PREFATORY CHAPTER—
SIR EDWARD MELLANBY

BY

B. S. PLATT

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MEDICAL RESEARCH COUNCIL

HUMAN NUTRITION RESEARCH UNIT

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PREFATORY CHAPTER

SIR EDWARD MELLANBY, G.B.E., K.C.B., M.D., F.R.C.P., F.R.S. (1884–1955): THE MAN, RESEARCH WORKER, AND STATESMAN

BY B. S. PLATT

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Sir Edward Mellanby had accepted a cordial invitation from the Editorial Committee of the *Annual Review of Biochemistry* to contribute this Prefatory Chapter. Unhappily, before he had completed his seventy-first year, he died suddenly on Sunday, January 30, 1955, about mid-day, after he had spent the morning at his research. His draft of the introduction to his contribution to this volume is printed below in the section "Background to British Biochemistry."

For nearly six years after retiring from the post of Secretary of the Medical Research Council, he continued to engage in research work and in many scientific affairs. He was, for example, active in the Royal Society, of which he had been a Fellow for 30 years, and he was one of its Vice-Presidents. Sir Henry Dale has recently completed an Obituary Notice of Mellanby for the Royal Society (1955);[1] this tribute is of such grandeur as perhaps only a man of Sir Henry's eminence could contribute, and I shall quote from this to give the weight of wisdom, experience, and knowledge to this chapter.

It has been said that until the First World War we in Britain were apt to assume that if foreigners did not understand or even like us, it was their fault and not ours. Various British statesmen from time to time have questioned whether this *laissez-faire* attitude was reasonable or rewarding, but it was not until 21 years ago that a committee was set up with the title "The British Council for Relations with Other Countries." It is indicative of Mellanby's broad interests that he took an active part in the work of what is now known as the British Council, and he was Chairman of its Advisory Medical Panel from its inception in 1942. One of the projects he initiated shortly before his death was the preparation of a special number of the British Medical Bulletin (1956)[2] on recent advances in vitamins. This number is the poorer by the fact that he was unable himself to contribute on his work on vitamins A and D; it is, however, to be issued as a memorial to Sir Edward Mellanby, and it contains among other notices of his work, a personal appreciation of him by Sir Charles Harington. Other appreciations

[1] Dale, H. H., *Biographical Memoirs of Fellows of the Royal Society*, **1**, No. 24 (1955).

[2] *Brit. Med. Bull.*, **12**, No. 1 (1956).

appearing shortly after his death in the British medical and scientific press[3,4,5] all make my task, if anything, in some ways more difficult. I still feel, as I felt some months ago when preparing a notice, as Mellanby himself said he felt when faced with the preparation of the Hopkins Memorial Lecture (91), that the task requires a "degree of knowledge, skill, judgment and sympathy . . . almost unattainable."

Most readers will be familiar with much of Mellanby's scientific work, and they will know something too, no doubt, about the influence he wielded as Secretary of the Medical Research Council of Great Britain. Whilst both of these topics must be given consideration in the chapter, I feel it would be interpreting the wishes of the Editorial Committee if a glimpse is given of Sir Edward's life before we look at his work.

A Biographical Sketch

"Nobody" writes Sir Henry Dale[1]

> 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. . . . 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 with 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.

He was born on April 8, 1884, in West Hartlepool, the youngest of a family of six children and the last of four sons, one of whom died in childhood. John Mellanby, his father, was the manager of a shipyard in the Furness-Withy Company, and his mother was born in Edinburgh. Dale describes the parents as "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." Mellanby's father, a Yorkshireman, was noted for his management of the men in the shipyard and for his ability in handling people, and he no doubt passed on some of this knowledge of human nature to his sons when he enjoyed his evening stroll with them; he was at one time amateur boxing champion for the north of England and he taught his sons boxing. At Barnard Castle School, Edward Mellanby excelled at sports; he won several jumping and running events and was captain of both cricket and football teams; he is described in the school magazine as "the best outside left we have had for some years." It was his reputation as an athlete that lived on to

[3] *Brit. Med. J.*, **I**, 355, 421 (1955).
[4] *Lancet*, **I**, 309, 359 (1955).
[5] *Nature*, **175**, 530 (1955).

impress Professor J. H. Burn of Oxford, when, as a new boy, he joined the school shortly after Mellanby left. At the Cambridge College sports in 1903, he won the Freshman's race of 200 yards, his time being 24⅗ seconds. Unknown to many of his friends and acquaintances of later life his interest in sport continued. He used to watch the Sheffield football teams on Saturdays, and he would interrupt his work on Saturday afternoons at the Nutrition Building to hear the Test Match commentaries. If his team was not doing well he would turn to his assistant and say "Come on, they can't play cricket nowadays, let's get on with some work." No doubt his early athletic activities helped to lay the foundation for the almost uninterrupted good health he enjoyed throughout life. He took a cold bath every morning to the day of his death!

His prowess in athletics was matched by his scholastic ability. He won the Upper School prize and a special prize for theoretical and practical physics and, like his brother before him, he took a Leaving Exhibition from school to go to Cambridge; there being three or four years between each of the brothers leaving school, the Exhibition was "a Mellanby possession" over a number of years. John Mellanby preceded his brother Edward to Emmanuel College, Cambridge, and it is on record that it was the particular bottle of acetic acid allotted to John in Hopkins' advanced practical class which, by leading to an anomalous failure of the Adamkiewicz colour reaction[6] for proteins, played a more or less direct part in Hopkins' discovery of tryptophan. John Mellanby held the Chair of Physiology at Oxford at his death; the eldest brother was Professor of Civil and Mechanical Engineering at the Royal Technical College, Glasgow. Mellanby's sister describes Edward in his early days as very lively, as always being in evidence in the home since he was the youngest, and a mimic of all the visitors. Throughout his life he enjoyed a joke and fun, and he had in his nature a strong streak of mischievousness. His discovery that canine hysteria was the result of the use of agene in "improving" wheat flour he kept to himself for almost a year before he sprung the news on the Physiological Society with almost impish glee. He was what we call in the north of England a "tease."

He loved children, and they loved him; he did in fact enjoy young people of all ages, and he would make a special effort, a little sheepishly, to see a new baby. One day he appeared at my kitchen window in muddy boots carrying an enormous cabbage he had grown himself which he presented with a smile as a fitting tribute to a family of seven. In his later years he took an increasing interest in the garden around the Nutrition Building, and with some pride and manifest delight he exhibited a wide range of produce from these gardens and more or less swept the board of the prizes and trophies at a show of the gardening club of the National Institute for Medical Research. One of his treasures which he obviously enjoyed was the framed original of a

[6] This reaction depends on glyoxylic acid which may be an impurity in acetic acid (see 91).

cartoon[7] from a Glasgow newspaper published in 1922 poking fun at the professor's work on the rickets-producing action of oatmeal.

He was in many ways eminently a sociable person. His colleagues recall with pleasure sing-songs at the Mellanby home in Sheffield, his own contribution being made on a tin whistle. He had a pleasing voice both in speaking and in singing, and when experiments were going well his voice might be heard echoing down the corridors of the laboratory in song. He was genuinely musical, with an inclination towards Bach and away from Bartók. He had, a colleague writes, "a boyish, genial manner, an exuberant zest for life and a sense of humour which made him a very likeable and stimulating colleague and chief." It is regrettable that to some who did not know him well, Mellanby might sometimes have appeared perhaps somewhat aggressive or arrogant or over-critical of other people and their work.

