Edward Mellanby, 1884-1955 / [Henry H. Dale].

Contributors

Dale, Henry H. 1875-1968.

Publication/Creation

London : Harrison and Son, 1938]

Persistent URL

https://wellcomecollection.org/works/dvcdfhu8

EDWARD MELLANBY

1884—1955

[Reprinted without change of pagination from
Biographical Memoirs of Fellows of The Royal Society,
Volume 1, November 1955]

E. McClanahan

EDWARD MELLANBY

1884-1955

DEATH came suddenly, and without recognized warning, to SIR EDWARD MELLANBY on 30 January 1955, before he had completed his 71st year. Nearly six years earlier he had retired, on reaching the official age-limit, from the Secretaryship of the Medical Research Council, which he had held for 16 years. During this period the range and the influence of the Council's activities for the promotion and support of medical research had undergone a most notable expansion, primarily in the United Kingdom, but widely beyond it also in the British Commonwealth; and Mellanby's enlightened and resourceful enterprise in proposal and planning, and his vigorous drive in administrative action, had undoubtedly been dominant factors in this remarkable development. Like his only predecessor in the appointment, the late Walter Morley Fletcher, Mellanby had been the Council's chief executive officer in much more than a merely official sense. Yet, during all the years in which he had carried that heavy load of official responsibility, he had succeeded in maintaining a direct and personal activity in the researches which had so long provided for him, and also for his devoted wife and scientific partner, the central aim and interest of their joint working lives. He could not, of course, have done this without the Council's active encouragement. When they invited him to become their Secretary, after Fletcher's untimely death in 1933, they had recognized, indeed, their duty to reduce to a minimum the inevitable interference of the duties of that appointment, if he accepted it, with the progressive contribution to medical knowledge which the Mellanbys had been making in Sheffield since 1920, working there in a research unit maintained largely by a grant from the Council's own funds, with additional support from the University and from the local medical community. That local attachment could clearly not be long maintained if Mellanby's primary duties were thenceforward to be in London; so the Council undertook to provide, on an estate, much of it then still vacant, which they owned at Mill Hill, a new laboratory especially designed for the purpose, to which, as soon as it could be built and equipped, the unit from Sheffield could be transferred. Mellanby might then again have ready access to his own research facilities, in such marginal time as might be left to him from his new duties. And, after some years of inevitable delay for planning and construction, during which the researches, even after Mellanby's removal to London, were still kept in being at Sheffield and actively pursued and stimulated during week-end visits there, the new

laboratory at Mill Hill had been completed and occupied. And, there, during the remaining years of his Secretaryship, even during the war years with all their new and tremendous preoccupations, Mellanby had found relief from the demands and responsibilities of organizing for the researches of others, and of giving advice and stimulating action to meet a wide variety of abnormal and urgent problems, by returning at every week-end to the peaceful air of his own laboratory, to work again at his own scientific problems with his own hands and brain. The conditions which made this possible were clearly exceptional. His own specially trained assistants were there during the week to carry forward much that he could leave to them, and their working times could be adjusted to meet his own requirements; and, even much more important, of course, Lady Mellanby was working regularly in the laboratory, and supervising the conduct of what was being continued for him, while carrying on her own special work. With all allowance, however, for those favourable factors, it remained a matter for general astonishment, that Mellanby could not only continue to do effective and productive research with such intermittent opportunity, but that he appeared even to find, in the week-ends spent so busily, a release and a refreshment, a recreation of his powers, comparable almost to that which others would find in complete rest, or in physical exercise in the open air.

When Mellanby retired from the Secretaryship, the Medical Research Council were glad to be able to arrange for him to continue his researches in the special laboratory for a further period, with full time at his disposal. He was thus at Mill Hill on the morning of Sunday, 30 January, to observe and record the results of experiments, in which he was then in happy and fruitful collaboration with Dr Honor Fell, F.R.S., of the Strangeways Laboratory, Cambridge.* Satisfied with the morning's yield, he had gone out to a small garden adjoining the laboratory, where he was cultivating fruit and flowers; and it was there that death suddenly overtook him, relaxed from an immediate and exhilarating contact with his researches.

Parentage and education

Edward Mellanby was born on 8 April 1884, in West Hartlepool, where his father, John Mellanby, was the manager of the shipyard of the Furness-Withy Company. Edward was the youngest of a family of six children, being the last of four sons, of whom one died in childhood. All the other three showed scientific ability of such an order that, at one time, they were simultaneous occupants of important academic chairs. The eldest, Alexander Lawson Mellanby (d. 1951), was Professor of Civil and Mechanical Engineering in the Royal Technical College, Glasgow. The second, John, who became F.R.S., had occupied for some years a London University Chair in the Sherrington School of Physiology at St Thomas's Hospital, moving then to succeed Sir Charles Sherrington in the Chair of Physiology at Oxford,

* Later information indicates that Mellanby on his last morning was working on a new line of experiments, which he intended to report to Dr Fell at their next meeting (see also p. 210).

but dying (1939) before he had held it long, and still at the height of his powers. Edward, as we shall see, held in succession a London University Chair of Physiology at King's (now Queen Elizabeth's) College for Women, and the Chair of Pharmacology at Sheffield University,* before he accepted his last and greatest opportunity of service to medical science, with the Medical Research Council.

The parents were members of a free-church communion, and the children were brought up in an atmosphere of evangelical piety, with austere standards, no doubt, of conduct and enjoyment, but tempered and enlivened by a robust independence and a genuine regard for intellectual achievement and enterprise. The father, John Mellanby, came from Yorkshire and his wife, Mary Lawson, Edward's mother, was born in Edinburgh. John Mellanby senior had been an amateur boxing champion of the North of England, and, naturally, taught his sons to box. It is on record that he was once asked how all his boys had done so well at school and university, and that he replied that only one can be first in a competitive examination, and that he knew no reason why a son of his, if a candidate, should not be that one. The life of the Mellanby household must certainly have been of a character favourable to the creation and strengthening of close family ties; for his friends in after years could not fail to become aware of Edward's strong feeling of affection for his brothers and sisters, his nephews and nieces; of his pride in their achievements, and his generous concern for their troubles. This staunch and active family loyalty was, indeed, a conspicuous and attractive feature of his character.

After early schooling in West Hartlepool, Edward Mellanby, at the age of 14, followed his brothers to Barnard Castle School in 1898, with the aid of a bursary, which each of the others had held before him; and he remained there till July, 1902. At that time the headmaster was the Rev. Francis Lloyd Brereton, and Mr Edward Dalrymple Walrod was the senior science master. Mellanby retained a grateful memory of what he owed to these teachers, and until Mr Brereton died he kept in friendly touch with him. His school record gives the evidence which we should expect, of ability and natural leadership. He won the Upper School Prize and a special Prize for Theoretical and Practical Physics, and he became Head Boy of the school. I think, however, that those who knew him only in later years would have been a little surprised, to find that he left at the school at least as great a reputation as an athlete. He won several events as a jumper and a runner, and was captain of both cricket and football; he was described in the School Magazine as 'the best outside left we have had for some years', and became 'Victor ludorum' in his final year. Professor J. H. Burn, who entered the same school in 1903, tells me that it was Mellanby's fame as an athlete which then survived there, strongly enough to attract the notice of a new boy. These early athletic triumphs on a relatively small stage would not, of course, have justified predictions of conspicuous achievement on a wider one. On the other hand, for one who had given such early promise in games and must have enjoyed them

* This post was combined with that of Honorary Physician to the Sheffield Royal Infirmary (see p.204).

keenly, Mellanby was rather exceptional in the completeness with which, very soon after going to Cambridge, he ceased to take an active part in any, though he always kept an interest in the successes of others, and in watching first-class events on occasion. In the later years his time and his thoughts must have become so preoccupied in other directions, that he could hardly have found leisure for games, if the inclination to play them had lasted. The school-time athletic activities, however, had doubtless contributed to the development of his handsome presence and well-knit figure, and of the robust physique and equable health which made it possible for him, during most of his active career, to work with so tireless a zest, with so few remissions, and without interruption by any serious illness, except for one brief period towards the end of the war in which signs of overstrain compelled him to take a rest.

In October, 1902, Mellanby entered Emmanuel College, Cambridge, with an Open Exhibition in Natural Science and a Leaving Exhibition from the school. His brother John had been at Emmanuel before him, so that the way was eased for his reception there and for the making of contacts, some of which were to mean much to him. Of particular importance was his association, thus early, with Frederick Gowland Hopkins, then acting as Medical Tutor to the College, as well as University Lecturer on Chemical Physiology. Hopkins, as teacher and friend, was to have a decisive influence on the direction of Mellanby's career. It was, in fact, the anomalous failure of the Adamkiewicz colour-reaction for proteins, with the particular bottle of acetic acid allotted to John Mellanby in Hopkins's advanced practical class, a few years earlier, which had led Hopkins more or less directly to the discovery of tryptophane. And this was to lead him in due course, while Edward Mellanby was still in close touch with him at Cambridge, to investigate the number and the nature of such pure constituents, needed to make an artificial diet adequate for maintenance and growth, and thus eventually to come upon the trail of the 'accessory factors' or 'vitamins'. And Mellanby himself would have been the first to acknowledge, proudly to claim indeed, that his close contact with Hopkins during this period, when the new idea of the detailed, qualitative adequacy of a diet was being born or engendered, was a most potent determinant factor in his own later research plans and ambitions.

