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SCIENTIFIC METHOD IN MEDICAL RESEARCH*

BY

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It was as long ago as December, 1949, that I was honoured by an invitation to give this lecture, as an introduction to the series then being planned. "Scientific Method in Medical Research" was suggested to me as a title; and, having no alternative of my own ready to offer, I accepted the suggestion with a procrastinator's easy optimism. Only more recently did I begin to recognize that, to deal adequately with the multitudinous applications of such a theme, a variously qualified syndicate would be required—a greater company of experts, indeed, than those who are to deliver the 40-odd lectures of this series on the "Scientific Basis of Medicine." My task, however, is to offer some kind of general introduction, and not to attempt a speculative review of what the following lectures will present in detail. And I should, further, not wish to be precluded from the discussion of some of the conditions of medical research which concern rather its general direction, or its more immediate aims, than its scientific methods. I hope that I may be allowed, therefore, some freedom in interpreting the title which I accepted. "Methods and Aims in Medical Research" would perhaps more accurately indicate the scope of what I have in mind to put before you.

The Beginnings of "Modern Science"

It will be one purpose of this lecture to bring to your notice the effective and still progressive penetration of the methods and the standards of scientific research into medical thought and practice, as a remarkably recent development; and the more remarkable in that for its origin we have to go back to the very beginning of experimental science in this country. It is not without significance, I think, that the great movement which brought about the new birth, in the sixteenth and seventeenth centuries, of the method of investigating Nature by direct observation and experiment which we call "modern science" had as its pioneers in this country two physicians—William Gilbert and William Harvey. Gilbert's *De Magnete*, published in 1600, provided a real starting-point for the development here of experimental physics some 60 years later, through the work of Boyle, Hooke, and other early Fellows of the Royal Society; and with Harvey's *De Motu Cordis*, in 1628, came the real beginning of experimental physiology and medicine for all the world. You remember Harvey's fervid advocacy of the experimental method—veritable battle-cries of his attack on a medicine which, till then, had been based upon the study and interpretation of ancient authorities—

"Not from books, but from dissections"; "To search and study out the secrets of Nature by way of experiment"; and, again, "Nature is herself to be addressed, the paths she shows us are to be boldly trodden; for thus only, and while we consult our own senses . . . shall we penetrate at length into the heart of her mystery."

It is noteworthy that Francis Bacon, who was Harvey's patient, paid so little attention to the great practical demonstrations which were given by these two, his English contemporaries, of what could be achieved by the method of direct appeal to Nature, which Bacon, himself no experimenter, was bent on proclaiming as the basis of a new philosophical system. The point of chief interest for our purpose, however, is that Harvey's great example and emphatic injunctions should have had so little apparent effect on his fellow physicians in England during the following 200 years. The unaided observational and descriptive study and naming of diseases as practised by Sydenham, whose career overlapped Harvey's, and by the many who followed him during this long period made very important additions, of course, to that aspect of medical knowledge; but they left problems of aetiology to crude and even fantastic speculation; while it is not surprising that the treatment of diseases should have so long remained so rarely effective and so often detrimental and dangerous. Such, however, was to be the general course of medicine for centuries. Harvey's experimental method passed, meanwhile, almost entirely into the hands of non-medical investigators. When the nature and mechanism of the circulation of the blood had been made clear, the next great step required for the advance of medicine—as Harvey himself had foreseen, though he made no real approach to it before he died—was the discovery of the nature of the respiratory process. This was very nearly achieved before the end of the seventeenth century by the group round Robert Boyle—Hooke, Mayow, and Lower, of whom only Lower had studied medicine—but science was then led astray by the dangerously plausible phlogistic speculation of Stahl. A physician, to be brought back to the true line of advance by the experimental chemist Lavoisier a century later.

