic resonance spectrometer a pharmaceutical company could send at least 20 mailings to all general practitioners.

Although there are always exceptions to every rule, it is much more likely that major advances will come from organizations with multi-million-pound research budgets than from the companies spending a few thousand pounds on a hunch. The smaller companies, who are unable to afford large marketing or research budgets, are much more likely to depend on minor developments or—if patents are not effective—on straight copies of the discoveries coming from the larger organizations. It would, however, be a useful confirmation of this hypothesis to know that it was in fact the science-based companies with large Research and Development budgets which also spend heavily in the marketing field, and that it was the formulators and copyists who tend to be kept out of the market by the high costs of marketing.

There may, of course, be some element of "chicken and egg" in this reasoning. The limited contribution to progress by small companies might

be due to their lack of funds for advertising, rather than to their lack of funds for research. In the economy as it is at present organized, growth without advertising is difficult to achieve. It would need a fundamental change in the whole economic structure of the nation to devise a system whereby companies could grow through research alone, unaccompanied by advertising. However, any such attempted revision would run contrary to the belief that it is fundamentally necessary to *sell* innovations, rather than merely to make them available.

Having discussed some of the arguments against advertising, and some of the alternative ways in which inventions can be publicized, I would now like to look at the role of marketing in a more positive light. First, I would like to discuss why I believe it plays a vital part in scientific progress, and then discuss some questions relating to the amount and type of advertising which is desirable.

There are two fundamental reasons why it is necessary to sell the results of research and innovation, and to create a demand for new products. The first is because the rate of academic and scientific progress depends on the speed and effectiveness of the publication of new data, and on the extent of the experience gained with the new products. The second is the commercial consideration that in a manufacturing industry the cost of innovation must generally be financed from sales revenue.

Under the first heading—relating to the encouragement and acceleration of scientific progress—I would like to distinguish three stages: publishing the results; publicizing the products; and gaining acceptance for them. It is the last two which make up the process of "selling" the discovery. It has been argued in relation to patents that delays in publication slow down progress. One research worker's published work may be the basis for further discoveries by another scientist. Delays in publication also increase the waste of scientific effort, because other researchers may be striving towards discoveries which have already been made elsewhere but which have not yet been published. However, to prevent waste and delay, publication must generally come—in the form of patent applications —some time before the product—or idea—is ready to "sell". Thus the marketing processes do not normally affect the earliness or completeness of the publication of new discoveries. They are concerned with the extent of experience gained with the new discovery. This experience is needed if further progress is to be soundly based.

The key to the importance of marketing in scientific progress lies in the fact that proven advances are often not adopted in practice unless they are "sold". Diphtheria immunization is one of the classic examples. Throughout the 1930's about 30,000 children died from diphtheria in Britain, because the diphtheria vaccine which was available was not being used; during most of that decade diphtheria in Canada had been virtually

eliminated by immunization. The demand for polio vaccination was also sluggish in Britain until the publicity surrounding the death of a famous footballer focused attention on the dangers of the disease. Computers for government and industry are another example of a scientific innovation which has proved hard to sell, despite the sales pressure by the electronics industry. Slightly outside the scientific field, there is domestic central heating, and air conditioning, which are still the exception rather than the rule in this country. These delays imply an apathy not only amongst the general public but also in the professions. Doctors largely ignored the vaccines; accountants and economists ignored the computers; and architects ignored central heating. They were not sufficiently "sold" on the innovations to overcome the objections to their introduction.

The significance of these delays is two-fold. First, the immediate benefits are postponed. Second, the opportunity to improve on the original advance is curtailed, not only commercially, but also because experience with the first innovation is too limited. It is therefore important to analyse the reasons for the delay.

First, there is suspicion and scepticism. This "fear of anything new" may be justified in some specific cases. The early Zeppelins, and later the Comets, proved that innovation in air travel was not without risks. Thalidomide was a tragic example amongst medicines. Early synthetic fibres were not invariably as satisfactory as the natural materials they replaced. Some agricultural chemicals have turned out to be more toxic than was anticipated. The carcinogenic properties of X-rays were recognized only after they had done much damage. In all these cases, people who held back and only adopted the innovation after others had acted as the "guinea-pigs" have been able to justify their action with hindsight.

But without risks, progress is impossible; and if early developments were not sold and used, further improvements would often be impossible. This is one reason why the benefits of new inventions must be publicized and why active persuasion is necessary to overcome the reluctance to "try something new". Generally the fears which have to be overcome have proved unjustified—as they did in the case of the strong initial antagonism to the use of antibiotics prophylactically in chronic bronchitis. Sometimes suspicion of innovation is frankly illogical as it was in the case of the ball-point pen. Examination candidates were advised not to use them, and it was thought dangerous to sign cheques with a Biro when they were first introduced. The fact is that the vast majority of people who are persuaded to try something new will benefit: but in the exceptional case something goes wrong—and when it does it may be serious. When dangers are *suspected*, the rational approach is not to prevent the new product from being advertised, but to introduce effective surveillance to make the maximum use of the experience gained, and to detect the dangers as early as possible,

should they prove real. The Dunlop Committee on the Safety of Drugs and the measures taken by the Air Registration Board in connection with new aircraft are good examples of intelligent safeguards to minimize risks.

Second, many people dismiss innovations as trivial or irrelevant. Their attitude is typified by the people who say with such conviction "—and anyway, who *wants* to be able to fly to New York in 3½ hours?" Central heating and air conditioning are classic examples when the spartan Britons have for years been denying that they wanted or could afford warm houses —and have even tried to justify their attitude by criticizing the complexions of American youth. It is only now being recognized that hypothermia due to the inadequate heating of our homes in Britain is an important cause of death amongst the elderly each winter. There was similar resistance to the introduction of car heaters, an "unnecessary expense", and "liable to send you to sleep at the wheel". It is only since the benefits of these "advances" have been forcibly sold that they have come to be accepted. In this sense, selling is the lubricant of change.

Street lighting, tape recorders, electric razors, electric toothbrushes, and anaesthesia for obstetrics are all innovations which have been dismissed as gimmicks, with the characteristic question "Whatever will they think of next?" A classic contemporary case is the Polaroid Land camera. Much of their advertising is now directed towards overcoming the idea that a camera producing an "instant photograph" is a rich man's toy with no practical applications. Historically I suspect that when roll-films replaced photographic plates they may have faced much the same conservatism.

This reaction to supposedly trivial advances becomes especially significant in view of the nature of innovation. Most of the examples quoted above are major innovations compared with those most often occurring in scientific progress, which usually depends on small steps forward. The majority of scientific and technical advances are not very important on their own, but collectively they add up to very substantial progress. The motor car is a much-quoted case. Present-day cars bear practically no resemblance to those of the 1900's; but there have been very few single steps in the process of innovation—such as the introduction of pneumatic tyres, disc brakes and the "synchromesh" gear box—which by themselves represented major advances. There is comparatively little improvement technically when one changes one's car for a new one developed two or three years later; but unless people are persuaded to buy each year's marginally improved model—and usually to pay a higher price for the small improvements—progress could be seriously delayed.

The question of price is the third obstacle to progress. New inventions are almost invariably more expensive than their predecessors. There will always be other competing demands for the extra expenditure involved in

buying the new product. Many of these competing demands will represent heavily advertised products or services, or else they may be supported by powerful pressure groups. If, by contrast, the fruits of scientific progress are not advertised or advocated, they will be at a substantial disadvantage when collective or individual purchasing decisions are made. Once again, it is possible to advocate central planning in place of the free market to overcome this problem. In practice, one falls back on the difficulty of who, in the event, would decide whether to spend available resources, for example, on computers instead of new factory space, or on new antibiotics instead of redecorating the hospital wards—always bearing in mind that neither the antibiotics nor the computers would have been advertised.

In summary, therefore, powerful publicity and persuasion almost invariably seems to be necessary to get new scientific ideas adopted. People who automatically adopt anything new as soon as it becomes available are very much the exception rather than the rule, and they become rarer in each generation as it gets older. But even for the younger age groups, a good deal of persuasion is needed to overcome their suspicion of novelties, innate resistance to change, and the "price barrier" which acts against newly introduced products. It is this persuasion which can be provided by the marketing men as well as by enthusiastic, independent reports on innovations.

Naturally, marketing techniques should only be used to stimulate the *appropriate* use of innovations, and this will very often involve discouraging the use of an older, and now *inappropriate*, product or technique. It is wrong to encourage the indiscriminate use of new inventions. This is bad marketing practice anyway, because a limited and specific claim for a new product is more effective than a broad omnibus claim. With medicines, there can be no excuse for advocating the unjustifiably widespread use of a new product, and in Britain, if any company did so they would be infringing the pharmaceutical industry's code of marketing practice.

Against this background, the second role of advertising in scientific progress falls into perspective. Not only can advertising directly accelerate scientific advance, it also plays a vital part from the commercial point of view, and indirectly makes possible further progress. The innovator must pay for the cost of his research, and this is a continuing and often very heavy prior charge on his earnings. He cannot recruit or discharge his research team at short notice, and he cannot expect a frequent and regular stream of new products from them. To the extent that he can sell the results of past inventions at a premium price, he is able to finance continuing research. The economic questions arising from this relationship between advertising, sales, prices, finance and research are outside the scope of this paper; but without the sales resulting from advertising it would clearly be necessary to raise the finance for research in other ways.

Returning to the mainstream argument of the need to sell inventions, two questions arise. First, to what extent does the community, individually or collectively, pay for the advertising? Second, how much should be spent on it?

The simple answer to the first question must be "they pay for all of it". It is cheaper for the individual or the community to buy an established product, which has borne no cost of innovation, and which has also probably borne little advertising costs, than it is to buy a new product. However, there is no easy way of separating out the various elements making up the higher price in the newer product. It bears the cost of research and development; it must often contribute to the higher capital cost of the new plant needed for its manufacture, which will have replaced older, fully depreciated plant; it bears the cost of training production workers to adopt new manufacturing methods; it bears heavy costs in connection with new product consumer trials; it may bear higher costs because it is an inherently more complex product; it must contribute to the higher profit expected because of the commercial risks inevitably associated with innovation; finally the product bears the cost of providing information on it, and the cost of persuading people to use it. If any one element is extracted from this structure, the new economic situation created will affect each of the other elements.

The community therefore pays for advertising of scientific inventions in the sense that it buys a more costly research-based product as a result of the advertising. If there were no advertising, one would not simply save the cost of the advertisements; to a great extent one would save *all* the higher costs associated with the use of new products—and of course, as a corollary, the community would no longer enjoy their benefits. When there was no advertising for central heating, for example, the effect was not to make central heating installations cheaper. For the vast majority of households it meant that their central heating installation cost them nothing at all, because they never had one. In the same way diphtheria immunization cost the community very little in the 1930's because children were not immunized. Once again, the effects of advertising and more widespread use on the unit price of central heating installations or of the diphtheria vaccine is a subject outside the scope of this paper.

The second question was "how much should be spent advertising innovations?" Provided advertising does not result in the inappropriate use of new products, the answer must be "as much as is commercially justified". Other things being equal, if an extra pound spent on advertising brings in an extra 21*s.* of net revenue, the advertising budget should be increased. It means there is sufficient demand for the new product, once people hear about it, to justify more extensive publicity for it. This principle applies not only to a single product, but is also true for the total advertising

expenditure on any group of products, such as the antibiotics, or television sets. However, having stated the principle, a problem still arises because it is never possible in practice to establish whether an extra pound spent on advertising will bring in at least an extra pound of marginal return. Even in assessing the results achieved with past advertising expenditures, one is dependent on assumptions as to what would have happened without any marketing activities at all. This is easy in the case of a new product—nothing—but once a product has been on the market for a year or two it becomes more difficult. Nevertheless, despite the assumptions involved, if past advertising expenditures are reviewed against this criterion, it provides a valuable guide as to whether they were too high or too low.

It is worth emphasizing here that there are special considerations in the case of some scientific innovations, and in particular of new medicines. The harm which can arise from their misuse is of a different order from that involved in many other scientific products. Therefore, although it is especially important that new medicines should be used as early as possible in appropriate cases, it is also especially important that advertising directed towards this end should not result—either deliberately or unintentionally—in their being used inappropriately. It is for this reason that increasing prominence is given to the contra-indications and the limitations of new medicines. The A.B.P.I. code of marketing practice requires "side effects and contra-indications to be clearly stated". It is only by vigorously enforcing this code that the industry can expect to avoid official control on the claims which they make in their advertising—such as that imposed by the F.D.A. in America.

In addition to this, of course, advertising and marketing must be as effective as possible per pound spent. Once again, this principle is easier to expound than to follow; but it is worth mentioning that innovations in marketing methods are just as necessary as innovation in other fields. The old-established advertising media are not necessarily the best methods of communication and certainly in the past much scientific advertising has been unsuccessful. There is plenty of scope for much more research into why people who could benefit from using new science-based products have not yet been persuaded to do so. This type of motivation research is accepted in the consumer field; there is no reason why it should not prove to be just as valuable in the scientific field. Why are computers still so little used? Why are only 10 per cent of domiciliary forceps deliveries carried out under local anaesthesia, when the proportion is four times as high in hospital? Why are four-fifths of the households in Britain still without a telephone? Why have contractors been so reluctant to introduce industrial building techniques? I suspect one answer is that scientific marketing should contain a very much higher element of instruction than it usually does. If you teach people how to do something new, they are more likely to be

persuaded to do it, provided they are reminded about its advantages a few times. If they do not understand how to apply a new scientific product, they are unlikely to use it however much they have been convinced of its advantages.

