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ACCIDENT AND OPPORTUNISM IN MEDICAL RESEARCH*

BY

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My title speaks of accident and opportunism, and it hardly requires to be said that the two must go together if accident is to have any value, if it, indeed, is to be anything but a hindrance to research of any kind. Perhaps it is one of the important qualifications for success in research that a man should know by the subconscious reasoning which we call instinctive judgment whether what appears to be an accident, a phenomenon presenting itself quite unexpectedly, is just a nuisance, the result of some trivial error, so that the further study of it will lead to nothing but waste of time and energy, or whether on the other hand it offers a possible clue to some new discovery of real importance which ought to be followed even at the cost, perhaps, of a diversion from the original objective. The same idea has often been expressed by saying that accidents fruitful in discovery happen only to those who deserve them—to those, we may say, in whom a natural aptitude has been reinforced by stored and ripened experience, so that a trained alertness, which does not distract the attention or weaken its concentration on the chosen objective, holds the mind ready to pounce on an unexpected opportunity. If we were called upon to construct a scale of values for the different kinds of scientific research we might feel bound to accord the highest rank to the kind of investigation which can be systematically planned in advance, such as one which sets out to interpret by mathematical analysis a set of astronomical or physical data, but accidents of the useful kind have sometimes been effective even in attracting and, as it were, refocusing the attention of some of the greatest of mathematical theorists. You will remember how Archimedes, the greatest mathematician of his own and one of the greatest, I suppose, of all ages, found the clue not only to the solution of the practical problem concerning the adulteration of the gold used for the king's crown but to one of the fundamental laws of hydrostatics in a sufficiently commonplace accident—the overflowing of his bath when he lowered his body into the water. Some nineteen centuries later the young Isaac Newton, driven home to Woolsthorpe from Cambridge by the arrival here of the plague, had been directing his astonishing powers to an attempt to discover a cause for the orbital motion of the moon round the earth and of the planets round the sun. Remembering later those years when he was yet only 23 to 24 years old, he wrote of himself: "I was in the prime of my age for invention and minded mathematics and philosophy more than at any time since"; and on that alert and receptive mind the sight of an apple falling from a tree in the Woolsthorpe garden acts like a trigger, and it comes to him in a flash that the gravity which pulls the apple to earth is holding the moon in its orbit; and he plunges into the calculations which, when some 20 years later they were given to the world in the *Principia*, were so completely to reshape men's ideas of the universe.

I could find other examples, if we required them, of the way in which theoretical and experimental investigators in the fields of pure physics and chemistry have on occasion been able to take advantage of accidental observations to make great new advances in their various special fields. Accident certainly played some part, though probably not so great a part as popular rumour has sometimes suggested, in those great discoveries a little over half a century ago of the *x* rays by Röntgen and of the radioactivity of uranium by Becquerel which together contributed so much to the launching of physics into its new era. Certainly they did not belong to the same class as the discoveries which most people were expecting to arise from the natural and straightforward development of the physical knowledge of the day. I have a very clear recollection of the interest which they aroused when the news of them first came to Cambridge in my second and third undergraduate years.

Röntgen's discovery of the *x* rays with their remarkable penetrating properties, enabling them to pass freely through flesh and to cast shadows of the bones on a fluorescent screen, was first made known here by reports in the daily press; and I well remember a friend of some seniority telling me that he had been at a dinner party at which this reported marvel had been the prevailing subject of conversation, of which the general tone was to ridicule it as a piece of journalistic nonsense; until the only member of the party whose knowledge and judgment gave him a real title to an opinion, J. J. Thomson, broke into the babble of sceptical merriment with a strongly expressed conviction that the report would prove to be true; so far from being nonsense, it was the kind of discovery which he would expect somebody to be making soon. And then in the following year, at a meeting of the undergraduates' Natural Science Club, my contemporary, R. J. Strutt (the late Lord Rayleigh), gave us an account of Becquerel's then new discovery that salts of uranium were continuously emitting a mysterious radiation to which a photographic plate was sensitive; and I well remember the sceptical protest of one of us who was later to become world-famous in theoretical physics and astronomy. "Why, Strutt," said he, "if this story of Becquerel's were true it would violate the law of the conservation of energy!" Such a reaction may well seem strange in these days, when the senior schoolboy can tell you about Einstein's theory of the convertibility of matter into energy and its realization in the atomic bomb. But it represented then a quite reasonable orthodoxy, and

