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ACADEMIC AND INDUSTRIAL RESEARCH IN THE FIELD OF THERAPEUTICS[1]

By Sir HENRY H. DALE

DIRECTOR OF THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH, LONDON, AND SECRETARY OF THE ROYAL SOCIETY OF LONDON

WE have to-day the privilege of assisting at the formal inauguration of these Research Laboratories, which the enterprise of a manufacturing house has brought into being. I know that I can speak for all those who are present, in saying to the directors whose enlightened policy has provided these laboratories, and to the distinguished investigators who will use them, that we wish them all the success which they desire and deserve. And in wishing them success, I have in mind not merely such as will directly increase the efficiency and extend the scope of the industrial enterprise with which these laboratories are associated, though that we may wish them without reserve; but we may also wish them a wider and more enduring success, in adding to the sum of life-saving knowledge, for the benefit of all mankind.

[1] An address delivered at the opening ceremony of the Research Laboratories of Merck and Company, Inc., Rahway, New Jersey, April 25.

The word "research" in relation to industry has been made to do duty over a wide range of meanings. You would probably find some manufacturers who apply the term to the mere experimental control of the details of an unprogressive technical routine, or of the quality of the materials used in it. At the other end of the scale, this great country, in particular, can show conspicuous examples of the far-seeing policy of great industrial enterprises, in providing opportunity for men of world-wide fame in science to follow freely the lead of their own original genius, without any immediate reference to the production of remunerative inventions. Results of the greatest theoretical importance to science have thus been obtained, which any university might be proud to claim as the product of its laboratories of pure research; but in some cases, at least, they have been obtained under conditions which only the technical resources of great industry could provide. I do not

think that we can have any doubt that, by such a policy, industry will not only render a proper service to the wider interests of the community from which it draws its support, but will also act in the essential interests of its own success and development. And it will do so, I think, not merely because some of the most important inventions, leading to really new lines of practical development, do in fact arise as incidental results of fundamental researches having no such practical aim, but also because the progress of such free scientific inquiry in any community creates the atmosphere of mental enterprise and the fount of ideas, which enable practical invention to thrive and to come to fruition.

There may be some who will see a danger here, fearing lest the opportunities offered by the research service of industry may come to make too large a draft upon the highest grade of scientific ability, so that the universities may be unable to make good their primary claim upon it, for the training and inspiration of the following generations. The danger is not one which could be treated lightly if there were any good reason to fear its development. For the scientific future of any country, in industry as well as in the academic sphere, must depend on the quality of the recruits which the universities can furnish; and that quality will be determined, not only by the effectiveness and the attractive influence of the formal teaching which they provide, but even more by the opportunity which they afford to their best students, of a living contact with the finest type of ability and achievement in research. If such a danger really existed, we could hardly put the responsibility for it only on industry. The great institutions, supported by private munificence or by public funds, and offering, to men selected for their achievement or promise as investigators, an opportunity to give the whole of their thoughts and energies to research, must share any responsibility of that kind. This country, through the unparalleled and enlightened generosity of its leaders of industry and finance, has led the world in this relatively new development of the endowment of research for its own sake. I myself have the honor now to be associated with an institute thus devoted entirely to medical research, with no formal academic contacts, supported from the public funds by the British Government. Earlier, after a relatively short academic experience, I had charge, for ten of my most active years as a scientific worker, of laboratories also concerned with various aspects of medical research—physiology, pharmacology, immunology, serology—and supported by the head of a great British pharmaceutical firm, Sir Henry Wellcome, who had migrated from your country to mine at an early stage of his career. I allow myself the apparent egotism of these personal details, only to make it clear that I have had the opportunity of viewing, from more than one angle, this problem of the relation between research in the universities, in endowed and public institutes and in laboratories supported by industry. And, so far as this experience has enabled me to form a judgment, I do not believe that there is any real or permanent danger of the universities losing, to whole-time research in endowed institutions or in laboratories associated with industry, the particular kind of scientific leadership and power of inspiration, which, in the interests of all kinds of scientific activity, it is essential that they should retain. So far as I can judge, I believe that, in general, this relatively new growth of whole-time research as a career is already effective, and is likely to become more so, in the reverse direction. In this, as in other spheres of human activity, supply must be largely determined by demand. The universities, in the nature of things, can offer only a limited number of major opportunities in science to their ablest and most enterprising students; and the more numerous the extra-academic opportunities for careers of distinction and of service to the community in research, the more readily will able men be willing to try their ability as investigators, before embarking on careers of professional practise or business; and the wider should be the field thus made available to the universities, in choosing the men they wish to retain and to promote. I do not think, then, that there is any real danger in that direction. Such difficulties as may arise, to hamper the development of the best and most helpful relationship between research in the universities and in the laboratories associated with industry, must come from causes of a different kind. In the field of medical science, which is that of my own direct experience, I am inclined to doubt whether the ideal relationship has yet been everywhere established, between research in the universities and the hospitals, on the one hand, and that associated with the pharmaceutical industry on the other. The finding and acceptance of a proper relationship, however, is vital to the progress of both alike, and to their union in an ordered advance, along the common front of medical science and its applications. It is a matter of special importance to an institution such as this, which starts to-day on its career, with the good wishes and the confident hope of us all. I hope, therefore, that I may be allowed to put briefly before you a few ideas as to the special kind of service which an organization such as this may render to medical science, and as to some of the difficulties which it may have to face.