In the context of the relationship between science-based industry and the State, these principles have a particular significance to which I referred earlier. Even if no cost is involved for the "purchaser", the demand for a new product does not arise spontaneously. Therefore, in fixing the level of marketing expenditure, one affects primarily and directly the extent of the demand for the product. The amount spent on marketing is comparatively irrelevant in its much more complex effect on the unit price. Whatever impact marketing expenditure does have on individual prices will be small compared with the effect it has on stimulating demand for higher-priced innovations. Any external restraint on advertising—for example on pharmaceutical products—would therefore have a quite different effect from the one often discussed. It would probably be very successful in reducing the Government's pharmaceutical expenditure because fewer new products would be prescribed. Such reduction in spending could be expected to far outweigh the actual reduction in advertising costs. This effect would therefore also exceed any possible reduction in the unit prices of individual products, which might even rise as demand and production fell. Such restraint is therefore only justified if individual companies are not applying a critical appraisal to their own level of expenditure along the lines described; or if some outside agency was able to make the present pharmaceutical marketing budgets more effective in "buying" more new sales for the same expenditure; or if doctors are incapable of deciding what are and what are not appropriate medicines to prescribe for their patients. There may indeed be room for improvement along these lines, but the right question to ask seems to be whether pharmaceutical advertising is sufficiently effective, rather than whether there is too much of it. Restraint on *efficient* advertising, in the sense in which I have defined it, can only delay medical progress.

At the risk of oversimplifying what is necessarily a complex issue, I would like to quote one example of the alternative pattern of progress which can occur in the absence of a free market and normal marketing activities. This concerns the Medresco hearing aids which were developed for use under the National Health Service. The original valve model was designed by the Electro–Acoustics Committee of the Medical Research Council to be satisfactory for the majority of the deaf. When first introduced it was technically more efficient than many models then on the market, and was adequate in design. The production of this standard model made it possible to supply the initial Health Service requirements for hearing aids relatively quickly and cheaply.

In the subsequent years, transistors became available, and the manufacturers of commercial hearing aids, which cannot be supplied on the Health Service, took advantage of these transistors to reduce the size and weight of their aids. Even if the transistor models were no more effective, they were incomparably more convenient and more elegant. This may be important because deafness is an emotionally charged disability, and many people who need a hearing aid may be reluctant to wear a conspicuous model. However, it was some 10 years after the first commercial transistor models were in production that the Health Service made available a standard transistor model to replace the obsolete standard valve models. It was a further three years before the valve sets had been generally replaced by the transistor models. In the meantime the more elegant "ear-worn" aids have been developed commercially, and it is becoming increasingly apparent that some of the small minority of deaf people who get no benefit from a Medresco aid could benefit from other models available outside the Health Service.

The results of this situation are two-fold. Some people who are entitled to hearing aids on the National Health Service choose to buy more modern designs privately and this has been reported to lead to abuses. Others who need aids cannot afford to purchase a more elegant or, for them, more effective model outside the Health Service; as a result they may go without. The present policy of supplying only the Medresco hearing aids under the National Health Service means there is little point in advertising more advanced designs to Health Service personnel. Although this example is not primarily concerned with the role of advertising, it does illustrate the dangers which may be involved when private innovators are not free to sell their products to public servants who should appropriately be ordering them. It undoubtedly results in economies for the Health Service; but it can be argued that this pattern of progress—demanding great leaps from one standard design to the next—may inhibit scientific advance which more often comes in the form of small steps, each constituting only a minor improvement. It certainly tends to ignore the fact that patients are not "standard", and that they may be best catered for by a range of different aids, none necessarily superior or inferior to the other, but each with characteristics appropriate to a particular group of deaf patients.

Since innovations are only very slowly accepted, advertising for established products may also stimulate progress, rather than hinder it. Advertisements for "discoveries" of 20 years ago may still be attracting new users, or encouraging those who have only tried the product on a limited scale to extend their use of it. At the same time other established users are being weaned off to newer discoveries, so that the net effect of the marketing activities may be to keep the level of sales for these older products more or less static. Certainly in the scientific field advertising for older

products should never be aimed to delay progress on to proven advances, and there is certainly no excuse for endlessly repeating outdated claims for outdated products. In many cases, however, it is possible to appeal to conservative consumers who are still several steps behind. Such people may be persuaded to change to a newer product which, although not the latest and best, is at least an improvement on what they have previously been using. On this basis, advertising for establishing products can also contribute to progress, and the proper level of expenditure on it can be established empirically on the same basis as that for new products. It is possible to judge the effectiveness of the advertising by seeing how sales react as the advertising budget is gradually increased or decreased over the years, bearing in mind the expected effect of other external factors. This may not give a very precise answer, but anyone who does not attempt such an analysis may be allocating their advertising expenditures very unwisely indeed.

Finally, it is worth pointing out that the pharmaceutical industry's advertising to National Health Service doctors is by no means the only example in which science-based manufacturers direct their advertising to a group of people who will influence the purchasing decisions, but not pay the bill. Architects concerned with local authority housing are told about innovations by all manner of suppliers. Schoolmasters are told about modern textbooks, teaching machines, and other electronic paraphernalia. Colour television manufacturers have been advertising to the public to educate public opinion, presumably so that it will influence the Government in favour of their system. The synthetic fibre manufacturers advertise direct to the public to support those who make clothes or furniture out of their materials; so do aircraft manufacturers, to support the airlines who buy their latest aircraft. All of these types of indirect advertising help to encourage scientific progress.

However, it is worth noting that advertising must often be aimed at many different targets if it is to succeed where it can do most good. Returning to my example of domestic central heating, the public, the architects and the local authorities all had to be convinced. The general public have now come to accept the advantages of warm housing, as a result of the massive combined advertising efforts of the oil, coal, gas and electricity industries, along with publicity from the actual manufacturers of heating equipment. Architects have probably recognized the benefits of central heating for many years, although they face client resistance to the higher costs involved. It is ironic that it is the local authorities, who are often responsible for housing the elderly, who have proved most difficult to convince about the need for adequate heating. Whilst they continue to resist the onslaught of the heating ad-men, the aged in their care will continue to be at risk from hypothermia each winter.

None of this, of course, answers perhaps the most fundamental question of all in relation to scientific progress. How much do we really benefit from the advances? To what extent do the dangers associated, for example, with nuclear weapons offset benefits in other directions? If marketing methods create demands for new scientific discoveries, are they always the most important discoveries? Would we, for example, have been better off without television, and will we be worse off when people are encouraged to spend their money on colour television? These questions involve value judgements, and for many of them different individuals will reach different answers.

However, in these lectures, we are looking at science-based industry mainly through experience with pharmaceutical innovation. This is one field where the overwhelming consensus of opinion must be that the benefits of progress have more than compensated for the costs involved, and for the setbacks suffered. In so far as marketing has created an awareness of, and a demand for, new and valuable medicines it has contributed to this overall progress. Although postgraduate education, and the non-commercial sources of information have played an important part, it is difficult to see how such rapid advances could have been achieved without advertising and salesmanship. The cost of the marketing processes, like all the other costs inherent in innovation and progress, must be set against the human and economic benefits which have been gained.

Where waste has occurred—as it undoubtedly has—it has generally indicated the need for both commercial and non-commercial channels of communication to be made more effective. It is simple to reduce the expenditure on innovations by delaying progress. It is incomparably harder to do so by increasing efficiency, whilst maintaining the rate of progress. But it is this latter objective towards which science-based industry and the State should be striving; and this applies not only to production and research, but just as importantly in the field of marketing. When the Government is paying the bill, it should not ask whether advertising is necessary. Instead it should ask whether it is effective.

Research and Safety in the Development of Medicines

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THE ethical side of the pharmaceutical industry, a high-risk and competitive industry, is more dependent than any other on successful research and new product development. Its very existence is contingent upon an adequate research effort; yet, oddly enough, it is this effort which brings about the risk—not only because of possible failure, but because success can create technical obsolescence either as a result of continued research in the inventing firm or in that of its competitors.

Three years ago, in a talk before the Pharmaceutical Society of Great Britain (1962), I said, "It frequently happens that a drug which is considered at one time to be a notable therapeutic advance and the most effective for a given purpose is unexpectedly eclipsed by a superior drug produced by a competitor. The publication of a patent for a new drug brings down the whole weight of world research on the product; it may then be superseded. This eclipse may wipe out three to five years or more of heavy investment in research and development, and even in expensive plant to manufacture the drug before the firm has had adequate opportunity of recouping its outlay. What was an asset is now converted into a liability." In spite of this, research and development expenditure in the pharmaceutical industry is unlikely ever to decrease. Although the levels may fluctuate from time to time, due to a variety of factors both political and economic, the general trend will always be upwards, provided there is government action to reverse the current erosion of patent rights. But the upward trend should not be taken to mean that the number of effective new drugs will also increase in proportion. Since future drugs will be more complex and sophisticated, there will be fewer new compounds per year; and the research overhead is bound to be higher.

It has been estimated that the annual research and development expenditure by the industry in the next decade will be of the order of £300 million on a world-wide basis; 60 to 65 per cent of this will be accounted for by the Americans. The present ratio of research expenditure between the U.S.A. and the U.K. is about 10:1, and if present trends continue it will be of the order of 15:1, or greater, within this decade. Due to the political environment

here, as exemplified by the Government's use of the outdated Section 41 of the Patents Act, research expenditure has levelled off at just over £8 million. The story from overseas is quite different.

In the recent Pharmaceutical Manufacturers Association (U.S.A.) report on Research and Development Activity during 1963–4, fifty-five member companies returned a company-financed research and development budget of £112 million for 1964 which is an increase of 11 per cent above the actual expenditures for 1963. About 5 per cent of this figure is budgeted for veterinary pharmaceutical research. That it should cost more to carry out the same tasks does not account for all the extra money. There was a 3·5 per cent rise in the strength of the scientific personnel in 1963 compared with 1962, and an estimated 7·6 per cent increase for 1964.

A similar rate of development is evident for the overseas research activities of U.S. company-financed prescription drug research. It rose from £4·6 million in 1962 to £6·77 million in 1963, and to a budgeted £8·32 million for 1964. The U.K.-based firms do not show a similar pattern, for there is, in fact, only a relatively small research investment in the Commonwealth and other countries abroad. I know of only one U.K. firm with a wholly-owned research facility in the States. British firms are dependent, therefore, upon their home-based research, particularly for human-end use, both for their home and overseas business. On the other hand, the leading Swiss firms, due to conditions peculiar to Switzerland, have large and well-staffed research facilities combined with manufacturing complexes in the U.S.A.

Research into ethical prescription drugs is almost entirely financed by the pharmaceutical industry; government grants or contracts account for only a small portion. In the last twenty years, 90 per cent of the new basic drugs have come from industrial laboratories, 9 per cent from universities and other academic institutions, and 1 per cent from government research establishments. While these figures are factual, they are not a measure of the relative significance of the contributions to our understanding, prevention or control of the disease process. The academic and industrial laboratories are interdependent in their efforts to discover truly worthwhile and more effective new drugs. The industry could not have made contributions of such magnitude had it not been for the truly remarkable advances in fundamental knowledge of living processes that have come from the university laboratories. Both groups are equally important and there is little to choose in the quality of the research staffs. While the facilities in many industrial laboratories may surpass those of the university, it is the environment together with the intellectual qualities of the research workers that determines success in either case. That this is recognized by both groups is demonstrated increasingly by the closeness of the collaboration apparent today.

Consultants drawn from the very top ranks of the academic world are a

potent force in improving relations and understanding between universities and industry. The research staff look forward to their visits and welcome the opportunity to demonstrate and discuss their findings with these experienced and erudite minds. The visiting is not a one-way traffic, however, for the consultants are often visited on their home ground to discuss particular problems which may arise between visits, or to display some aspects of research policy.

Many consultants operate on a world-wide basis, visiting pharmaceutical firms abroad as well as at home. They have, of course, made contacts all over the world, and often introduce industrial scientists to work currently in progress before it has been published. Considering the long delay in publication, this knowledge can accelerate progress in research by avoiding unnecessary work or altering the course of the investigations. Incidentally, if the research side of the industry is as bad as its detractors claim, would it really be able to attract these first class men of such high standing?

The exchange of ideas is also fostered to a greater extent than previously by frequent visits to each others' laboratories, by industrial scientists serving on committees and editorial boards of scientific societies, and contributing to them by reading communications and publishing in the scientific journals. Another important factor leading to better understanding is the secondment of research workers from industry to university laboratories and other research institutes at home and abroad. This usually occurs where the particular academic department is pre-eminent in a field cognate with the industrial laboratory's interest. The subject may be fairly broad, e.g. the metabolism of drugs; or it may be narrow, e.g. some particular field of chemistry or the study of a disease. In either case, the resultant knowledge is made available to the whole world, sponsors and competitors alike. Chain (1963) pleads for much more support by both government and industry for research projects not favoured by fashion and of no apparent practical use, particularly in the biological field. He continues, "It is frequently quite difficult to raise funds for this kind of investigation—and this applies not only to Europe, but also to the United States—and yet nearly all the great advances in drug research have their origin in observations of biological phenomena." In supporting this, I would suggest, however, that financial aid given to academic departments for this type of work should be under conditions similar to those pertaining to the funding of the Medical Research Council in this country. Once the M.R.C. has obtained a grant it can, within very broad limits, spend it as it deems fit in the light of its own scientific assessment. These general grants in aid by industry are separate, of course, from those more directly related to the industry's project research. Academic and other research institutions abroad are also the recipients of industrial support which is, in addition to financial or technical aid, given in relation to clinical trials.

The international nature of medical and pharmaceutical research means that new drugs are likely to come from any of the countries in which this research is done. Generally speaking, the likelihood of any particular country making new drug discoveries will be related to the intensity and quality of its research effort. Gordon Fryers, in the first lecture of this series, stated that the pharmaceutical industry in Britain had produced a share of the world-wide total of new medicines roughly proportional to its share of the total expenditure on research. Scientific achievement cannot really be measured in terms of the money spent on research; the money spent only gives some indication of the magnitude of the effort. However, I think most will agree that the U.K. record, industrial and academic, is somewhat better than the relative expenditure would indicate.