Progress in the Nineteenth Century

In this long period, and well into the nineteenth century, Harvey's experimental method seems, indeed, to have commended itself to surgeons more than to his fellow physicians. John Hunter was passionately devoted to the making of experiments; his pupil, the country surgeon Edward Jenner, followed Hunter's suggestions and promptings in the experiments from which came not only a practical protection against smallpox but a seed of knowledge from which were to germinate, much later, the progressive

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experimental sciences that now deal with specific immunity and with the viruses. You remember Hunter's letter to Jenner, with its provocative questions: "But why think? Why not try the experiment?" As late as the 1830's, such advancement of medical knowledge as was due to experiment seems still to have been largely in the hands of the surgeons. Charles Bell, in that decade, recognized afferent and efferent nerve fibres, and the different functions of the spinal nerve roots—an observation which was confirmed and extended, indeed, by the almost simultaneous researches of the French physiologist Magendie, in Paris. Of comparable importance, indeed, was the experimental work on reflex action of a physician, Marshall Hall, published by the Royal Society in its *Philosophical Transactions* in 1833, but received with scepticism and ridicule by leaders of contemporary medical opinion. It was an American Army surgeon again, William Beaumont, who in that period made the first systematic experimental studies of the secretory functions of the stomach and the digestive properties of its juice, using with a brilliant opportunism a gunshot accident which gave him a co-operative patient with a permanent traumatic gastric fistula.

From the middle years of the nineteenth century onwards the advancement of essentially medical knowledge by researches in the experimental laboratories was to provide one of the main currents in the gathering flood of general scientific discovery which characterized that period. First came the great revival of experimental physiology, due to the researches and the inspiring influence of Magendie's great pupil and successor in Paris, Claude Bernard, and, a little later, to the great school of Karl Ludwig, in Leipzig—a movement which, somewhat later again, was to spread to this country, largely at the hands of men who had been the pupils of these Continental pioneers. Then bacteriology, with its later outlet to immunology, was opened up to experimental research as an essentially new domain by the work of Louis Pasteur—who, though not medically qualified, had studied under Claude Bernard—and in Germany by that of Robert Koch, and then by the great host of those who followed the lead thus given; and among the early followers was Joseph Lister, who transformed the whole prospect in surgery by researches based on the analogy between surgical infection and putrefaction, the microbial origin of which had been demonstrated by Pasteur.

Discoveries by British Medical Men

Meanwhile, however, this outburst of activity, this great ferment and expansion of ideas, in the experimental sciences so nearly contiguous in their interests to medicine, would appear to have had much more effect on practical developments in public health administration and of technical aids to diagnosis than on the attitude of clinical authority to experimental research as a method by which medical knowledge could be advanced. British medicine of the middle and later nineteenth century could point, indeed, with justifiable pride to the discoveries then being made by keen observation of disease at the bedside, and by correlation of signs and symptoms with morbid changes in particular organs as seen post mortem. The skill and insight displayed in researches conducted on these slow observational lines by men like Richard Bright, Thomas Addison, or, on the surgical side, James Paget, and the scientific interest and importance of the discoveries thus made, would have justified a claim to distinction in medical research for any period in any country. Nor is it to be doubted that there are important discoveries still to be

made by this patient method, which waits for Nature to make the experiments, in directions unpredictable and under conditions of unknown complexity, and contents itself with a faithful record and correlation of results.

One aspect of Harvey's injunction it obeys, in addressing its inquiry direct to Nature. On the other hand, it may be suspected that the very successes achieved by this purely expectant observational method, in this period of the middle and later years of the nineteenth century, may have been among the influences which kept clinical medicine so long aloof, made it seem, indeed, to drift further away from the widening stream of experimental discovery which was fulfilling the other, and major, principle of Harvey's policy. And meanwhile there were changes in the social status of practical medicine which would not, I think, have been conducive to the maintenance of a lifelong devotion, such as Addison had shown, to research by any method. William Gull, Addison's pupil, having won early fame by his work on thyroid defect and myxoedema, achieved it in another direction with the revelation, after his death, of the size of the fortune which an immense and various consulting practice had enabled him to accumulate. Whatever the reason, the cleavage between clinical practice and the experimental researches contributory to medical knowledge tended to become deeper.