Let us recognize, in the first place, that investigation in that group of sciences which contribute to medicine entails certain special obligations. The practitioners of medicine are bound, by a tradition of

long and honorable history, to place any new knowledge, gained in the practise of their art, freely at the disposal of their professional brethren, without any concealment or any attempt to restrict its use for private advantage. This tradition has no connection with any formal code of professional etiquette governing medical practise. Its basis, I think, is a recognition of an essential condition for the advance of medical science; and in recent years, as such advances have come in increasing measure from the research laboratories, the workers in these, whether medically qualified or not, have in general shown themselves eager to embrace this great medical tradition and to accept this freedom of the great medical brotherhood. Without committing ourselves too hastily in advance to the details of its application over the whole field of enterprise, I think we must accept this tradition as embodying a true ideal, and one which we can not afford to lose or to see obscured. For medical research differs from that in other fields in this respect, that its ultimate aim is the provision of knowledge which will find its application in the relief, the cure or the prevention of human sickness and suffering. Further, while all medical research, however remote from any immediate thought of such application, preserves this ultimate aim, no practical development of the results of medical research can be made, no therapeutic invention can be completed, without a full and frank cooperation with those engaged in clinical practise. Those who are engaged in the task, vitally important to the progress of medical science and practise, of translating the new knowledge of natural laws and principles into terms of practical therapeutics, as the workers in these laboratories will be, require the fullest confidence and cooperation of those, on the one hand, who are freely exploring new avenues of knowledge, without an immediately practical objective, and those, on the other hand, who are directly responsible for the care and the treatment of the sick. And in order that this frank and full cooperation and confidence may be established, between all those engaged in furthering medical discovery and its application at these different stages, they will need to convince one another that they are bound together in a common cause and by loyalty to a common tradition.

I think that we must frankly face the fact that those whose contribution to this common end is made by research in laboratories such as these may find a special difficulty in carrying that conviction. These laboratories have been founded by industry, and their maintenance and progressive opportunity of service to medical science will depend on the extent to which industry receives the proper reward of its enterprise. I have no fear that the directorate responsible for these laboratories will reckon that reward by any narrow calculation, based merely on returns from directly remunerative invention. But you men of science, who have accepted the opportunity which these laboratories offer, will probably find some among your academic or clinical colleagues who will be ready to assume that your researches, henceforward, will be directed merely to the promotion of some trade interest, to securing some advantage to the manufacturing house supporting you over its competitors and not to the advancement of the common cause of medical science. I say that you will probably find some ready to take this attitude, and to regard you as engaged in, at best, an inferior order of medical research; but it may be that I am wrong, and I hope that I am. I was speaking from the analogy, perhaps a misleading one, of my own experience in another country, and now nearly 30 years ago. I suspect, however, that human nature and academic traditions do not exhibit any fundamental differences over those parts of the world where our common language is spoken and that they do not change completely in the course of thirty years. If there is anything in my suspicion, it will be your task, as it was mine, to show these colleagues that they have been wrong in their assumptions; that work in these laboratories supported by industrial enterprise, though differing from theirs, perhaps, in the nature of its immediate objective, can be as genuinely inspired by the ideals of the advancement of medical science, and of service to suffering humanity; and that even in researches undertaken in the interests of some immediately practical development, the alert investigator, given such freedom as you will surely have here, will find the opportunity for making additions to the common fund of scientific knowledge, which may be as fundamentally important as those which come from the academic laboratories. They have had examples before them, indeed, for many years, from other laboratories established and maintained by great pharmaceutical houses in this country; and it must surely be generally recognized that some of the great advances in medical knowledge, which have in recent years come from American universities, have been made possible by the cooperation which only industrially supported research could give. But prejudice dies hard, especially when it has its roots in a tradition which we all acknowledge and respect; and I suspect that you who are to work here will find that there is, for yourselves and your colleagues in other similar institutions, something yet to be won, of the full confidence and cooperation which you need from the academic investigators and which they as certainly need from you. You will win it, when they see that your work differs from theirs, not so much in its quality or its ultimate aim as in the nature of