That the industry as a whole must gamble on research is accepted, but the significance of the stake is very great when we get down to individual companies. No company has resources vast enough to cover every possible field. Choices have to be made, and the judgement required for making them is based on an assessment of present knowledge combined with an insight into the significance of new knowledge. The choice will be conditioned, therefore, by technical feasibility and commercial potential; the latter could also be expressed as medical need. The recognition and satisfaction of this need is a primary factor in ensuring success.

The greater proportion of new drugs should come from the U.S.A. As already stated, their expenditure is greater, and there are more firms in the business. In spite of considerable research overlap, which is all to the good in relation to the incidence of new drug discovery, there is a better chance of more fields of investigation being covered. The Swiss firms are second in importance in the world of drug business. They spend in Switzerland about £8 million out of the £30 million for all European countries other than the U.K. Like ourselves, most of the Swiss research expenditure is accounted for by only a few firms. These statements are supported by the breakdown of the N.H.S. drug bill of which approximately 52 per cent is paid to American-owned firms, 20 per cent to Swiss firms and other foreign-owned firms, with 28 per cent to British firms.

The industry is frequently accused of directing too much of its research effort to minor molecular changes—"molecular roulette" or "me-too-ism". Minor variations summated over a period of time can and do result in a remarkable improvement over the original compound; furthermore, the slight chemical variations may not only produce marked variations in biological response, but complete alteration in the therapeutic effect. The sulphonamides are a classic example; chemical modifications of the original sulphanilamide not only resulted in improved antibacterial action with varied properties of absorption and excretion, but in derivatives with entirely new effects. Following the clinical observation of the diuretic

effect of sulphanilamide and the elucidation of the mechanism of this action at Cambridge University, extremely powerful and useful derivatives such as diamox and chlorothiazide were developed by industry. Not only were they an improvement over the older mercurial type of diuretic in effectiveness, but they were safer and more consistent in action. The thiazide derivatives have been found to be valuable as an adjunct in the treatment of cardiovascular disease, both when used as an orally administered diuretic in the treatment of cardiac decompensation and when used to enhance the effects of antihypertensive agents in the treatment and control of high blood pressure. Other substituted sulphonamides were observed to possess blood-sugar lowering activity. Derivatives, devoid of antibacterial action, such as tolbutamide, are useful oral hypoglycaemic agents for the control of the milder forms of diabetes mellitus which cannot be controlled by diet alone.

The steroids are yet another example of the profound biological effects of molecular manipulation and of the success of very close academic and industrial collaboration. The original academic work on the physiological action of the two main groups, the sex hormones and the corticosteroids, was developed with the aid of industry—first, by large-scale extraction and purification of the hormone from natural sources, and secondly, by synthesis. A listing of the academic and industrial collaborators in the above examples reads like an international "Who's Who" of medicine and industry. At least seven countries and twenty firms have been involved at some stage or another. The remarkable collaboration of Hench and Kendall of the Mayo Clinic with Sarett of Merck & Company, and the chemical contributions of Reichstein of the University of Basle, laid the foundations of corticosteroid therapy. The industrial contribution, mainly in steroid synthesis, has produced agents having an eclectic range of therapeutic activity.

Therapeutic effectiveness cannot be claimed without adequate clinical trials in man, and these trials cannot be carried out unless the laboratory has produced sufficient evidence to convince clinical pharmacologists and clinicians that they are not subjecting their volunteers or patients to undue hazard. There is, of course, a definite element of risk when a drug is given to the "somebody who has to be first". This is minimized, however, by beginning with fractional doses under carefully controlled conditions by experienced clinicians backed up by adequate facilities.

Investigating the action of drugs in humans is an honoured and respected calling—a calling that has been followed by some of medicine's greatest names. . . . The study of drugs by clinicians is a part of clinical investigation (Dowling, 1964). The testing of drugs on man is as old as medicine itself, and as the clinician quoted by Lessing (1963) said, "We must face up to the fact that someone has to be first or we could have no new drugs."

The advent of more powerful and sophisticated drugs with a remarkable degree of specificity in modifying organic functions in a profound manner (essential for the treatment of diseases of organic dysfunction or deep-seated degenerative diseases) has increased the emphasis on toxicity studies in depth. A sense of urgency, and perhaps frustration, was added by the thalidomide tragedy in 1962. It triggered off, on both sides of the Atlantic, new legislation, the setting up of commissions and committees, and societies and symposia, to study current methods and suggest new ones. There has been complete freedom of discussion between the representatives of different firms with the authorities of medical science and governments on an international level.

The drug industry, both here and in the U.S.A., took the initiative in sponsoring non-industrial bodies to study drug toxicity. On this side of the Atlantic, we have The European Society for the Study of Drug Toxicity whose President is Dr. D. G. Davey of the Pharmaceuticals Division of I.C.I. It was formed in Zurich in September 1962, at a meeting attended by twenty-six scientists from some of the major pharmaceutical companies in the U.K. and Europe. The objects of the Society are:

1. To encourage and extend research in the field of drug toxicity.
2. To establish working groups with a view to the 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.
4. To undertake any form of scientific work connected with drug toxicity.

The officers of the Society, and the Committee members, are drawn from Czechoslovakia, France, Germany, Holland, Italy, Sweden, Switzerland, and the U.K. The Committee consists entirely of academic authorities, and receives financial support from eighteen pharmaceutical companies. The Society has been remarkably active, and published its first volume of the Proceedings of a Symposium held in Paris on "The Effects of Drugs on the Foetus" in January 1963. Other meetings have taken place in Leyden, Lausanne, and Cambridge, England. The Proceedings have been published in each case.

Dr. Davey points out that the Society is a purely scientific society, open to all individuals interested in the subject of toxicity. Its membership is drawn from universities, medical schools, research institutes, and government institutions, as well as from the pharmaceutical industry. It provides a forum for open scientific discussion of all problems of drug toxicity, and its success is evidence, if evidence is needed, that the first loyalty of a good scientist within the pharmaceutical industry is still to science.

The Commission on Drug Safety was established in America in August 1962 with a grant from the Pharmaceutical Manufacturers Association.

This support was offered and accepted under the conditions of an award to an academic institution, providing for an independent body that determines its own plans and objectives. Lowell T. Coggeshall, M.D., Vice-President of the University of Chicago, was its Chairman. He assembled, as members of the Commission, fourteen top-ranking medical and scientific authorities, five of whom were drawn from the industry. All were doctors of medicine except one, who was the Director of the National Primate Centre, University of California. Seventeen Sub-Committees were established in 1963; each was charged with the responsibility of examining and reporting on specific areas directly related to drug safety. There were 150 nationally recognized authorities on these Sub-Committees. The Commission has completed its work and published its report. Some of its findings are referred to in the course of this paper.

There is real danger of a controlling agency demanding arbitrary tests of drug safety which would not only waste time and expensive professional effort but, above all, give a false sense of security. Mandatory tests must be meaningful. There are, at the moment, genuine differences of opinion among the highest authorities with regard to the duration of chronic toxicity experiments; but most authorities are now agreed that extension beyond a year contributes nothing towards reducing the likelihood of human toxicity that is not already apparent within the first three to six months. The mere increasing of the numbers of animals, additional species, or more administered doses over longer periods, contributes little to the solution of the problem. We must not delude ourselves that scientific progress is attained by expanding current procedures or doing more of the same thing. There is no doubt that due to our lack of knowledge, we are carrying out a large number of useless experiments which shed no additional light on the likelihood of the occurrence of toxic reactions in man. We are all agreed, however, that more fundamental biological or biochemical knowledge is required; it is equally true that there are new experiments to be done which cannot be designed until this knowledge is available. The degree of safety of a drug is a consequence of this knowledge which embraces the understanding of drug action, drug metabolism and chemical structure, in relation to living processes. *So far, no laboratory or animal test can guarantee an effect, or lack of effect, desirable or undesirable in man.*

Any biologically active substance must, by its very nature, possess toxic properties under appropriate conditions. It is unlikely that any completely non-toxic substance will have therapeutic activity; therefore, restrictive legislation and increased severity of control will never remove the hazard of unexpected human toxicity. The safety of a drug must be judged in relation to its therapeutic use. The criteria for a life-endangering disease will be different from those applicable to an analgesic, or for those diseases

of organic dysfunction requiring prolonged medication over a period of years. The Commission on Drug Safety commented that "Drug safety itself is not and cannot be the first consideration of the manufacturer, nor the physician. The governing principle must be to provide the best possible therapy for the patient, and this means that the possible risk inherent in new compounds must be weighed against potential gains in efficacy. The seriousness of the illness, quite clearly, dictates the margin of allowable risk. If safety *per se* were the over-riding factor, few compounds would reach the clinical test stage. . . ." The ultimate responsibility for the initial clinical trial in man rests with the physician; he must have all available pre-clinical information concerning the potential drug to guide him in coming to a decision; he must be satisfied with regard to the scope and adequacy of the data, and demand further experiment if he is not.

The clinical investigation, in turn, must be properly designed and controlled to permit accurate observation, and must be accompanied by careful documentation. The first trial in man, and the subsequent establishment of efficacy, are a continuation of the laboratory research project which is not completed until efficacy and safety are substantiated. An adverse reaction record will continue as long as a drug is prescribed. The F.D.A. requirements for substantial evidence of efficacy are clearly stated: "Evidence consisting of adequate and well-controlled investigations . . . by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

It should be realized that when a drug reaches the prescription pad, it has attained this status by the joint efforts of the medical profession and the drug industry. The onus of providing effective and safe medicines is, therefore, collectively shared between the pharmaceutical industry, the controlling agency, and the medical profession. When unwanted reactions appear, the medical profession must also accept its share of responsibility associated with the jealously guarded right of prescription. It is, of course, the responsibility of the industry to follow up and investigate all reports and complaints of suspected adverse reactions, and to carry out additional laboratory tests which may either explain or give guidance in avoiding these unwanted results.

The substantiation of drug-related side effects is not so easy as it would appear at first sight, for even double-blind clinical trials have shown the placebos to produce the same toxic response as that attributed to the drug; the effect, therefore, cannot be drug-related.

The 1962 Amendments to the Federal Drug Laws in the U.S.A. increased the scope of the F.D.A.'s responsibilities. Substantial evidence of efficacy was added to proof of safety. Data concerning the qualifications of technical and professional personnel employed by the manufacturers was required, and of those carrying out clinical trials. The Commission on Drug Safety

comments that the paper work and other controls have reduced the research effort in some quarters . . . and that they have brought about a slowing down of development and marketing of new drugs, thus depriving physicians of more effective weapons at their command with which to fight disease. While nobody could possibly disagree with the object of releasing only safe and therapeutically effective drugs, the regulations to achieve this may require redrafting and modification.

All these regulations have resulted in a considerable increase in the cost of producing a new drug. In his special report on the industry, Kiefer (1964) quotes figures showing the magnitude of the increase in the U.S.A. It is estimated that the toxicity and clinical tests for an N.D.A. begin at around £75,000. To this must be added the cost of the paper and administration requirements. Smith, Kline and French estimate the additional expenditure to be £175,000 a year. To bring a new drug to the market requires a minimum of £175,000 for research, development and testing. Most firms now agree that £750,000 to £2 million is nearer the mark and could be considerably higher for a drug treating a chronic ailment.

The present French system which came into force in 1959, although a considerable advance on the previous one, is still far from perfect. Even though it was designed for safety purposes, it is so bound up with red-tape and cost that the inevitable delays may tend to work against the public interest. The net result is that many discoveries made by the smaller companies or individual research workers can never find their way onto the French market, and the bigger companies are penalized in that the great number of delays allow competitors, particularly with unpatented products, to take advantage of other people's work.

The first procedure is to have toxicological trials on animals and analytical work carried out, but unlike any other system such as the F.D.A. and the Dunlop Committee, this work cannot be done either by the industry in its own laboratories or by recognized academic authorities unless they happen to be on the approved lists. The firm must select experts from the lists of "accepted experts" prepared by the French Ministry of Health. Only three non-Frenchmen are at present entered on these lists.

The firm submitting the application must join a queue to get the preclinical work done. Furthermore, each expert charges from £750 to £2000 for the work he does, according to the complexity of the product. When the toxicological work is done and the analytical controls are defined, each by two separate experts, the way is open for clinical trial. Again, the clinical trials can be carried out only by an accepted expert from the official lists. Once more there is a competitive search to find the clinical expert, and again there must be payment of a substantial fee for the service. If the expert is not particularly interested in the product, the firm will find itself in a position where it is difficult for it to obtain official documentation.

The basis of the French scheme is that the experts themselves accept responsibility for the work they have done and, in theory, this is supposed to present the public with an unbiased check, independent of the manufacturer and of the Government, before the new drug can be offered for sale. In practice, as distinct from theory, arising as a result of the Stalinon and Baumol powder cases where a large number of tragedies occurred, some experts in France today are reluctant to accept this responsibility and are hesitant about giving clearance. As a result, more tests and checks than are necessary are carried out, and it is difficult with a new product to obtain a clearance by the expert within a reasonable time.

Obviously the delays are considerable, and although one cannot prove it, there are those who have serious doubts about how confidential the information is kept in view of the small numbers of experts each working for more than one firm, and the difficulty of ensuring that junior staff do not reveal confidential details. For example, in a recent case, before the originating manufacturer's tests were completed, the company was approached by a French company who had learned, in France, of the work that was being done. This company suggested there might be an exchange of information and expert tests, and that both should market within France. This is a typical example of what can occur.

In this country we now have the Committee on the Safety of Drugs. The setting up of this Committee is described by Dunlop (1965). It is organized on the basis of the three clearly defined stages in the testing of a new drug, namely:

1. Toxicity tests on animals to ensure that a therapeutically promising drug is reasonably safe for clinical trial.
2. Clinical trials to establish efficacy.
3. To collect and analyse adverse reactions.

