Jubilee of the Medical Research Council

The National Insurance Act of 1911 provided for a fund to promote research. The Medical Research Committee was set up in 1913 to carry out this purpose. By the Ministry of Health Act of 1919 responsibility for the direction of research was transferred to a committee of the Privy Council. The committee then assumed its present title of Medical Research Council. The responsibilities of the M.R.C. were reaffirmed by the National Health Service Act, 1946. The Minister of Science, as Chairman of the Committee of the Privy Council, is responsible to Parliament for the Council's work.

To celebrate the jubilee of this remarkable British institution we have invited three distinguished authors to provide a retrospect and prospect of medical research. And to this we have added four pages of photographs of faces and places which summarize much of the history of what is widely known as "The M.R.C."

Fifty Years of Medical Research

BY

SIR HENRY DALE, O.M., G.B.E., M.D., F.R.C.P., F.R.S.

I should have felt obliged, in any case, to accept an invitation to take a part in celebrating the Medical Research Council's Jubilee, if only by lasting gratitude for my life's great opportunity, as one of the first whole-time research workers to be appointed by the Council's embryo, the Medical Research Committee of 1913. Nobody at that time could, of course, have foreseen with what gathering speed, or in how many new directions, the Council's undertakings were to multiply and spread during its first half-century.

I have been invited to offer my tribute under the title "Fifty Years of Medical Research," and I have gladly accepted that suggestion, but only in the sense in which it was made. For it is obvious that no brief appreciation could begin to give any idea of the extent and the variety of all that has been discovered and applied, during a period which has witnessed such an outburst of world-wide activity in medical research; or even, indeed, of all that the Medical Research Council's now widely ranging enterprises have been contributing to this great world movement. In this country, perhaps more obviously than in some others, this movement has been transforming clinical medicine from the traditional, empirical art, which was still so largely its status fifty years ago, until now, while it continuously extends and enriches its practical equipment from the discoveries of many of the experimental disciplines, it is rapidly acquiring that character for itself. It is evident, indeed, that this great forward surge of medical research and practice must to a large extent be considered also as a phase, in many directions even as a consequence, of the revolutionary developments during the same period, in a wide range of the natural sciences. Even fifty years ago there seemed still to be, as it were, a close curtain of aloofness between the interests of those who were then working in different major sections of the scientific field; but in these recent years this partition has happily been losing its earlier density, so that with active support and encouragement from the Medical Research Council, it is becoming freely permeable, and in both directions.

I must not, however, spend more of my tribute on such general features of this great advance; for the invitation most kindly suggested that my part in the celebration might suitably have a reminiscent character, referring especially to some features of the Medical Research Council's first enterprise, the National Institute for Medical Research, and recalling some typical projects of its earlier years. When I first heard about the Medical Research Committee, then under Lord Moulton, they had already decided that this, their new Institute, was to have four Departments.

Each was to have its own Director, with an assistant or deputy, and to be separately responsible to the Committee. There was to be such a Department of Bacteriology and Pathology, under Sir Almroth Wright, with Captain Stewart Douglas; another of Applied Physiology and Hygiene under Sir Leonard Hill, with Professor Benjamin Moore; another of Medical Statistics, under Dr. John Brownlee; and one of Biochemistry and Pharmacology, which I was then being invited to form, Professor George Barger being suggested as my principal colleague.

Years of the First World War

These appointments were eventually made to date from July 1, 1914, together with that of Walter Fletcher as the first and very great Secretary of the Committee, and eventually of its successor, the Council. And then, just over a month later, the outbreak of the first World War called for a sudden and drastic revision of all our plans and arrangements; and by the time the war ended in 1918 several members of this original staff of the Institute were no longer available. Sir Almroth Wright was naturally unwilling by then to leave his long-established and famous Department at St. Mary's Hospital for the few remaining years. His place in the reassembled Institute was therefore to be taken by Captain Douglas; and a generous, wise, and co-operative colleague we were all to find him. Professor Moore, very sadly, had died during the war; while George Barger had meanwhile found his major opportunity elsewhere, as the first holder of a new Professorship of Chemistry in relation to Medicine, at the University of Edinburgh. And, in view of later developments, it is of interest to recall that one of his first research colleagues there was to be Charles Harington, then a young Cambridge graduate in Chemistry, who was later, as a Professor in the Medical School of University College Hospital, London, to make his historic isolation, structural identification and synthesis of the thyroid hormone, "thyroxine." Many years later, in 1942, Dr. (now Sir Charles) Harington was to succeed me as the second Director of the National Institute, and as such to preside over its development during the next twenty years, from the small dimensions and tentative character of its adolescence at Hampstead, into the great and widely famous centre which it has now become, in its much larger and more permanent quarters on the Ridgeway, at Mill Hill; and he was then, only last year, to transfer it to the charge of its third Director, Professor Peter Medawar.