Mellanby's student career showed a record of the straightforward successes which were to be expected, with college prizes to mark them. He was placed in the first class of both parts of the Natural Sciences Tripos, his special subject for the second part being physiology. Perhaps the attraction of Hopkins's teaching and inspiration would have led him to choose biochemistry, if the subject had by that date achieved recognition in Cambridge as a separate discipline. We cannot be certain, however, that he would have chosen thus; for, though all the researches of his later career had a background of biochemical ideas, his approach to his problems was essentially from the side of biology and experimental medicine. In a preface, partially drafted at the time of his death, to the Chemical Society's *Annual review of biochemistry*, and

containing a glowing tribute to the influence of Hopkins, he was still urging with great conviction the importance of maintaining an effective co-operation between biochemistry, on the one hand, and experimental biology and clinical medicine on the other.

I myself first met Mellanby while he was a Cambridge student, and before he graduated. It was in the summer of 1904, and I was visiting his brother John, who was then finishing an appointment which he had held for a few years in the Wellcome Laboratories, while waiting for a studentship to enable him to return to Cambridge. And there, in John Mellanby's laboratory, I first met Edward, and was immediately attracted, as many others must have been, by the vigour and the straightforward friendliness of his manner, and the evidence of an active and independent mind. I had been prepared for this favourable first impression by what Hopkins had told me of this 'second Mellanby' who had come to Emmanuel; and it was an impression which all later encounters were to deepen, though these were not to be really frequent till we become officially associated, nearly 30 years after this first meeting.

Rumours had reached me also of some of his doings and interests at Cambridge, outside the range of his formal studies. The University Natural Science Club—a small group of the more serious students and recent graduates in that faculty, meeting in one or another's rooms on Saturday evenings to hear papers and indulge in discussion—appeared to have been rather shocked, though evidently not disagreeably, by a paper which the young Mellanby had read to them on the subject of 'Sin'—presented, no doubt, from what in those days was an unexpectedly wide, biological angle. There was even a rumour—probably with no real foundation—that the fame of this discourse, spreading beyond its proper audience to certain College authorities, had had an adverse effect on Mellanby's prospect of election to a Fellowship. In any case, the talk about it gave strength to my own impression of a new recruit to science, with a courageously enterprising mind.

Researches

With the tripos behind him, and a Research Studentship at Emmanuel to support him, the young Mellanby entered at once, in 1906, upon the activities in research which, with only such interruption as that due to the further clinical studies required for medical qualification, were then to continue for nearly 50 years till his life ended in 1955. In that later period of his scientific career which we should, perhaps, regard as its culmination, this direct and personal activity in medical research was to be overlapped, as mentioned already, by his simultaneous achievements as the chief official promoter and organizer, in this country, of opportunities for a great army of other workers in that general field. But, while it should further be recognized that his services to medical research along each of these two lines could not have been without an effect of some kind upon the other, it will be convenient here to follow their courses separately, and to deal first with the personal researches, beginning with the completion of his formal studies at Cambridge.

Research at Cambridge

In the review article mentioned above, which he left unfinished, Mellanby recalled the conditions under which he served his first apprenticeship to research, in 1906-7. In the old Physiological Laboratories at Cambridge, only one small room, with incredibly poor equipment by modern standards, could then be assigned for any researches in that department which dealt with the chemical aspects of the subject. Yet it was in this room that some of Hopkins's most brilliant researches had been done, and were even still in progress; and it was in it, alongside Hopkins, that Mellanby also was to work for the next year. The inevitable inconveniences of such overcrowding, however, must clearly have been substantially offset by the privilege of working in such regular and stimulating contact with Hopkins and his ideas; for Mellanby's output, in this first year of his research experience, showed no sign of being hampered by the conditions, even though they were such that no research worker to-day would regard them as tolerable. It is significant, I think, that Mellanby's first effort in research, while he was still thus working in Cambridge under the direct influence and guidance of Hopkins, dealt with an application of biochemical methods to a definitely medical problem, in investigating the changes produced by diseases in the excreted products of a certain line of metabolism. A published abstract of his first communication to the Physiological Society in 1907, the year after he finished his Tripos examinations and when he was 23, dealt with 'The excretion of creatin and creatinin in hepatic disease'. Neither cirrhosis nor venous engorgement of the liver, he found, caused any important departure from the normal condition, in which creatinine only of these two bases is excreted in the urine; in cancer of the liver, on the other hand, much of this normal creatinine is replaced by creatine.

And a year later, in 1908, came Mellanby's first substantial publication, on 'Creatin and creatinin', in which the whole question of the origins and reciprocal relations of these two bases in the vertebrate animal body was re-opened, and thoroughly investigated. A number of ideas then current, and supported in some cases by eminent authority, were re-examined by newly available and better methods, and decisively rejected. The conclusion was drawn that creatinine is the direct product of the primary metabolism taking place in the liver, while creatine is normally produced from creatinine for storage in the voluntary muscles; and, in accordance with that conception it was found that in very young animals, whether newly hatched chickens or newly born babies, there is no excess of creatinine left to be excreted, until this capacity of the muscles for storing it as creatine has been satisfied. Mellanby's work did not touch, of course, the question of the function of this creatine in muscle, the nature of which did not come to light till many years later; but there was abundant promise of further achievements in this paper, the record of a young man's first full trial of his hand at research, with results making possible the clear and decisive removal of the grounds for a series

of misunderstandings and controversies, which, till then, had encumbered and obscured its subject.

Before this first full-length paper was published, Mellanby, in 1907, had left Cambridge for London, to complete his medical course by clinical and pathological studies at St Thomas's Hospital. Even before that, he appears to have gone to Glasgow during a Cambridge Long Vacation, to take a course in pathology under Professor (now Sir Robert) Muir.

Research at St Thomas's Hospital

During the next three years we find no record of further publications dealing with research. Then, in 1911, he published a paper on cyclical vomiting, describing clinical observations made on the condition and using, in connexion with it, his earlier experience on the metabolism of creatine and the significance of its appearance in the urine. He considered also the possibility that the vomiting might be connected with some cyclical change in the intestinal flora, leading to an excessive production of histamine, the powerful activities of which, and its occurrence in the intestinal mucosa, had then recently been made known by work in my own laboratory. Having by then graduated in medicine and obtained a position as demonstrator in the Department of Physiology at St Thomas's Hospital, and having become thus interested in the possible effects of bacterial activities in the intestine, Mellanby began a collaboration with the late F. W. Twort, of the London Hospital, already a man of great experience in bacteriology, and one who was later to make discoveries of great importance in that field. Twort was then acting as Superintendent of the Brown Institution, in South London. Together they isolated in pure cultures, from intestinal contents, more than one strain of bacteria which attacked such substances and produced such changes as to give them a special interest for Mellanby. A strictly anaerobic, Gram-staining bacillus was thus found, which rapidly and completely destroyed creatine; and the extent to which this action might occur in the intestine clearly required to be taken into account, in assessing the results of metabolic experiments in which creatine was given by the mouth. A little later, in this joint enterprise with Twort, a bacillus of the typhoid-coli group was isolated, growing either aerobically or anaerobically on ordinary laboratory media and actively decarboxylating histidine to produce histamine. Mellanby and Twort's main deduction from this was that the histamine which Barger and I had found, as a constituent of the washed mucosa of the intestine, was probably the product of such bacterial action. The suggestion was plausible enough at that time, though it was later made much less so by the discovery of histamine in many other tissues. Mellanby continued for some years to be interested in the possible participation of histamine, if produced by conditions favouring the growth in the intestine of the appropriate bacteria, in the genesis of such conditions as infantile diarrhoea and vomiting; and he published a paper presenting evidence in favour of such a possibility as late as 1916. Mention should also be made of another investigation in

which he used biochemical methods and clinical opportunity for a study of the metabolism of lactating women, the results of which were communicated to the Royal Society, and published in its *Proceedings*.

The date of the publication last mentioned, 1913, brings us to another and major turning-point in Mellanby's scientific career. So far, it may be suggested, he had been largely feeling his way into the life of research, guided by a general instinct to use the biochemical methods, in which the association with Hopkins had awakened his enthusiastic interest, for the study of problems having some bearing upon the conditions of human health and disease. During this trial period he had held a demonstratorship and, later, a Beit Memorial Fellowship. The resulting researches, without leading to particular discoveries likely to attract wide notice, had clearly given abundant evidence of his capacity for dealing with a variety of problems, with devotion and accuracy, with alertness of interest, and with a resourceful ingenuity. He was marked already, in short, as a recruit of great potentialities to the then relatively small army of the devotees of medical research, waiting for a problem worthy of his powers and his equipment, and for an opportunity to give him adequate scope.

At King's (now Queen Elizabeth's) College for Women

The opportunity was to come in a quarter which might have appeared to be even curiously detached from the clinical association in which Mellanby had so far tended to find his subjects for research. He accepted appointment, in 1913, to a Chair of Physiology of the University of London in the King's (now Queen Elizabeth's) College for Women, founded to provide an education in household science with a genuinely scientific basis and a full academic status. The course for its students of physiology might, accordingly, be expected to be unusually detached, in its aim, from the requirements of clinical medicine, though its bearing on the general health would be clear enough. The research opportunities, though otherwise good, could obviously not be expected to facilitate clinical contacts or co-operation. Mellanby, however, like the rest of us in those days, had to take the opportunity for research where he found it; and his desire to establish himself in a career, without further delay, would naturally be quickened by the prospect of marriage. For a student friendship with May Tweedy, at Cambridge, had early ripened into a clear understanding that they would marry, as soon as conditions made their union wise and reasonable. Miss Tweedy herself, meanwhile, had made a promising start in physiological research at Bedford College, London; and so they were married, in the year following Mellanby's appointment at the King's College for Women, and began their long and happy partnership.