the incentive and in the kind of opportunity offered by the conditions under which it is done.

There is one matter, affecting the question of loyalty to a common medical tradition, which I must mention more explicitly, if only to free myself from the suspicion of shirking a difficulty. I refer to the question of patents for inventions having therapeutic value. I shall make no attempt to conceal my own wish that we could do without them. I am convinced that a general recognition of their use by research workers in the medical field would be unfavorable to open confidence and to the free interchange of experience and materials among such workers, including those whose part in a common investigation is concerned with the human patient. The whole basis of such cooperative work would be endangered by any suspicion that it was being used for the enrichment of some individual or institution, and not for the advancement of medical science for the common benefit.

That being said, I should make it clear that I am not among those who condemn the use of patents in medicine with a kind of dogmatic fervor and without reference to its object and its effect. The object of any patent law is to further the progress of science and its applications, by stimulating invention and by providing the conditions which will make its results available to all who need to use them. I believe that a general use of patents in all parts of the field of therapeutic research and by investigators in all kinds of institutions would definitely hinder, rather than promote, such progress. That belief, however, does not entitle me to suggest that the protection by patent of any kind of therapeutic invention, under any conditions and in any country, must of necessity have that detrimental effect. So far as I can judge the situation, the danger of it seems to me to be greatest in connection with discoveries relating to remedies of the biological type, for which the practical application is apt to present itself as a stage in the general advance of knowledge, to which many, in different institutions and countries, have made essential contributions. I believe that there is a definite danger here from the difficulty of distinguishing between scientific discovery and practical invention, and from the temptation to use the opportunity which a patent affords, not only to endow a particular institution in which a practical development happened to begin, but also to dictate to the whole world an orthodoxy in its application, and thereby to restrict the freedom of further advance. Frankly, I am inclined to regard the medical patent as a peculiarly dangerous weapon when it is wielded by the good intentions of the academic amateur.

On the other hand, I do not see the same danger in the use of patents for inventions related to really new substances of therapeutic value produced by chemical synthesis. I can not ignore the argument that an immediate and complete freedom to all the world for the manufacture and sale of such a substance might have the result of its not being produced at all, because nobody could justify the expenditure necessary to organize its efficient production and to make its value known to those who could use it. I think it could be urged that, under the conditions of modern pharmaceutical industry, in some countries, a patent for a definite invention of this kind may be used in accordance with the very purpose of medical tradition, to make the new knowledge available to all who need to use it. I think that it can also be urged that such a policy may enable an industry to support research leading to further and more important inventions. Without such incentive and guarantee it is hardly likely, I think, that the great pharmaceutical industry of Germany could have embarked on a policy which, after many years, has led to the production of substances representing the first clear advance in the treatment of malaria along new lines since the Jesuit Fathers brought cinchona bark from Peru in the seventeenth century; or that the pharmaceutical industry of this and other countries would have enriched the resources of medicine with all the new general and local anesthetics which now help to reduce the sum of human pain. If the industry of any country tells me that it can only promote research and apply its results, in this synthetic field of therapeutic invention, by the use of patents, I can not presume to contest the statement. But I am certain that patents in the medical field will do no service even to industry, unless they are so used that they serve also the great medical tradition, so that industry wins and retains the confidence of the academic laboratories and the clinics. No invention in the medical field can be completed or brought to use without the cooperation of the physician and his patients. I believe that such cooperation will be readily and properly given so long as it is clear that the aim of industrial research is the real increase of knowledge for the ultimate benefit of mankind and not the promotion of some narrow commercial aim.