In one department of medicine, indeed, that of neurology, this cleavage seems always to have been little if at all effective. Clinical knowledge here was conscious of its need for the analysis of nervous functions, which only the experimental laboratories could provide; while there were responses, especially on the sensory side, of the higher nervous centres which could be studied only by applying an experimental method to the reactions of a co-operative human patient. And so we find a Ferrier or a Horsley working always in the laboratories as well as in the wards, while the clinical researches of Hughlings Jackson were making an essential contribution to the physiology as well as to knowledge of the disorders of the central nervous system. And I have no doubt that cases here and there could be discovered, by search in the more general fields of medicine and surgery in that period, of such conscious co-operation and reciprocal fertilization of ideas between experimental research in the laboratories and practice and observation in the wards. G. R. Murray's discovery, in 1891, of the treatment of myxoedema by administration of thyroid gland comes to mind as an example; its inspiration came even more clearly from Horsley's experiments on monkeys than from Gull's clinical observations; but the very fact that it so readily suggests itself indicates to me that this was a rather conspicuous exception.

Aloofness to Experimental Research

I do not believe that I misunderstand or exaggerate the position in suggesting that, in medicine and surgery as a whole, including most of their special departments, there was in the period under discussion a growing tendency to this aloofness of interests and aims, this progressively dominant assumption that experimental research, and indeed the attempt to apply scientific criteria of evidence with any rigidity, was a matter for the laboratories; and that the practice of the wards, on its part, must be based upon a separate empirical art, ready on occasion to incorporate technical contributions from the research laboratories into the routine of diagnosis or treatment, but basing itself essentially on a body of esoteric experience, trained skill, and acquired instinct—an art, a craft, almost a priesthood, not properly a science of any kind, and least of all one seeking to advance knowledge "by way of experiment."

Perhaps there was a connexion between this attitude and the tradition, still current in my student days, that a physician should use no apparatus which could not be carried in his pocket or in his conveniently rigid and capacious tall hat. Even the clinical thermometer was under suspicion, indeed, of causing the loss of a special skill. The earlier physicians, it was claimed, had been able to discriminate among the causes of a fever by the quality of the feeling of heat communicated by the patient's skin to the experienced hand. I believe that that great observer Thomas Addison had been the first to claim that the skin in pneumonia gave a peculiar sensation of a tingling heat. Far be it from me to deride such a claim as incredible; my only concern is to emphasize the absence of any impulse to raise it above the level of such empirical observation. Scientifically, such clinical lore was, indeed, little better than the practice of a prescientific manufacture, depending for its test of the quality or consistency of a product on the experienced eye, nose, or thumb of the old foreman. The clinical attitude threatened to become, indeed, not merely unscientific, but even explicitly antiscientific.

When I say "explicitly" I have in mind the injunction which met me on the threshold of such clinical experience as I was destined to obtain. "When you enter my wards," said Dr. Samuel Gee, "your first duty is to forget all your physiology. Physiology," said he "is an experimental science—and a very good thing, no doubt, in its proper place. Medicine is not a science, but an empirical art, and it is as such that you may learn something of it here." He added that some day medicine, too, might become an experimental science; but that this would not be in his time.

Now Samuel Gee was a fine and scholarly physician—a late representative, and a very good one, of a tradition which then showed no sign of losing its authority. He had made his own distinguished contributions to medical knowledge by the accepted, observational method; his description of the condition which he named the "coeliac disease" was, I believe, as perfect as could be given until the experimental discovery and differentiation of the vitamins provided what was necessary to complete the aetiological picture. Like other honest physicians of his period he was cynically sceptical about most of the medicinal treatment then available; but he prescribed with judgment those few remedies in which his own experience gave him confidence. A case of "Barlow's disease" was admitted to his ward—infantile scurvy, in the first recognition of which, indeed, he had himself been associated with Thomas Barlow—and Gee ordered, not any drug, but raw meat juice and as many oranges as the child could suck. The empirical fact that such a treatment was effective in scurvy had, of course, been discovered, forgotten, and rediscovered in each of several previous centuries, and even made the basis of regulations by the Admiralty and the Board of Trade; but without the authority of the controlled experiments which have more recently established it on a basis of rational scientific meaning it might still be subject to these alternations of recognition and oblivion.