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I like to remember the enterprising spirit of Strutt's rejoinder: "Well, all I can say is, 'so much the worse for the law of the conservation of energy,' because I am quite sure that Becquerel is a trustworthy observer." And, of course, none of us had then any inkling of the enormous expansion of knowledge for which discoveries such as these were to provide the points of origin, or of the whole armoury of physical resources which would thus be brought to the service of medicine. This is even now receiving a reinforcement of yet unmeasured magnitude from the forward leap which knowledge in nuclear physics has made in these recent years, and on the uses of which so much of the world's hopes and so much of its fears are now centred.

Medical Research

The mention of such applications to the service of medicine brings me at last to the subject of my paper—the part played by accident and opportunism in medical research, which is the field of scientific activity of which I can speak from some personal experience, and the one which we may regard as specially appropriate to this occasion. Medical research as we know it to-day has spread its tentacles widely, and there is hardly any branch of experimental science now which may not find itself seized and pressed into the service, constrained to contribute from some angle, either directly or from a distance, to the scientific basis of modern medical knowledge and practice. That, however, is a very recent development; modern medical research as an experimental science, or a varied group of experimental scientific disciplines, had not begun a hundred years ago, and was only just beginning to get really under way at the beginning of the present century. Yet medical knowledge was making important advances at the end of the eighteenth and in the first half of the nineteenth century at the hands of the great physicians of those days, who used to the full the opportunities which they encountered by accident in their practice, enabling them to observe the regular recurrence of symptoms and conditions which others had passed unnoticed. Thus the immunity from smallpox of those who had infected their hands with the cow-pox appears to have been a matter of common belief with the dairymaids and other country folk among whom Edward Jenner practised in Gloucestershire. None of the other medical men of the neighbourhood, however, had observed the fact, much less recognized its significance; they even threatened, jestingly we may hope, to expel Jenner from their Convivio-Medical Club if he continued to bore them with such nonsense. So he waited for many years, accumulating data as accident gave him opportunity, until at length in 1796 he followed the advice given long before by his friend John Hunter and tried the experiment, inoculating a boy with cow-pox and, when that had passed, proving him to be completely refractory to inoculation with smallpox. Jenner, then, in the light of later developments may be regarded as having found already, long in advance of his time, the bridge between the method which waits for opportunities of observation to be provided by nature and encountered by accident and that which puts a possibility to deliberate test under the critical and controlled conditions of experiment. And I propose now to bring to your special notice a few out of a large number of possible instances of the way in which the use of opportunity provided by accident has made contributions, some of them of the very highest importance, to the progress of medical knowledge by research even in its more recent and still flourishing experimental period.