The idea of cooperation involves some differentiation of function. It would not be in the general interest of science that the academic institutions and laboratories such as these should be following exactly similar lines of investigation, with the same kind of immediate objective. Broadly, we may distinguish their respective functions, I think, by saying that the primary task of those academic laboratories, which are concerned with the ultimate advancement of therapeutics, is the increase of our fundamental knowledge of the problems involved, without any immediate or insistent thought of its practical applica-

tion. The function of science in the universities seems to me to be well expressed in the old formula, which, since its foundation in the seventeenth century, has defined the purpose of the Royal Society of London —"the improvement of natural knowledge by means of experiment." That tradition has not needed any artificial importation into the universities of this country. One of the first and greatest of American citizens, Benjamin Franklin, was himself a distinguished fellow of the Royal Society. Your primary task in these laboratories, on the other hand, will be to find applications for the laws governing therapeutic action, as fundamental inquiry reveals them, and to translate them into the practical terms of remedies ready for the treatment of the sick.

Broadly, I think, this differentiation can be made, and I believe it to be important that it should be kept steadily in view. On the other hand, it is natural and proper that, from time to time, these functions should largely overlap. The academic investigator must certainly not be inhibited or called off from his quest, if its natural line of development should lead him to a discovery which is directly applicable to the prevention or treatment of disease. On the contrary, it is right that he should be the more encouraged to pursue his investigation, by the thought of its promise of immediate benefit to mankind. I suppose that we shall agree that the discovery, in the past century, which had the most revolutionary and transforming effect on medical science and practise was that of microorganisms as the cause of infective diseases; and its real starting point was the interest, awakened in the mind of a man of genius, Louis Pasteur, by the relation between the optical rotations of the different tartaric acids and the asymmetry of their crystals. He followed the clue through the differential fermentative action of moulds and of yeasts, to open a new world to investigation, in the bacterial origin of putrefaction and of many diseases. But, out of an unbounded admiration for that great man and for his wonderful gift to mankind, I am sometimes tempted to wonder whether that gift might not have been even greater, and in some of its phases more permanent, if the clamor for practical application had not led him, in later years, so far into the unfamiliar field of therapeutics, and away from his more fundamental inquiries. When Michael Faraday, patiently seeking the improvement of natural knowledge, with an inspired curiosity, discovered the phenomenon of electromagnetic induction, he probably had little thought that it would find any practical application; if he had had any prevision of the kind of civilization which, a hundred years later, would have arisen on his discovery, the thought would probably have appalled him. It will surely happen in the future, as in the past, that free and fundamental researches will often lead to the most important practical discoveries; and we need not grudge his good fortune to the academic investigator whose work has such a result. I do think, however, that there is a definite danger lest he should be diverted by it from his proper task of further free inquiry and should devote his interest to the practical development and application of a discovery already made, which, in many cases, he had better leave to others. The concentration of popular enthusiasm on discoveries which are immediately applicable in therapeutics is natural and intelligible. We need have no fear of its effect, provided that a proper balance of recognition is preserved within the universities themselves, between the achievement of a practical success and the fundamental advancement of knowledge. I have no right, and no desire, to criticize here a particular line of policy, which some of the universities of the North American continent have adopted in recent years, in order to secure to themselves funds for the endowment of further research, from the proceeds of practically useful medical discoveries which have come from their respective laboratories. It is for them to judge their needs and the proper way to meet them. I mention the matter, not from any desire to make or to imply a criticism of action already taken, but because of its direct bearing on a view which I desire to emphasize, namely, that the primary and special function of research in the universities is to build the main fabric of knowledge by free and untrammelled inquiry and to be concerned with the practical uses of it, only as these arise in the course of a natural development. I suggest that we should watch carefully the effect of any line of action which might lead the scientific departments of the universities to give encouragement and promotion to the practical inventor at the expense of withholding it from a potential Michael Faraday or Willard Gibbs. If that should happen, there would be a real danger of the university departments neglecting their own proper part in the cooperative scheme, and encroaching on that more proper to the laboratories supported by industry.