A student, recalling memories of Mellanby as a professor 30 years ago, stresses how Mellanby had become to him:

> the prototype of the professor of real life instead of that odd creature, the professor of fiction. In no way absent minded, nor in the clouds, nor academic in the futile impractical way in which this word is now misused, he was large, healthy, robust, with a memory like a dictionary and a seemingly inexhaustible knowledge of physiology, chemistry, and biochemistry, not to mention pharmacology [of which he was professor]. And practical above all things.

Mellanby was in his later years much sought after as a lecturer, as the number of important named lectures in the appended bibiliography testify. His old student retains the impression that his professor in his lectures "took nothing for granted, but brought always a fresh outlook to everything which came to his notice. Never shall I forget" he writes "his lecture upon alcohol. 'Let us examine the facts which have been proved, whether we like alcohol or not' " opened an hour's undergraduate lecture which is still remembered clearly by his student who claims he has not heard anything better worth listening to since. As a young student of 23 years he was impressed with a number of incidents: Mellanby's remark on research and committees "If you want to find out anything, don't imagine you'll do it by talking about it at a committee meeting. You'll have to do some work on it, and hard work too"; his reply to a student who asked why a certain drug acted as it did, "science does not explain why: it tries to answer how"; and the only time when he was seen to be really annoyed, when a Scottish professor denied the results of Mellanby's work on the rachitogenic factor in oatmeal—he could have forgiven a different opinion, but "this creature had denied the facts." To the student waiting for examination Mellanby must have indeed seemed formidable; our informant recalls waiting his turn in the corridor of the department when the professor's wife passed by and evidently seeing signs of strain said "Are you going in for your viva? Oh, you'll be all right—he's really much nicer than he sometimes sounds."

I find myself reluctant to attempt to give a complete, detached, and

[7] This is reproduced as Figure 42 in *A Story of Nutritional Research* (96).

objective portrait; chiefly, I think, because to Mellanby I was—as many people even older than myself were—"young man." I can imagine him at this point coming out with some apt quotation, accurate and probably from the Scriptures, though it might equally be a line or two from a ditty of the music halls of decades ago, and his remark at this point might well be "Judge not that ye be not judged." Mellanby was a man for whom one could have the profoundest respect, admiration, and affection, yet he had a forthrightness of manner that alienated some, particularly those of a gentle or timid temperament. He demanded of others qualities which he himself possessed: wisdom, devotion to discovery, integrity of character, competence at work, and courage. He had little use for persons who did not have these qualities and often expressed his contempt for those who showed their antitheses—stupidity, indifference, untrustworthiness, and ineptitude. There were individuals he did not like, but he never allowed such dislikes to affect his decision to invite such a person to do a job if he judged him to be the right person for it. I know that it came as a surprise and sometimes as a shock to him to be accused of being deliberately unkind or unjust, when he had thought that he had been consistently helpful. The aggrieved person was often one who happened to be about, possibly failing to understand, or being out of sympathy with, some important principle Mellanby was out to establish, or some major measure which he was pushing through. His qualities as a man of affairs, in my view, are summed up in the term "statesman," and I have a letter from one the most eminent Civil Servants of our time and a man of exceptional judgment saying "I am glad you describe him as a statesman."

Two main streams are distinguishable in Mellanby's career, but just as in attempting to discover the origin of a river, so it is not entirely clear where Mellanby could be said to "rise," probably from a spring in Cambridge. His early days there are described by himself in the next section. The course of his life's work was, however, directly, if remotely, affected by the following programme drawn up in 1913 by the Medical Research Committee, forerunner of the present Medical Research Council:

> A list of major disabling diseases besetting the country at that time was prepared and those individuals who had shown a particular interest in any of these or were judged to be fitted for the task were asked to investigate one or more of the diseases from some specific angle. Among the items listed were tuberculosis, rheumatism (including acute rheumatic infections and chronic arthritis), rickets and oral sepsis (96).

According to the first report of the Medical Research Committee for 1914 to 1915 "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." Mellanby began this work whilst holding the Chair of Physiology at King's (now Queen Elizabeth) College for Women. The work was continued in Sheffield where he held the Chair of Pharmacology and a post as Honorary Physician to the Sheffield Royal Infirmary. This post he prized because in addition to facilities for laboratory work he also had a number of patients in his care, and this gave him opportunities for extending his investigations and teaching into clinical fields.

In 1933 he was invited to become the Secretary of the Medical Research Council. His work in this position was not in fact a separate stream so much as a powerful current in the mainstream of his career, for his research continued throughout the 16 years that he was Secretary, and indeed after his retirement, until his death.

Mellanby and his work were well-known in many countries in the world, and his eminence was recognised by the conferment of Honorary Degrees by many Universities, of distinctions and prizes from many scientific and other bodies. "These awards and high honours" said Lord Hankey at the address given at the Memorial Service to Sir Edward Mellanby "add undying lustre to Mellanby's career and testify to the world-wide esteem in which he was held;" but he says "Mellanby won the greatest prize of his life by marrying May Tweedy, thus doubling his efficiency, for she was already a research scholar and lecturer at Bedford College and was ideally equipped to halve his troubles and double his joys."[8]

BACKGROUND TO BRITISH BIOCHEMISTRY

The main part of this section is Sir Edward Mellanby's own introduction to the present prefatory chapter; it is reproduced substantially unaltered:

In writing the prefatory chapter to previous *Annual Reviews of Biochemistry*, my distinguished predecessors have discussed many of the salient developments in this subject during the present century in Germany and the United States. The invitation to write the present chapter can only be regarded as a gerontological distinction to one who has had the opportunity of seeing and appreciating the same kind of magnificent development of the subject in the United Kingdom, for the most part as a biochemist in the suspended chrysalis stage. Had fate been kinder, or at least different, the present writer might at least have been able to write with a little of the distinction of his predecessors; but whereas the trend of events has made the modern biochemist into a specialist chemist, those who entered the field in the earlier years of the development of the subject were more biological in outlook and their chemical skill and knowledge were elementary. The chemist of 1905 was not interested in biological phenomena, and he never for one moment considered it possible that the future of chemistry itself would be revolutionised by knowledge of the chemical processes which were encountered in biological material. It can be said with assurance, however, that those of us who were actively engaged in the study of physiological processes at that time realised to the full that the essential condition for progress was the enticement of first-class chemists into the biological field as active collaborators. Our prayers have been abundantly answered, indeed, more than answered, for the pendulum has swung the other way, and whereas chemical skill in biochemistry has become predominant, biological knowledge and outlook in the subject has either tended to fade away or to isolate itself from that of the chemists. This present-day dichotomy is

[8] Address given by The Rt. Hon. Lord Hankey at the Memorial Service to Sir Edward Mellanby, March 17, 1955.

viewed with regret by those, such as medical men, whose duty it is to deal with the practical problems of living. They realise to the full the great intellectual pleasure brought by discoveries of biochemists in, for instance, the subject of intermediate metabolism, and they appreciate greatly the advances in knowledge of carbohydrate metabolism, but they also know that they can do little more for their diabetic patients now than they could do 30 years ago, when insulin was first discovered by physiologists and the carbohydrate cycle was undreamt of. Nor can the gouty patient be greatly assured when he is told he is suffering from a biochemical disorder and that biochemistry is the most successful of all modern scientific subjects. There is much to be said for the view that biochemistry is a discipline in its own right, but there is still a great need for workers in the subject to direct their attention to the great practical problems of biological function. In such matters it is just as likely that the scientist will make a great scientific discovery by a study of the practical problem as it is for him to make a great practical discovery by studying a purely scientific problem; indeed, experience has shown that it is more so. Whereas in Germany and France it would probably be claimed that biochemistry had its origin predominantly in chemistry, in the United Kingdom there is no doubt that physiology was its progenitor. Thus in Germany, Liebig and his school; and in France, Pasteur and the pharmaceutical chemists, were outstanding leaders in chemistry who applied their great skill to problems of biological interest. In England we had no such distinguished scientists turning their attention in this way. Indeed, where such a person appeared, as in the case of MacMunn who made many fundamental discoveries in the chemistry of haemoglobin and blood pigments, his work passed unnoticed for 50 years or more, largely, it is presumed, because there was nobody in the country interested in this aspect of biological chemistry.