This revolutionary change in the methods of advancing medical knowledge began, as I have suggested, in the second half of the nineteenth century; and if anybody was asked to name the important factors of its beginning and its promotion he could not fail to give to the work and the discoveries of Louis Pasteur, and to the whole science of bacteriology which grew out of them, a leading place among these factors. Everybody knows that it is to the discoveries of Pasteur that we can trace the first clear recognition of living and self-multiplying micro-organisms, yeasts and bacteria, as responsible for the familiar processes of fermentation and putrefaction, and then for diseases transmitted by infection and contagion. I do not think, however, that it is so generally known that accident—a whole series, indeed, of accidental and extraneous circumstances—played a very prominent part in engaging and focusing Pasteur's attention for the remainder of his life on studies which were widely divergent from the line of his original scientific interests and activities. For Pasteur began his scientific career as a mineralogist and a crystallographer. His first great discovery concerned the crystallography of the two isomeric forms of tartaric acid and revealed their true relation to racemic acid. It was he who discovered that the two forms which in solution rotate the plane of polarized light in opposite directions have crystals with forms related to one another as that of an unsymmetrical object is related to its image in a mirror—a discovery as fundamental to organic chemistry as to crystallography, and one which might well, one thinks, have occupied the rest of his life in its direct development. But a mould, a *Penicillium*, grew by accident on his solution containing both the forms of a tartrate; and Pasteur found that, as it grew, it selectively used and destroyed only the form producing right-handed rotation of the plane of a polarized beam, so that the left-rotating tartrate remained. And then, with his mind thus rendered alert to the new idea of a selective fermentation as due to the action of living and multiplying organisms, Pasteur was given additional stimulus and opportunity in that direction by his appointment to a chair of chemistry at Lille, where practical problems of fermentation in the local distilling industry were waiting for his ripening genius to begin the great clarification. And soon his success led to appeals to him to investigate the causes of the variable results encountered in the fermentative production of vinegar and in the brewing of beer, and he was summoned then to deal with the diseases of wine in his own native countryside; and in every case he was able to identify and to separate the micro-organisms responsible for the desired fermentation and to show the way to eliminate those which diverted it harmfully. And then, of course, his success with the diseases of wine involved him in insistent pleas that he would direct his researches to the elimination of the infectious disease known as "pébrine" from silkworms. And thus the train was laid for the great revolution in the pathology and eventually in the treatment of infectious diseases through the further work of Pasteur himself and his immediate pupils in Paris, of Koch in Germany, of Lister in this country, and of all the great host of their disciples and followers throughout the world, right down to the present day, who have caught and carried forward the flame first kindled from the interest of a man of genius in the crystallography of the tartaric acids and in the accidentally observed effect of a mould which grew on them.

Beginning of Endocrinology

As another leading factor in the great change which has come over the whole aspect of medical knowledge and research we should certainly mention the rise of experimental physiology and, later, of biochemistry. And among the special fields of investigation in the general domain of these, which have had a specially direct influence on knowledge of diseases and their treatment, we might well mention those concerned with the hormones and the vitamins. And here again, if we look at the beginnings of experimental activity in both these fields, we shall find the exploitation of happy accident playing a part of real importance.

The real beginning of scientific endocrinology, the study of the internal secretions or hormones, may be found, I suppose, in the brilliant use which great English physicians of the middle of the nineteenth century made of their opportunities, presented by accident, for accurate observations at the bedside and in the post-mortem room: when Thomas Addison described the malady known by his name and recognized its regular association with destructive disease of the suprarenal gland, and when William Gull described myxoedema as a kind of adult cretinism and traced it to atrophy of the thyroid gland. But nobody in 1889 had any idea that the much commoner disease diabetes mellitus had any connexion with the defect of a gland or the lack of an internal secretion. In that year Professor von Mering, of Strasbourg, asked his assistant professor, Minkowski, to remove the pancreas from a dog by operation in order that they might study the absorption of fat from the intestine in the absence of that gland. So, purely by accident, it was discovered that the dog without a pancreas showed an abnormal hunger and thirst and passed large volumes of urine, which Minkowski found to be loaded with glucose. Naturally he turned aside to investigate the condition more closely, and point by point he found it to correspond with a severe diabetes mellitus as this had long been known in the human patients whom it afflicted. But more than thirty years were to pass before this discovery was made fully effective for medical practice by the determined enterprise of two young Canadians, Banting and Best, who, after many experienced investigators had failed, demonstrated the possibility of preparing the missing hormone, insulin, from the pancreas and therewith changed completely the prospect of the sufferer from diabetes. More than that, I think that it cannot be doubted that the stimulus due to Banting and Best's success was an important factor in the astonishing advance which research began at once and continues still to achieve over this whole field of knowledge of the endocrine glands and their hormones. Let me mention just one item. But a few years ago the disease known as pernicious anaemia, or sometimes as Addison's anaemia, was as completely beyond the reach of effective remedy as diabetes had earlier been, when a team of physicians in Boston (Mass.) discovered that a hormone could be prepared from the liver by the use of which the prospect of the sufferer from pernicious anaemia has been transformed as completely as that of the sufferer from diabetes by insulin. The senior member of that Boston team, Professor Minot, is himself a sufferer from diabetes, and insulin had come just in time to save him from a premature death and to fit him to take a leading part in the discovery which is now saving others from pernicious anaemia. Is it fanciful, then, to find in Minkowski's enlightened use of the opportunity which accident offered him in 1889 the real starting-point for work which has now led to the effective treatment of more than one disease regarded till a few years ago as beyond any hope of remedy?