Each stage is the responsibility of a Sub-Committee whose activities are co-ordinated by the parent body. Benefiting no doubt by the experiences of other countries, they have evolved a combination of technical competence and responsibility with a straightforward procedure. The expert medical and secretarial staff who serve the Committee show the high sense of duty we have come to expect of the British Civil Service, and there are certainly no reservations to make on security of confidential information. The Committee itself consists of voluntary unpaid scientists and physicians. The manufacturer may use any reputable source of information for his documents; and work from the laboratories of companies of high-standing is usually accepted. The only delays occurring in the Dunlop system are those due to shortage of the staff required for formal clearance of paper work within the Committee. This has resulted in some slight delay during the past few months, but staff is being increased and we expect little or no trouble in future.

The voluntary nature of the Dunlop Committee and its freedom from statutory regulations makes it possible, at present, to approach those administering the scheme for informal discussions on resolving questions and difficulties before they cause delay within the formal machinery of clearance. Even if and when made statutory, one would expect this to continue; such informal approach has always been available within the Therapeutic Substances Act Regulations. Even the F.D.A., though subject to considerable regulations, allows non-political scientific discussions with its officers, but the French system allows no discussion whatsoever.

The procedure in France requires the documentation and formal request for approval to be deposited at the French Ministry of Health. All further communications and citations against the dossier are formal and subject to routine office delay. As a result, the time taken for final approval is prolonged because further work required to satisfy the authorities cannot be put in hand until the official citation is received. It may well be, under the French system of clearing, that after nine months of waiting in the files, one is required to start other work.

The Common Market Six, through the official Campet Commission, are working now on the harmonization of drug control, and it is proposed that the major safety steps be based on the system of accepted experts. The French are strongly for it and are supported by the Belgians and the Italians. The Germans, supported by the Dutch, have been against this system. The German industry have convinced their Parliament that to support this would be harmful to their flourishing pharmaceutical industry and retard research. They point out how few discoveries have come from France in recent years. It has just been announced that a compromise has been reached, but no details are yet available.

The medical profession and the industry must do all they can to ensure that the Government does not legislate discovery out of existence. In respect of safety, Lawrence Lessing's timely article "Laws alone can't make drugs safe" demonstrates the difficulties we are up against. It is interesting to note that this article, which appeared in the magazine *Fortune*, was read into the Congressional Record of the 88th Congress during the same month in which it appeared—March 1963.

It is to be expected that there will be variations from country to country in the average time required by the controlling agency to release a new drug for clinical use. The F.D.A. now have a period of 180 days as against the previous 60 for initial consideration after filing. This period, as previously, can be considerably prolonged if more information is requested. Bambach (1964) of the P.M.A. has shown that F.D.A. clearance is taking much longer. In 1958, the average processing time for an N.D.A. was about 100 days; three years later this period had doubled, and in 1963 it had soared to 327 days. These figures apply to all drugs which eventually

won approval. It is only fair to point out, however, that Mr. Larrick, the F.D.A. Commissioner, has said that some firms really have only themselves to blame, because they submit poorly documented and incomplete N.D.A.s without sufficient supporting scientific data. He further maintains that well-organized N.D.A.s with adequate scientific data to permit proper evaluation can be processed in half the time required for a poor one. It is salutary to realize that only 5 per cent of the N.D.A.s received by the F.D.A. can be approved without amendment or additional information.

The average delay between the manufacturers' submissions to the Dunlop Committee and their clearance has not exceeded eight weeks during the last year; about a quarter of the submissions had to be referred back for further information. The lesson in both cases is clear—the manufacturers must, in their own interests, help the agencies to carry out their work efficiently by sending in carefully prepared, well-documented submissions containing adequate pre-clinical and clinical data. Time spent on a critical examination of the documents will be well rewarded by an earlier entry to the market and less likelihood of technical failure at a later date.

Proper and complete evaluation of the properties of a new drug by controlling bodies will obviously require advanced methods of recording, storing, retrieval, assessment, and other processing of vast amounts of data. These data will come not only from many different centres in a country, but from many different countries of the world. How vast this can be is evident from the now-familiar picture of an industrial co-ordinator for F.D.A. affairs standing alongside a single N.D.A. stack of volumes, usually shoulder-high, three deep, and probably weighing around a quarter of a ton. Currently, the medical assessors of the F.D.A. have to read and evaluate some two million pages of clinical data per year. Add to this the problem of recruiting adequate numbers of suitably experienced medical men, and it will be appreciated that there is an urgent need for a workable system of computer processing of clinical data.

The F.D.A. realized that with the increased demands for more experimental data, more clinical observations and documentation, something had to be done if it was to process with efficient and reasonable rapidity the information it now requires—otherwise the Government, through its controlling agency, might find itself accused of being the bottle-neck of scientific progress in medicine. To avoid such accusations, the F.D.A. have embarked upon a pilot project known as "Project Rapid". They state: "Our ultimate goal is to achieve an automated drug information centre and also to enable the Food and Drug Administration to more efficiently and speedily process new drug applications." An admirable objective.

In collaboration with the A.M.A. and members of the industry, they are developing a coding system beginning with Adverse Reactions, Acute

Toxicity and Sub-acute Toxicity in Animals. The full development of this project has exciting possibilities with regard to the logical processing of the mass of data which is considered essential before a new drug can be properly launched and used without subjecting the patient to any undue hazard. It will mean not only a more rapid processing of the data, but an increase in technical efficiency and assistance to the medical assessors in exerting their medical and biological judgement.

At the moment, this coding system refers only to the U.S.A., but the international nature of new drug development requires co-ordination with other schemes being studied on a world level. Within the next ten years, the new drug requirements for Europe alone will be greater than those of the U.S.A., even if only on a population basis. The existence of the Six and the Outer Seven will, of necessity, require a far greater interchangeability and acceptance of data than occurs at the moment. To make this really effective and internationally acceptable, a common technical language is required. What could be better than the development of machine compatible systems of recording, together with an internationally recognized and acceptable code to achieve this? There must be agreement, of course, in the description of the patient response, of clinical and adverse toxic reactions, of the dosage régime, and of the terminology linked to the code. The system of coding and storing must be highly flexible and capable of accepting programmes and data both planned and different from those envisaged at the time; and it must have the ability to feed back information and derived instructions to modify the experiments or trials in being. The reporting participants will not only use the coding system index for international uniformity but also as a check-list to decrease the possibility of errors by omission.

Finney (1964) defines monitoring of drugs as any systematic collection and analysis of information pertaining to adverse effects or other idiosyncratic phenomena associated with the normal use of drugs. He emphasizes the necessity of the computer giving an early warning when the accumulating evidence suggests that a drug has adverse side effects, and not waiting until the evidence is overwhelming. A properly planned computer would screen a large number of records in respect of a wide range of variables, thereby enabling the medical assessor to exert his medical expertise in interpreting the medical data processed by the computer. While there will be a considerable saving of time and a more efficient deployment of the limited number of medical experts working in this field, no machine, computer or other device will reduce the biological constants of man or experimental animals.

Whether we like it or not, clearance of a drug by the F.D.A. in the States, or by the Dunlop Committee, in this country does not result in reciprocal clearance; nor, for that matter, does it apply to any other country

with a regulatory system such as France. Nevertheless, there are many other countries without an indigenous research-oriented industry and possibly less advanced medical facilities that are considerably influenced by U.K. or U.S.A. clearance, even though they still demand local clinical trials. There is no reason for believing that the results of clinical trials carried out in one country will be willingly accepted, if at all, in some other countries. This cannot, or should not, arise, however, because of ignorance of modern clinical trials procedures, for all these have been well publicized and documented during the past decade.

It is expected before long that each sophisticated country or political territory will set up a licensing or approving authority like the F.D.A. or the Dunlop Committee, and demand that submissions placed before it must conform to these modern concepts. Theoretically, the judgement of any of these approving bodies should be acceptable to all the others—and at some time in the rather distant future this will happen. It is too idealistic to suppose, of course, that this type of international acceptance is just around the corner; but there are indications that developments are proceeding along these lines, for in the case of pre-clinical data from the more responsible firms, there is a relatively high degree of international acceptance. There will no doubt be an interim period during which the medicals of some countries will improve their critical faculties, and the pharmaceutical houses be strengthened in their resolve to produce only safe and effective products. In other words, there will be a general levelling upwards of medical skills.

It is obvious that commercial exploitation of new products must be preceded by technical penetration, and this can be achieved only through the medium of the local clinical trial; these will, in turn, be facilitated by Dunlop Committee and/or F.D.A. clearance. Further support can be given either by a member of the firm's medical department presenting a résumé of the knowledge and clinical experience to date of the new product, before medical gatherings, or by the visit of an authority in the particular field from the country of origin.

The establishment of a new drug frequently involves the organization of a symposium at the international level. Contributions are made by research-oriented clinicians from different centres of the world who are brought together to display their findings, pro and con, and to exchange information concerning the effects and modes of action of the drug. The symposium should, for preference, be held at, or as close as possible to, the firm's research establishment, thereby permitting the collaborating clinicians to meet the research men and see some of their work going on in the laboratory. Furthermore, a symposium has the additional advantage of the proceedings being published and bringing current knowledge and opinion together in one publication.

It is not surprising, perhaps, that the repository of the greatest amount of knowledge and experience in pre-clinical toxicity lies within the files and staff of the ethical drug researching firms. Many millions of laboratory animal tests, involving thousands of compounds of a wide diversity of chemical types, have been carried out in the last twenty-five years in industrial laboratories. Much of the credit for the development of methods and the establishment of standards must be given to the industry. The researching firms, by their uncompromising rejection of potential drugs which exhibit unacceptable toxicity in one or more species of laboratory animals, have shown a high degree of responsibility in maintaining such tight toxicity control. It may be that the manifestations were species-specific, and it is possible, therefore, that good drugs have been lost to medicine; but in the light of current knowledge, there is an understandable policy to play safe by considering man equivalent to the most sensitive species. More knowledge of the metabolism of the potential drug and its mode of toxic action would probably have saved some. The rejection rate of compounds at the final pre-clinical stage can be as high as five out of every six tested —and after much money and possibly many man-years have been put into the synthesis and biological screening of the chemical compound. I wonder if it would be worth while trying to retrieve a portion of the vast amount of data on chemical structure and biological response by using modern methods, including computers, to reprocess it? This might lead to an improved evaluation of toxicity tests and the development of ones which would yield data predictive of human toxicity.

The industry has also met its responsibilities in a conscientious manner by producing drugs of the highest standard of purity, potency and quality. Many of the standards have, in fact, been established by industry in collaboration with the official agencies. In other cases, industry has both raised and maintained standards of quality generally above the B.P. or U.S.P. requirements which are usually set at a minimal acceptable standard.

The responsibility for quality, potency and effectiveness of a drug lies absolutely with the manufacturer. Since it is a responsibility that he is proud to assume, both success and complaint should be attributable to him. The only satisfactory way in which this can be achieved is by means of the brand name, which identifies both the product and the manufacturer, whereas the generic name merely identifies the ingredient.

There have been disturbing complaints of unbranded drugs, particularly the imported ones, not being up to standard (*Lancet*, 1958, 1959; *Canad. Med. Ass. J.*, 1963). Obviously it is wrong for a doctor to discover, by patient reaction, that a drug is substandard.

Government or hospital laboratories are not places to test the quality of drugs—irrespective of price. The proper place for complete quality control is the manufacturer's laboratory, where controls with all the modern

facilities of analysis, physical chemistry, sterility and the like, are imposed during the manufacturing and finishing processes. Chemical analysis that meets pharmacopoeial requirements is not enough, for differences in formulation of a single therapeutic agent may produce every effect—from complete reversal of action to no action at all. In their survey—"Pharmaceutical Formulation and Therapeutic Efficacy"—Levy and Nelson (1961) concluded that "in some cases, choice of dosage form and manufacturer's brand may be as important as choice of the actual therapeutic agent".

An editorial in the *Journal of the Americal Medical Association* (1964) suggested that doctors should use generic names in teaching or communicating with their colleagues. "Physicians should be encouraged regularly to use non-proprietary names, recognising, however, that such usage is solely for educational purposes and does not provide assurance of the quality and potency of products prescribed. . . . The physician who prescribes meprobamate as such, has no way of knowing that his patient will receive the drug in a form of highest quality and expected potency. Careful prescription writers provide the necessary assurance in one of three ways: by writing the non-proprietary name plus the name of a manufacturer known to be reliable, by writing the desired brand name, or by writing the non-proprietary name plus the desired brand name. When the physician uses a brand name or a manufacturer's name to designate the source of supply, he is fulfilling a part of his obligation to his patient. Having decided that medication is required, he should assume the responsibility for selecting a manufacturer who will supply the drug in a therapeutically-effective form at the lowest possible cost to the patient."

The reputable manufacturer must maintain the doctor's confidence, or the doctor will never again prescribe his products. The same applies to those exporting their branded products; failure, on grounds of quality or lack of quality control, can have serious repercussions on product acceptability. In those countries where it is necessary to carry out the final processing stages locally, a check on the effectiveness of local quality control is achieved by the return of random samples to the firm of origin.

A drug is prescribed when there is a true need for it. Proper evidence provided by the medical profession and publications by reputable clinical investigators in good medical journals create the demand for the drug—*not* immoderate or inadequately supported therapeutic claims by the manufacturer. Here the medical profession and more responsible members of the industry are at one. Austin Smith (1963), President of the Pharmaceutical Manufacturers Association, referring to unneeded drugs, said: "It seems to me that the best way to resolve this issue is to let the doctors decide, through practical experience, what they want. What is not wanted will be dropped by the drug makers." From the profession in this country, Sir Derrick Dunlop (1965) has stated: "If we do not prescribe new drugs

and preparations until good evidence has been presented in support of the claims made for them, it will cease to be profitable to market them without such evidence . . . and if our wishes are expressed on prescription pads they will be heeded." Similarly, from the States, Walter Modell (1964) writes: "Remember there is no guarantee that a new drug is better than an old one. . . . Therefore until the evidence is in, until after a drug's probationary period is over, I suggest the value of experience be held in proper esteem and take precedence over shakily established claims and hurried use of new drugs." He continues: "Good drugs will always be recognized if they are placed in proper hands—they will make themselves felt promptly—they will be recognized for what they are, and they will survive."