Research on rickets

Mellanby had not long been settled in the new position and opportunity, when a subject of research presented itself, worthy of all his effort, and

congenial to his instinct for a biochemical approach to a problem of human disease. The Medical Research Committee (predecessor of the Medical Research Council), then newly appointed to administer the first of such Government Research Funds, held a meeting in the early part of 1914, at which I was present by invitation, to discuss possible schemes for expenditure. The proposal of the nature and causation of rickets, as a suitable subject, was put forward by Hopkins as a member of the Committee, and was at once accepted; and the meeting proceeded immediately to discuss apparently numerous possibilities, each of which might be investigated by a suitably qualified worker. The field seemed widely open; but Hopkins made a special case for asking somebody to make an experimental study of the metabolic defect in rickets, and recommended that Mellanby should be invited to undertake this; and both these proposals were very readily accepted. I remember, too, that with his shy hesitation—and it may well have been only in a whispered aside to me—Hopkins even speculated on the possibility that rickets might prove to be due to a lack of one of the new 'accessory food factors', or 'vitamins'. This, however, was clearly not meant for transmission to Mellanby, who told me, indeed, in after years, that no such suggestion reached him; and the First Report of the Medical Research Committee, for 1914-15, records only (p. 26) that 'Dr Mellanby was given part-time work, with an assistant supplied by the Committee, for the study of experimental rickets and its relations to conditions of oxidation'. Whatever that may have meant, it clearly offered no direct hint of a dietary defect of any kind as the cause; and Mellanby had yet to effect a great clearance before he was able, about 1916, to find and to follow that clue for himself.

Mellanby was soon at work, therefore, on the problem of rickets, so challenging and, at the same time, so congenial to his interests. The extensive histological and biochemical investigations were largely carried out in the King's College laboratories, at Kensington; but accommodation had to be found for many of the dietary trials on dogs, which provided the experimental back-bone of the research, in the Field Laboratories of Cambridge University. A large series of controls was needed to deal with the competing claims which were still being made for lack of exercise, for forms of infection, etc., as causes of rickets, and then to obtain the clear evidence, which Mellanby was eventually able to produce, first for a dietary deficiency as the primary and essential cause, and then for something present in animal fats, specially abundant in cod-liver oil, but lacking or weakly represented in vegetable oils, as the factor which must be present in a diet. Rickets regularly appeared when this factor was absent or deficient, and was rapidly cured by its administration. It corresponded closely in its distribution with what was then still known as 'the fat-soluble vitamin A', containing, of course, as was discovered some years later, the carotene-derivative now known as vitamin A, as well as the product of irradiation of certain sterols, now recognized as the essentially antirachitic vitamin D. Infections, lack of exercise and all the other suggested causes of rickets, were thereby firmly and finally relegated to

their proper role as contributory factors, capable of weakening the protective effect of marginal quantities of the antirachitic constituent in the diet, but not of causing rickets when that protective factor was given in a normal abundance. And it may be noted, in passing, that there was no suspicion yet of a production of the antirachitic factor by ultra-violet rays; so that there could be no consideration at that stage of the possibility that liberation for exercise, if it allowed any considerable exposure of the animals or their food to sunlight, might accidentally supplement a deficient antirachitic component of the diet.

Altogether then, this work of Mellanby's, the first really scientific attack on the problem, with its long series of carefully planned and controlled experiments, had effected a great and most wholesome clearance of a mass of conflicting arguments and observations, which had hitherto obscured and confused the issue; and, in so doing, it had placed the essential factor properly in the centre of the picture. When once the real nature of the cause of rickets had thus been discovered and presented, this main position was never again to be seriously threatened, in spite of certain obstinate rearguard actions in defence of earlier beliefs. On the other hand, the way was now open, especially with the added facility afforded by the experimental dietary production of rickets in rats, for others to separate the vitamin D, to link its production with the antirachitic effect of the ultra-violet rays, and, many years later, to isolate and identify more than one such vitamin D from the products obtained by irradiating different sterols. It was Mellanby's laborious and accurate experiments on dogs, however, which had enabled him to make the initial and crucial discovery. And this had not only become the essential starting point for all the later developments; it had already provided knowledge which, by itself, and without waiting for these further and consequential advances, could be directly and easily applied to the prevention and cure of human rickets, till then so disastrously prevalent among the children of the urban populations of our industrial civilization.

Mellanby's first public mention of what he had discovered about rickets was made in short notes, recording communications made to the Physiological Society, at the beginning and the end of 1918; and his first full report on his findings, to the Medical Research Council, did not appear till 1921. The time of these announcements, at and soon after the ending of the First World War, could not be regarded as propitious for a quick recognition of their importance. Nevertheless, the success with which the discovery was applied in practice was not only remarkably complete, but even dramatically rapid. Rickets, as a serious menace to the general health, was so soon and so effectively eliminated, that the direct memory of its former malign prevalence, and of its prompt disappearance, is already beginning to fade. Not many years later, when it became necessary to assay the potency of the first pure vitamin D (Calciferol) directly, in the treatment of human rickets, a search made in all the London hospitals failed to discover a single case in which the mother, guided by a welfare clinic, had not already given effective

treatment with cod-liver oil. The search had to be carried to a pocket of unemployment in the industrial North, before a few suitable cases could be found. I have always regarded this work of Mellanby's as one of the high peaks, one of the outstanding points of new departure, in the revolutionary advance of therapeutic knowledge and practice by research during the present century—comparable in its direct success, and in its stimulating influence on further enterprise in research, to the earlier discovery of salvarsan, and the later ones of insulin and penicillin. Of course, when once the discovery had been made scientifically, it was recalled, by Mellanby among others, that cod-liver oil had earlier been suggested as useful in rickets, more than one surgeon being credited with having recommended it for lion cubs at the Zoo. It was beyond dispute, however, that such empirical indications had had no serious effect on theory or practice in human medicine, whereas Mellanby's evidence was such as to carry immediate conviction, leading to prompt and effective application.

Further researches

As was to be expected, the immediately important results of this, Mellanby's first major undertaking in research, made it the starting point for investigations, too numerous even for an estimate, by workers all over the world and along a number of different lines. And he was content to leave to a succession of such other workers the further separation and, eventually, the complete chemical identification of the anti-rachitic vitamin. Of his own further research activities, those which we may regard as the four principal ones—on a pro-rachitic dietary factor, on the pathology of nerve degenerations caused by a deficiency of the vitamin A and consequent anomalies of bone development, on a toxic action of flour conditioned with 'agene', and on the effects of an excess of vitamin A on embryonic organs in artificial culture, all these will call for separate mention, in relation to the further successive phases of his career. And it may be noted that these major lines of his further researches can all be traced in origin, more or less directly, to questions already opened by his first work on rickets. Reference, however, to the full bibliography at the end of this notice, will show that this was by no means true of all the different experimental enquiries on which, at different stages, he embarked. It will not be possible here to make even separate mention of all these, additional and unrelated as they were to the main nutritional current of his researches. Those interested, for example, in Mellanby's experimental approach to the cancer problem, must be referred to the relevant original papers, which are fully listed.

Absorption and fate of alcohol

One of these aberrant research enterprises, however, and the earliest of them, should receive a more specific, though brief, mention. The late Viscount D'Abernon, as Chairman of the war-time Liquor Control Board, was anxious to have all the well-founded scientific evidence about the action

of alcohol made easily available. The Scientific Committee, which he had appointed, found that more definite information was needed about the comparative rates of absorption of alcohol into the blood from different kinds of drinks, and when taken in different relations to food of various kinds. I think that I was responsible for suggesting that Mellanby should be asked to undertake the required experimental study, with the support of the Medical Research Council. In any case, he readily accepted the invitation. The research, carried out at the end of the war, partly at King's College for Women and partly at the London Hospital Medical School, was very successful in its prompt production of clear-cut and definite information, on the different points which he submitted to experiment. Lord D'Abernon himself found great pleasure and interest in the visits which he paid to the laboratories in Whitechapel, to see the Mellanbys at this work and to discuss the possible significance of its results for his Board's policy; so that when Mellanby became Secretary of the Medical Research Council some fourteen years later, Lord D'Abernon having then become Chairman of that body, they started their official relationship on a footing of friendly confidence, already long established.