I have suggested, as the primary concern of the laboratories supported by industry, the development to a practical outcome of the fundamental discoveries which the academic and endowed institutions may be expected, in the main, to furnish. But just as the academic worker ought not to be restrained from following freely the line of his inquiry, because it happens to lead to a practical application, the investigator in an industrially supported laboratory ought to have a large freedom, to follow a clue to new knowledge of a fundamental kind, if it presents itself in the course of his practical investigations. Indeed, I think it is probably of great advantage to an

industrial laboratory that its staff should have always in hand a substantial body of investigation having no direct relation to any practical development. My own personal experience, if you will pardon a further reference to it, perhaps influences my views unduly. If the head of a great pharmaceutical house, who gave me my first real opportunity as an independent investigator, had been inclined to judge me by my output of therapeutic novelties directly remunerative to his firm, I think he must have concluded that I was a very unprofitable investment. If he did so, he never let me suspect it; on the contrary, I received a steady encouragement to follow, with my colleagues, the natural lead of the problems which our initially practical investigations had presented. And I believe that such a policy is undoubtedly the right one. If necessity is the mother of invention, the spirit of free investigation is most certainly its father. The men who work here will need it, to preserve their active interest in what is happening in the larger world of science, and to maintain their contacts with men of like interests in the academic world.

In a very large proportion of cases, when we come to look at the results, it will be difficult to say whether a particular discovery would come more appropriately from an academic or from an industrial laboratory. Permit me to illustrate the difficulty by an example which has some personal interest for me, as well as for these laboratories. Many years ago my friend, Dr. Reid Hunt, now professor in the Harvard Medical School, thought that he detected the presence, in an animal organ, of some unstable derivative of choline, of greater physiological activity than that substance. An examination of a series of artificial derivatives, with Dr. Taveau, led him to the discovery, in acetylcholine, of a substance having at least one thousand times the activity of the parent base. Some five years later, in the Wellcome Laboratories, I was still following up certain lines of inquiry on the pharmacology of ergot, which had been suggested to me as a subject when I entered that service. A remarkable type of activity showed itself in certain peculiar ergot extracts, and cooperative work with my colleague, Dr. Ewins, led to the isolation of the substance responsible for it, which proved to be acetylcholine. Acetylcholine thus passed from the class of synthetic curiosities into that of natural substances, and a fuller study of its action showed a remarkable relation between its effects on different organs and those produced by parasympathetic nerves. This work, in an industrially supported laboratory, had brought us no nearer to practical therapeutics than Professor Reid Hunt's original discovery had done; but it arose from a chance observation, for which only the industrial connection could have provided the opportunity and of which we were able to take advantage through our association with large-scale work. After another interval, created by the war, the next step was taken in an academic laboratory, when Professor Loewi, in Graz, showed that stimulation of the vagus nerve produces its effect on the frog's heart by releasing something remarkably similar to acetylcholine in its properties; but the quantities were far too small for direct identification. After another interval of years, now in an institute supported by the public funds, another chance observation enabled Dr. Dudley and myself actually to isolate acetylcholine from an animal organ, in quantity sufficient for complete identification. So that now we had evidence that this substance, the most powerful dilator of the arteries of which we have any knowledge, actually occurs as a natural constituent of the body, and almost certainly intervenes in the natural control of its functions. But still its instability, and the consequent evanescent nature of its action, while fitting it supremely for such a natural function, made it of very doubtful value for artificial application in therapeutics. And so the scene shifts again to the industrially supported laboratories, and the systematic search begins for allied esters of choline, with a similar but more persistent action. And already there is news of the discovery of several; of one from the laboratories of the ancestral house of Merck in Germany; of another, apparently of real therapeutic promise, from the research laboratories of this younger house of Merck, for the inauguration of which in their new form we have been invited here to-day. The pharmacological properties of this new substance, however, were first made clear by Simonart, working under academic conditions, in the laboratories of my friend, and for a time my close comrade in research, Professor A. N. Richards, of Philadelphia. I congratulate these laboratories on securing the cooperation and advice of Professor Richards in relation to their activities in fundamental research. The association, as you will see, has a double interest for me; but I take almost as much in tracing the successive stages of this investigation, from the academic to the industrial laboratories and back again, and in finding myself unable to suggest that the nature of the researches at any one stage was specially suited to an academic institution, and at another more appropriate to the function of an industrial laboratory.