When every physician depended on his own experience, in most cases quite vague and unorganized, each was entitled, of course, to treat a condition of doubtful aetiology according to his own fancy. The situation was similar in the case of rickets. The treatment of this condition with cod-liver oil had been mentioned as early as 1840; in the period of which I am speaking, at the very beginning of this century, it was current gossip that the eminent Bart's surgeon Sir Thomas Smith had recommended it for the rickety lion cubs at the Zoo. Yet in default of controlled

experimental evidence the physician could still pick and choose among the suggested causes of rickets, and vary his treatment accordingly. The favoured aetiologies then, so far as I remember them, were an intestinal infection and a defective absorption of fats; the latter being based, possibly, on some vaguely apprehended analogy with Gee's "coeliac disease." Meanwhile, in such a confusion of competing speculations and unorganized experience, rickets continued to flourish in our industrial communities, with nothing effective done to treat it, and nothing at all to prevent it. Well might the community have cried aloud, with John Hunter, "But why think? Why not try the experiment?" The experiments, however, which would at last give definite evidence concerning the origin of rickets, and provide a basis for the action which would practically eliminate it, were not to be made till some 15 years later by Sir Edward Mellanby, who is to give the first of the special lectures of this series.

To what, then, are we to attribute this aloofness, even antagonism, of the predominant clinical attitude of those days to the same application of the experimental method to problems in the field of medicine as had been so successful in other departments of natural science? Instinctive defence of authority from subversive intrusion would no doubt account in part for the reaction. A priesthood does not readily share its privilege, or accept additions to or corrections of its doctrine from outside the pale; while the advocates of the scientific method, on their part, would inevitably, with Harvey, react against authority as inimical to its spirit. But I think that we may find a further clue to this antagonism in a warning which, as late even as 1932, was given to his students in a lecture, and repeated with emphasis, by one who was assuredly no opponent of the proper use of the scientific method in medical research—the late Wilfred Trotter. "A practical art," he warned them, "which pretends to be an applied science does not show itself to be progressive, it only shows itself to be quackery." And I think it can hardly be doubted that such shallow pretence to find direct application, in the clinic, for experimental results, even when their soundness and their meaning were still largely matters of conjecture, was too obvious in the practice of some physicians early in this century; and contempt for such posturings must surely have sharpened the reaction of the sound physician of the old school, conscious that, within its own limitations, his cautious if unduly complacent empiricism had really more of the true spirit of science, in spite of his emphatic disclaimer.

A Change in Outlook

Our proper concern to-day, however, is not with the causes contributory to the position half a century ago, but rather to inquire into the causes of the remarkable change, the veritable transformation, which began not many years later, leading to to-day's increasingly co-operative relation between genuine research in the wards and researches in a large and still growing number of the natural and experimental sciences. How has it now become possible and natural to plan for such a series of lectures as will follow this one, dealing with so many aspects of "the Scientific Basis of Medicine," and to refer, without apology or hesitation, to "Scientific Method in Medical Research"? We cannot expect to recognize or to evaluate all the various factors which have contributed to this change. I must be satisfied to draw attention to a few.