Nutrition and Biochemistry

There has been a good deal of discussion, in an entirely friendly spirit, concerning the real starting point of the researches which led to the recognition of the vitamins and thus to the specific and effective treatment or prevention of a number of other formerly mysterious diseases now known to be due to the lack of one or another of these trace-constituents of a normal diet. There is one accidental observation, used to remarkable purpose by the late Sir Frederick Gowland Hopkins, which must, I think, be regarded as the first link in a chain of discoveries by which that great investigator was led to his first recognition of the factors which we have come to call the vitamins. One student in Hopkins's early advanced class at Cambridge, the late John Mellanby, who was long afterwards the distinguished occupant of the Oxford Chair of Physiology in succession to Sherrington, was curiously unable to obtain the colour reaction for proteins which a certain Adamkiewicz had described, and Hopkins himself found that with the particular bottle of acetic acid on Mellanby's shelf it was indeed unobtainable, though that from all the other bottles in the laboratory gave it readily. He did not put the matter aside as one of those queer anomalies and content himself with telling Mellanby to borrow the reagent from his neighbour; he recognized, with his remarkable instinct, that here was something of potential importance; and with the assistance of another member of the class, S. W. Cole, he immediately began the investigation which led them to the discovery that the reaction was due to glyoxylic acid, which almost all specimens of acetic acid contain as an impurity. Then, with a more effective reagent, they were able to isolate the constituent of proteins giving this and another well-known colour reaction and to identify it as a new amino-acid, tryptophane. And then Hopkins undertook experiments to determine the degree to which each of the different amino-acids which had then been identified, tryptophane among them, was a necessary constituent of a diet for maintenance and growth, and thus he was led further to the discovery that young rats could not grow, or even maintain their weight, on food made up from all the *known* constituents of a complete diet in abundance if these had been elaborately purified. So it was made clear that there were unknown factors of a normal diet, minute in quantity but essential to make the food adequate in quality for normal nutrition; and biochemistry was launched upon what soon became a world-wide expedition of research, still in progress, in pursuit of the vitamins.

Many of you, I think, will have heard of "Ringer's solution"—a watery solution of salts in carefully adjusted proportions with which the late Dr. Sidney Ringer was able to maintain the heart removed from the body of a dead frog in vigorously beating activity for hours. Ringer was a physician to University College Hospital, and, in such time as he could spare from his practice, one of the pioneers of pharmacological research in this country. In his early experiments he had found that a solution containing only pure sodium chloride, common salt, in the proportion in which it is present in the serum of frog's blood would keep the beat of the heart in action only for a short time, after which it weakened and soon stopped. And then suddenly the picture changed: apparently the same pure salt solution would now maintain the heart in vigorous activity for many hours. Ringer was puzzled, and thought for a time that the difference must be due to a change in the behaviour of the frog's heart with the season of the year—until he discovered what had really happened. Being busy with other duties, he had trusted the preparation of his solutions to his laboratory boy, one Fielder; and as Fielder himself, whom I knew as an ageing man, explained to me, he didn't see the point of spending all that time distilling water for Dr. Ringer, who wouldn't notice any difference if the salt solution was made up with water straight out of the tap. But, as we have seen, Ringer did notice the difference; and when he discovered what had happened he did not merely become angry and insist on having distilled water for his saline solution, he took full advantage of the opportunity which accident had thus offered him and soon discovered that water from the tap, supplied then to North London by the New River Company, contained just the right small proportion of calcium ions to make a physiologically balanced solution with his pure sodium chloride; and when, guided by further analysis, he had also added the correct small proportion of a potassium salt, Ringer's solution was complete, and with the later modifications which Locke, Tyrode and others introduced to make it suitable for the tissues of other animals it has become an essential reagent for everyday use in an immense range of medical and biological research procedures.