I have spoken of the broad differentiation of aim and of function between academic and industrial research, and of the different types of ability and of temperament suited to each. There are men, indeed, of whom we could say with confidence that the associations of academic life are necessary for their happiness and their efficiency in research; and there are others of whom we could say with equal cer-

tainty that their best work would be done under such conditions as these laboratories provide. I believe, however, that the men so easily classified are relatively few, and that for a large majority the choice will be determined by the accident of opportunity, rather than by aptitude. For some of this majority, I suspect that the best conditions for the full development and maintenance of their powers of serving science might be provided by a successive or an alternating experience of the conditions of academic and of industrial research. The investigator who has been digging himself to a standstill in an academic groove, might find a new mobility in the less conventional surroundings of an industrial laboratory; while his colleague, whose inventive energies have grown stale from too long contact with a variety of practical problems, might find them refreshed and renewed by migrating for a period to the calmer atmosphere of fundamental research. I believe, then, that a freer interchange of suitable personnel, if it were possible, between the academic laboratories and those supported by industry, might have an invigorating influence on both; but I speak of ideals, without knowledge of practical possibilities. I am sure that even a short experience of the kind of opportunity that these laboratories will afford would make some of your academic colleagues envy the elasticity of organization, the adaptability of equipment and readiness of expansion to a large scale of working which the industrial association can give.

There are several advantages which you will have here over some institutions supported by memorial endowments. I am sure that this country must have had examples of a type of large-hearted testator or pious founder, familiar to us in England. He rightly believes that he can create the most worthy memorial to himself or to those dear to him by the endowment of medical research; but too often he wrongly believes that his generous impulse brings with it a scientific vision and a prophetic wisdom, entitling him to restrict, for all time, the application of his benefaction to research on some particular problem in medicine, which has enlisted his personal sympathies or stimulated his imagination. You who work here will be free to choose your problems, according to the needs of the time and the promise of advance offered by current progress in science; you will be able to give intensive cultivation to the fertile areas, to raise the crops which are likely to give good yield and put in the sickle where the harvest stands ripe for gathering. You will have the great advantage that your buildings can be designed and equipped, with the sole aim of making the most efficient provision for the work which you have in hand or in near prospect. You begin with an equipment perfect for your present needs, and will be able to expand it as your program and your staff expand. I can hardly resist a feeling of envy at the opportunity which Dr. Major, Dr. Molitor, Dr. Engels and their coworkers will have, to concentrate their thoughts on their researches, without distraction by duties of administration or teaching, in laboratories designed so admirably for the needs of research and so readily adaptable to changing requirements.

Whole-time research, however, whether in an endowed or an industrial laboratory, has its own special anxieties and psychological needs. Research workers in an institution such as this can only give of their best, if they can escape from any feeling of isolation from the general scientific community, and can feel an assurance that their work is making an essential contribution to the general advance of medical science and practise. They will need, and I am confident that they will have, all the encouragement and friendly cooperation which their scientific colleagues in the academic laboratories and the clinical centers can give them. We wish them all success, and we congratulate the president, Mr. Merck, and all who have been associated with him, on an enterprise which we now launch, with high hopes, on a career of service to science and to the industry which supports it.

OBITUARY

FRED E. BROOKS

FRED E. BROOKS, associate entomologist of the U. S. Bureau of Entomology and nationally known writer on nature subjects, died at French Creek, West Virginia, on March 9. He had been in ill health for several years and the immediate cause of his death was a heart attack. Mr. Brooks' first scientific work was done as associate entomologist of the West Virginia Experiment Station, where he did notable research work with insects affecting grapes. For some time he also worked with small mammals. In 1911 he became associated with the U. S. Bureau of Entomology, where his main work was with wood-boring insects, especially those working on apple. He also conducted research with codling moth, the grape curculio and several nut insects. Most of his research work is published in bulletins of the West Virginia Experiment Station and of the U. S. Department of Agriculture. In addition to entomology he was keenly interested in nature generally and published many papers covering his observations in journals such as *Nature, Country Life in America, The Rural New*