We ought first to note the rapid spread—thinking of Harvey, we ought to call it a revival, perhaps—of the belief that a direct study of disease in the human patient can

partake of the nature of a genuinely scientific research. It may be purely observational, it may be experimental in its method; but, in either case, it is ready now to accept the controls and submit to the discipline of the scientific method, and no longer seeks escape from these on a plea that medicine is, and, by implication, can be content to remain, an empirical art and not a science. What has brought about the change? It has had enthusiastic advocates, like the late Sir Thomas Lewis, who insistently claimed for clinical research the status not merely of a science but of a separate *experimental* discipline, as independent, in its aims and its methods, of the physiology and pathology of the laboratories as these of other experimental sciences. I am sure that Lewis, with his burning conviction, did invaluable service to the encouragement in this country, lagging behind some others in that respect, of interest in clinical research as a career, and of enterprise in the provision of opportunities for it. It seems to me, on the other hand, that, with his own research activities concentrated on the physiological analysis of symptoms, he tended to exaggerate the possibilities of experiment on the human subject. There are obvious and natural limitations to experiments directly on man, in researches on aetiology, for example, and even, until a final and confirmatory stage, on therapeutics. Overemphasis of the scope of the experimental method in the clinic may tend, I think, to obscure the most important feature of the new and more general development, which so many of the lectures of this series will illustrate—namely, the progressive obliteration of the earlier deep division, the reciprocal aloofness, between the researches directed to the advancement of medical knowledge in the clinics and those making equally essential contributions to it from the experimental laboratories.

We must recognize, further, that the approach to this easier understanding has been made from both sides. Not only has there been a rapidly increasing readiness on the part of the clinics to adopt, or to interpret, as Wilfred Trotter would have it, the new knowledge pouring from the experimental laboratories; an increasing number of researches in a widening range of the experimental sciences have been undertaken with a conscious orientation towards the advancement of biological and ultimately of medical knowledge. But the most important result, I believe, of this more intimate understanding has been a growing recognition of the need and the duty to interpret the evidence produced, whether it comes from clinics or laboratories, whether from opportunist observations or from deliberately framed experiments, by common and rigid standards of scientific validity and significance.

I spoke of researches in the experimental sciences which have had in view the possibility of service to medical knowledge; it seems hazardous, however, if not impossible, to predict of any scientific discovery to-day, however remote its immediate or conscious objective, that it can never find medical application. Who would have foreseen that the effect of a magnetic field on the path of an electron, or the fission of heavy atomic nuclei under neutron bombardment, would have any special bearing on medical researches? Yet the electron microscope and the newly available radioactive isotopes seem, so far, to have found their readiest and perhaps their most important applications in researches contributory to medicine. Plenty of other examples could be found, and many, indeed, will be furnished by special lectures of this series. I must be content, however, to mention a few of the more general developments in experimental science which seem to me to have exercised an especially potent influence on the course of medical research and on the growth of the

newly co-operative relations between the clinics and the laboratories.

The Influence of Biochemistry

I think that I should place first, for influence in that direction, the rapid penetration, by chemical ideas and chemical methods, of experimental physiology, pathology, therapeutics, and, indeed, a much wider range of the biological sciences. Biochemistry, as we know it to-day, is essentially a creation of the present century. When I was a student at Cambridge, chemical physiology, as we called it, was in relatively low esteem even with the physiologists, and in lower still with the chemists—a Cinderella in the scientific household. "Tierchemie ist Schmierchemie"—animal chemistry is a chemistry of messes—was an aphorism widely quoted and attributed to the great Emil Fischer, then the recognized European leader in organic chemistry. Yet Fischer, by applying the methods of exact chemistry to attack the complex structures of the sugars, and then of the proteins, was himself becoming one of the pioneers of a development which in a few decades was to give to the new biochemistry a place of central importance among the medical and biological sciences.

And then, just before the new century began, the late Frederick Gowland Hopkins came to Cambridge, where, by the influence of his own researches and teaching, and by his steady championship of its potential significance and scope, he was to play a leading part in the movement which has enabled biochemistry so rapidly to permeate and to give a new orientation to ideas and methods in medical research, in the clinic as well as in the experimental laboratories. And, in years more recent, the results which biochemistry was thus achieving by use of the more fundamental chemical disciplines have brought a major and progressive part of organic chemistry, with great new resources of knowledge and of methods acquired in other studies, back to its original aim—the investigation of substances of biological origin and interest—and thus into contacts, now ever more numerous and intimate, with medical research and with clinical medicine.