Professor of Pharmacology at Sheffield

It will, of course, not be possible here to make individual mention of the researches by other workers than himself, which grew more or less directly from Mellanby's work on rickets. Even Lady Mellanby's highly important researches, pursued with such enthusiasm and success for so many years, on analogous nutritional mal-developments of the teeth and the relation of these to liability to caries, must be regarded as an independent enterprise from the point of view of this Memoir, although it was carried out, of course, in close consultation with her husband. Here we must restrict our detailed consideration to the further researches on which Mellanby himself was already actively engaged, and for which his removal to Sheffield in 1920, to occupy the Chair of Pharmacology, was soon to give greatly improved facilities. Apart from the normal laboratories of his University Department, he was now to have the field laboratories which have been already mentioned, at a convenient distance; and it had further been arranged with the University and Hospital authorities that, as Professor of Pharmacology, he should be given the honorary rank of Physician in the Sheffield Royal Infirmary, with beds at his disposal, enabling him to extend his investigations and his teaching into the clinical field. The offer of this clinical opportunity was, indeed, an important factor in Mellanby's decision to accept the Sheffield invitation out of several which he received at that time. This interest of Mellanby's, in clinical opportunities for research, was not, in fact, to find extensive representation in his original publications. Perhaps the nearest approach which he made to a clinical discovery, arose from an observation made in the early days of his nutritional studies on dogs in Sheffield. He noticed that many of the dogs on the poorer kinds of diet, and

especially on those which did not include cod-liver oil, developed goitres, the histology of which was like that seen in Graves's disease. He found that cod-liver oil had, indeed, a remedial effect on the goitres in such dogs, and tried it then with success on Graves's disease in human patients, with the addition, following an indication from the work of Marine, of small doses of iodine; and then, in co-operation with Dr Cowell, a more systematic study was made of the favourable, though impermanent, effects of small doses of iodine alone, and a description of the results was published in the *Quarterly Journal of Medicine*, in 1929. So that Mellanby was one of those to recognize and investigate, at an early stage, the iodine treatment which was to prove so valuable, especially as a preparation for surgery, in exophthalmic goitre.

Mellanby was also responsible for one of the first clinical applications of insulin in this country, after its discovery by Banting and Best. Dudley and I, after a visit to Toronto, had circulated details of suggested methods for preparing and standardizing emergency supplies of insulin on a laboratory scale, while its factory production was being organized. Mellanby was one of the first to act on this suggestion, and was able, with insulin prepared in his own laboratory, to treat a sufferer from diabetes in an advanced stage, who, being rescued thus from a death which could not otherwise have been long delayed, is now a successful and prominent citizen of Sheffield, active and generous in his support of medical enterprises.

The pro-rachitic action of cereals

The first problem which was tackled by Mellanby under the new conditions, provided at Sheffield, and which was destined to occupy much of his attention for years, arose from an observation which he had made and recorded in his first research on rickets. He had found that rickets became more easy to produce, more severe, and more difficult to prevent or to cure, with increase of the proportion of bread, flour, or cereals of any kind in the diet. There was no question here of the removal of a vitamin by milling, for white flour was less rachitogenic than whole-meal flour, and oatmeal was the most pernicious of all. His own earlier work had already made it clear that rickets was not due simply to the absence of the protective factor, but to some dietary imbalance which that factor was needed to correct, and which might require more or less of such correction, according to the composition of the diet in other respects. Now, with the vitamin D identified as the protective agent, he came to the conclusion that there was a positively toxic constituent of cereals, and of their germs in particular, which directly antagonized the effect of this vitamin, requiring it to be added in corresponding excess to prevent or cure rickets. He had referred to this antagonist as a 'toxamin', and for many years he was engaged in trying to track it down, having found early that it was easily destroyed by acid hydrolysis. An understanding of the many aspects of this research must be sought in the original documents, and especially in Mellanby's second 'Report on experimental rickets' to the Medical Research Council, and his later papers on the subject, one with

Professor D. C. Harrison, in 1939, and the last by himself alone, in 1946.

A first clear indication of what proved, eventually, to be the real clue to the nature of this pro-rachitic effect of cereals, was given by Bruce and Callow in 1934, in describing a relatively limited study which they had made—as a sequel to their contribution to the isolation of Calciferol—of the conditions affecting the production of rickets in rats by a high calcium-low phosphorus diet, and the action of the vitamin D upon it. They found, essentially, that when this unbalanced ratio between the total calcium and total phosphorus in the diet was kept constant, the inclusion of cereals made the imbalance effectively worse, and thereby increased the rachitogenic action, because the phosphorus which these contributed to the total was in the very poorly absorbable form of salts of phytic acid—inositol-hexaphosphoric acid. The significance of this observation, made on the rickets thus produced in rats, for the interpretation of Mellanby's imposing array of evidence, obtained from dogs rendered rachitic by diets with a low calcium-high phosphorus ratio, was not immediately obvious. Mellanby with his co-workers, however, proceeded to make further studies directed to the testing of its relevance; and thus he came to discover that phytic acid and its salts, as contained in cereals, was also, indeed, the cause of the pro-rachitic effects of adding these to the low-calcium diet of his dogs. The presence of phytic acid, he found, restricted also the absorption of calcium by forming the unabsorbable calcium phytate. McCance and Widdowson had also extended the significance of this effect to human diets, showing that the absorption of calcium by man could be definitely impaired by the phytates in brown bread. In the end, therefore, it was clearly established that the phytic acid in cereals was responsible for the 'toxamin' effect which Mellanby had discovered, so far as this effect was pro-rachitic and antagonistic to the vitamin D.

Effects of deficiency of vitamin A; nerve degeneration and bony malformation

Many years before the nature of this pro-rachitic effect of cereals had been finally elucidated, Mellanby had embarked upon the third of his major programmes of research. The separation of the vitamins A and D had raised, for him, the question whether all the symptoms which he had observed in the dogs with rickets were due to the lack of vitamin D, or some of them, perhaps, to the inevitably associated lack of vitamin A in the experimental diet. As soon as vitamin D became available in a state of purity, and vitamin A as its precursor, β-carotene, he could begin to put the possibility to the test of experiment; and it thus became clear that a deficiency of vitamin A alone could produce a severe ataxia, which could be traced to degenerative nerve changes, affecting chiefly the sensory fibres, and most conspicuously those of the cranial nerves of the special senses, the olfactory, optic and auditory (8th) nerves, and some of the upper spinal nerves, together with central tracts corresponding to these. Later, these degenerative changes were traced to distorted developments of bones of the skull and the vertebrae, with resulting compression of the nerves, and of their sensory ganglia in particular, at the

foramina by which they pass from the cranial cavity and spinal canal. And these bony mal-developments were traced again, in remarkably beautiful detail, to displaced and unbalanced activities of the osteoblasts and osteoclasts. Here again, reference must be made for full details to the original publications; and, in this instance, an admirable first-hand account of the researches and their results is readily accessible to Fellows of the Royal Society, through the publication in *Proceedings* B (1944, **132**, 28) of the brilliant Croonian Lecture which Mellanby gave in 1943. A large proportion of the researches therein presented had been the product of his work at week-ends, during war years, in which his week-days were crowded with administrative demands and national responsibilities. It was my privilege on that occasion to comment, from the Chair, on that astonishing achievement, and on the special conditions which had made it possible, even for him. This study of the results of vitamin A deficiency, while less immediately dramatic, in its consequences for the general health, than the earlier work on rickets, must surely take very high rank among all Mellanby's major contributions to medical science.

Canine hysteria and 'agenized' flour

It was in 1946, when Mellanby was still giving full-time service to the Medical Research Council as their Secretary, so that his opportunities for research continued to be practically restricted to his week-ends at the Mill Hill Nutrition Laboratory, that he found the cause of a troublesome condition, long known to dog-fanciers and veterinary surgeons as canine 'hysteria', or 'running fits'. There had been no indication, so far, as to whether this condition was due to an infection, or to some other and unknown cause. Mellanby was able first to trace a regular association between outbreaks of it among his experimental dogs, and diets containing high proportions of wheat flour, as bread or dog-biscuit. Enquiry then produced evidence that the flours so incriminated had all been 'improved' and bleached by the so-called 'agene' process, consisting essentially of its exposure to a dilute vapour of nitrogen trichloride. Since a very high proportion of the flour used in this country was treated by this process, the publication of Mellanby's finding excited a natural and anxious interest, in circles widely beyond those normally concerned with scientific research. In any case, the discovery was of a kind to give it more of the 'news value' of a brilliant piece of detective work, than most of those which fall to the lot of the research worker. It was obviously of pressing interest to know whether this toxic action of 'agenized' flour was limited to the only species, the dog, in which its effects had so far been observed. Mellanby found that, of the animals readily available for experiment, only the ferret showed a sensitiveness to the poisonous product similar to that seen in the dog. There was no evidence at all of any comparably acute action of the agenized flour on man, at any rate in the quantities in which it would be taken in a human diet; but there remained, and still remains, an open possibility that some chronic deleterious action may yet be

found to be associated with its continued use. Mellanby's striking experimental evidence had certainly given a signal of warning to all those responsible for public health policies in such matters; and at the end of 1954 he was writing to Lord Hankey to congratulate him on the reward of his 'missionary zeal', in securing the abolition of the 'agene' process.

He also took the first steps towards the identification of the poisonous constituent, showing that it was produced by action on the gluten of flour, that it was resistant to acid hydrolysis when it had once appeared, but was no longer formed from the products of a preliminary hydrolysis, if these were exposed to the 'agene' treatment. After that stage he wisely shared the further chemical investigation with others who had the special experience and facilities which it required. With Campbell and Work, of the National Institute for Medical Research, the poison was separated and characterized as a product of some methionine-complex in the gluten; and workers for the British Millers' Research Association, under Dr Moran, then further identified it as methionine-sulphoximine, and confirmed the identification by synthesis. Mellanby thus had the satisfaction of seeing an investigation of peculiar interest, which had had its origin in his own alert use of opportunities for observation and his brilliant initiative, brought early to a definite conclusion.