Adrenaline and Acetylcholine

Some fifteen years later another observation, also of far-reaching effect on the progress of physiology, was made in the same laboratory at University College in circumstances which, if not entirely accidental, had at least something of that character. Dr. George Oliver, a physician of Harrogate, employed his winter leisure in experiments on his family, using apparatus of his own devising for clinical measurements. In one such experiment he was applying an instrument for measuring the thickness of the radial artery ; and, having given his young son, who deserves a special memorial, an injection of an extract of the suprarenal gland, prepared from material supplied by the local butcher, Oliver thought that he detected a contraction or, according to some who have transmitted the story, an expansion of the radial artery. Whichever it was, he went up to London to tell Professor Schäfer what he thought he had observed, and found him engaged in an experiment in which the blood pressure of a dog was being recorded ; found him, not unnaturally, incredulous about Oliver's story and very impatient at the interruption. But Oliver was in no hurry, and urged only that a dose of his suprarenal extract, which he produced from his pocket, should be injected into a vein when Schäfer's own experiment was finished. And so, just to convince Oliver that it was all nonsense, Schäfer gave the injection, and then stood amazed to see the mercury mounting in the arterial manometer till the recording float was lifted almost out of the distal limb.

Thus the extremely active substance formed in one part of the suprarenal gland, and known as adrenaline, was discovered. And in due course there came to light the curious correspondence between the effects produced by this potent substance and those produced by nerves of the so-called sympathetic system ; and Professor T. R. Elliott, then a postgraduate research student in Cambridge, was led to make the brilliant suggestion that these sympathetic nerves produce their effects by liberating small quantities of adrenaline at the points where they end in contact with muscle fibres and gland cells. Some ten years later it came to my notice by sheer accident that a particular extract of the drug known as ergot of rye exhibited a curious and very potent type of activity. With the co-operation of my chemical colleague at the time, Dr. Ewins, the substance responsible was isolated from the ergot extract and identified as the acetic-ester of the base choline, acetylcholine. And when the actions of this came to be examined in detail they showed as suggestive a correspondence to the effects of other nerves as those of adrenaline had shown to the effects of the sympathetic nerves in particular. At that time there was no reason at all to believe that acetylcholine was a natural constituent of the animal and human body ; but my late colleague, Dr. Dudley, and I found it there some 15 years later, again by accident, when we were looking for something else. And meanwhile my friend of many years, Professor Otto Loewi, then of Graz but now in New York, by experiments of a most elegant simplicity had directly demonstrated, in confirmation of Elliott's much earlier suggestion, that impulses passing down the fibres of different nerves to the frog's heart do in fact produce their effects by liberating at the junctions of the nerve with the muscle fibres one or the other of two substances ; and these two substances were found to be identical with adrenaline and acetylcholine in all the properties for which they could be tested. And further developments, in which I have again taken a part, entitle me to believe that even at this moment impulses passing down nerve fibres are liberating tiny charges of acetylcholine where these fibres end in the muscles of my tongue, my lips, my larynx, and my diaphragm and are throwing these into the complicated and varying patterns of speech, which, I hope, contrives none the less to be reasonably articulate.