The export of pharmaceuticals from the U.K. to more than one hundred countries overseas attained a record figure of £60 million for 1964. It clearly shows the extent of international penetration of the products of research originating in this country. We export more than eight times the value of the drugs we import. That the State should jeopardize this national asset, either by new legislation or by invoking outdated laws, is beyond comprehension. Continuation of such a policy can be based only on ignorance or political dogma. We are not alone in the export drive. In the U.S.A., foreign markets account for 25 per cent of their vast turnover in ethicals, and within about ten years, the leading U.S. firms expect their overseas business to contribute 50 per cent of their total return. These firms already have over ninety plants in foreign lands.

Discoveries, after they have been shown to be effective and safe, attain their full development when they become readily available throughout all countries of the world. Consequently, a superior or therapeutically effective drug that has been added to the doctor's armamentarium will be in universal demand by the medical profession and the general public. Let us hope that the industry in this country will be encouraged and given the opportunity of making and developing a fair share of these discoveries.

REFERENCES AND RELEVANT LITERATURE

BACH, F. (1959) *Lancet* **1**, 50.

BAMBACH, KARL (1964) Pharmaceutical Manufacturers Association quoted from *C. & E. N.*

BAYLISS, R. I. S. (1959) *Lancet* **1**, 98.

BINKLEY, HOWARD L. (1964) *Pharmaceutical Industry Research and Development Activity, 1963–1964.* Pharmaceutical Manufacturers Association, July 1964.

BOGUE, J. YULE (1962) The organisation and economics of research in the pharmaceutical industry, *Phamarceutical Journal* **188**, 27.

CHAIN, ERNST B. (1963) Academic and industrial contributions to drug research, *J. Roy. Soc. Arts*, III, 856.

DOWLING, HARRY F. (1964) *J. Amer. Med. Assoc.* **187**, 212.

Drug Safety Symposium. *J. Amer. Med. Assoc.* **187,** 340–51.
Dunlop, Derrick (1965) *Practitioner* **194,** 5 (Special number on drug toxicity, pp. 5–125).
Editorial (1963) *Canad. Med. Ass. J.* **88,** 94.
Editorial (1964) Illicit Traffic. *Barron's,* 13 July 1963.
Editorial (1964) *J. Amer. Med. Assoc.* **190,** 542.
Finney, D. J. (1964) *J. Chronic Diseases,* **17,** 565.
Harris, Charles (1964) The physician and the drug disputes. *Science* **146,** 717.
Kiefer, David M. (1964) *Chemical & Engineering News* **42,** 68 and 114.
Lasagna, Louis (1964) Problems of drug development. *Science* **145,** 362.
Lessing, Lawrence (1963) Laws alone can't make drugs safe. *Fortune,* March 1963; *Proceedings of the 88th Congress,* 1st Session, March 28, 1963.
Levy, G. and Nelson, E. (1961) *J. Amer. Med. Assoc.* **177,** 689.
Modell, Walter (1964) *J. Amer. Med. Assoc.* **190,** 141.
Report of the Commission on Drug Safety 1964. Distributed by the Federation of American Societies for Experimental Biology.
Rosenheim, M. L. and Ross, E. J. (1958) *Lancet* **2,** 1371.
Smith, Austin (1963) *Drugs and Man's Welfare.* Pharmaceutical Manufacturers Association.
Stevens, C. C. Regulations in Europe. Personal communication.
Symposium on Evaluation of Drug Toxicity (1958). Editors A. L. Walpole and A. Spinks. J. & A. Churchill Ltd., London.

Government Relations with Science Based Industries

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THIS is certainly an appropriate moment in which to consider the relationship between government and the research based industries. So many aspects of this relationship appear to be undergoing change. There are, most obviously, the changes deriving from the Trend report on the organization of civil science, as modified by the present administration. We now have a Ministry of Technology, with a sponsoring role for four industries—electronics, telecommunications, computers, and machine tools, and continuing responsibility for the more industrially orientated activities of the Department of Scientific and Industrial Research, now in process of being wound up after a career that by July this year will have lasted exactly forty years. The first child of this new Ministry appeared less than ten days ago: a four-point programme to assist the computer industry.

We also have the Development of Inventions Bill going through the House of Commons, providing considerably increased powers and finance for the 17-year-old National Research Development Corporation. Both the Corporation and the Ministry intend developing the fairly recent technique of civil development contracts as a stimulant to industrial innovation. At the same time we have the reappraisal of the aircraft research and development programme, to be followed probably by the demise of the Ministry of Aviation, the biggest dispenser of public funds for research and development that industry has ever seen—except that only a few industries ever saw some of these funds. The role and activities of the Atomic Energy Authority, now a mature and possibly a trifle flabby 11-year-old, is under close scrutiny for the second year running and by the second government running. And, the sponsors of this series of lectures will hardly need reminding, there are also the repercussions of the last Minister of Health but one, recently etched into the permanent record by an epochal judgement of the House of Lords.

All these events reflect changes—or more precisely shifts—in policy as well as changes in organization. For some years now there has been growing concern about both the scale and the priority of this country's research effort, and increasing acceptance of the opportunity open to the public

purse to do more both as a catalyst in particular areas where not enough research is being done now and as a prime mover in directions—like the direct generation of electricity for example—that cannot be adequately covered or afforded by existing research arrangements, both public and private.

But the role of the Government certainly does not consist only of the provision of funds for research and development. For a good two decades now the public sector has been a major customer for a wide range of goods and services. In 1963, to cite the latest fully documented year, central and local government and the public corporations accounted between them for at least a fifth of all purchases of goods and services in Britain, including more than two-fifths of all new capital investment. There are few industries that do not encounter government in either or both of these roles. And those that do not are always liable to be influenced by acts of government in its conduct of fiscal and tax policies, in its post-Keynesian role of regulator-in-chief of the national economy, and in such matters as tariffs, standards, patent law, and so on.

I propose, therefore, to divide the main part of this paper into two parts. First of all, I shall discuss some aspects of the government role in its relationship with research based industries. Then I shall consider the relationship from the point of view of two particular research based industries—electrical plant and aircraft. I have chosen only two industries for a number of reasons. Firstly, I do not want to make this paper too long. Secondly, I feel ill-equipped to be drawn into a discussion of the pharmaceutical industry among so many people who know far more about it than I can ever hope to do. And, thirdly, I am keen to avoid having to attempt a precise definition of what is a research based industry.

There are certainly not many. On the test of research ratios—the ratio of total spending on research and development to net output and the ratio of qualified scientists and engineers to total employment—only five industries stand out: aircraft; chemicals, in all its branches; scientific instruments; electronics; and in substantial measure the electrical industry in general.

Of these the chemical industry is in a slightly different position from the rest. If one excludes pharmaceuticals and mineral oil refining, few of its products—certainly well under a tenth—are bought directly by the Government and an even smaller proportion of its research effort is financed by public money. The electronics industry also presents problems in this context. Apart from computers, telecommunications equipment, and radio and television receivers, where the role of government has a very marked influence in one form or another, most electronics products go into something else—like aero-space and defence equipment. The same is also true of scientific instruments, though for both industries the Government is a

fairly major provider of research funds. That leaves, apparently, only the two industries I have chosen for individual discussion.

But is it right to say that there are only five research based industries? They are generally counted as such, they have all grown up in parallel with the sciences on which they are based, and between them they account for two-thirds of the qualified manpower engaged upon research and development in private industry and three-quarters of the spending on research and development. But can one so lightly dismiss all of the traditional or craft based industries that grew to maturity before the scientific phase of the industrial revolution? What about steel, for instance? Whatever view may be held about the adequacy of its research effort, the British steel industry, like its counterparts in North America and on the Continent, is undergoing a technological transformation at the present time quicker than in any previous period since the days of Bessemer, Siemens, and the others. True, the rate of change in steel melting practice is largely determined by the rate of scientific advance in understanding what goes on inside the furnace and rule of thumb pragmaticism still appears to have a bigger role than methodical analysis, and so not everyone would consider the industry as science based. But it is certainly one where the role of government is bearing down somewhat heavily at the present time. However, if I pursued that line of thought I would be getting well beyond the ambit of this paper.

It has taken forty years for the British Government to evolve the present concept of its role in stimulating a high and vigorous rate of innovation for the economic defence of this country. Until the outbreak of the First World War it could be said that its policy on scientific and industrial research and development for civil purposes was certainly clear-cut. It would have nothing to do with it at all. The Government accepted full responsibility for defending the country against any foreign power or the frontiers of empire from any marauding tribesman. And it naturally followed that it would pay for any research to improve the performance of ships, guns, shells or rifles. But responsibility for technological advance outside military requirements it left to private industry. And why not? The industrial revolution had shown that there was vitality and ability in plenty among individual scientists and entrepreneurs.

But Britain had no monopoly of scientific innovation or of business enterprise and other countries, notably Germany and the United States, were soon developing their own industries behind the protection of tariffs. By the time that the political divisions of Europe hardened into the siege lines of 1914, this country had become dangerously dependent upon foreign powers for supplies of vital manufactures, like optical glass, dye stuffs, magnetos, drugs, tungsten and zinc. So in the following year the Government took its first step in support of civil science and research by creating the Department of Scientific and Industrial Research. In its

historic white paper of July 1915, the Coalition Government explained this sea change of policy in these words: "If we are to advance or even maintain our industrial position we must as a nation aim at such a development of scientific and industrial research as will place us in a position to expand and strengthen our industries and to compete successfully with the most highly organised of our rivals." In other words, the Government not only accepted responsibility for this country's military defence: it also accepted a role in helping forward technological advances contributing to our economic defence. During the twenties and thirties, DSIR established a number of its own research stations and provided finance for research associations created by individual industries or groups of industries on a co-operative basis. And, after the Haldane report on the machinery of government had emphasized the importance of research in the formulation of government policy, a number of individual government departments set up their own research establishments and research councils were created for medicine, in 1920, and agriculture, in 1931. But the scale of government support was still relatively small.

Since then both the scale and the depth of government commitment to civil research and development have grown considerably. The Second World War, on the one hand, accelerated the development of radar, the gas turbine and nuclear fission, three major discoveries originally sponsored for military purposes which subsequently have had considerable repercussions in the civil field. On the other hand, that war accentuated the weakness of Britain's position as a trading nation. And, with the more recent emphasis in economic policy discussions upon the desirability of faster growth, this has helped to focus attention upon the possible correlation, both for firms and probably for nations, between economic growth and technological innovation. More specifically, this has led under the present Government and its predecessor to the reconsideration of governmental organization that I mentioned at the outset of this paper, and to the idea that the Government should use its powers of patronage, both as a provider of research finance and as a purchaser of goods, to stimulate both a higher rate and a better balance of industrial research effort in this country.

Unfortunately all this attention has not yet led to the provision of what I would call really adequate figures about the scale and pattern of our research effort, on which proper judgements could be based. But certain trends are clear. In the first place, the total effort put into scientific and technical research and development in this country, both civil and military, has certainly been growing quite sharply in recent years. Between 1955–6 and 1961–2, according to the surveys carried out for the Advisory Council on Scientific Policy (which, incidentally, disappears under the present reorganization), the total amount spent on current and capital account more than doubled, from £300 million a year to £634 million a year. As a

proportion of the gross national product, research spending rose from 1·7 per cent to 2·7 per cent in these six years. By now the total must be within sight of £800 million a year or between 3 per cent and 3½ per cent of the gross national product. Secondly, proportionately more is going on civil research. Total effort in the civil field grew three-fold between 1955–6, when £122 million was spent, or less than what was then spent on defence research, and 1961–2, when £388 million was spent, rather more than that year's outlay on defence research.

Since the late fifties more has been spent on civil research than on military. By 1961–2, the last year for which full figures are available, defence accounted for only two-fifths of the total, as against three-fifths six years before. Today it probably accounts for only just over a third. All told, civil research spending has probably risen between four and five-fold in the last ten years, from some £120 million a year to between £500 million and £550 million a year. Although government support for civil research has grown substantially since the war, from £6½ million a year in 1945–6 to £45 million ten years later, and to £204 million in the present financial year, the share provided by industry has been steadily increasing. Ten years ago it was barely a quarter; today it is probably over half. In actual figures it has quadrupled in these ten years, from £68 million a year to probably about £280 million a year. I might add that all these figures for the position today are my own estimates, drawn in the case of government expenditure from the civil estimates and for industry's own spending from random indications of the rate of increase in outlays in certain industries, since the last comprehensive estimates were published for 1961–2 following the Board of Trade enquiry for the Advisory Council on Scientific Policy.

All these trends are distinctly encouraging but three most important points must be made. They concern what one might describe as the lop-sided nature of some of this country's civil research effort. The first arises from the distribution of government support for civil research. Of the total sum of £204 million that the Government reckoned it would provide in the present financial year, well under £10 million has gone to industrial research associations and on development grants to individual firms—that is, less than 5 per cent. Another fifth, about £40 million, has gone to finance work at the Government's own research establishments or channelled through the research councils. Another fifth has gone to the universities directly and about £5–6 million has gone to assist research work overseas in the Commonwealth and elsewhere. That is probably a reasonable distribution, as far as I have taken the story. But it covers not quite half of the £204 million being spent. The rest has gone towards nuclear research of one sort or another—about £60 million or nearly a third—and to civil aero-space projects—about £50 million or roughly a quarter, mostly for work on space research and the development of civil transport aircraft. A good half of all

government funds for civil research therefore goes on these three—dare I say, prestige?—programmes. A half seems an awful lot.

The second way in which our civil research programme appears lopsided partly arises from this distribution of government money. The pattern of research spending between different industries is very uneven. With three-quarters of research in the aircraft industry paid for by government, that industry naturally stands very high on the list of research based industries. The latest reliable figures of net output research ratios—the ratio of research spending to net output—are unfortunately those compiled by the Federation of British Industries in 1960 with the assistance of the National Institute of Economic and Social Research. At that time the aircraft industry had a net output research ratio of as high as a third, way above electronics' 13 per cent, the 4–6 per cent level at which one found scientific instruments, electrical engineering and the chemical industry, and the 2 per cent mark where non-ferrous metals, rubber and mechanical engineering were listed. The average for manufacturing industry as a whole that year was just under 2 per cent, if one excluded aircraft.