In the United Kingdom the man who did most for the official recognition of biochemistry as a discipline in its own right was Benjamin Moore. The first chair of biochemistry in England was founded by Liverpool University (the Johnston Chair of Biochemistry) in 1902, and Moore was the first incumbent. In 1920 the Chair of Biochemistry was founded in Oxford University by a Mr. Whitley, an intimate friend and former colleague of Moore's, and Moore was again the first professor. His early death in 1922 was followed by the election of R. A. Peters (now Sir Rudolph Peters), a pupil of Hopkins, as professor of biochemistry. An even greater service to biochemistry in England was the foundation in 1906 of the *Biochemical Journal* by B. Moore in co-operation with Edward Whitley. The journal was edited by Moore until 1912, when its control was taken over by the Biochemical Society. However, the real stimulus to British biochemistry came from Cambridge University, and in particular from its physiological department. Michael Foster had been imported to Cambridge by T. H. Huxley and ultimately became the first professor of physiology. As is now well known, Foster himself was no great scientific discoverer, but he had many other qualities of greatness, particularly those of appreciating the value of experimental investigation and, what is of greater importance, an eye for picking men with outstanding qualities in research and persuading them to devote their life to their studies. When I went to Cambridge in 1902, Foster had just retired and devoted all his time to parliamentary work (and to his garden). Langley had succeeded him as professor, and the small laboratory was filled with men of the highest distinction—these included Gaskell, W. B. Hardy, H. K. Anderson, Keith Lucas, T. R. Elliott, J. Barcroft and most important from the present point of view, F. Gowland Hopkins. It was a wonderful galaxy of talent, and any young man who had the privilege of entering and being accepted by this circle was thereafter doomed to a career of research and investigation.

Hopkins was not originally a Cambridge man, and his importation at the age of 40 years, on the basis of a few publications of work done at Guy's Hospital, was a stroke of genius and one of the most fruitful incidents that can ever have happened in the world of science. Hopkins was made reader in physiology and was also given a post as director of studies in medicine at Emmanuel College. Entering that College in 1902 as a medical student, it was my great fortune to be brought at once under his scientific care, a relationship which continued first as student, later as research associate until 1907, and until his death in 1947 as close friend. After I had taken my bachelor's degree in 1905, Hopkins invited me to continue as a research worker in his laboratory. He had at this time completed his work on the detection and isolation of trytophan and was engaged, in association with Edith Willock, in experiments on growing mice to see what special part this substance played in animal nutrition. It was this work on tryptophan metabolism, published in 1906, which opened up the whole field of differences in protein quality, and so replaced the view that protein in itself was a nutritional entity; it also directed Hopkins' attention to the physiological importance of accessory food factors in general, which led to his classical publication on this subject in 1912. I remember with great interest the remark he made on a number of occasions in those early years that "Somebody was soon going to make an enormous fundamental discovery in nutrition." Little did he seem to recognise that, with his work on the nutritional needs of tryptophan and of other "accessory food factors," he himself had already made the necessary fundamental observations which were going to transform biological science and indeed to lead to a new science affecting the nutritional condition of the whole world. If anybody doubts this statement, let him read a physiological text-book on nutrition published before 1907.

After 1907 it was never my good fortune to work with Hopkins again, as I left Cambridge in order to become medically qualified. In 1920, when he became the first professor of biochemistry at Cambridge and obtained a laboratory which was worthy of him, he invited me to become his first reader, but by this time I had become so involved in medical research as the result of some investigations on rickets which he had urged me to undertake on behalf of the Medical Research Council (at that time Committee) that I decided not to return to Cambridge. This was a crucial decision (and probably a wrong one), and hereafter I could no longer be regarded as a biochemist. Indeed, my occupation was now as physician to a general hospital and as professor of pharmacology at Sheffield University—a subject which at that time did not make large teaching demands and so allowed time for investigation.

Up to 1914 Hopkins had to do his work in the Physiology Laboratory under what would now be regarded as ridiculous restrictions as regards space and laboratory assistance. He had one small room in which to carry out his investigations, and this I shared with him during 1906 and 1907. I remember with interest that all our clean glass (cleaned by ourselves) had to be kept in one cupboard, which remained locked to prevent raiding by fellow workers. In order to obtain any glass article from the permanently locked cupboard, it was necessary to remove an upper drawer and dig in the darkness for the particular flask or beaker required. In 1914 the physiology department obtained a fine new laboratory. Hopkins was raised to the status of professor of biochemistry and was allowed to use the whole of the old physiology laboratory. After the first war, biochemistry was recognised as a separate subject for Part II of the Natural Sciences Tripos, and in 1925 Hopkins for the first time was provided with an excellent institute for biochemistry, and it became possible for him to receive into his laboratory a group of research workers who formed a good nucleus for the training of many of the biochemists who now form a significant part of the leaders of this subject in the United Kingdom. By 1925 Hopkins was 64 years of age, but fortunately his Chair was founded before the University rule of retirement at 65, so that he got the opportunity not only of extending his own great investigations but also of building up his well-known school and exerting his inspiring influence on biochemistry until he retired from the chair in 1943.

It would be impossible to exaggerate the magnificent part played by Hopkins not only in the development of biochemistry in England but also in setting a standard of investigation which very few can attain or even copy.

In 1948 Mellanby delivered before the Chemical Society the Hopkins Memorial Lecture. In it he relates an incident which is an interesting footnote to his appreciation of Hopkins. He said

Hopkins had a great stimulating power on young people. A particular instance of this kind happened at an early stage in my undergraduate career at Cambridge, when he introduced to a class taking the Tripos in Physiology a discussion on the volume of blood in the body. He succeeded in rousing in me a state of enthusiasm sufficient to make me confine my whole attention to this problem for a fortnight to the detriment of my other work in order to find a method to decide whether the blood volume was 1/13 or 1/20 of the total body weight. This was an exaggerated reaction of the kind with which I was constantly affected in the few years in which I was intimately associated with him in the laboratory.

An Autobiographal Sketch of Research

The Editorial Board emphasise the great value of these prefatory chapters to the younger generation of biochemists and especially of the autobiographical sketch of the life of the person as student, teacher, and investigator. Mellanby, in his Abraham Flexner Lectures which have been published under the title of *A Story of Nutritional Research. The Effect of Some Dietary Factors on Bones and the Nervous System*, has already given an autobiographical account (96) of "a series of investigations which systematically developed from observations made early in his career, observations which played a prominent part in the birth of the science of nutrition and which have continued on and off over a period of thirty years." The "story" runs to well over 100,000 words with many diagrams and tables; to summarise it would defeat the purpose of the story. Sir Edward intended it to be read through and to be a source of inspiration; as a demonstration of the triumph of determination over the difficulties of biological research, it will undoubtedly become a classic in the literature of science.