Experiments on embryonic organs in artificial culture

In the first two years after he retired from his Secretaryship, 1949-50, Mellanby's expected freedom for research in the Nutrition Laboratory at Mill Hill was rather compromised by his acceptance of invitations, first to India, and then to Australia and New Zealand, on advisory missions lasting for three months, or more, in each case. He was able in those years, nevertheless, not only to finish his own active part in the agene research, but even to devote increasing attention to a new venture, in which he had begun to use the method of studying the growth of isolated embryonic organs in artificial media. His immediate object was to examine further the mechanism of the action of vitamin A in promoting an orderly development of the bones in the living young animal, and of the abnormal development resulting from its deficiency, which he had discovered in the researches earlier mentioned. Did the vitamin act directly on the tissues of the growing bones, or on some other organ, responsible for a nutritional or endocrine action required for the normal development? Some preliminary experiments were made to observe the effects, on embryonic bone rudiments, of growing them in artificial media deficient in vitamin A; but these, for some reason, gave negative results. Mellanby then arranged to continue the work in co-operation with Dr Honor Fell of Cambridge, who had an unrivalled experience of the artificial cultivation of isolated organs and tissues, and of its details and possibilities. They decided, in the first instance, to make the easier experiments, in which the bones of embryo chickens and mice were cultivated in media containing an excess of the vitamin A. The result was dramatic. The

matrix of the cartilage of the rudiment lost its characteristic staining properties and then disappeared, and the shaft of the bone shrank and disintegrated, till nothing was left of the supporting matrix but crumbs of debris, scattered in a sheet of actively growing and migrating cells, derived from the former cartilage and bone cells. This process was not a necrosis; it did not occur if the bone rudiment was dead; it appeared rather to represent an over-stimulation, by the excess of vitamin A, of one aspect of a normally balanced physiological complex, in which the earlier cartilaginous matrix is absorbed as new bone is laid down round it. The effects thus observed were, in fact, in line with already known effects of an excess of dietary vitamin A, in producing an abnormally rapid absorption of cartilage and bony tissue in the bones of young animals. The effects now seen *in vitro* made it clear, therefore, that this action was due to a direct effect of the vitamin on the components of the skeleton, and not an indirect effect of its action on some other organs.

In the next phase of this study, dealing with direct effects of the vitamin A on other growing tissues, reactions were encountered which had still more of the exciting character of the unexpected. It was known that deficiency of vitamin A in a living animal produces, among other effects, a squamous metaplasia and keratinization of mucous membranes. It was accordingly of interest to observe the influence of the vitamin on the development in isolated culture of ectoderm from a chicken embryo, taken from such a part of the body that it would normally acquire the character of a stratified epidermis, with a surface layer of horny scales. In explants of such ectoderm grown in a normal medium, this development took place in a typical manner; and deficiency of vitamin A in the medium did not prevent this and might even accentuate it. In media containing excess of the vitamin, on the other hand, similar explants had failed after a week's cultivation to show signs of the keratinizing change, and the cultivation was continued further, to see whether this inhibition was only temporary. After about ten days a layer of sticky secretion had formed on the surface of the explants, and chemical tests showed that this had the character of mucin. When the explants were then examined histologically, the unexpected discovery was made that the ectoderm had been transformed, not, as normally, into a stratified epidermis, but into a columnar epithelium, containing goblet cells which produced the mucous secretion. Still more surprising, even exciting, was the discovery that other cells of this epithelium were bordered with actively beating cilia, similar to those of the epithelium of the chicken embryo's respiratory tract. Also unexpected, perhaps, was the further observation that, when such explants were then transferred, from the medium containing an excess of vitamin A, to a normal medium, the mucus-secreting and ciliated cells of the columnar epithelium were not replaced from below; on the contrary, they ultimately died and were shed, the basal cells having meanwhile formed a squamous, keratinizing epidermis underneath them.

These studies of the direct effects of vitamin A on epithelia were extended to other structures of ectodermal origin, the otocysts and retinae of 4-day

chicken embryos; but no comparable metaplastic changes were observed in these, though the effect on the cartilaginous capsule of the otocysts was like that on other cartilages.

An offer of further collaboration from Dr S. R. Pelc, of the Medical Research Council's Radiotherapeutic Research Unit at Hammersmith, enabled the analysis of the direct effects of vitamin A to be carried a stage further. By the use of sulphates containing radio-active sulphur (^{35}S), and thin autoradiographs from sections of the tissues, so superimposed on the actual sections that both could be seen together under the microscope, it could be demonstrated that the uptake of sulphur by cultivated explants of ectoderm and bone rudiments, and its distribution in their tissues, are profoundly modified by the addition of vitamin A to the medium.

Mellanby had earlier begun a study of the effects of thyroxine also on isolated bone rudiments in culture, and had observed an inhibition of growth, especially in the long bones of the leg. When the co-operation with Dr Fell began, they found that, as *in vivo*, the addition of thyroxine at first accelerated the development and maturation of the cartilage in the explanted bone rudiments. Later it induced degenerative changes; but these appeared to be due to an excessive stimulation of the metabolic requirements of the growing tissue, since they were checked by increasing the glucose in the medium. The observations were extended to the action of tri-iodothyronine, which was found to be similar to that of thyroxine, but about three times as potent, as in comparisons of their activities *in vivo*.

The mention of these last collaborative investigations brings us to the point at which Mellanby's activities were so suddenly cut short by his death. The experiments on the effects of thyroxine and tri-iodothyronine, and those on the effects of the vitamin A on sulphur metabolism, were still in progress when he died, though nearing completion in both cases. We are left with a conviction that this new field, into which, by a natural and logical development from his earlier work, he had extended his researches in these last years, was, and still is, rich with promise of further harvests of discovery.

Even at the time of his death Mellanby had some new experiments in hand, in which he was using developing chicken embryos and tissue cultures for further observations on the actions of methionine-sulphoximine, the poisonous product of the 'agene' treatment of flour.

Last thoughts on and plans for research

The essential novelty and the special interest of the results, which his own most recent work had thus continued to produce, gave no indication that Mellanby was not still at the height of his powers as an investigator. He seemed to have lost none of his gift for instinctive recognition of the lines of advance likely to be practicable and rewarding, or of his eagerness to exploit the new methods, which the general advance of scientific knowledge was so rapidly making available. It might have been hoped that he would still have some working years before him, in which to take a principal part, with both

hand and brain, in the further development of this new scientific territory into which he had led the way, and to enjoy, perhaps, a growing co-operation with younger colleagues, able to contribute specialist knowledge of the new techniques which would certainly continue to emerge. In his last report to the Medical Research Council, on the researches in which he had been engaged since his retirement from the Secretaryship, he had appeared to envisage, as a desirable policy, an increasing use of such opportunities of co-operation, with workers attached to other research establishments receiving the Council's support. It is sad that an enterprise so full of promise should have lost his stimulating initiative and the guidance of his ripened experience at so early a stage of its progress; but we may be glad to think of him as enjoying to the full, and to the last minute, this brilliant 'Indian summer', at the end of so many years at productive research.

Reference has already been made to the special circumstances which rendered it possible for Mellanby to continue his researches without a break, through the period in which other pre-occupations could hardly have failed otherwise to make an interruption. Throughout their married life, indeed, though each of them during most of it had his and her own separate problems and plans for research, Lady Mellanby and he had worked alongside one another with such an intimacy of understanding, that the effects upon his research work of prior calls on his time and attention could be reduced to a minimum. It should further be made clear, in the same connexion, that an account of his research career would be seriously defective, without a tribute to the devoted and understanding co-operation which he received from a succession of highly qualified technical assistants; and special reference should be made to the skilful and versatile contribution thus made to his work, especially in the later years, by Mr R. J. C. Stewart.

Secretary of the Medical Research Council, 1933-1949

When Sir Walter Fletcher died, in 1933, the Medical Research Council's undertakings, starting on a very small scale less than twenty years earlier, had already undergone a remarkable development during his enterprising and enlightened Secretaryship. There was no reason to suppose that this expansion of the Council's activities had yet been completed; it might, on the contrary, be expected to continue at an increasing rate, with similarly able guidance. It was clear, then, that the appointment of a successor to Fletcher would be one of the greatest importance to the prospects of medical research and its support from the public funds in the United Kingdom, and beyond it in the British Empire. When it was learned, therefore, that Edward Mellanby had accepted the appointment, there was a widespread feeling of satisfaction, that a man of his well-known ability and force of character, and with so direct and intimate a knowledge of the needs and the possibilities of medical research, had consented to shoulder this heavy burden of responsibility for the promotion of medical science, and for the interests of his fellow

research workers. For some, however, this feeling of relief and approval was tempered by one of regret, for what appeared to them to be the practically inevitable sacrifice of Mellanby's own very important personal activities in research—even though it was known that the Council had undertaken to enable him to continue his researches with their full support, concurrently with the discharge of the responsible duties of their Secretary. I confess to having been among the sceptics; however sincere the intentions, it seemed to me that, with two such different claims on his thoughts and interests, one or the other must suffer from the attempt to meet both at once, and that the claim of his new appointment would inevitably win. How wrong I was in this judgment has already been made abundantly clear. I do not think, however, that it was wrong in principle, or in a general application; my mistake was to have underestimated so widely what Mellanby, in particular, would be able to achieve.