Histamine and Penicillin

The intimacy of direct experience may to some extent justify this mention of incidents involving my own activities alongside the examples of the far-reaching importance of the part which accident may play in medical research which I have cited earlier. If further excuse is needed, I may plead that the function of acetylcholine as a transmitter of nervous effects figured prominently in a discussion meeting held here yesterday in one of the scientific sections of the British Medical Association. There is even something of the nature of an accident in the fact that this morning another of the sections had a discussion on a novel group of remedies called " Antihistamine substances " ; for histamine is another base which came to my notice by accident, some 40 years ago, as accounting for the special activity of another kind of extract from the same curious drug, ergot of rye. When histamine had thus been isolated and identified by my late colleague, Professor George Barger, it proved to have an action reproducing most of the symptoms characteristic of an " anaphylactic " or " allergic " reaction —a type of reaction which will be familiar to most of you in the special forms of hay-fever, nettle-rash, and some forms of asthma. Then I had another stroke of luck. I was studying a rather weak activity of a similar kind which fresh blood serum exhibited when it was applied to strips of involuntary muscle taken from a dead guinea-pig, and I suddenly encountered a strip of this tissue from one particular guinea-pig which responded with a contraction of peculiar violence when it was treated with a mere trace of horse serum, though it behaved quite normally in the presence of blood serum from other animals—cat, dog, rabbit, sheep, or man. And it occurred to me that many guinea-pigs in that laboratory were used for testing the strength of antitoxic horse serum, and that an economically minded colleague might have provided me with a survivor from such a test. The verification of that suspicion gave us a new idea about the meaning of the anaphylactic or allergic condition ; but it took many years more, and a great deal of work in many laboratories in different countries, before we were able to establish the fact that histamine is a natural constituent of most cells of the living body which is normally held harmless and inactive in their interior but is released, so as to produce its characteristic effects, if the living cells come into contact with some substance from a plant or animal—grass pollen, scurf from a skin, and so forth—to which they have become abnormally sensitive or allergic. And now, here in Cambridge, only this morning we have been discussing the action of " antihistamines " —substances for which it is claimed that they relieve the symptoms by preventing the action of histamine when this is set free by the effect on allergic cells of the substances for which they have acquired a specific sensitiveness.

There is one more example which I must mention, even if only because it will certainly, and most properly, be already in the minds of many of you—the discovery of penicillin. The contamination of a bacterial culture growing upon a plate of solid nutritive medium by the spore of a mould falling on it while the cover is removed for examination must be a frequent and usually no more than a mildly annoying incident of bacteriological practice. It was the chance coincidence of three conditions which made its occurrence on a particular plate in 1929 the starting point of a discovery of first-rate importance. (1) The contaminating spore was that of one particular mould species, *Penicillum notatum* ; (2) the culture on the plate was that of a staphylococcus, susceptible to the restraining effect of an antibacterial agent which this mould produced ; and (3), most important of all, the worker concerned was Professor Alexander Fleming, with the eye of a medical naturalist, alert to detect the unusual phenomenon of a kind of halo round the spot where the mould colony grew, free from colonies of the staphylococcus which grew abundantly over the rest of the plate. Sir Alexander Fleming, as you know, picked off the mould colony and cultivated it in a broth, and found that the broth contained an antibacterial agent which he named penicillin. Then, as happened with Minkowski and the pancreatic hormone, neither Fleming nor anyone else for some years could hold out any hope of the chemical isolation or even of a substantial purification of penicillin, to say nothing of its eventual production in a form and in a quantity enabling its therapeutic possibilities to be critically tested. Such a possibility had in fact been practically written off the account and almost forgotten until, like Banting and Best with insulin, Sir Howard Florey and his chemical collaborators took it up with determined energy and with brilliant and resourceful enterprise ; and now the research chemists and the organized therapeutic industry of half the world have combined to exploit and develop this gift of an alert opportunism and to make it a practical reality for human need. And the chemists have isolated several penicillins, determined their constitutions, and even made one of them by synthesis. And this success has had value not merely for its own sake, it has opened up a most hopeful vista of other and perhaps equally important discoveries in the same field, streptomycin, chloromycetin, and others yet to come.