Rickets was, as already mentioned, the subject allotted to Mellanby by the Medical Research Committee in the days immediately before the First World War. The state of knowlege of the disease at that time is indicated by the nature of this assignment, which was to investigate the part that processes of oxidation might play in the aetiology of the disease, and, in the early stages of the experiments which began in 1915, tests were made with diets of high specific dynamic action to see whether increasing the intensity of the oxidation by this means affected bone formation. In 1919 to 1920 it was demonstrated that a fat-soluble vitamin controlled calcification of bones and teeth. In course of time it became evident that the vitamin A of those days was a complex of two vitamins, one retaining the name of vitamin A and the other now called vitamin D. In his Flexner Lectures, Mellanby showed how

these two entities work together in close association. First vitamin A controls, or at least influences, the activity of the osteoblasts which lay down the soft bone matrix. Vitamin D then attends to the calcification of this osteoid tissue, and finally vitamin A again steps in and sees that any superfluous calcified bone is removed by osteoclastic action and that the bone shape is correct. Thus . . . these two inseparables, vitamins A and D, the David and Jonathan of nutrition, whose faithful alliance in distribution and similarity of many chemical and physical properties has caused so much trouble to hosts of physiologists, biochemists and other scientists, work in harmony and on the same structures at the time of their active careers in the animal body. Although their functions are different, they unite in directing and controlling the building up and maintenance of bone structure.

With these words Mellanby concludes his account of a series of researches. Selecting from Chapter X of this book an illustration of his treatment we read that he sets out "to find the cause of the ataxia and incoordination of movement that developed in growing animals fed on diets, which so far as was known were complete except for vitamin A and carotene." In the earlier chapters of the book he has described "the development of the research and the gradual unravelling of the factors involved as the work progressed." Whilst from this work, "it is probably easy to judge" he says, "where and when progress was made and generally to group and evaluate the positive results, it cannot be easy to understand the doubts, difficulties, disappointment and mistakes that have been major factors in work which has continued intermittently over a period of about 25 years."

He refers

to a brief account of experiments which failed to open up the problem, but the narrative would hardly bear a full review of all the other will-o'-the-wisps that were pursued in the course of the work. Yet, failure fills a much larger part in biological investigation of this nature than in the more scientifically developed chemical and physical fields. The solution of a biological problem when worked out often seems so reasonable and so simple that wonder is expressed that any other sequence of events could be contemplated, but those who think along these lines can have had little experience in opening up new fields of biological enquiry. Such work involves constant speculation and formulation of ideas, most of which, on testing, do not reach the stage of being acceptable as working hypotheses. It is even worse when the speculation becomes a working hypothesis only to be rejected after months or years of further work.

One other general remark may be permitted. It is obvious that there is no end to an investigation of this nature. The final results [as he has described them] will no doubt form the basis for other work. The facts as described will probably be for the most part, correct, but it is rare for biological discoveries to be interpreted in the right light or in their true perspective in the early stages. There is no reason to believe that the present work will differ in this respect from many other advances in biological knowledge.

After summarising the changes attributable to the presence or absence of vitamin A in growing bone, demonstrating so clearly how important a task vitamin A has in ensuring the normal moulding and shaping of bones, he writes

It will be generally agreed that Nature has done well to provide the central nervous system with a strong bony protection. Its safety from assault is essential both for the survival of individual and the race. Those who build the walls and ramparts must, however, plan their activities in accordance with the size and growth of the citadel to be protected. The central nervous system is a citadel and as it grows the protecting walls are normally moved farther out. As the bones of the skull and vertebrae grow bigger the space they surround is enlarged by absorption of the inner surface and deposition on their outer surface. Now if the director (vitamin A) of building operations disappears, it might then be expected that the brick layers (osteoblasts) and demolition squad (osteoclasts) would either go on strike or work in a completely disorderly way, but this does not happen in the bony ramparts. It is rather as if the place of vitamin A as a wise director of operations were taken over by that worst kind of director—the energetic man with no wisdom, whom we all know so well nowadays—who says: "I am going to show you how things should be done; now you will see something really happen." His directions are: "You must work harder than ever, but in a different way. You builders (osteoblasts) must lay down bricks wherever there is a foundation (periosteum). You demolishers (osteoclasts), working nearest the citadel, must leave that position and continue your labours elsewhere."

The result is that the walls, instead of enclosing a greater area as the citadel grows, now encroach on the nerve control stations, lines of communication and the administrative centres and squeeze all the vital structures into so small a space that work inside the citadel is impossible. Parts of the citadel (the central nervous system) are destroyed and the city (animal) with it. There has been no slacking and no anarchy among the building operatives but, by working at the wrong place and in the wrong direction, they have converted a protective structure into one of destruction. Thus, vitamin A, by regulating the activities of the bone cells in this position coördinates a beautiful adjustment of bone and nervous system growth. How important this function is to animal development can be appreciated by the drastic and dramatic effects produced when the mechanism goes wrong in the absence of the vitamin.

The second half of *A Story of Nutritional Research* is devoted to a study of the anti-calcifying or rachitogenic action of cereals. Mellanby starts at the point where rickets is accepted as being a result primarily of a deficiency of the vitamin D moiety whose main function is to harden the bones by controlling the deposition of the calcium-phosphate compound in the osteoid tissue laid down by the osteoblasts. He points out that

Prior to the Great War of 1914–18 . . . among a vast number of other hypotheses it was stated by clinicians that carbohydrate-containing foods, including cereals, had a rickets-producing effect on children. This view was largely founded on the fact that excessive consumption of such foods produced fat babies and in those days fat babies were more prone to develop the disease. Rickets was at that time rampant in both the U.S.A. and Britain and the indictment of this large class of foodstuffs by clinical experts was widely accepted . . . while their assumption had real foundation, the explanation of the rachitogenic effect of cereals was not so simple as it then appeared, namely that the carbohydrate was the responsible factor.

He found two main effects of cereals, one on growth promotion which has not been elucidated and is, he says

undoubtedly . . . a subject which will repay further study.

The second one, to which most attention is given, is the property of interfering with the calcification of bones of young animals. Ultimately it was demonstrated that a chemical substance, phytic acid, plentiful in some cereals such as oatmeal, corn, and wholemeal wheaten flour, and sparse in others such as rice and wheat flour, has the property of interfering with calcification of growing bones and teeth. This substance interferes

with calcium metabolism when there is a deficiency of vitamin D, causes the production of rickets in young growing animals and, in adult animals, a decalcifying effect which may lead to osteomalacia . . . phytic acid or inositol hexaphosphoric acid, [is] a compound which has long been known to exist in cereal grains and, indeed, in all seeds in the form of the insoluble Ca and Mg salt—phytin. Phytin itself is not rickets-producing but oats and almost certainly other grains contain phytic acid which is not wholly satisfied by Ca and it is this form which has the toxic anti-calcifying action. It was found early in the work that the phytate action could be largely antagonised by the addition of extra calcium to the diet, especially in the first weeks of the experiment, while the presence of vitamin D completely preventeu rickets, although as shown later it did not necessarily prevent the predatory effect of phytate on calcium . . . more recent experiments have consisted of metabolic studies of the close interaction of three substances which are themselves, or which contain, elements essential for calcium metabolism, namely vitamin D, Ca and phytate, a rich source of P. If nature had supplied more phosphorus as inorganic phosphate and less in the form of phytate, the investigation would have been unnecessary. As it is, phytate provides much of the P essential to animals and its unhappy property of combining with Ca in the intestine and so making this salt unavailable to the animal is the cause of much physical abnormality. It would be wrong however, especially from a scientific angle, if all interest in phytate as a physiological study centred round its property of immobilising Ca in the gut. As a rich source of inositol, an essential dietary constituent in many animals, and a well recognised constituent of nervous and muscle tissue, phytate is clearly of some importance from another angle.