Mellanby's task as Secretary did not, of course, involve a start from nothing, as Fletcher's had done. He had succeeded to a well-developed organization, with an able and enthusiastic staff already experienced in its working. He was not the man, however, to be content with the mere consolidation of such an inheritance, and he soon began to give proof of his capacity for a vigorous and independent initiative. It was evident that, in response to his stimulus, the range of the Council's enterprises would expand in new directions, and that there would be pruning where it was judged to be needed, as well as planting. A survey in detail of the researches promoted, or reinforced, by support from the Council's funds, even during the first six years of Mellanby's Secretaryship, before the war, would involve the listing of a very large proportion of all the medical researches then in progress in this country, as recorded in the Council's Annual Reports. There were some who appeared to believe that they could detect certain new general tendencies in the Council's policy, and that these, not unnaturally, were of a nature congenial to Mellanby's own interests and ideals in medical research. They would watch, for example, for indications of a growing tendency to encourage research in the clinics, and on problems, such as those of nutrition, which might have a relatively immediate bearing on the conditions of human health. I believe, however, that, if there was really any such change of emphasis in the Council's policy, it could with equally good reason have been attributed to a natural alinement with a more general, indeed a world-wide tendency of medical research at that time. What was certainly clear was that, while the Council, with Mellanby's prompting, might well be giving additional attention to investigations more directly related to practical medicine and health policy, they were not doing so at the expense of their support for more fundamental studies. Mellanby's influence, in fact, was clearly in favour of casting the net widely, taking the long view, and making the Council's encouragement and support available to any well conceived and expertly manned enterprise in the whole field of medical research, whether it promised to yield an early harvest of practical results, or only to enrich the soil with

fundamental additions to knowledge. I may briefly mention examples, out of a great range from which choice could be made, of research projects of these different kinds, which attracted the Council's support during Mellanby's term of office, and which I know that he viewed with special pride and satisfaction. The Council were directly concerned, on the one hand, with the first organized clinical trial, under conditions of scientific control, of the then new 'Prontosil' and its active moiety, sulphanilamide, in the special unit which they had founded for research on puerperal fever, under the direction of Dr Leonard Colebrook; and the result was so decisive as to awaken medical interest all over the world in the potentialities of sulphanilamide, and then in those of its more active derivatives. Some three years later, the Council were again interested, from an early stage, in promoting the new investigation, by Sir Howard Florey, Dr Chain and their team, of the properties of Fleming's then almost forgotten penicillin, resulting in its separation and purification, and in the triumphant demonstration of its supreme remedial value in so many general infections. The Council's active concern with these, the two chief starting points of the revolutionary advance, still continuing, in the treatment of bacterial and similar infections, was largely due to Mellanby's prompt and enthusiastic recognition of their immediate and prospective importance. I know that Mellanby, on the other hand, would have found equal reason for pride in the foundation by the Council, during his term as their Secretary, of the unit of research under Professor Krebs, originally in Sheffield, and recently transferred with its leader to Oxford, for the fundamental study of the enzymatic mechanisms of oxidative metabolism. The 'Krebs cycle' is now well known, as a major component of the rising structure of fundamental biochemistry, and has been recognized by the award of a Nobel Prize and a Royal Medal of the Royal Society; but it required an enlightened vision to foresee the eventual importance of researches of that order for practical medicine, even in a distant future. And we who were members then of the staff of the National Institute for Medical Research, had abundant reason to know that the Council showed no abatement of its interest in the more fundamental aspects of medical research while Mellanby was their Secretary.

Mellanby, like Fletcher before him, was engaged, during an important part of his secretarial term, in the special organization of medical research to meet the needs of a world war. In both cases the Council and its staff were called upon to meet a forced extension of the demands for their activities, and therewith of their opportunities and resources; and, though many of these war-time activities were of special kinds, they had yielded, being medical in their general aim, an unusually high proportion of new scientific knowledge and experience which would have a more permanent, peace-time value. The Council had accordingly emerged, from each of the wars, with its range and resources greatly enlarged and its reputation greatly enhanced, so that there was no demand for a shrinkage of its activities to the former dimensions; and, in both cases, it was evident that a major share in a widely

applauded achievement was attributable to the resourceful and devoted labours of the Council's Secretary.

In other ways the experiences of the two had differed; unlike Fletcher, on whom the 1914 emergency had been sprung without warning, and only a month after he had taken office, Mellanby had six years of service in which to watch the advancing shadow and to prepare for the call, before it came in 1939. He had been busy at an early stage of his new appointment, making contacts with the official authorities in the different relevant departments. A very important contact of that kind was with Sir Maurice (now Lord) Hankey, who was then Secretary to the Committee of Imperial Defence, and to the Cabinet, as well as Clerk to the Privy Council, to which the Medical Research Council is officially responsible. In a moving address, which he delivered at the Memorial Service which followed Mellanby's death, Lord Hankey has told of an early appeal which he made to Mellanby, for some action to improve the standard of health among men presenting themselves for military recruitment; and of Mellanby's reply that 'the problem could be solved, but only on a long-term basis, and by drastic reform in the national diet'. Lord Hankey asked for a memorandum; and, to Mellanby's astonishment, a day or two later it came back to him in the form of a Memorandum to the Cabinet. This heartening experience, coming to Mellanby at a moment when he was feeling baffled 'by the well-nigh insuperable difficulty in getting research work translated into action', opened the way to an invaluable collaboration behind the scenes, on confidential preparations for the demands for medical research, and for its products, which would be made immediately, if and when the threatened war began. A more open preparatory move, of importance not only for war, was the appointment by the Air Ministry, in response to Mellanby's vigorous representations, of a committee to deal with the physiological problems of aviation. From what I heard from the other side, the officials of the Ministry thought that they had 'trumped Mellanby's ace', by insisting on his becoming the chairman of this committee; but I have no doubt that he regarded the trick as taken by himself. When the war came, therefore, much of the planning, for the organization of special medical researches from the Council's office, had already been done. Professor Topley, from the London School of Hygiene and Tropical Medicine, joined the headquarters staff, and an Emergency Public Health Service was organized, in collaboration with the Ministry of Health, as Sir Arthur McNalty has recalled.

Mellanby himself was constantly at work behind the scenes and on advisory committees, pressing successfully, and with scientific warrant, for the appropriate reinforcement of margarine, bread and other staple articles of diet. The long delay of active belligerency, after war had been declared, gave time to put the prepared machinery into action, and special research committees on medical problems of the war came into being, in such number and variety as to preclude any attempt at detailed reference. Special mention may be made, however, of the new emphasis on physiological problems

concerned with the maintenance of health, apart from measures against infection and other known causes of disease, in men who would be exposed to a wide variety of abnormal stresses and conditions, on land, or sea, or in the air; so that a range of expert committees was appointed, to consider and advise upon normal and emergency rations, clothing for a wide variety of climates, maintenance of fitness in marching, or during service in submarines or tanks, problems of deep diving, and on many others newly created by the changing conditions of warfare.

The war had helped to give Mellanby a position of power, and opportunities of service on high-level official committees, which did not disappear when it ended. One of his most important interdepartmental functions, until he retired from his position as the Council's Secretary, was that of Chairman of a Committee on Colonial Medical Research, appointed jointly by the Medical Research Council and the Colonial Office. As he gained the confidence of the departments, he was more and more consulted on their various medical problems.

Among other matters of the Council's policy during Mellanby's Secretaryship, mention should also be made of the decision to remove the activities of the National Institute for Medical Research to a new building, to be erected on their estate at Mill Hill. The eventual need to increase and improve the Institute's accommodation had long been recognized; and action was accelerated by the announcement of a special increase of the Government's annual grant, to make possible a large extension of the programme of researches on chemotherapy, in response to a memorandum which Mellanby had presented to the Treasury on behalf of the Council. Important new accommodation for chemotherapy would evidently be required by the Institute, and it was administratively undesirable to provide it at a distance from the main building. So, after a number of abortive attempts to plan appropriately for further building on the Hampstead site, the decision was taken to move the Institute as a whole to new quarters at Mill Hill. Building eventually began not long before the outbreak of war; but when the main carcase was completed, in 1941, and before work on the internal fitting and equipment could be begun, it was requisitioned for what was regarded as a prior war-time need—the preliminary instruction of successive flocks of recruits to the W.R.N.S. And so it came about that the new Institute, with its internal planning and equipment redesigned, to its great advantage, by my successor Sir Charles Harington, who was able to take advantage of many great advances due to war-time researches, was not ready till 1950 for its formal opening by the late King George VI and his Queen; and there was general regret that this should not have been possible till a year after Mellanby's retirement from the Secretaryship. For it was during his term of office that the decision for this new building had been made, and its planning and construction, after the war-time diversion, had been brought very nearly to completion before he retired.

Other activities and distinctions

Much could be written about other aspects of Mellanby's work. Apart from the researches which he undertook from time to time, in addition to those of which a more detailed mention has been made, some reference is due to his qualities as a teacher. The obligations of formal teaching and organization, in connexion with the university chairs which he held, were probably lighter than those of many, and thus left him with more freedom for his own researches. Nevertheless, he obviously enjoyed the contact which regular teaching gave him with young and eager minds, and letters from his former students have given glowing testimony to the attractive, unconventional and inspiring quality of his lectures; while those who had the privilege of collaborating in his researches have spoken, with a like enthusiasm, of his unassuming friendliness and open-hearted sharing of experience and ideas, and of what they learned from him of the principles and the spirit of scientific research. And reference may be made to the attached bibliography for evidence of the extent to which he was in demand as a special lecturer, both at home and abroad.