Of course there are plenty of other instances to be found of opportunity coming to an attentive worker in research through what we have to regard as chance or accident ; and, apart from the many which could be collected, there must be innumerable cases which will never be recognized because no record of them has been preserved. I hope, however, that my choice of a subject and citation of examples will not bring me under the suspicion of suggesting that accident is the principal factor of success in research of any kind, or of medical research in particular. Accidents of the kind which we have been discussing do not, in fact, happen to the merely fanciful speculator who waits on chance to provide him with inspiration. They come rather to him who, while continuously busy with the work of research, does not close his attention from matters outside this principal aim and immediate objective but keeps it alert to what unexpected observation may have to offer. I certainly do not believe that any research work of permanent value is done, or any discovery of importance soundly established, without a great deal of hard, systematic, and conscientious work.

Then I should not like to be misunderstood as suggesting that mankind would have been left in permanent ignorance of any of the items of scientific knowledge, great and small, which I have cited through default of the accidents which were in fact associated with their discovery. If Archimedes' bath had failed to overflow, or the falling apple to catch Newton's attention, the principles which they gave to the world would not have remained hidden for ever, and probably not for long. We know in fact that Hooke, Wren, and Halley were actually competing in speculation about an inverse-square law of gravity and the moon's orbit without being able to calculate the relation ; and that it was the news, indeed, of such an approach to its independent discovery which acted as a stimulus to Newton, leading him to publish at last what he had known in principle and worked upon intermittently for over 20 years. We cannot be so certain in other cases, but it does not seem likely that the effects of removing the pancreas, or of injecting a suprarenal extract into a vein, would have remained very long unknown even if von Mering had not called on Minkowski to perform the one for another purpose, or if Oliver had not goaded a reluctant and sceptical Schäfer into trying the other. Incidents of the kind which I have described may greatly advance the date of a discovery or may associate it with the name of a particular investigator, but I do not believe that they will ever produce discoveries which would not eventually be made without them. They may provide, however, touches of highlight in the varied landscape of science, of decoration to its solid building, or of light relief to the more serious drama of its normal and logical advancement. And if they have thus lent something of life and colour and everyday interest to an hour of talk about medical research they have helped me to achieve a large part of my intention.

THE PROBLEMS OF CLINICAL RESEARCH

BY

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First-class clinical research has been and is being done by men busily engaged in practice. For examples in my own generation I think of J. W. Brown's work on congenital heart disease, Cookson on thyrotoxicosis, or Sheldon on haemochromatosis. In a delightful article called " Clinical Research with a Notebook " Alvarez (1946) has illustrated the good research work done by what he calls small-town doctors. The man in practice has the best opportunity of carrying out clinical research in depth, the intimate and prolonged study of people to learn what happens to individuals with certain constitutions or chronic diseases. If in the rest of this article I refer to clinical research by whole-time workers in hospitals or institutes it is not that I forget these facts but rather that I am addressing myself to those who wish to make clinical research their career or major interest and to those who should provide the facilities for them. I must ask to be excused, likewise, for quoting examples from the work of my own department.

Simon Flexner (1939) said that one of the essentials for successful clinical research was the power of the researcher to command his time for the patients, from whom the research problems are derived, and for the laboratory, in which those problems are investigated. No man in a busy practice can command his time, and for this reason great men like Richard Bright have found it impossible to continue clinical research when they have made a name in practice. The young man who wishes to engage in clinical research in this country should usually work whole-time in a hospital or a research institute. The opportunities for this type of employment have been greatly enlarged by the increased funds which are now at the disposal of the University Grants Committee and the Medical Research Council. Nevertheless, whereas medical practice may be regarded as a stairway, in which the opportunities do not diminish as a man advances in years, the academic and research