It is impossible to study the calcification of bones in growing animals without being impressed by the dominant position held by vitamin D. Take all vitamin D away from the food and ultimately, when the reserves of this substance are lost, the animal cannot retain sufficient Ca, however much is added to the food . . . when what appears to be a relatively small amount of this vitamin is supplied to the body further additions do not increase the powers of the body to absorb and retain calcium. This does not mean that the additions have no effect on the bones, for it was shown that increasing the vitamin intake resulted in an improvement in bone quality even when it had no effect on calcium absorption. It does this by controlling the proportion of organic to inorganic substances.

Although vitamin D has been shown to stimulate "the absorption of Ca from and hydrolysis of phytate in the gut," it seems certain

that this does not explain all the action of the vitamin, and that it also plays an important part in promoting the deposition of the calcium-phosphorus compound in the osteoid tissue of the growing bone and in producing perfect bone structure.

Mellanby concludes his "story" by discussing some of the evidences of

the present improvement in calcification processes in the population of Britain during and since the war . . . in spite of the greater relative consumption of [cereals], involving as it has, the higher intake of phytate. Here, then, is some evidence of a practical nature, taken from the life of the community, showing that the teachings based on the results of animal experiments . . . are correct and that cereals with high phytate content, although in themselves harmful and even dangerous to life, and especially early life, can be made innocuous by including in the diet other foods rich in calcium and containing vitamin D.

Half a Century of Research

In 1905 Mellanby started research in Gowland Hopkins' laboratory; he worked for two years on creatine and creatinine metabolism. In a paper published in 1908, evidence was presented which decisively disposed of a number of current notions about the behaviour of these substances in the body. The first signs of his life-long interest in biological problems are to be found in this paper; he examined the creatine content of various animals, and its occurrence in the course of development in several of these, in an attempt to discover whether from ontogeny and phylogeny light might be cast on the evolution of vertebrate animals. A bibliography of Mellanby's work is appended, with titles, so that the range and scope of his work can be appreciated. An attempt will be made here to indicate how the various researches may be linked.

The sorts of strands of thought running through much of his research are best appreciated from the work described by Mellanby himself in *A Story of Nutritional Research*. One feature is the way he follows up one piece of work with another. In his earlier papers for example he returned from time to time to the study of creatine in metabolic processes; this is to be seen in a paper on the metabolism of lactating women which Gowland Hopkins read before the Royal Society in 1913. An incidental observation that creatine is destroyed by bacterial action led to a study, with F. W. Twort, of the effect of bacteria from the gut on creatine; this work led to the discovery that histidine was decarboxylated by an intestinal organism to form histamine. These threads are picked up again in a paper on the investigation of diarrhoea and vomiting of children.

Another theme of considerable importance is what he calls "the interaction of clinical and experimental work" which he used as a sub-title to his book *Nutrition and Disease* (58) published in 1934. He says in the introduction to this book

Some lay stress on the importance of the clinical aspect of medical science, others on the provision of laboratory facilities. Only too often there is a distinct cleavage between the respective adherents of these two schools of thought.

His book is offered as "a chance, by reviewing the work done, of showing how the two methods can react on one another to their mutual advantage."

Some of his work seems to derive from his desire to maintain a sense of balance, a reflection of his sense of propriety and level-headedness; this emerges, for example, in his chapter on "Toxamins in Food" contributed to *Perspectives in Biochemistry* (67). He opens the chapter with this paragraph:

It is curious how biological research is influenced by vogues and fashions: probably not to the extent of dress, but still greatly. Nor is this altogether a bad thing. It means that a profitable idea is often pressed until it looks like a squeezed lemon, but, unlike the lemon, it is not really dry and is only put aside and not thrown away. After a moribund period the original line of investigation is taken up from another angle, the old fashion is revived, and all the workers in the subject are after it again.

Remarking that this is a phenomenon particularly apparent in nutritional investigations he refers to the fact that Chatin in 1850 put forward the first instance of deficiency disease when he ascribed simple goitre to deficient intake of iodine in food. This ". . . excellent work" he points out, "was discredited, partly by the French Académie des Sciences, and partly by the success of the Pasteur investigations on microorganisms which led the medical world to believe that all disease is due to a *materies morbi*," only to be revived later with Baumann's discovery of iodine in the thyroid gland. Mellanby gives evidence to show how in the first part of the present century

. . . the pendulum swung towards the deficiency theory of nutritional disease with a vengeance, and well has the theory served its purpose. The object of the present contribution, however, is to swing the pendulum back a bit and emphasise the view that some so-called deficiency diseases are not simply due to the deficient intake of dietetic entities but depend also on the action of certain positive toxic factors which are normally present in food (67).

Another powerful influence in his work was the practical and humanitarian benefits that he recognised might accrue from medical research. His investigations in the earlier part of his career into the physiological action of alcohol, for example, did much to influence opinion and policy in regard to the social evil of drunkenness in this country. He took an active part in one of the earliest campaigns on cancer research and himself engaged in investigations into the cancer problem in which he was still interested in his last years, as a quotation from an unpublished report given later will show. It is not surprising that working in the district in which "Derbyshire neck" (goitre) was common, he should engage in work on this subject, and here again his interest continued as will be seen from recent publications with Dr. Fell on the effects of substances from the thyroid gland on living tissues cultured *in vitro*.

In a Presidential address to the Indian Pharmaceutical Association (100) he recalls that when a

. . . medical student doing clinical work in the years 1907–10, I constantly wondered at the attitude of my clinical teachers towards individual cases in hospital. Infinite pains were taken to diagnose the illness, and teaching at the bedside of diagnosis was very thorough. This was excellent. But after the diagnosis was made, I looked forward to learning the proper treatment of the condition. To my surprise, the physician either passed on to the next case without mentioning the subject, or in a perfunctory manner issued a few orders to the house physician and left the case. There was no teaching on what I thought ought to have been the main object of the physician, namely, to cure the patient. Only slowly did I understand this method of procedure, but looking back it is clear that his omission to discuss treatment was only too often due to the fact that there was no adequate treatment for these sick people. In many cases the physician said with a smile that this was a case for "expectant treatment" —clearly an expression of the hope that having diagnosed the complaint, Nature would play her part and cure the patient. Nature fortunately often rose to the challenge and cured the patient but this was by no means always the case.

Mellanby was one of the first persons in this country successfully to employ insulin.

An interest in infections and the possible role of good feeding in combating them constantly recurred. One of his most recent statements (86) on this subject reads

Nothing seems to be more certain than that nutritional defect is at least part of the aetiological basis of many of the more common illnesses, and yet, in most of these cases, this is only conviction without satisfactory proof. . . . To what extent, if any, dietary factors will be found to have a specific anti-infective action remains for future investigation. Some investigators on nutrition have already had experience in the search for this El Dorado, and in consequence regard the problem with more respect.