As already indicated, the outbreak of war, early in August, 1914, had scattered our new, skeleton staff of the

National Institute, before it had been possible to assemble it, in the laboratories to be made from the wards and offices of the former Mount Vernon Hospital at Hampstead, which the Committee had acquired for that purpose. Sir Almroth Wright had departed early, with several of his associates, to carry out researches in the Army hospitals established at Boulogne, on the pathology and treatment of wound infections. Sir Leonard Hill and Benjamin Moore were soon fully engaged in investigating the hygienic problems of wartime factories, and especially that due to the chronic poisoning which was affecting the workers hurriedly drafted to fill shells with the then new high-explosive, trinitro-toluene—"TNT."

With Barger and his former assistant, Arthur Ewins, I had good temporary quarters in the Lister Institute; and there I had found myself immediately responsible for applying and improvising standards and tests for controlling the safety and the potency of the remedies which were then being hurriedly produced by British and French industry, to replace the many—salvarsan as a prominent example—for which this country had been entirely dependent on Germany. Ewins was thus brought into contact with Messrs. May and Baker, who offered him an opportunity which, even in the national interest, he was bound to accept; while Barger was soon to leave me for Edinburgh. Not till after the end of the war was I able to fill these vacancies, by the appointment of H. W. Dudley, earlier an intimate biochemical colleague with H. D. Dakin in New York, and of Harold King, a former colleague of my own, whose structural organic chemistry was later to contribute greatly to the new Institute's record of achievements.

Meanwhile, however, while attempting still to deal with a series of wartime therapeutic emergencies, I was trying to collaborate with my former colleague, P. P. Laidlaw, in research on the newly urgent phenomenon described as "wound-shock," to which his earlier work with me on the actions of histamine seemed to offer a possible clue: but other duties, for each of us, had prevented us from following this effectively, until friends in the U.S.A. arranged for us to be joined by Dr. Alfred Newton Richards, the distinguished Professor of Pharmacology in Philadelphia. Our work together then led to the suggestion of a traumatic toxæmia as the cause of the functional oligæmia, characteristic of the "wound-shock" conditions.

Not till some 10 years later was any direct evidence to be obtained of the existence of histamine as a natural constituent of most of the body's organs and tissues; but, meanwhile, it had interested the Director of the Council's first Unit of Clinical Research, the late Sir Thomas Lewis, in connexion with his "threefold reaction" to local injuries, shown by the minute blood-vessels of the human skin. Even after the end of the war, in 1918, we had still to wait for two years, till the Mount Vernon Hospital building could be vacated, and then re-conditioned and fitted for our occupation; but we were able meanwhile to begin some of our peacetime researches in, or from, our temporary quarters. Sir Leonard Hill and his assistants thus began to develop his evidence for the health-giving actions of fresh and moving air, and of the ultra-violet component of sunlight. By transatlantic co-operation with H. D. Dakin, I took part in a preliminary study of the chemical basis of the specificity of otherwise similar proteins, as anaphylactic antigens; and then, with Harold Dudley, in the separation, as distinct though similar peptides, of the hormones responsible for the vasopressor and oxytocic activities of the neurohypophysis.