Plane making is, of course, a labour intensive and not a capital intensive industry. A comparison of the ratio of qualified men working on research and development to total employment might therefore show a different picture. Not all that much. Here we have the figures of the Advisory Council on Scientific Policy for 1961–2, still out of date, but not quite so much so. On this test the aircraft, electronics and chemical industries all had research ratios of about 15 to 17 qualified research staff to every thousand employed. The ratio for instruments was about 10 per 1000 and for electrical engineering about 9 per 1000. After these five research based industries the figures fall sharply: non-ferrous metals is the next with a ratio of 5 per 1000. For manufacturing industry as a whole the average ratio four years ago was just under 5 per 1000 including aircraft manufacture: just over 4 per 1000 excluding it. The figure for chemicals, I might add, excludes mineral oil refining, one of the most highly capital intensive industries, with a research ratio correspondingly high at 26 qualified research staff per 1000 employed.

As I have said before, five industries stand out way above all the rest in these comparisons, which may not be the best way of measuring research mindedness but, in the absence of any other, will have to suffice. It is notable that for four of these industries the Government provides an appreciable proportion of their total research funds. For aircraft, the proportion is about three-quarters. For electronics, electrical engineering, and instruments, it amounted, at the time of the FBI survey nearly five years ago, to about 40 per cent, though, according to the National Economic Development Council, the proportion in electronics has been just over half since 1961. Without getting involved in fruitless discussion about what is the right level of research spending in any particular industry, and allowing

for the possibility that the uneven pattern of industrial research effort in this country may perhaps have been smoothed out a bit amid the considerable upsurge in industry's own outlays during the last five years, surely we can agree that this extreme imbalance is not a good thing. For instance, the construction industry spent barely £2 million on research in 1961–2, counting in the Building Research Station's budget, out of a total turnover in Britain of nearly £3000 million a year. Again the ability of the electronics industry to promote the application of electronics to machine tools must be hampered if the machine tool industry does not have a broadly corresponding research and development effort. The machine tool industry, I must say, has been taking steps to increase its research effort in the last few years. But its effort to market new tools of advanced design must, in its turn, be hampered if the research and development effort of the engineering industry generally is not in broad correspondence. Industry's spending on new equipment and plant, now in process of rising to a new peak this year, must likewise be hampered if the rate of innovation and technical improvement in the engineering industry is not as high as it could be.

The engineering industry has been stepping up its own research effort in the last few years. But it illustrates my third and last point about the balance of our research effort. This is, that by far the greater part of our research spending is done by the larger firms. According to the FBI survey again, about 350 firms employing more than 2000 people apiece did over 90 per cent of the total in 1959–60. The position could not have changed much since then. The same picture of concentration of research effort is found in the United States. There, too, about 350 large firms accounted for about 85 per cent of total industrial research in 1958. In Britain the engineering industry is a heterogeneous industry with a high proportion of smallish and middle-sized firms. Despite the creation of the Machine Tool Industry Research Association, there is still evidence that the improvement of research and development activity in engineering generally is hampered by inadequate external research facilities.

Engineering, of course, is one of the older-type industries and it does not have the Government as a major customer—except for those firms making railway equipment, mining machinery and gas making plant. Defence purchases do not bulk large in its order books. It is, of course, the requirements of military procurement that help to explain the high rate of research effort and the high rate of government finance for research in aircraft, electronics and instruments. Defence is a form of competition where the only economic limits are set by the total capacity of the economy and by politicians' willingness to allot resources to a technical race, as against the mundane limits of potential commercial return that private companies have to set, however roughly, upon their research efforts. The same might be said of nuclear physics and space as of defence.

A high rate of sales to the public sector does not, however, necessarily mean a high rate of research spending. The construction industry, for example, gets nearly half of its work from public authorities of one kind or another, but it spends very little indeed upon research. Conversely, the absence of the public sector as a major customer does not lead to a low rate of research effort. Look at the chemical industry. But generally speaking, apart from chemicals, the research based industries do have public authorities as a major customer. The heavy electrical plant industry almost entirely so: about four-fifths of its home sales and a good 70 per cent of its total sales. In telecommunications equipment, the Post Office and the two broadcasting authorities are virtually the only big buyers. In electronics, defence contracts are generally reckoned to account for about a quarter of the home market or just under a fifth overall. In the case of drugs and pharmaceuticals the health and hospital services buy about a third of the total output. And of all oil products refined in this country, the public sector buys about a quarter.

When the State buys such high proportions of an industry's output and pays for a good part of its research and development, it does not have to own the industry in order to exercise a marked influence upon its performance, rate of growth, efficiency and its technological progress. In the case of the heavy electrical plant and aircraft industries, private firms are hardly able to increase their home sales by their own efforts. What the electrical plant makers sell to the public electricity supply industry in Britain is largely determined by Whitehall's decisions about the level of capital investment in the public sector. What they make, too, is largely determined by one group of people in one organization, the Central Electricity Generating Board. If the CEGB decides to put in nothing but 500 megawatt generating sets, then that is what the manufacturers have to make. If the Government decides to go in for a nuclear power programme, then treble it, then cut it back, then lengthen it out, and then ask for tenders based upon American designs for the second generation of power stations—which is what has happened in the ten years since 1955—then the electrical firms making up the nuclear power consortia have to conform. Likewise, if the Government asks the public electricity supply industry to postpone a price increase, which has the effect of encouraging demand for electricity, and within twelve months—as happened in the mid-fifties—pares back the electricity supply industry's capital investment programme, which means cutting down the provision of plant to meet future demand, then the electrical plant makers can only pull wry faces. Too bad if all this chop and change in the power station programme, both conventional and nuclear, leads to years of surplus manufacturing capacity. And too bad also, if the sharp jump in the size of generating sets required, from 60 MW ten years ago to 500 MW today, means making equipments too powerful

to be really suitable for most of the relatively few customers overseas that are allowed to import. Although the first 500 MW set built in this country happened to go to the United States, a considerable gap has now opened up between the kind of equipment required by the industry's customers at home and the kind that sells most readily abroad.

A similar gap has been created in the aircraft industry, though for different reasons. Because there are four major public customers for aircraft in Britain—the RAF, the Navy, BOAC and BEA—as against virtually only one for generating plant, the problem of diverging specifications between the home and export markets is, in that respect at least, less acute. But the VC 10, the TSR 2 and the P 1154 vertical take-off fighter are only the most recent examples of tailor-made aircraft that will fit virtually no other customer. Making products that will sell both at home and abroad is far more necessary in fact in aircraft than in electrical plant: exports are vital to break even. It is costing more and more to develop each new generation of military and civil machines. Two decades ago it cost only £6 million to build the first and only Brabazon. Nowadays it costs £300 million to build the first TSR 2 and apparently more still to send up the first Concord. Sales have to reach very large numbers indeed to recoup this order of development cost. But the chances of getting long runs are becoming fewer and fewer. Each new generation of aircraft is not only costing more to develop, it is also capable of doing far more work. In military aviation, today's aircraft have far more strike capability than whole armadas of their Second World War predecessors. On the civil side, new airliners are both bigger and faster. Since 1958, when the first civil jets came into service, the output of the world's airlines has doubled, yet their airliner fleets have grown in number by only a fifth. Chasing after aircraft performance has brought its own bitter harvest: it is becoming harder and harder to break even on each new design.

The trouble about the dominant role of the public sector as a customer and as a kind of rich uncle for research in both the aircraft and heavy electrical plant industries is that it provides an easy alibi for allegations of inefficiency. Certainly no honest friend of either industry would deny that both have their weak spots. But, whichever yardstick one uses to judge efficiency—profitability or export success, and neither gives a very encouraging picture for either industry—one is led back to arguments about the share of the blame attributable to decisions of the industry's major customers.

One can never be really happy, however, about an industry's efficiency when it lacks the stimulus of price competition. Admittedly, it is hard to envisage how one could get price competition in the aircraft industry nowadays—that is, for the three-quarters of its output that goes to the armed services and the two state airlines. One cannot expect to have two

types of supersonic airliner built and test-flown in this country, and then buy the cheaper. It is as much as we can do to afford half of one. And recent events have not given us grounds for confidence in the overwhelming efficiency of the Ministry of Aviation's cost control techniques and price negotiating skills. One must be fair about this: the task of assessing realistic costs in modern aircraft development and manufacture is exceptionally difficult.

In the case of heavy electrical plant making the possibilities of creating genuine price competition are as difficult as in aircraft manufacture, though for different reasons. Here the absence of competitive tendering is not caused by the sheer complexity and expensiveness of new equipment, but by the CEGB's dominating position as virtually sole buyer. Although price fixing and market sharing arrangements have a comparatively long history in this industry, going back certainly to the 1930's and in some instances further back still before the electricity supply industry was concentrated, the Restrictive Practices Court has accepted CEGB's dominant role as sufficient grounds for upholding the arrangements at least of the water-tube boiler-makers, which involve price exchanging and some element of market sharing. In the case of high voltage cables, the Generating Board has arrived at an arrangement with the manufacturers whereby the bulk of its requirements are supplied at negotiated prices with full disclosure of profits, and for the rest—about a quarter—to be met by competitive tendering, open in part at least to firms overseas. But in large transformers, turbo-alternators, and switchgear there is neither competitive tendering nor price negotiation with disclosure of profits. And as long as the plant makers complain of low profits in comparison with other industries and the Generating Board complains of high prices in comparison with foreign equipment, one cannot be really happy about the efficient working of the relationship between buyer and seller. Nor, in particular, about the level of efficiency in the industry itself.

This complaint about the softness of price negotiations by the public sector may seem somewhat odd to an audience only too familiar with the recent House of Lords judgement on the legality of unlicensed drug imports for the hospital service. But the point I want to make at the conclusion of this paper is that, if the State chooses to utilize its considerable powers of patronage as a buyer of goods and services to stimulate a higher rate of innovation in industry, it should be careful how it sets about doing it. It would be a pity to stimulate technological advance at the cost of an industry's operating efficiency or financial tautness.

Where Does the Public Interest Lie?

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MY ROLE is to try to appraise the papers given in this series in the light of the general public interest. I approach this task as an economist with no expertise in the field of drugs or the pharmaceutical industry: this has disadvantages which will no doubt become clear as the paper develops. The advantages, if any, are those stemming from having previously been identified with no committed position. I cannot be comprehensive, and propose no final answers: I can only record what strikes me as important, or useful or misleading about the papers, and form some questions that still appear unanswered. I shall be critical but in, I hope, a constructive way.

Mr. Lee pithily summed up what one might call the popular indictment of the pharmaceutical industry. "Through patent protection and product promotion, the industry is charging high prices for products that could be made more cheaply in standard form. The medical profession is persuaded into prescribing branded products instead of standard preparations, by commercial pressure. The price difference between a branded and a standard product is used to finance this massive selling programme." Undoubtedly, the revelations about the American drug industry in the Kefauver anti-monopoly probe have helped sharpen public questions about the operation of the U.K. industry. On reading the American evidence it is hard to disagree with the view that the costs of advance in the drug field are high there. In a sense, much of the material in the present series of lectures can be seen as an extended answer to anyone who wishes to draw an analogy between the U.S. and the U.K. industries, and who may come, without sufficient evidence, to a similar conclusion about the U.K. industry. On the other hand, the papers have done much to reinforce the other popular view—taken when the public is contemplating the benefits side—that progress in the discovery and marketing of drugs is an activity of almost boundless worth. This does, and indeed should, engender a sharp respect for aphorisms about geese and golden eggs. We must be cautious in advocating reform, but we cannot ignore the question—can we get more benefits for the same cost or the same benefits for less? This, broadly, is what the public interest must mean.

We can approach this question by first looking at the interrelationships between the structural features of the drug industry and its use of scientific

manpower, and then broaden (and I fear necessarily loosen) our discussion to encourage some of the other implicit issues—e.g. the question of how far that manpower should be increased (in economists' terms, what are the opportunity costs of expansion of medically oriented research and how is it best achieved?) and issues such as the effect upon the U.K. balance of payments of encouraging the growth of this research, a topic which has been touched on by several speakers, in the guise of comparisons between U.K. and foreign levels of research expenditure.

The previous papers have indicated a fear that the growing use of Section 41 of 1949 Patents Act by an increasing number of trading concerns to acquire compulsory licences on patent protected medicines (an increase first noted in the A.B.P.I. Annual Report of 1961/2) will lead to a diminution of industry-based research, either as a share of the world's medical research activity, or even absolutely. (I am not clear, for example, which sense Dr. Fryers intended.) This follows the use by the Minister of Health of Section 46 of the same act to obtain certain medicines for the hospital service from unlicensed suppliers. One can only suppose that the recent House of Lords judgment on that case will reinforce these fears, for it appears seriously to weaken patent protection in U.K. drug markets.*

Let us first look, then, at the arguments in the papers directed to show the connection between the industry's present manufacturing, selling and promotion structure and its level of research and innovating activity.