Look at the list of the lectures of this series, and observe how large a proportion of them deal with medical advances involving applications of exact methods and fundamental principles of chemistry—lectures dealing not only with problems of animal and human nutrition, metabolism, excretory and respiratory functions, with hormones and vitamins, but with conditions of bacterial growth, tissue defences, immunity reactions, and with the chemotherapy of infections. I make only a quick selection as I glance at the list.

Immunology and Chemotherapy

In connexion with advances in immunology and chemotherapy, which have produced in recent decades so conspicuous a revolution in the methods of preventing and treating infections, we may note again how dominant was the influence of chemical knowledge and chemical conceptions on the pioneer investigations, and, indeed, on the whole of the experimental strategy, of the late Paul Ehrlich and of those who have followed his inspiring lead. And could we find anywhere a more complete illustration of the influence of chemical ideas and discoveries on the progress of medical knowledge, or of effective co-operation between researches in the clinics and in the laboratories, than that offered by the recent work of Hench and Kendall, of the Mayo Clinic, on the remedial effects of cortisone and A.C.T.H. on rheumatoid arthritis, on rheumatic conditions in general, and on a still widening range, apparently, of abnormal protective or allergic reactions? Dr. Hench is.

in fact, lecturing on that subject at this moment at the Royal Society of Medicine. Clearly no approach to a discovery so brilliant in its immediate achievement and in its promise of further developments could have been made without the years of systematic laboratory researches by Kendall and others on the difficult and complex chemistry of the hormones of the adrenal cortex, or without other experimental knowledge of the effects of chemically differentiated specific hormones of the pituitary anterior lobe on the activities of different ductless glands. But, on the other hand, to bring all this wealth of discovery from the laboratories to this particular focus and practical trial evidence was required, which only expert clinical researches could have supplied, concerning the remissions of rheumatic or allergic conditions occurring regularly in circumstances which had been shown to raise the output of the adrenal cortical hormones—an observation made possible, once again, by the application of chemical knowledge and chemical methods to material made available by the use of clinical opportunities. Those of you who attend the full series of these lectures will have the opportunity of observing many other examples of the part thus played by chemical methods and ideas in medical research as we now know it.

Biophysics

Good cases could be made, no doubt, for the significance, in the development which we are considering, of advances in other departments of fundamental science. Physics, for example, was very early represented by the rapid exploitation of the x rays in diagnosis; more recently it has offered many applications of the modern resources for amplifying and recording small variations of electrical potential, as in electrocardiography and electroencephalography. I think, however, that it can fairly be suggested that such advances in physical knowledge and technique have hitherto been largely used in medicine as devices for record and diagnosis, and that physical ideas in themselves have so far not so powerfully affected the general direction and outlook of medical research as have those derived from biochemistry. The fundamental physiology of muscular and nervous activity has, of course, been immensely enriched by use of the methods which modern physics provides. These have enabled us to recognize, to record, and to measure fleeting and otherwise imperceptible changes and to make proximate analyses of natural complexities of these into unitary components; but always with the presumption that the electrical changes thus detected and analysed are but signals of ultimately biochemical phenomena. The coming generation may, nevertheless, find biophysics rivalling or even replacing biochemistry in its influence on the course of medical research and the directions of medical thought.

The Science of Statistics

If, however, I were asked to choose one other among the more fundamental scientific activities as a competitor with biochemistry in these recent decades, for depth and range of influence on thought and practice in medical research, I should name the science of statistics. Quietly but irresistibly, it seems to me, statistical methods and principles have been exercising and establishing their corrective influence, substituting a numerical measure of the evidential significance of data obtained in ward or laboratory, whether from opportunist observations or deliberately planned experiments, for the vague and speculative methods of appraisal which formerly prevailed.