Mount Vernon Building

At last, in 1920, we members of the four Research Departments were able to move into our chosen sections of the readapted Mount Vernon building, which was then to be the only home of the National Institute for the next thirty years. It must have been much easier then, and enormously cheaper than it would be to-day, to take such an oldish building, designed for entirely different purposes, to refurnish its rooms and provide them with such conventional services and equipment, as to turn them into adequate laboratories, for any such range of researches as our different departments might then have had in view. In fact, the kinds of special research equipment then available seem, in retrospect, to have been astonishingly few and simple, in comparison with the ever more complex and costly requirements of to-day. We started with an adequate supply of ordinary microscopes, desiccators and simple centrifuges, a spectroscope, a couple of kymographs, and such like. We were fortunate in having with us Mr. J. E. Barnard—a distinguished amateur, experimenting with a microscope to work with ultra-violet radiation; and also Dr. Edgar Schuster, of the Council's staff, a fine-mechanic of great parts in his spare time, who used his hobby to great purpose in co-operation with our researches. In general, however, our methods and apparatus were simple, and we still depended largely on improvisation. We were very far, indeed, even in imagination, from these days when electron-microscopes, ultracentrifuges, nuclear-magnetic-resonance spectrometers, radioisotopes and the apparatus for using them, even calculating machines, seem likely soon to be recognized as the conventional tools required by almost any medical research.

The Council's generous policy had seemed, so far, to leave us free to follow our own ideas, in framing departmental programmes for our peacetime activities. On those lines we could be promptly at work; but it seemed natural to expect that the Council would from time to time find it proper to bring special directions to our notice, in which the research qualifications of one or another of our departments might appropriately find new opportunities. This was in fact to happen, and in more than one direction, when we were still in our early years at Hampstead; but all such requests and proposals were made with a sympathetic understanding of the needs and the possibilities of true research, so that the result was in every case to strengthen the Institute's contribution to the general advance of medical science. Here I can only attempt to illustrate this manner of its development, and those of its research activities, by choosing a few examples. And it will be understood, I hope, that these must be taken from the 22 years at Hampstead until my own retirement in 1942, and that the choice may well have been affected by a capricious memory.

Insulin and Biological Standards

I found myself soon engaged in a further study of the anaphylactic condition with the late Charles Kellaway, who was then supported by a Research Studentship from the Royal Society. In September, 1922, however, a pressing invitation came for me to cross the Atlantic, with my colleague Harold Dudley, to report more directly to the Council on the then recent discovery of insulin by Banting and Best, and especially on the possibility of making it available for general use in Britain, with the help of information which was becoming available, in Indianapolis as well as in Toronto. On our return we had to carry a rather heavy load of responsibility and contrivance, even with good co-operation from the British pharmaceutical

industry. Dudley, however, succeeded, incidentally, in providing me with a purified sample of insulin in a perfectly dry and stable condition—an achievement till then regarded as impracticable. And this met an immediate need for yet another enterprise, which had been waiting for my return.

Dr. Thorwald Madsen, the eminent Danish immunologist, was waiting for me to join him in a project, under the auspices of the newly founded League of Nations, to provide a new set of international standards for the antitoxic sera, and for any other remedies requiring standardization by biological assay. And I thus found it possible, through successive international conferences at Edinburgh and Geneva, to secure the adoption of our dried insulin preparation, and of another containing the neurohypophysial principles and provided by Dr. Voegtlin, of Washington, as permanent standards for defining the units of activity of these potent hormones.

My department of the Institute, and the Medical Research Council, thus early acquired a new national and international obligation, to prepare, provide, and control the application of such reference standards for antitoxins, hormones, digitalis, and any other important remedies which might yet require such measurement and control by biological assays and tests. And out of all this was to come the Therapeutic Substances Act, and an extensively revised *British Pharmacopoeia*, and, eventually, a special Standards Department of the National Institute, first directed by my distinguished colleague the late Sir Percival Hartley; and a part of this special department is still at Hampstead, while another part is now at Mill Hill. But the Toronto mission had yet more widely scientific results for me and my colleagues. Dr. Charles Best came twice to take part in researches at the Institute; in 1925 to work with some of us on the detailed manner of the actions of insulin, and two years later, with another group of us, on the occurrence of histamine as a constituent of normal cells, in most of the organs and tissues of the body.