For the purposes of discussion—and as a matter of conviction—I shall accept one assumption on which the arguments have been conducted, namely that invention without innovation is useless; and that innovation—the actual marketing of new products—requires, at the very least, a strong economic incentive. I also accept that the economic incentive will be the more effective if connected with private rather than State enterprise. I accept, that is, that the whole market and other strategy of firms is closely bound up with the innovatory process, and that to bring the simple maxims of micro competitive theory to bear on certain dimensions (e.g. price) only

* See Lord Wilberforce's dissenting judgment, in which he said that "an enormous breach was made in the rights of the proprietors of patents and drugs. The Crown had attempted to persuade their Lordships of its moderation by disclaiming any intention to use the drug (Tetracycline) outside the hospital services. His Lordship looked with a little reserve upon self-imposed limitations or concessions of that kind." *The Times*, 2 February, 1965, p. 5. He also argued that it was the Legislature's province to define the Crown's rights "on a fresh consideration of the respective interests of the public and of the inventor". But the M.O.H. is surely unlikely to abandon all the other criteria on which it agrees drug prices in favour of the single one of import prices. It is more likely to use the probability of import to keep up a downward pressure on prices, and not to pursue a deliberate policy of undermining patent protection. Nevertheless, the long-run effect may be to do so. It should also perhaps be made clear that M.O.H. pays royalties to patent owners on the drugs in question.

is likely to mislead. In all this, I merely repeat what Schumpeter said long ago. But the realistic question is whether the existing structural features, while they may be sufficient to produce a given level of research activity, are all necessary. And we must also enquire whether, with moderate reform, the rate of innovatory activity may be raised, or at least accomplished more cheaply.

The most contentious part of the industry's activity is probably its advertising and promotion activities. Mr. Teeling-Smith made a plea which, in effect, said that the resources devoted to these enjoy very high social value because the substitute methods of informing consumers about innovations imply, or would imply, a much lower rate of absorption of innovations. I do not think he has made out his case on the substitutes: for example, it may well be true that information is, in a sense, a collective good, which will not be provided in sufficient quantity in a competitively organized information industry unless some outside agency intervenes. In other words, consumers will not, left to themselves, pay enough for informatory journals. Mr. Teeling-Smith's "outside agency" is advertising by drug companies; but might we not consider other means of subsidizing journals, e.g. by arranging a compulsory levy on "consumers"—the doctors, or even considering it a charge on the N.H.S.?

Other parts of his arguments also bother me. He has, I think, a high opinion of doctors' ability independently to assess information about drugs and, indeed, if there is one group of consumers for whom one is entitled to assume this, it is surely the doctors. He thinks it insults doctors to suggest they should not be exposed to rival claims for different drugs, and he argues, I think rightly, that no company intent on long-term survival can afford to claim too much for its products. But on this, I would point out that Section 2(b) of the Code of Marketing Practice in effect specifically debars manufacturers from what one might describe as the "knocking" of competitive products. This clause can only be interpreted, I think, as meaning that no adverse comparisons should be made at all and, if so, it discourages the most important information a doctor needs—frank comparisons. Without these, it is quite possible that repeated, *true* claims are disfunctional in that they reduce the ability or willingness to take an independent view.

Again, one would have more sympathy with Mr. Teeling-Smith's claim for advertising if it could be shown that just as much—or more—effort per £ of sales was put into export markets as in the home market. This is not a balance of payments point, but simply to observe that the *information* argument applies to all markets, and that in view of the fact that in many British overseas markets the standard of medical knowledge is lower than at home, and the practitioners fewer, it might well be expected that the need for information-spreading was higher overseas on average. Similarly,

if the industry's aim really is to maximize the "appropriate" use of its products, as he desires, one might predict that the industry would spend a lot of money supporting *independent* pharmaceutical refresher courses, paying for doctors' time off by organizing locums, etc.—with the end of increasing the consumers' ability to appreciate drug innovation.* Perhaps these indeed could be shown.

In the absence of *relative* costs of advertising, etc., in different industries it is difficult, in general, to assess the argument that, as in other technologically based industries, enthusiasm and expense is necessary to overcome various forms of inertia. The question is whether, in relation to these other industries, the £8·9 million or so a year which the pharmaceutical industry spends on sales promotion (rather more than it spends in Britain on research itself) reflects consumers of greater than average inertia—because the industry must surely be among the highest spenders of all industries per potential consumer. (We must of course define consumers as the "prescribers".) I must confess I remain sceptical; and Mr. Teeling-Smith's other arguments about increasing the effectiveness per £ spent on advertising of course largely depends on what one thinks of the basic justification for this expenditure.

Even if one regards the benefits of advertising and promotion sceptically, however, one could still argue that they are a necessary cost which the community has to bear in order to get the gains of innovatory activity. In spite of Mr. Lee's strictures about the inappropriateness of conventional economic analysis the general argument is well known to economists: perfect competition in Mr. Lee's sense may be inimical to innovation for at least two main reasons. First, the competitive firm by definition earns only enough to pay for its factors of production, including management and capital, and has no uncommitted profits. Borrowing or new issues are circumscribed by the uncertainty of innovatory returns (borrowers' and lenders' expectations diverge), so some monopoly profit is essential to the supply of risk capital. Second, the firm itself needs an inducement; some prospective escape is needed from the forces of competition—from Schumpeter's "perennial gale"—which otherwise would quickly "wash away" the gain of innovation. Entire escape from the "perennial gale" would, it is recognized, be just as inimical to innovation in the long run. The balance is struck by possibilities of product competition, limits to the duration of patents, changes in technology and new research discoveries outside the industry.

Applied to the pharmaceutical industry, protection from competition is achieved in two principal ways—the practice of branding products and the

* To refer to his analogy, the reason why computers are not as widely used as they might be is partly price, partly rate of technological change, partly increasing consumer uncertainty, and partly sheer inability to use the machines effectively.

use of patents (though advertising and promotion costs are also important). Their function is to discourage entry into the industry: the risks of innovation are lowered. Let me say at once that I think that the practice of branding can only be justified, if at all, by the market advantages it conveys. There seems no reason whatsoever why the testing of all drugs should not be accomplished by a governmental or quasi-governmental agency via random sampling devices supported by international agreement if necessary. I notice that Dr. Yule Bogue remarks that, where it is necessary to carry out final processing stages in a foreign country, a "check on the effectiveness of local quality is achieved by the return of random samples to the firm of origin". This is a useful principle, capable of wide adaptation.

On this analysis, attack on any one of the props against competition could weaken innovation, and it is in this light that we are asked to view the spread of compulsory patent licensing. It also seems to be held that the present balance of monopolistic and competitive forces in the industry is about right (though certain reforms are, of course, not ruled out by earlier contributors). This view *may* be correct, but it is not unassailable. Let us first grant that we do not wish to see *industrial* based research into pharmaceuticals and, consequently, innovation, reduced, i.e. let us for the moment accept the view that fewer research resources employed in the industry either would lead to a lower proportion of basic research in the total research activity directed to this area of medical advance and thus a loss in the rate of innovation, or they would be directed at high social cost into non-medical activities. (We may have to challenge these views later.)

The first question to ask is a qualitative one. One possible result of the industrial structure described may be to produce too many innovations of low social value—a familiar result in the analysis of monopolistic competition, where, traditionally, advertising outlays result in wasteful atomizing of the total market. To assess this, the best we can do is to appeal to American evidence, covering an industry at least very similar in its general economic features to the British, and certainly spoken of with approval by Dr. Yule Bogue. J. W. Markham has quoted William Comanor's study of the pharmaceutical research as developed in 57 firms over the years 1951–60.* From this it appears that 4632 new products were marketed in that time. Of these 432 were new chemical entities, 760 duplicate products, 1064 new dosage forms and 2376 compound products. The first category was found to be strongly associated with the employment of professional research personnel; and the higher individual firm expenditure was, the more such entities were produced. (This finding, together with the apparent

* New product patenting is more important than the process patenting—at a rate of 80 : 20 (Ref. 1).

pay-off to concentration in a relatively few therapeutic classes, seems to favour Mr. Teeling-Smith's rather than Mr. Lee's view of increasing returns to scale in research—but more of this later.) The impression given is that the industry structure as a whole *does* produce many innovations of relatively low social benefit, and that concentrated research in part of the industry (probably associated with size of research effort) provides most of the innovations of high social benefit. (It seems that "molecular manipulation" which Dr. Yule Bogue defends is included among the new chemical entities.)

We certainly do not wish to lose the baby of new chemical entities with the bath-water of the other new products, and so it is interesting to speculate—supposing the situation in the U.K. to approximate to the American—how we might increase their number. If, in the process, we can produce conditions which also tend to lower the price of drugs, so much the better, but that is probably a secondary consideration, though we should never underestimate the traditional function of price reductions in spreading the consumption of new products; and, even if it is true that demand for particular drugs is often inelastic, there may still be gain by getting drugs cheaper rather than dearer.*

The problem is essentially one of shifting research resources into more basic research whilst retaining the economic incentives which result in quick application of research break-through. As R. R. Nelson puts it, this problem is partly what economists know as the "classical external-economy problem"—"first, research results are often of little value to the few that sponsor them, though of great value to another firm, and second, research results often cannot be quickly patented",[2] i.e. cannot command a commercial return within a time consistent with recovery of costs, given normal attitudes to discounting time. It is clear, then, that any policy to increase "basic" research cannot entirely rely on harnessing commercial incentives. But a rearrangement of the incentives within the industry may do so. On reading the papers given in this series so far, it seems to me that the encouragement of two developments would help. Firstly, innovatory risks can be lessened by aggregation of different research efforts—applying the insurance principle. Also there are increasing returns to scale in research productivity—at least so far as experience now goes—but this means concentration on a relatively narrow therapeutic field. Clearly then, we want industrially oriented research laboratories of larger scale which are themselves combined through ownership. (How many the industry in the U.K. alone would support is a question for debate but the arguments

* I doubt very much whether the demand for individual drugs is as inelastic as is often supposed, especially where world markets are concerned. Undoubtedly they are at least income elastic in many markets.

put forward later require that sufficient be established to maintain competition between them in research activity. The required number may be very few, because of international research competition.)

Second, it seems clear from Dr. Fryers's paper that the tie between manufacturing, selling and research—the "integrated" firm—can be an obstacle to the widespread adoption of innovations. In negotiating a licence, it appears there is a conflict between attaining what is regarded as satisfactory profits on the integrated firm's whole activities and setting royalties which would be attractive to other manufacturers.

It is easy to see why this conflict is particularly acute in the pharmaceutical industry: without the protection which the combination of research, branding, promotional and advertising activity conveys to profit levels, the return to manufacturing would fall to a level set by potential competitors' manufacturing costs. There seem to be few obstacles to entry to manufacturing from the technical side, and no one claims important economies of scale in manufacturing. (This extreme "vulnerability" on the manufacturing side distinguishes the pharmaceutical from most other "science-based" industries, where considerable obstacles to entry to manufacturing exist even without patent or other protection.)* Dr. Fryers canvassed various ways of mitigating the effects of this dilemma without being able to eliminate it. A possible answer is obviously disintegration. This does *not* mean—*pace* Mr. Lee—that yet another economist is suggesting that "the research function should be delegated to some non-industrial or state institution", or that "science and industry should be divorced". What I have in mind is Mr. R. R. Nelson's "industrially oriented laboratories not owned by specific industries but doing research on contract for a diversified set of clients,[2] licensing the fruits of their own independent research. Examples of such firms already, of course, exist in the world industry. (If there really *are* research advantages to this kind of organization, one would expect the latter to become their most important function.)

But *could* more of such "research firms" make a living? A.B.P.I. thinks that "royalty income is not an adequate subsitute for the effective exercise of patent rights. The granting of a compulsory licence means a loss of part of the firm's market, with the result that capacity may become idle and have to be carried by a smaller volume of sales. . . ." This is to restate the dilemma of the integrated firm, but the passage continues "the inadequacy

* Here one should perhaps remind Mr. Jones that necessary conditions for price competition are to be found in the structure of the supplying industry: whether the industry faces a monopsonistic buyer or not is immaterial. The Post Office facing a highly competitive supply for postmen's clothing has operated for years without major complaints—because the level of prices is determined by cost plus normal profits, i.e. the successful bidders' opportunity costs. Disputes arise when monopsony is faced with collective oligopoly or monopoly, which in turn depends on the entry conditions.

of relying on royalties to support research or development is illustrated by the experience of the National Research Development Corporation ... it has found that royalty income is totally inadequate to support even the development of new products, let alone the original research."[3] There are many reasons why N.R.D.C.'s experience should not be held to be evidence about the viability of the type of firms we are considering. First, it is specifically concerned with inventions *not* having clear industrial application; second, it has to operate as a public corporation, open to all who wish to submit inventions; third, of its nature it cannot develop expertise in localized industrial fields; fourth, it is saddled with the compulsory exploitation of all inventions offered to it by government departments; fifth, it cannot attract risk capital. Even so, it admits that "one or two real 'winners' could alter this situation" (of being unable to balance its accounts).[4]

The principal determinant of the profitability of "research firms" would be the pricing policy they are allowed to pursue—the terms on which payments for the use of their inventions are made. One possibility would be to require a firm to grant exclusive rights to one manufacturer. The two firms would then share in the prospective profits of exploitation. The only difference from the present situation would then presumably be that rather more profits are siphoned into research than would otherwise be the case. Since the long-run viability of the research firm would depend on keeping its inventive level high, the extra profits would be ploughed back into research, with net gain to society.

But if we were solely interested in increasing the level of research activity, the appropriate policy would be to allow the "research firm" complete freedom of contract. In that case, one would expect it to take advantage of the division of the final drug market into branded and generic drugs by pursuing a policy of discrimination in licensing to different manufacturers, negotiating exclusive contacts where it saw fit, licensing at different royalty rates to manufacturers having a secure branded market, and licensing to "generic" drug manufacturers if that strategy appeared to pay off. (To get in the best bargaining position, the research firm would presumably have the function of performing the clinical trials for new drugs—and there may, as it appears from Dr. Yule Bogue's paper, be some advantage from the point of view of safety in having this function centred in what would be organizations necessarily devoted to "accurate observation", "careful documentation", etc.)