His greatest titles to fame, however, will still be found in the record of his own major enterprises in research, and of his service to medical research in general, as a great administrator and public official. Other instances could, no doubt, be cited, beginning perhaps with that of Isaac Newton, of men who, having risen to great eminence as scientific investigators and discoverers, have later found opportunity to show a different aspect of their powers, as great public servants. It was Mellanby's special title to greatness that, having achieved high rank as an investigator of great originality and distinction, he continued to hold it, by maintaining the high level of his own activity in research, when he became, in addition, a great administrator of the public funds provided for the general support of research in his own field of the medical sciences, and a most determined and forceful advocate, in official circles and widely beyond them, of the proper use and application of the results of such research, for the promotion of health in the nation and throughout the world.

Nobody, I think, who had dealings with Edward Mellanby could fail to be attracted by his big, handsome, friendly personality, which, in his happier moods, had retained something of a boyish exuberance. His character was strong and independent, and, when he considered the opinions of others, he looked at them on their merits and with little reference to the standing or the dignity of their advocates. In most cases he appeared to form his own opinion; and when he had done so, and taken a stand, you were likely to find it difficult to move him from it if you happened not to agree with him; but you could be certain that it was his own and not one tamely accepted from others. I think that, like other great men with a sense of a mission, he was apt on occasion to weaken his own influence by faults of manner, which were essentially due to an excess of good qualities. When his convictions were

strongly moved, or if he felt that his plans were being hampered by a conventional timidity, his reaction could be explosive and provocative, when it might have served his purpose better to be persuasive and adroit. Perhaps the early discipline in boxing with his father had left its mark on his reactions; for, if one of his outbursts was met by a counter-attack of like pugnacity, he took it in good part, and he cherished no grudge, if, at the end of an encounter, he had to accept defeat. He was staunchly loyal to his own co-workers; but his well-justified pride in the effectiveness of the organization which he had been called to administer, and in what it was achieving as it continued to grow under his hand, was apt to overflow into criticism and resentment of efforts by other and less experienced organizations to play a part in the promotion of medical research. But nobody who knew Mellanby at all could attribute such a reaction to anything but an excess of his consuming zeal for the great cause which he had espoused, or could suspect him of any concern for his personal interests. He was a doughty champion of the interests of medical research, as he saw them, and a man of great personal achievement in its performance; and, with it all, he was a man of simple, generous and lovable character, who could be tender in his sympathy for a friend in trouble, as well as fierce and impetuous in his drive for what he believed to be right and important.

Mention has been made of advisory missions to India and Australia which Mellanby undertook after his retirement. Even earlier, in 1947, leave from his official duties had enabled him to accept an Abraham Flexner Lectureship at Vanderbilt University, Nashville, Tennessee, for which the lecturer is under obligation to reside for three months in Nashville, so as to have opportunity for informal contacts and discussion with the staff of the University, in addition to the delivery of more formal lectures. He was still in office also in 1948, when he attended, on behalf of the British Government, the meeting in Washington of a Commission appointed to consider the practical implications of his own discovery concerning the effect of the 'agene' treatment of flour. As the result of the Commission's report, the 'agene' process was prohibited in the U.S.A. The British Government accepted the recommendation in principle, but, as already mentioned, some years were required to make it effective. In 1948 again, he went to South Africa to advise upon the organized promotion of medical research at the invitation of the South African Council of Scientific and Industrial Research, and in 1949, still before his retirement, he attended the African Scientific Regional Congress on behalf of the Colonial Office.

Among many important Committees of which Mellanby was Chairman, special mention should be made of a conference under his chairmanship which was convened in London by the Health Section of the League of Nations in 1931, when he was still a Professor in Sheffield, to consider the standardization of the vitamins already then known; with the result that a number of international standards for these substances were accepted, and units of biological activity defined in terms of them. Mellanby continued to

preside over subsequent conferences, summoned in 1934 and 1949, to keep these important international agreements abreast of further advances in that field. He was also Chairman of an International Technical Commission on Nutrition, and, in co-operation with Professor E. V. McCollum, of Baltimore, he produced a very influential report on the relationship of human nutrition to agriculture.

In addition to the Abraham Flexner Lectures already mentioned, Mellanby gave the Croonian Lecture to the Royal Society, the Oliver Sharpey Lectures, the Croonian Lectures, and the Harveian Oration to the Royal College of Physicians, the Linacre Lecture and the Rede Lecture at Cambridge, and the Withering Lectures at Birmingham. The Royal Society awarded him the Royal and the Buchanan Medals, and he served on its Council in 1932-1934 and 1953-1955; from the Royal College of Physicians he received the Bisset-Hawkins, Moxon and Baly Medals. He was Hon. Sc.D. of Cambridge; Hon. D.Sc. of Sheffield, Oxford, Belfast, Chicago and Oslo; Hon. LL.D. of Birmingham, Glasgow, St Andrew's and Melbourne; Hon. M.D. of Witwatersrand and Adelaide. He was a Fellow of the Royal Danish Academy of Sciences.

Mellanby was created K.C.B. in 1937, and G.B.E. in 1948. In 1947 he became Officier de la Légion d'Honneur (France); he was also awarded the American Medal of Freedom with Silver Palm, and made a Commander (1st Class) of the Swedish Royal Order of the North Star.

The portrait facing p. 193 is from a photograph taken by Elliott and Fry Ltd in 1927, when Edward Mellanby was 43 years of age.

I am deeply indebted to Lady Mellanby and, through her, to many others, for help with information and reminiscences, which have greatly contributed to this notice. The attached bibliography was most kindly prepared for me by Miss Jeannette R. Taylor, Librarian to the National Institute for Medical Research.

HENRY H. DALE

BIBLIOGRAPHY

1907. The excretion of creatin and creatinin in hepatic disease. *J. Physiol.* **36**, xxiii.
1908. Creatin and creatinin. *J. Physiol.* **36**, 447.
1911. A short chemical study of a case of cyclic vomiting with some remarks on creatinuria and acidosis. *Lancet*, **2**, 8.
1912. (With F. W. Twort.) On the presence of β-imidazolethylamine in the intestinal wall; with a method of isolating a bacillus from the alimentary canal which converts histidine into this substance. *J. Physiol.* **45**, 53.
1912. (With F. W. Twort.) On creatin-destroying bacilli in the intestine, and their isolation. *J. Physiol.* **44**, 43.
1913. The metabolism of lactating women. *Proc. Roy. Soc.* B, **86**, 88.
1913. The excretion of creatin as an aid to the diagnosis of cancer of the liver. *XVII int. Congr. Med.*, Sub-Section III (a), Chem. Path. Pt. II. Independent Paper, 11 August, 1913.
1916. An experimental investigation on diarrhoea and vomiting of children. *Quart. J. Med.* **9**, 165.
1918. Diagnosis and treatment of dysentery occurring in the British Salonika force. *Lancet*, **1**, 162.
1918. The part played by an 'accessory factor' in the production of experimental rickets. *J. Physiol.* **52**, 11P.
1918. A further demonstration of the part played by accessory food factors in the aetiology of rickets. *J. Physiol.* **52**, 53P.
1919. Discussion on the importance of accessory food factors (vitamines) in the feeding of infants. *Proc. R. Soc. Med.* **13**, Sect. Stud. Dis. Child., p. 57.
1919. Alcohol: its absorption into and disappearance from the blood under different conditions. *Spec. Rep. Ser. med. Res. Coun., Lond.* No. 31.
1919. An experimental investigation on rickets. *Lancet*, **1**, 407.
1920. Accessory food factors (vitamines) in the feeding of infants. *Lancet*, **1**, 856.
1920. Alcohol and alcoholic intoxication. *Brit. J. Inebr.* **17**, 157.
1921. Experimental rickets. *Spec. Rep. Ser. med. Res. Coun., Lond.* No. 61.
1921. (With M. Mellanby.) The experimental production of thyroid hyperplasia in dogs. *J. Physiol.* **55**, 7P.
1921. The application of the results obtained in experiments on the hyperplasia of dogs' thyroids to the treatment of exophthalmic goitre (Graves' disease). *J. Physiol.* **55**, 10P.
1922. Some common defects of diet and their pathological significance. *Brit. med. J.* **1**, 790, 831.
1922. Discussion on alcohol as a beverage and its relation to certain social problems; the action of alcohol on the human economy. *Brit. med. J.* **2**, 195.
1922. Discussion on the etiology of rickets. *Brit. med. J.* **2**, 849.
1922. The rickets-producing effect of dried thyroid. *J. Physiol.* **57**, 2P.
1923. (With H. Chick *et al.*) Discussion on nutritional diseases in animals. *Proc. R. Soc. Med.* **17**, Sect. Comp. Med., p. 19.
1924. (With S. J. Cowell.) The effect of iodine on hyperthyroidism in man. *Quart. J. Med.* **18**, 1.
1924. Deficiency diseases, with special reference to rickets. *Brit. med. J.* **1**, 985.
1924. Diseases of nutrition in animals. *Lancet*, **1**, 229.
1925. Experimental rickets: the effect of cereals and their interaction with other factors of diet and environment in producing rickets. *Spec. Rep. Ser. med. Res. Coun., Lond.* No. 93.
1925. Diet and disease; with special reference to teeth. *Amer. dent. Surg.* **46**, 620.