Research on Viruses

It was also in 1922 that the Institute received another request, in this case direct from the Council. The late Sir William Leishman had proposed that our staff should be asked to consider a scheme of research, on the mysterious and controversial nature of the then still ultra-microscopic infective agents, now so familiarly known as "viruses." After discussion, in which Captain Douglas was so good as to include me, we proposed to begin with dog distemper; and then, through friendly contacts, I discovered that research on this disease was already being advocated by masters of foxhounds, with a fund to be raised by the weekly journal, *The Field*. Our project could thus be supported from two sources; and we were further fortunate in discovering a largely derelict farm on the Ridgeway, Mill Hill, which could then be bought cheaply. This was eventually to provide the site for the present National Institute; but when we first acquired it, it was needed only for the erection of kennels and hutments where healthy dogs and ferrets could be bred, in guaranteed freedom from infection and from immunity to the highly contagious distemper. For this investigation the staff of Captain Douglas's department was then notably augmented by the appointment of my trusted colleague of many earlier years, Dr. (later Sir) Patrick Laidlaw, and of a veterinary expert, Major G. W. Dunkin. Between 1926 and 1929 they had isolated and identified the virus of distemper, and had then shown the way to produce an effective inoculum giving full protection against the disease—to the

great satisfaction of the many owners and lovers of young dogs.

At the same time, much valuable experience had been gained of methods for dealing with and identifying a virus, and of determining the size of its submicroscopic units. A very valuable contribution to the equipment for such measurements was made by the "gradocol" filtering membranes produced by W. J. Elford, a then recent graduate in physical chemistry who had joined Laidlaw's team. And this was then to be further strengthened by the appointment of Drs. Christopher Andrewes and Wilson Smith, and later of Dr. Stuart-Harris, before the arrival of an epidemic of human influenza, in 1931. The experience obtained in the distemper research, together with the most fortunate discovery that our clean-bred ferrets were readily infected also with influenza, enabled this enlarged research team to isolate and describe the influenza virus in the next two years. And it seems to me reasonable to claim that the Institute had therewith already made an important contribution to the launching of the campaign of research on the viruses, which is still in such vigorous and world-wide progress; but now, of course, with the aid of all the electronic and other types of advanced equipment which the intervening thirty years have made available.

Vitamin D and Sterol Structure

A fruitful collaboration in another important direction had been opened in 1926 between Dr. Otto Rosenheim, the distinguished amateur of research in biochemistry who had then recently added his wide experience to the strength of my department, and Mr. T. A. Webster, of Sir Leonard Hill's staff, who was already at work on the effect of ultra-violet radiation on food, in producing the antirachitic vitamin D. They found that, while ordinary cholesterol could thus be made antirachitic, it lost this property when completely purified from traces of other sterols; and it was then not long before, at Harold King's suggestion, ergosterol had been tried and found to be indeed the radiation-sensitive pro-vitamin D. Larger-scale work then, by Bourdillon, Callow, and Webster, produced a pure vitamin D from irradiated ergosterol, with the name "calciferol" to identify it. Meanwhile another joint inspiration, shared by King and Rosenheim, produced a new conception of the ring-system of cholesterol, common to the structural formulae of all the sterols and the bile-acids. This was generally accepted, and its applications have since been invaluable, in the further studies of a wide variety of substances of biological interest and medical importance—including saponins, cardiotonic glucosides, and the steroid hormones of the adrenal cortex and the gonads.

Chemical Transmission at Synapses

And one other development may be mentioned, closer to my own earlier interests in research. Before 1914 I had recognized the suggestive nature of the actions of acetylcholine, as qualifying it for the function of a junctional transmitter of the effects of nerve impulses; and Otto Loewi's brilliant experiments on the frog's heart, which began in 1921, had practically established this conception for the peripheral effects of the vagus and similar nerves. But the other actions of acetylcholine, on ganglion cells and voluntary motor end-plates, were still waiting to be considered. And it seems to have required Dudley's isolation and chemical identification of acetylcholine as a natural constituent of an animal organ, in 1929, and then the addition to our team, in 1933, of Dr. W. Feldberg, bringing new ideas and methods, to start us on the quest for evidence of a "cholinergic" transmission at these other

junctions; but convincing evidence came then in some two years and later, with the co-operation, at different stages, of J. H. Gaddum, Marthe Vogt, G. Lindor Brown, F. C. MacIntosh, and yet others after my own retirement. And I think that it would be generally admitted that, here again, the Institute programme had contributed to the opening of a new field for much wider cultivation, and with results having again important practical implications, in this case for clinical neurology, as well as for experimental physiology. And again we can trace a connexion with Harold King's chemistry, when he isolated D-tubocurarine, and identified its structure, and thus made, as it seems to me, an essential contribution to the recent spectacular improvement in anaesthesia, and, therewith, to the great advances now being made in surgery.