Two lectures of this series, by Professor Bradford Hill, will furnish detailed illustration of this salutary influence

of statistics on medical research. This bracing discipline was as badly needed in the laboratories as in the wards; and from both sides came signs of shivering discomfort, as an early reaction to the cold jet of statistical reason. It must indeed have been painful to a mind proudly reliant on the experience of half a lifetime to submit to the imposition of control experiments and statistical evaluation of results as a protection against an unconscious bias of its judgment. To name an example of topical interest, it may be regarded as practically certain that uncontrolled clinical testimony would, but a few decades ago, have given an extended currency, at least, to confidence in the proved value of the antihistaminic substances as suppressive remedies for the common cold.

On the other hand, the value of a statistical criticism of methods and results has been at least as obvious in the experimental laboratories of medical science. It was especially needed, I think, in connexion with the common type of experiment in which an attempt is made to determine the smallest quantity of a remedy, or other preparation, producing death or some other limiting reaction—what my former colleague, Professor Gaddum, conveniently termed a “quantal response.” The problem was first presented in its true perspective, I believe, in a paper in which results obtained by the late Sidney Rowland with a plague-bacillus toxin were analysed by the late Professor Major Greenwood, to whose influence and teaching during many years medical science has been immensely indebted for the clarification of its ideas in this direction. Professor R. A. Fisher's investigations and writings have also achieved the authority of classics in a wider range of biology; while as contributors, in this country, to the building of a scientific statistical basis for the procedures involved in the “biological standardization of remedies,” the names of Trevan, Gaddum, Emmens, and, most recently, Perry are worthy of special recognition.

Earlier to-day I was waiting at a multiple bus-halt at which buses of every line due to stop there seemed to arrive in rapidly repeated succession, except that which I wanted. And it occurred to me that a conclusion, that my line had somehow been eliminated, could have been based on reasoning not very different from that which passed muster not only in the wards, but often in the experimental laboratories, in my early days as student and research worker. And when I had despairingly departed in a taxi my successor at the halt would probably have concluded that buses of the line for which I had waited in vain predominated among those stopping there; and so we should have had the familiar and discouraging conflict of scientific evidence.

Even now I suspect that there may still be found, here and there, authors of medical publications, both clinical and experimental, whose tentative sips at the Pierian spring of statistical method have produced in them little more than a conviction that the occurrence of a particular event—death, say, or recovery—in two out of three instances will become scientifically precise and significant if they record it as a percentage—66.6%. In general, however, I am sure that the calm and ruthless logic of the statistical method has had an influence of inestimable value, in giving a higher level of scientific authority to the planning of investigations and the appraisal of their results, over the whole field of medical research; and that, in thus imposing common standards of scientific validity and quantitative significance on researches in the field, in the wards, and in the laboratories, it has been a most potent factor in the newly co-operative relationship.

Opportunities for Research Work

Let me now make brief reference to the important part in promoting this growth and integration of scientific activities in medical research played by the great changes which have occurred in the source and the scale of the material provision available for its support. Those of us who wished to try our hands at research in the medical field at the opening of the century competed hopefully for the rare crumbs of brief opportunity, which then fell infrequently from a few small private endowments. You know how profoundly that position has been altered. With much larger funds available from private generosity, and with even more important and steadily expanding grants of public money, administered by the Medical Research Council or dispensed through the University Grants Committee, no man with a genuine impulse and with an adequate equipment of training and temperament for medical research need fail now to find an opportunity to prove his aptitude, and, if the result be favourable, to give medical research then at least a prominent place in his life's plans and ambitions. I am one of a great number who have reason to be grateful for the opportunities which have been created under this new dispensation.