One of the best known of Mellanby's discoveries is that agenised wheat flour causes "canine hysteria" and that the toxic substance, methionine sulphoximine, produced by the action of nitrogen trichloride on gluten, has toxic effects on the central nervous systems of all the species of animals tested. This work has contributed to the present day interest in the effects on human health of chemical additives deliberately introduced into or present unintentionally in foods. Mellanby, in a lecture on "The chemical manipulation of food" (99), has sounded a warning against the dangers of leaving the field of food technology entirely in the hands of the "food scientist"; the "actions and reactions of the human body are so unpredictable, and knowledge of them so meagre, that the confidence and clear-cut views of the chemists may often be dangerous." One of the conclusions of his survey of the use of chemicals in the preparation of foods emphasises this warning.

The triumph of medical science in the prevention and control of disease during the present century has been impressive, and care must be taken that, at the time of gaining such control, new habits of living which cause ill-health should either be prevented or, if they arise, be controlled. Such errors in living are undoubtedly developing at the present time, and it is the duty of medical science to find out their relative disease-producing importance. The chemical manipulation of food may well be the basis of some of these errors, and the problem requires investigation (99).

The bulk of his work was, however, more or less directly related to his first important problem, i.e., rickets. This is true, of course, of all his work on bones, of the action of vitamins A and D, and work on toxamins, especially phytate; of his interest in diseases of the nervous system; of his experimental work on vitamin A and infections; and even the work on thyroid arose out of a similarity in histological appearance that he and his wife had observed between the hyperplastic thyroids of dogs under experiment and those of patients suffering from exophthalmic goitre (19).

The culmination of Mellanby's work on vitamin A came after he had delivered the Abraham Flexner Lectures. This work, which was part of a plan to examine the direct effect of substances on tissues in culture, he developed with the expert help of Dr. Honor Fell of the Strangeways Research Laboratories, Cambridge. They found that bone grown in plasma with a high vitamin A content showed some striking changes.

> The matrix of the cartilage first lost its metachromatic staining properties and then rapidly disappeared, leaving the healthy cartilage cells collected together like a bunch of grapes. The bone shaft then began to shrink and to disappear so that at the end of ten days or so nothing remained but a few crumbs of debris scattered in a sheet of actively growing and migrating cells.[9]

Chick ectoderm grown in plasma with a high vitamin A content developed not into normal skin, but into more highly developed mucous-secreting ciliated respiratory epithelium, and, when returned to normal plasma, it reverted to normal skin. Likewise, on culture in high vitamin A plasma, corneal epithelium became hyperplastic like the conjunctiva. Commenting on these results on metaplasia of epithelium, Mellanby writes

> The action common to skin and bone seems to be, therefore, that the effect of the vitamin A is on the basal structural cells both of the ectodermal and mesodermal tissues. If this is the right interpretation, vitamin A might be regarded as a "director" of basal cell development. This recalls the action of "organisers" in embryological growth. . . . It may well be that the developmental and differentiation changes of all organs, tissues and cells have their specific chemical controllers. In the case of cells, these controllers may normally continue to exert their influence over structure and function throughout life, and, only with their reduction or disappearance due to age or other circumstances, the cells may suffer metaplastic and degenerative changes.

He envisages the possibility that his results

> may ultimately prove to have a bearing on pathology and medicine. . . . The most prominent medical problem of metaplasia is seen in cancer, and it would certainly be beneficial to the scientific advance of studies in cancer if the biological mode of control of cell structure were understood. . . . The fact that various levels of a substance normally circulating in the blood and essential to life can have such remarkably different effects on the structure of living cells of different origins, and that these or some of them, can be analysed by a simple *in vitro* method, opens up the field of metaplasia to further study.
>
> Apart from metaplastic disease, it is possible that other diseases which involve degenerative and other changes of structure due to altered metabolism may be investigated by this type of work.[9]

At the time of his death, he was investigating with the help of colleagues in other Medical Research Council laboratories the effects of vitamin A on the metabolism of the sulphur-containing elements of skin epithelium, cartilage and bone[9]. Summing up in 1953 his attitude to his own research[10] he wrote:

. . . there is a tendency in work of the kind done in this [his own] laboratory to allow its chemical and biochemical aspects to become dominant. This I have resisted, and although chemistry has had to have its place, I have endeavoured to make it subsidiary to the biological objectives and to limit its expansion. It seemed to me that while the physiological field in its wider aspects is probably not receiving sufficient attention in this country, biochemistry on a large scale is developing rapidly into a special branch of chemistry and only too rarely with any direct relation to biological function. Thus, at the present time a large number of chemical substances have been isolated from living tissues, which are known to be essential to life yet there is little or no knowledge of the part payed by them in the animal economy. A knowledge of their functions might revolutionize our present-day physiology and pathology.

Statesmanship

It is most regrettable that Sir Edward Mellanby as one of the "elder statesmen" of medical research could not himself have recorded in this section his advice and experience. To his work as Secretary of the Medical Research Council he brought the qualities of a statesman—sagacity, far-sightedness, and skill in the management of practical affairs—in unusual measure. In a Minute of the Council on the occasion of his death, it is recorded that he

. . . took the leading part in the difficult tasks of deploying the Council's scientific resources in support of the national effort during the Second World War and of reconstructing and notably expanding the organisation thereafter. To these responsibilities he brought an intense regard for scientific truth, a wide knowledge and deep understanding of medical problems, a sure sense of what was important in research, and a constant desire to encourage all who showed ability as investigators and ideas likely to lead to real discoveries. His endeavours had great success.

We have already seen that he had been in close contact with work of the original Medical Research Committee in, for example, his researches on rickets and also on alcohol. He was indeed in many ways intimately connected with the activities of the Medical Research Committee from its earliest days. In a letter written to Mellanby in August 1913, Hopkins wrote

My job is to research after researchers. The new [Medical Research] Committee is going to be no joke. Indeed I want to ask you the biggest favour I ever asked of you

[9] Lady Mellanby tells me that although this statement is correct, his chief interest was in his experiments on methionine sulphoximine, the effects of which he was studying by means of injections into fertile eggs and by tissue culture. He was, she says, thrilled with the results so far achieved, and he was proposing to extend the work and to include tests on cancer growth.

Some observations on the effects of sulphoximine on the growth of bones in tissue culture, on the development of fowl from injected eggs, and on cancer growth are being prepared for publication posthumously.

[10] Unpublished report (Medical Research Council) by E. Mellanby (1953).

. . . it is no less than this that I propose to ask—I wouldn't ask it only it is a job which you will almost have to do yourself. I want you to try and appraise the current chemical work in physiology, pathology and pharmacology. . . . If by the end of the first week in October you could prepare some sort of document pointing out the main lines on which chemical research is likely to help practical medicine you would be doing much for me and for chemical research. . . . What I am asking is really rather a big thing but I feel that the matter is important. What we do during the next year may determine the fate of that £60,000 [the Treasury grant] for a long time to come. To make a strong case, I want a young and alert mind to help my rusty one and it is to you alone that I can turn.