Broad-minded Policy

I have cited these few examples, to illustrate only some of the directions, in which the research staff of the still young Institute had found scope for their initiative and imagination. One steady source of encouragement, of which we were all fully aware, was the broad-minded policy of the successive Councils, with their distinguished Secretaries and administrative staff, in assuring for us so continuous a freedom of opportunity, and in their generous appreciation of our efforts. And I believe that all of us would have given a special place, among the many reasons for our gratitude, to the readiness shown by the Council

and its staff so to modify the administrative pattern of the Institute, in the light of experience, as to enable us eventually to pass it to our successors, as still, indeed, a young and immature, but already a vigorously viable and intimately co-operative organism.

Since 1942, and especially since the building at Mill Hill was ready at last to receive it, in 1950, the National Institute and the range of its research activities have undergone a remarkable expansion and development, under the wise and inspiring direction of Sir Charles Harington, and now of Dr. Medawar, and with a continued generosity of encouragement from the Council. Meanwhile, although the National Institute has continued until now to hold its pride of place as the largest single item among the now multiple units and enterprises which the Medical Research Council has already created, or has agreed to support, it is obvious that the number and the variety of these have long ago lifted them beyond the range of any reasonable comparison, with the modest aims of the original Committee of 1913, or even, for many years, with those of the Council which replaced it in 1919. And I am proud indeed to have been given this opportunity of joining in the Jubilee celebration of what has become so splendid an achievement. He would be a bolder speculator than I, who would venture on any prediction of what our descendants may be expected to be celebrating, when another half-century of such nationally supported medical research has been completed.

ORIGIN AND DEVELOPMENT OF THE MEDICAL RESEARCH COUNCIL

BY

Sir LANDSBOROUGH THOMSON, C.B., D.Sc., LL.D.

Late Second Secretary of the Council

A governmental agency exclusively for the promotion of medical research was fifty years ago something new. Before that, since the middle years of the nineteenth century, there had been a trickle of State support for medical research through various channels. The beginnings of this were in the field of preventive medicine, at that time more definitely a public responsibility than provision for the treatment of patients. The notable landmark was the research policy of Sir John Simon as Medical Officer of, successively, the General Board of Health, the Privy Council, and the Local Government Board. He arranged for numerous investigations by specially employed experts, and in 1864 obtained authority to initiate laboratory investigations in addition to field inquiries; in 1870 Parliament for the first time voted £2,000 for "auxiliary scientific investigations," and this was maintained for many years at about the same level.

The first year of the twentieth century saw the appointment of a Royal Commission to inquire into the Relations of Human and Animal Tuberculosis. This body took the remarkable step of deciding not to hear evidence—that is, opinions—but to conduct experimental investigations of its own, to determine facts; and for that purpose it was provided with funds enabling it to employ a scientific staff and meet other costs. In a sense, within the limits of its subject, the Commission was a true precursor.

Medical Research Committee

The crucial step was the inclusion in the National Insurance Act, 1911, of power to provide money for research. This was done in a section dealing with sanatorium benefit, which suggests that there may have

been an early intention to restrict the provision to research on tuberculosis. If there was such an idea, someone—tradition says Dr. Christopher Addison—had the wisdom to have the limiting words deleted from the draft of the Bill. The power was permissive, and allowed one penny per annum for every insured person in England, Scotland, Ireland, and Wales to be applied to research; this was from moneys provided by Parliament, not from insurance contributions. The "four pennies," as they were called, were estimated to yield about £57,000 per annum, which was a substantial sum by the standards of those days and enormously more than had ever before been provided for the purpose from public funds.

Much of the public thinking about implementing this provision was done by the Departmental Committee on Tuberculosis, appointed by the Local Government Board in 1912 and finally reporting in 1913. This body made definite recommendations for the establishment of a single organization for the promotion of medical research in the United Kingdom. The power was vested in the National Health Insurance Joint Committee, which proceeded to make Regulations appointing a small executive Medical Research Committee and a large representative Advisory Council. The former was a slightly smaller counterpart of the Medical Research Council of to-day; the latter was a cumbersome piece of machinery (unofficially known as "the forty thieves") that may have been politically necessary at the outset but was destined to fade out of existence within a few years.

The Medical Research Committee met for the first time on June 20, 1913, under the chairmanship of Lord Moulton