1926. Diet and disease; with special reference to teeth, lungs and pre-natal feeding. *Brit. med. J.* **1**, 515.
1926. The presence in foodstuffs of substances having specific harmful effects under certain conditions. *J. Physiol.* **61**, 24P.
1927. Duties of the State in relation to the nation's food supply; research on nutritional problems. *Brit. med. J.* **2**, 633.
1928. (With H. N. Green.). Vitamin A as anti-infective agent. *Brit. med. J.* **2**, 691.
1928. A rat technique for demonstrating the interfering effect of cereals on bone calcification. *Biochem. J.* **22**, 102.
1928. (With E. M. Surie & D. C. Harrison.) The antirachitic effect of ergot. *J. Physiol.* **65**, 29P.
1929. (With H. N. Green.) Vitamin A as anti-infective agent; its use in the treatment of puerperal septicaemia; preliminary communication. *Brit. med. J.* **1**, 984.
1929. (With E. M. Surie & D. C. Harrison.) Vitamin D in ergot of rye. *Biochem. J.* **23**, 710.
1930 (With H. N. Green.) Carotene and vitamin A: the anti-infective action of carotene. *Brit. J. exp. Path.* **11**, 81.
1930. (With S. T. Harrison.) The inhibition of lactic acid formation in cancer and muscle. *Biochem. J.* **24**, 141.
1930. Diseases produced and prevented by certain food constituents. *Trans. Sect. Dis. Child. A.M.A.*, p. 193.
1930. A lecture on the relation of diet to health and disease; some recent investigations. *Brit. med. J.* **1**, 677.
1930. Relation of diet to health and disease; some recent investigations. *Med. Stand.* **53**, 10.
1930. Some recent investigations into relation of diet to health and disease. *Kenya E. Afr. med. J.* **7**, 29.
1930. Maternal mortality. *Public Health Congress*, Paper No. 7.
1930 (With A. F. Watson.) Tar cancer in mice; technique of comparative experiment. *Brit. J. exp. Path.* **11**, 267.
1930. (With A. F. Watson.) Tar cancer in mice; condition of skin when modified by external treatment or diet, as factor in influencing cancerous reaction. *Brit. J. exp. Path.* **11**, 311.
1931. (With H. N. Green, D. Pindar & G. Davis.) Diet as a prophylactic agent against puerperal sepsis; with special reference to vitamin A as an anti-infective agent. *Brit. med. J.* **2**, 595.
1931. (With S. T. Harrison.) A note on the inhibitory effect of monoiodoacetic acid on lactic acid production by cancer tissue. *Biochem. J.* **25**, 770.
1931. Diseases produced and prevented by certain food constituents. *J. Amer. med. Ass.* **96**, 325.
1931. Diet and health. [Hastings Lecture.] *Brit. med. J.* **1**, 85 (Supplement).
1931. The experimental production and prevention of degeneration in the spinal cord. *Brain*, **54**, 247.
1932. Remarks on clinical applications of the recent work on bone disease. *Brit. med. J.* **2**, 865.
1933. The fat-soluble vitamins—their significance in nutrition. *Edinb. med. J.* **40**, 197.
1933. Nutrition and child-bearing. [Lloyd Roberts Lecture.] *Lancet*, **2**, 1131.
1934. The treatment of subacute combined degeneration. *Proc. R. Soc. Med.* **27**, Sect. Neurol., p. 31.
1934. Report on work on cancer carried out in the Pharmacological Laboratory, Sheffield University. *Brit. Emp. Cancer Campaign, 11th Ann. Rep.* p. 81.
1934. Xerophthalmia, trigeminal degeneration and vitamin A deficiency. *J. Path. Bact.* **38**, 391.
1934. *Nutrition and disease. The inter-action of clinical and experimental work.* Edinburgh: Oliver and Boyd.

1935. Lesions of the central and peripheral nervous systems produced in young rabbits by vitamin A deficiency and a high cereal intake. *Brain*, **58**, 141.
1935. Report on work on cancer carried out in the Pharmacological Laboratory, Sheffield University. *Brit. Emp. Cancer Campaign, 12th Ann. Rep.* p. 99.
1935. The Huxley Lecture. *The advance of medical science since Huxley's day.* (Delivered at Charing Cross Hospital Medical School, 28 November, 1935.)
1936. Report on work on cancer carried out in the Pharmacological Laboratory, Sheffield University. *Brit. Emp. Cancer Campaign, 13th Ann. Rep.* p. 100.
1937. Report on work on cancer carried out in the Pharmacological Laboratory, Sheffield University. *Brit. Emp. Cancer Campaign, 14th Ann. Rep.* p. 77.
1937. Vitamin A deficiency and deafness. *Chem. & Ind.* **56**, 1054.
1937. Durch mangelhafte Ernährung bedingte Erkrankungen des Nerven-systems. *Schweiz. med. Wschr.* **67**, 349.
1937. The choice of a career. *Univ. Coll. Hosp. Mag., Lond.*, May-June.
1937. Toxamins in food. In *Perspectives in biochemistry.* Edited by J. Needham and D. E. Green. Cambridge Univ. Press. p. 318.
1938. The transmission of the Rous filterable agent to chemically induced tumours. *J. Path. Bact.* **46**, 447.
1938. The transmission of the Rous filterable agent to the normal tissues of fowls. *J. Path. Bact.* **47**, 47.
1938. Nerve degeneration and bone hypertrophy induced in young animals by diet. *J. Physiol.* **93**, 42P.
1938. The experimental production of deafness in young animals by diet. *J. Physiol.* **94**, 380.
1938. State and medical research. [Harveian Oration.] *Lancet*, **2**, 939; *Brit. med. J.* **2**, 821.
1938. Methods of discovery in the fight against disease. *Robert Boyle Memorial Lecture.*
1939. (With D. C. Harrison.) Phytic acid and the rickets-producing action of cereals. *Biochem. J.* **33**, 1660.
1939. Neurological aspects of the avitaminoses, with special reference to the peripheral nervous system. *C.R. III Int. neurol. Congr.* Copenhagen. p. 797.
1939. Further observations on bone overgrowth and nerve degeneration produced by defective diet. *J. Physiol.* **96**, 36P.
1939. The experimental method in the conquest of disease. [Stephen Paget Memorial Lecture.] *The Fight Against Disease*, **27**, 1.
1939. *Recent advances in medical science. A study of their social and economic implications.* [Rede Lecture 1939.] Cambridge Univ. Press.
1941. Skeletal changes affecting the nervous system produced in young dogs by diets deficient in vitamin A. *J. Physiol.* **99**, 467.
1942. Viscount D'Abernon, P.C., G.C.B., G.C.M.G., F.R.S. *Nature, Lond.* **149**, 43.
1943. The effect of bone dysplasia (overgrowth) on cranial nerves in vitamin A-deficient animals. *J. Physiol.* **101**, 408.
1943. Medical research in wartime. *Brit. med. J.* **2**, 351.
1944. Nutrition in relation to bone growth and the nervous system. *Proc. Roy. Soc.* B, **132**, 28.
1944. Phytic acid and phytase in cereals. [Letter.] *Nature, Lond.* **154**, 394.
1944. Nutritional science in medicine. *Brit. med. Bull.* **2**, 202.
1946. Diet and canine hysteria. *Brit. med. J.* **2**, 885.
1947. Further observations on the production of canine hysteria by flour treated with nitrogen trichloride (agene process). *Brit. med. J.* **2**, 288.
1947. Vitamin A and bone growth: the reversibility of vitamin A deficiency changes. *J. Physiol.* **105**, 382.
1947. Further investigations on the anticalcifying or rickets-producing action of cereals. *XVII int. Physiol. Congr., Oxford.*
1948. The Hopkins Memorial Lecture. Delivered before the Chemical Society on 19 February, 1948. *J. Chem. Soc.* p. 713.

1949. The rickets-producing and anti-calcifying action of phytate. *J. Physiol.* **109**, 488.
1949. Jenner and his impact on medical science. *Brit. med. J.* **1**, 921.
1950. (With P. N. Campbell & T. S. Work.) Isolation of a crystalline toxic factor from agenized wheat flour. *Nature, Lond.* **165**, 345.
1950. (With H. B. Fell.) Effect of hypervitaminosis A on foetal mouse bones cultivated *in vitro*. Preliminary communication. *Brit. med. J.* **2**, 535.
1950. The story of nutritional research; the effect of some dietary factors on bones and the nervous system. *Abraham Flexner Lectures*, ser. No. 9. Baltimore: Williams & Wilkins.
1951. (With P. N. Campbell & T. S. Work.) The isolation of a toxic substance from agenized wheat flour. *Biochem. J.* **48**, 106.
1951. (With H. B. Fell.) The effect of vitamin A on skeletal tissue cultivated *in vitro*. *J. Physiol.* **115**, 4P.
1951. The chemical manipulation of food. [Sanderson-Wells Lecture.] *Brit. med. J.* **2**, 863.
1951. Modern advances in therapeutics. *Indian J. Pharm.* **13**, 8.
1952. (With H. B. Fell.) The effect of hypervitaminosis A on embryonic limb-bones cultivated *in vitro*. *J. Physiol.* **116**, 320.
1953. Metaplasia produced in cultures of chick ectoderm by high vitamin A. *J. Physiol.* **119**, 470.
1954. (With H. B. Fell & S. R. Pelc.) Influence of excess vitamin A on the sulphate metabolism of chick ectoderm grown *in vitro*. *Brit. med. J.* **2**, 611.
1955. (With H. B. Fell.) The biological action of thyroxine on embryonic bones grown in tissue culture. *J. Physiol.* **127**, 427.

PRINTED IN GREAT BRITAIN BY HEADLEY BROTHERS LTD
109 KINGSWAY LONDON WC2 AND ASHFORD KENT