A letter dated October, 1931, to Sir Walter Fletcher, the Secretary of the Council, shows Mellanby's continuing interest in the work of the Council of which by that time he was a member. Fletcher had evidently asked him about a committee to look into the possibility of advancing the application of biochemistry to medical problems. Mellanby writes

The lack of status of the biochemist in the average hospital is only an instance of the bigger problem of which you are fully aware, namely, the small recognition given to any scientific work inside the hospital. The status of the pathologist and bacteriologist inside the hospital is generally not much better than that of the biochemist although individuals have by their personality or by their research sometimes obtained well-recognised positions. The biochemists are not free from blame as regards their lower status than the pathologists and bacteriologists; so many of them refuse to get a medical qualification or even to study physiology that the choice to fill hospital posts is lamentably small. When qualified they often are attracted to the flesh pots thought to be associated with private practice. Scientific medicine has a long furrow to hoe before it arrives; that it will do so I have no doubt at all. It must however justify itself and the quicker it does this the more quickly it will be recognised. The most certain method it can adopt to do this is by making valuable discoveries and making itself pre-eminent. Able biochemists must get medically qualified and meet the clinician on equal terms even on his own line. He has a virgin field for discovery and ought to recognise that a biochemical discovery in a clinical subject has the great advantage not only of shedding light on the diagnosis and treatment of disease, but also opening up new academic lines of investigation. I am, as you know, a blatant advocate of medical research for this reason, but except for yourself there is almost a complete absence of such recognition even among scientific men.

It would have been interesting to read why Mellanby accepted the invitation to become the chief executive officer of medical research in this country. At the time he was appointed he was enjoying good facilities for research, and there were assured prospects for him of a more important post affording still better opportunities for research. There may have been a number of reasons for his acceptance, but it does seem likely that he took the job because he knew what he wanted to do and because he thought he could do it well. As his experiments on rickets influenced the course of his researches, so his experience with the study of the disease and of the application of the results of research in eradicating it, may well have helped to determine his decision to engage in administration.

When he started work on rickets, there were many and varied views on its aetiology. Among these was indeed good evidence of the efficacy of cod liver oil and butter fat as therapeutic agents, as will be seen in the lecture on rickets by Cheadle (1906)[11] who emphasises that "the only constant factor, always present, is the food factor." Notwithstanding such teaching, however, in the 1910's "a concoction called Marylebone Cream, an emulsion of linseed oil, was being distributed in London welfare centers for the cure of rickets" (53). Soon after Mellanby had established that rickets was a dietary deficiency disease, a revolution occurred. In London over three quarters of the school children had been found to have some signs of rickets (14), but when it became necessary in the early 1930's to determine the effects of calciferol on the disease in the human, no case of rickets could be found in the London clinics that had not already been prescribed proper treatment; the investigators had to go to a depressed area in the north of England to find cases on which to conduct their trials. No wonder Mellanby subscribed so strongly to the view expressed by Lord Moulton when he wrote (61) "Where we are reduced to observation, science crawls. Where and in proportion as you can use experiment, science advances rapidly."

The main function of the Medical Research Council has been defined as the promotion of "scientific investigations for the acquisition of knowledge likely to be of value for the prevention, diagnosis and treatment of disease, and for the maintenance of normal health and full human efficiency."[12] In his Harveian Oration in 1938 (72) Mellanby showed how state control of medical research can be compatible with freedom to the investigator.

> In this country, and even more so in the United States of America, scientific research is not supported by the public, even the enlightened public, on intellectual grounds but because it has been found to deliver the goods often enough to deserve special encouragements. . . . Wise men, both in public life and in industry, saw that scientific research was the life blood of modern existence—a means of providing easily the needs of mankind and the knowledge necessary for healthy existence under modern conditions . . . it was good business to throw a sprat of expenditure to catch a mackerel of large profit.

Into this background of realism he fitted his concept of how research should be developed

He repeatedly insisted on the importance of the use of the experimental method, which he has described as "the most important discovery that the human mind has yet used and developed." He maintained that Claude Bernard's point of view was the correct one, that is, that all experimental medicine was applied physiology. But, he says,

> . . . it is no more unlikely that discoveries of first-class scientific interest will result from work directed to the solution of practical problems of disease than that discoveries of first-class interest to medicine will result from the study of academic physiological problems (61). Every man working on a problem from either angle ought to be familiar with the other aspect (79).

[11] Cheadle, W. B., *Artificial Feeding and Food Disorders in Infants*, 6th ed. (Smith, Elder & Co., London, England, 274 pp., 1906).

[12] Report of the Medical Research Council for the Years 1945–48 (His Majesty's Stationery Office, London, England, 1949).

Once when asked what the Council's policy was in financing research workers he said (72) they had none except "to find the right men and back them in every possible way." He recognised that "the limiting factor in this progress (of medical discovery) will be the men of genius to make the first-class discoveries." He had described the right men as

> . . . limited in number and cannot be appreciably increased by any known method. They must in general be what is known as clever men, but cleverness alone accounts for little. In addition they must be men of strong character, capable of hard and often disheartening work, with power to distinguish truth from falsehood, prepared to spend their lives with limited social contacts and to forego riches.

One might add that this is something of a self-portrait. Such men he recognised are rare and he considered that one aspect of the Council's work was, short of this ideal

> . . . to attract able men, and by providing financial assistance and ensuring the proper kind of training, helping them to a career of medical research.

Although the discovery of suitable investigators was a limiting factor, the difficulty he foresaw was not that of obtaining knowledge but that of its application to human needs.

In nutritional matters, in a paper in 1927 on the duties of the state in relation to the nation's food supply, he foresaw a number of what have been comparatively recent developments in applied nutrition. On one point he stands firm: "no nutritional policy adopted by governments can be wrong if it places the health and the needs of the community as its first and guiding principle."

In the broader field of human welfare he saw that

> For every problem—social and economic—raised [in his Rede Lecture] the only solution is more knowledge and more wisdom to use this knowledge. There is no limit to the amount of knowledge to be gained if the medical scientist is given the opportunities and facilities for his work. Would that the same could be said about the wisdom necessary to make the best use of this knowledge.

Mellanby was fortunate from the early days of his appointment with the Medical Research Council.

> At the time of Mellanby's appointment [in 1933]

says Lord Hankey,

> I was Clerk of the Privy Council, to which the Medical Research Council was attached for administrative purposes. I was also Secretary to the Cabinet and to the Committee of Imperial Defense.
>
> In the latter capacity, soon after his arrival, I asked him whether something could be done to improve the health of volunteer recruits for the army, some 50 to 60 per cent of whom were being rejected every year for medical and especially dental reasons. Mellanby, as he recalled to me as recently as January 20th last [1955] replied that the problem could be solved, but only on a long term basis, and by drastic reforms in the national diet. I asked him for a Memorandum on the subject, and to his astonishment, as he also recalled on January 20th, a day or two later it came back to him in the form of a Memorandum to the Cabinet. At the moment, he had been

feeling baffled and exasperated, like many another distinguished Scientist has been, by the well-nigh insuperable difficulty in getting the results of research work translated into action. In terms of rare emotion, at this, our last meeting on earth, he told me that this episode had given him new hope and inspiration.

This episode,

continues Lord Hankey, was

the beginning of our long and valued friendship. It was also a prelude to even closer collaboration, in which Mellanby took a leading part, between the Medical Research Council and other Government Departments concerned, including the Committee of Imperial Defense [when appropriate], with a view to the common aim of safe-guarding our people, should need arise, against those hidden foes of mankind, which in past wars so often brought nations and armies to disaster—disease, malnutrition, contaminated water, biological and microbiological pests of all kinds—the risks of which had been greatly increased by the menace of air bombardment. In the five years before the war, and in the six war years, I was a privileged witness and sometimes a collaborator, as Chairman of Committees or otherwise, in much of that work.[8]

It is quite impossible to do justice to the work which Mellanby accomplished as Secretary of the Medical Research Council. Some idea of the immense scope and intensity of activity may be obtained from reading the Reports of the Medical Research Council for the years 1939 to 1945 and 1945 to 1948. The Council itself, commenting on his period of office, states[13] that it

. . . had been one of exceptional difficulty and strain, during which the Council's programme had to be reorientated to the needs of war and again to those of peace, and the Council's organisation and resources were increased several fold.