Yet a third alternative is some form of compulsory licensing. The term itself is, of course, ambiguous so far as pricing is concerned. Compulsion is of minor effect if it allows the terms of a licence to go unspecified. What previous speakers have intended by "compulsory licensing" is, I think, "most favoured firm treatment", i.e. the granting of royalty terms

is the private concern of the contracting parties, yet newcomers can claim to get no worse terms than their predecessors. At all events, I construe it so here. Compared with the other alternatives we have canvassed, the effect of this would probably be to reduce the profits of the research firm but would ensure the widest possible dissemination of an innovation. This might well be the best of the three worlds. So long as our intuitions about the effects of scale and specialization in research are correct, and so long as process development (which might indeed be harmed by the adoption of the arrangements we have been discussing) *is* of relatively minor importance, the net result might be increasing profits to research plus a greater rate of production of socially useful drugs. Since entry into manufacturing would also be encouraged, there would probably also be a fall in the average price of drugs—though this would depend partly on how fast innovatory possibilities emerge.*

This prospective modification of the industry's structure would also tend to resolve the dilemma facing the Government as major buyers of a research-oriented industry's output—a dilemma pointed out by Mr. Jones when he said, towards the end of his paper, that if the State chooses to use its considerable power of patronage to stimulate a higher rate of innovation in industry "it would be a pity to stimulate technological advance at the cost of an industry's operating efficiency or financial tautness"—by which he meant that the State must be tough in negotiating prices. The State buyer is put in an impossible position if he has to judge the effect, in particular price negotiations, of the allowed rate of profit on future innovations; and it is in part because of similar uncertainties that it seems to me probable that the Ministry of Health will use very gingerly indeed its apparent power to undermine the patent structure in the drug industry. For efficient performance of its duties the State must basically rely on competitive bids: it must be able to *assume* that the general industrial structure is such as to remunerate innovation adequately.

It may well be said that the growth in the practice of compulsory licensing is already tending to produce a research-firm oriented structure, and certainly it *could* be used to bring it about. But clearly there are conditions for, and costs of, bringing about this result which must be recognized, and I cannot pretend to be able to foresee them all. Most important, it is essential to ensure that income from licensing new products will, in fact, accrue to the licensors—and this requires, at the very least, that drugs are not sold unless bearing a "most favoured firm" royalty, acondition which would

* It could happen that the new structure was so productive of innovating possibilities that, in the short run, the switch of manufacturers to new products would lessen pressures to reduce prices and costs of old products. This is unlikely to survive for long in a very profitable industry.

require international action to this effect for all countries who now uphold patent rights. I agree with Dr. Fryers that in compulsory licensing it is essential not to discriminate between foreign-based and British firms. This is a minimum first step to international improvement in this area. Another important condition is that some system of official (random) sampling of drugs is devised, because under the new structure envisaged, the pay-off to branding drugs would be lessened. If these conditions are met, the use of a compulsory licensing system may well, in the end, have beneficial effects on the industry's structure. Any change brings costs, and there may well be a period when resources devoted to drug research in general, and more basic research in particular, are lessened. But given, as I have no reason to doubt, that the U.K. is a relatively favourable place in which to set up, and profit by, medical research activities, the longer run will see a considerable expansion. In this context, some of Dr. Fryers's proposals for patent reform look more attractive. First, his case for extending patents to natural compounds is reinforced. Second, since I envisage more strongly research-oriented firms, in which there is some, though I believe little, danger of adverse consequences because of concentration of knowledge, it may be important that patent coverage be narrowly construed. In turn, Dr. Yule Bogue's emphasis on the importance of international collaboration in testing drugs would, one imagines, find a ready response in the firms I have described.

I conclude this section with some comments on particular points raised by Dr. Fryers's "model" concerning the effect of shortening patent life, and Mr. Lee's warning about making judgements about the ratio of profits to capital when the latter excludes research expenditure. Dr. Fryers's conclusion, that were a patent life shortened to an "effective four years" from its present "effective life" of twelve, it would "mean initial prices approaching double those indicated by this model under present circumstances", entirely depends on assuming that the price elasticity of demand for a new drug is zero. In spite of the vast amount of evidence given on the Kefauver hearings and elsewhere about the prices of drugs, I know of no evidence which would satisfactorily test this hypothesis. (Evidence about the increase of amount sold over time as price falls, while suggestive, is not good enough. What is required ideally, is a test in separate markets at one time, in which a drug is sold at different prices and in which other parameters such as incomes are known.) But the often attested fact that manufacturers try to introduce a new product at a price near that of an old product which it may wholly or partly replace is certainly evidence that manufacturers behave as if there were considerable price elasticity (i.e. advertised drug prices reflect manufacturers' fears of price retaliation). This is a very important issue to resolve, because if greater quantities of the drug can be sold by reducing price, it may be just as easy to remunerate

research with the lower price—indeed, the return to the research effort may turn out to be greater, though one *would* expect the return on manufacturing activities to fall.

Mr. Lee's warning is well taken—but it points towards the whole absurdity of trying to work with rigid categories labelled "capital" and "other expenditure". If this argument is also meant to imply that research expenditure should rank for tax relief, then one's view on this must, of course, depend on being sure that "research" expenditure is itself well directed, to which my earlier remarks are relevant, and on whether, looking outside the "research-oriented industry", the public interest would be served by diverting scientific resources from activities which would not enjoy tax relief (and this includes most, if not all, other institutions in which research is done). This brings us to Mr. Jones's paper.

Mr. Jones maintained a self-denying ordinance in not seeking to draw out of his discussion inferences for the pharmaceutical industry or medical research in general. Unfortunately, that rule—however hazardously—must be breached now. In one respect it seems to me that the dangers he saw in relationship between government spending and research response do not apply to our area of discussion—namely, the unfortunate tendency, when the Government is the chief customer of an industry, for that industry to concentrate upon innovatory activity which results in rather too narrowly marketable products (to put it kindly). As an outsider, I see no great danger of this in pharmaceuticals. However, his other points do contain lessons for us.

As he points out, the main determinant of the distribution of research resources between the main institutions—industrial research associations, private firms, government research institutes and universities, is government spending. Many writers, and notably E. B. Chain, have stressed the importance to invention in drugs of the contributions of differing types of institutions—a conclusion reinforced in general by studies of innovatory processes such as Jewkes and Stillerman. Mr. Jones, I think, feels that so far as research innovatory activity at large is concerned, the Government's civil research expenditures are distributed among the institutions fairly satisfactorily. He did not address himself to medical research in particular, but he certainly gave the impression—which many will share—that too much government money is devoted to nuclear research and civil aerospace projects. It is indeed difficult to resist the view, looking at the matter from the point of view of potential benefits to humanity, that a reorientation of effort towards medical research, including drugs, is overdue.

In discussing this, we can really do no more now than point out some of the unanswered questions. One obvious difficulty is the relatively high specificity of research personnel. An effective switch of activity demands scientists and technologists of specialized training. Mr. Jones gave a picture of a

recent but healthy growth in national research activity, but illustrated how success in research is cumulative—research money attracts further research money and the scientists to go with it. Clearly, a government determined to encourage a massive break-through in medical research would have to decide on a promising area and focus its financial support accordingly, while keeping in view the need for a balance among institutions. This means, possibly, increasing direct research contracts with industry. (In the field characteristically more important for medical research than for other research areas—the charities—keeping the balance may imply a differential encouragement of this particular area of benefaction—e.g. by extra tax relief to donors.)

In selecting these research areas, it may be asked, what principles should the Government adopt? We are faced here with the difficulties noted at the end of O.H.E.'s pamphlet on the Finance of Medical Research, which poses the problem of the relative claims, for example, of poliomyelitis, cancer and mental health, a problem similar to that encountered by Dr. Fryers when he spoke of the difficulties of "authoritative evaluation of the value of possible products". In resolving this, weight must, of course, be given to expert advice on the prospective "cost effectiveness" of research in the different areas: but on the benefits side, the paradoxes involved in trying to compute "savings" from avoiding illness and death, give highly unsatisfactory answers, as students of the analogous problem of computing benefits from investments (e.g. in roads) designed to avoid accidents know. However, would not careful research into the public attitude towards various illnesses reveal a remarkably consistent ranking of preferences for certain research areas, at least, among healthy people?* Or, if this fails, a similar study of doctors' preferences for research, based on their experience in general practice in particular, may reveal something approaching unanimity in ranking. If so, this would be a useful, if partial, guide.

To discuss how the extra money might be administered would be to take one even further from my area of competence: but one should, I think, also stress that arranging for extra demand for medical research is only one side of the question. The other is the supply of appropriately trained personnel. Already the expansion of demand upon scientific manpower noted by Mr. Jones is showing defects in training processes—as in the unfilled places for applied science students at Universities and Colleges of Advanced Technology. If the extra doctors and scientists are to be forthcoming, a considerable revision of attitudes and practices in the education system—reaching back, perhaps, into the sixth form—will

* The charities, I take it, are not a perfect reflection of consumer preference in research but their relative size is some indication at least of major donors' preferences.

probably be necessary; and certainly universities will have to reconsider the balance of their student numbers as between disciplines.

The case for increasing pharmaceutical research, in particular, as put in the preceding papers does not rest, however, solely on its potential in relieving suffering, though that, rightly, has been the dominant theme. A strong secondary theme has been the industry's performance in promoting exports and (by implication) saving imports—and it has been asserted that pharmaceutical research pays off strongly in these terms. It seems to me, though the case cannot be proven, that the arguments are stronger here than those derived from humanitarian interests. For the latter is really a question of getting done as quickly as possible somewhere in the world the necessary research to whose products we, as consumers, get access. I do not take as axiomatic the proposition that Great Britain's pharmaceutical research activity must grow: the optimal division of world research activity in medicine may, on the contrary, require a brain-drain towards, say, America and Switzerland, whilst we specialize in other aspects of medical research, perhaps with a reverse brain-drain. Or it may require foreign sponsored research in Great Britain, which may have no favourable effects on our balance of payments at all. Only a very careful account of present discoveries and trends, together with a detailed study of the disposition of research resources and the speed of innovations and terms of access to them, could tell us.

(I notice that Dr. Yule Bogue says that U.S. company-financed prescription drug research outside the U.S. has risen sharply lately. I suppose that the predicted growth of future U.S. research sponsored activity may well spill into Great Britain. This will be small comfort for British pharmaceutical firms "dependent on home-based research" but it may reflect a better international diversion of labour.)

Humanitarian and national economic interest do not necessarily coincide. Nevertheless, at least on the surface, the pharmaceutical industry's recent import–export record has been good, though here again there are great statistical difficulties. Mr. Jones concentrated on two "research-based" industries—electrical plant and aircraft. Taking the 10-year period from 1954 to 1963, what one might call the "crude trade balance"—exports minus imports (of finished products)—has been rising much faster in pharmaceuticals than in electrical plant (and about at the same rate as in electronics). The aircraft industry's "crude balance" is, of course, dependent in an unusual degree upon "buy British" policies; but at least pharmaceutical exports have kept pace proportionately with them over the whole period, and the pharmaceutical industry has not suffered the decline in exports which the aircraft industry has been showing since 1959. (One needs a very much longer period to judge aircraft export performance than that of most other industries, but few would argue that the halcyon days

of 1955–9 will be soon repeated.) This relative stability in export earnings may well have been particularly valuable in a period marked by recurring crises in the balance of payments. A proper appreciation of pharmaceuticals, as of any other industry's record, would have to take into account indirect effects on imports and exports, and in particular the import content of suppliers to the industry. Should such an appreciation be made, one imagines that pharmaceuticals would compare still more favourably. When this appreciation comes—as one hopes it will—to be done, clarification on two matters in particular will be welcome—the position of invisible earnings and payments, and the precise relationship between exports, imports and the research activity of the U.K. firms.

Invisible earnings and payments—the transactions between and within firms that do not enter into the Trade and Navigation accounts, and probably most important here for payments on account of research services —might modify the picture. I have in mind the fact that nine-tenths of the research activity in pharmaceuticals is done outside the U.K. (Dr. Fryers). Prospective changes in the level of innovatory activity would have to be viewed against changes in the balance in invisibles. One would also like to see some analysis of the composition of (especially) exports in terms of the U.K. research content, as compared with products sold at home. I realize this involves definitional and other difficulties, but if it could be done it would throw light on two of the arguments presented in these papers—including one of my own. If the "research content" of exports is substantially greater than it is of products sold at home, this is support for the argument implied in many preceding papers (and in particular, Dr. Yule Bogue's) that the pharmaceutical industry is an efficient converter of British research into national earnings. If, on the other hand, it turns out that the "research content" is relatively low, it weakens that case, but also weakens one of my earlier arguments about the relation of selling expense to exports.

One of the great difficulties of relating research effort to exports—or, indeed, to output as a whole—is that of identifying the lag between research input and its results. Presumably the recent fall in the rate of growth of research expenditure, which concerned earlier speakers, will have delayed effects. There was a very swift increase of research expenditure in the pharmaceutical industry between 1954 and 1959. There is no sign yet of a comparable spurt in exports; many will be watching the export figures with great interest to see whether this occurs, and even more for a demonstration of the connections between the events.

I am aware, in concluding, that what I have said leads to a beginning of a set of research specifications for appraising the pharmaceutical industry's performance rather than a set of positive solutions. I am even more aware now than when I undertook this job of how difficult it is to

define the public interest. I fear I have done less than justice to the other speakers' arguments; and in particular I have not given to Dr. Yule Bogue's most interesting proposals for the further development, by international action, of tests for toxicity of drugs, the consideration that they deserve. On this, and on other like issues, of course, the economist can have little to say. I hope, however, that I have shown that, while it is possible to discern, if dimly, some of the economic changes that would be beneficial in the British industry, the "popular indictment'" with which we started is indeed superficial, but not without uncomfortable implications. One of the most welcome signs that criticism, far from being silenced, is valued is surely the very existence of this series of lectures, and another is the great help given by the staff of the Office of Health Economics to all speakers. They have helped us in every way they could, and we are grateful.

References

1. *Economic Incentives in the Drug Industry: Drugs in our Society*, edited by Paul Talalay, John Hopkins, 1964, pp. 174–5.
2. The simple economics of basic scientific research. R. R. Nelson, *Journal of Political Economy*, June 1959, p. 306.
3. *A.B.P.I. Annual Report, 1963–64*, pp. 8–9.
4. *Nat. Research Dev. Corpn. Report, 1961–62*, p. 5.

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