There have been and may still be some, however, who, while they would acknowledge that the results, so far, appear to have been broadly beneficial, are doubtful and suspicious concerning the ultimate effects of this predominant support from public funds on the freedom of medical research, and therewith on its long-range effectiveness, as well as on its scientific spirit. Up to a point I can understand this anxiety, considering what might happen under an administration less wise and sympathetic, less expert and independent, than that which has hitherto been responsible for the effective decisions.

The anxiety in question is not unconnected, I think, with a more general discussion, now current, of the proper aim of research in all departments of science. You will no doubt have heard it argued by some that the proper aim of research is to discover truth for its own sake, and by others that it is to discover means for the material improvement of the lot of mankind. If you follow the arguments in detail, however, you will find that those who advocate the pursuit of knowledge for its own beauty and excellence often support their claim by evidence that this has led to the widest and most beneficent of practical developments; while those who insist that material benefit is the proper aim justify encouragement of the most abstract researches as an eventual contribution to that practical end. One begins to wonder, indeed, whether there is much to choose between these rival creeds. It has to be remembered however, that the advocacy of material human benefit, as the only acceptable aim, has associations with a particular political philosophy, and thus with plans for a central, authoritative direction of research. Theories, like people who seem innocent in themselves, may prove to be dangerous through the company they keep.

The Ultimate Aim

In dealing with medical research, in particular, material benefit to human life and health must surely be accepted as the ultimate aim; I can find no other meaning for the word "medical" in such a connexion. And our chief concern must be to ensure that the public funds directly granted for medical research continue to be administered and allotted, as hitherto, by a Council composed predominantly of experts who know the meaning of research, and who can be trusted to recognize the ways in which its truly

scientific pursuit can most effectively be encouraged, without either facile enthusiasm or obstinate caution. Such administrators will know from their own experience that, while the consciousness of the ultimately philanthropic purpose must be retained, and may even provide a valuable stimulus, success in medical research very often depends on an investigator's freedom to seize and to follow an unexpected clue, even when it appears to lead far from the original objective, and in a direction offering no visible likelihood of practical developments. They will be aware of the danger of short cuts, taken in the hope of reaching some dramatically practical result, without submission to the full and exacting discipline of science; and they will know how to hold and adjust the balance between the claims of researches undertaken to develop existing knowledge for medical uses and of those which plan bolder adventures into the unknown. While the administration remains safely under such expert and independent control, the support of medical research from the public funds, now an indispensable condition of its pursuit in this country on the present progressive scale, will continue to be protected from any serious danger to its freedom and integrity. Such danger could arise only if the distribution of the available funds were to become subject to political pressure, seeking to influence its direction in order to satisfy some popular clamour or sentiment, to meet some official convenience, or to enhance some Minister's prestige.

LABORATORY AND CLINICAL EXPERIENCE WITH TERRAMYCIN HYDROCHLORIDE

BY

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A comparatively recent addition to the field of chemotherapy is the new antibiotic "terramycin hydrochloride," first reported in America by Finlay *et al.* (1950). This substance was obtained as a pure amphoteric compound from the growth of a soil actinomycete, *Streptomyces rimosus*.

There is already an extensive American literature, and much is in course of publication, on the physical, chemical, bacteriological, and clinical properties of terramycin (Finlay *et al.*, 1950; Hobby *et al.*, 1950; Welch *et al.*, 1950; Herrell *et al.*, 1950; Bliss *et al.*, 1950).

Terramycin hydrochloride is a sulphur-coloured compound with a bitter taste. It is sparingly soluble in water at pH 7, but can be readily dissolved by the addition of NaOH to pH 8.3-8.5, forming the sodium salt, or by adding HCl to lower the pH to 2, when the hydrochloride becomes soluble.

Stability

In contrast to "aureomycin," terramycin is a relatively stable antibiotic in solution. We have found that the acid solution at pH 2 maintains its potency for up to 30 days when kept at 0° C. as judged by assay against a standard staphylococcus. The alkaline solution maintains its potency for about seven days at 0° C., but it slowly deteriorates thereafter, turning dark brown in colour, and forms a