The Council recognised the debt which not only they but medical research in general owe to him. They say

He showed a firm grasp of the general principles governing the progress of scientific research. To these he held fast among the multitudinous problems with which he was confronted, so that his advice was far-sighted and his action effective. During his time as Secretary many important medical discoveries have been made or have come to fruition. Modern chemo-therapy and the anti-biotics have revolutionised medical treatment. The science of nutrition has become a major branch of preventive medicine. Personnel research is achieving the recognition its importance deserves. Nuclear physics has brought its profound influence on society. Mellanby's ready appreciation of the significance and possibilities of different lines of research, even when the investigations were in the embryo stage, has been a formative factor in the progress of medical research in this country, and indeed in the world.

In his work, generally, Mellanby was never content unless he could ensure that the practical fruits of research should be reaped. This attitude is found in his work in the international sphere, and from 1930 he was intimately connected with the Health Organization of the League of Nations, and he was Chairman of the international conferences for the standardisation of vitamins in 1931 and 1934 and of the International Technical Commission

[13] Report of the Medical Research Council for the Years 1948–50 (His Majesty's Stationery Office, London, England, 1951).

on Nutrition sponsored by the League. With Professor E. V. McCollum, Mellanby represented nutritional experts on the medical committee of the League of Nations which was responsible for the classical report that led to "the marriage of nutrition with agriculture." The United Nations Organizations now concerned with nutrition owe much to this early spade work, a debt which has probably not been sufficiently acknowledged.

Research abroad owes much to his influence, and in recent years he visited Africa, India, Australia, and New Zealand for the express purpose of advising on research. Earlier he had been to Canada and on other occasions to the United States.

For many years he was active in the development of medical research in British Colonial territories. Not only did he recognise the great need for the application of medical science, but he also foresaw what has only recently been widely recognised as a major problem, namely the need for relating the rapidly increasing population to the supply of sufficient food. He insisted that ". . . most of the political, social and economic difficulties in tropical countries are and will continue to be of a biological nature and the sooner the fact is recognised, the sooner will these difficulties be controlled or dispersed, and we can only pray that there is sufficient wisdom left among us to use the fruits of science properly" (79).

Philosophy and Motivation

Much of what is written above might well have been included in this section. Inadequate and incomplete as the account may be, there is space for only a few more thoughts. One friend, recalling a lovely moorland walk with "E. M.," remembers the latter saying "There are few subjects you cannot get something out of if you really get down to it." This he followed with a quotation from the last words of the celebrated Laplace "What we know of things is little—what we are ignorant of is immense." "A sobering belief in no finality to knowledge" his friend says, "produced in Mellanby an enthusiasm for work which in turn he was keen to impart to his workers, this making him an ideal leader in research." Glimpses of this attitude are to be found throughout his work; for example, in 1933 in his Cameron Prize Lecture (53) he said "the whole subject of nutrition in relation to tissue structure and function is at present almost uncharted territory." Eleven years later (86) considering biological problems, he says

> Surveying now the general field of nutritional science, what do we find? We see that physiologists and biochemists, mainly by means of experiments on young rats, have detected a large and increasing number of chemical substances which must be present in the diet, often in minute quantities, either for the maintenance of life itself, or for proper growth. The chemical constitution of most of these vitamins is known. The chemists' success has indeed been great. But what about the biological side; can it be said why these substances are essential and/or in what way they work? From this angle the success has not been so outstanding: a biological problem is usually much more difficult than a chemical problem. The living cell in the animal body will not limit itself to actions by the known rules and regulations of the chemist's laboratory. . . . Thus there is hardly any knowledge of how the vitamins work in

performing their function . . . clearly this is a great challenge to all interested in experimental biology—physiologists, biochemists, pathologists, pharmacologists and clinicians.

He recognised to the full "the enormous difficulties of the experimental method in biological investigations due to the complexity of the interacting materials" [Paget Memorial Lecture (78)]. It is of special interest to some of us that in his Hopkins Memorial Lecture he gave an illustration of the difficulties encountered in biological work. He relates that the growth curves shown in Hopkins' publication in 1912 on the nutritive value of tryptophan were reproduced in all parts of the world, yet

. . . neither Hopkins himself nor anybody else was able to repeat the particular experiments—that is, the growth stimulus supplied by 2–3 c.c. of milk per rat per day. There was apparently some unknown condition in the experiments essential for their successful repetition (a state of affairs not uncommon in biological research). This fact . . . greatly troubled Hopkins for many years and it was only in 1945 [over 30 years later] that he returned to the subject and claimed to have found out the cause of the difficulty of repeating the early work. The secret apparently was that in the earlier work he used potato starch in the synthetic diet and this had led to a condition later known as refection (91).

It is perhaps appropriate here to recall his insistence on the proper appreciation of the experimental method: "Most of us know what we mean," he writes, "when we use [the words, observation and experiment] but there is still evidence of confusion in the minds of some people as to the difference between" them. . . . "An observation leads to knowledge of itself, and it is true that, for an experiment to be fruitful, it must be followed by observation. The experiment, however, consists essentially of changing a condition or conditions by active interference whereby any effect produced by these changes can be tested. . . . The words 'good' or 'bad' in connection with an experiment have no meaning at all, except in so far as they reflect the goodness and the badness of the experimenter." "Long experience has taught me," he says in his Harveian Oration, "that it is seldom in the facts of discovery but rather in the interpretation, especially in the first interpretation, mistakes are made (72)." He follows up this theme in a lecture he gave on Jenner in 1949 (93), and his observations on unjust criticism are well worth reading. Amongst his observations is this piece of advice:

If a man thinks that the facts described by an investigator are wrong, then it is no good simply writing about them. The critics must go into the hospital or laboratory, make observations or better experiments in order to prove his contention.

He had one motto he offered to laboratory workers—a positive version of the saying that "chance favours the skilled observer"—it was his injunction to "treasure your exceptions."

He was a fine and indeed a great man and in the words of a contemporary

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.[1]

With all, to use a sentence written by an old student, "He was so very human," and this is the note on which I would wish to end. He could be pleased and proud as when he found in the distortion of bone growth the explanation of nervous symptoms in his experimental animals, or as when, with enthusiasm and pride, he found, having almost achieved his "three score years and ten" that he could still make discoveries; notably that in high vitamin A plasma, epithelial cells were converted into mucous secreting cells. He could, however, also be pleased, as on the occasion of his election to an Honorary Fellowship of the Royal College of Surgeons of Edinburgh, after several eminent people "had said a few words," when his turn came he said "As a duly qualified surgeon, I now propose to perform here and now my own operation: 'cackle-ectomy'; I shall cut out the cackle." Upon which he sat down.

One quality which I had not, I confess, fully appreciated until re-reading much of his work, was his doggedness. Genius is admittedly rare and if it is no more than an infinite capacity for taking pains, he was indeed a genius. It is some consolation to some of us that he maintained that he was a slow thinker. Those who associated him with quick repartee or a challenging evocative question would tend to be puzzled by his own assessment of himself, but by reading his writings and by appreciating the amount of thought that led to the foreshadowing of some of his discoveries and his general observations, the truth of his own assessment becomes apparent.

Like vitamin A in the growth and modelling of bone he was the "wise director" in the growth and development of medical research and, as will no doubt be found of vitamin A, he was, as can be seen from his personal record of research, an integral part of the operation.

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