OBITUARIES

Sir Edward Mellanby, G.B.E., K.C.B., F.R.S.

Statesman for a quarter of a century, scientist for half a century: one feels in preparing this notice as Mellanby himself said he felt when faced with the preparation of the Hopkins Memorial Lecture, that the task requires a "degree of knowledge, skill, judgement and sympathy . . . almost unattainable"[1].

Sir Edward left the stamp of his skill as a statesman on the work of the Medical Research Council, of which he was secretary for sixteen years. The present members of the Medical Research Council have in the following words recorded "their high appreciation of his great services to medical science. As Secretary of the Council from 1933 to 1949, after being a Member since 1931, Sir Edward Mellanby 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 discovery. His endeavours had great success"[2].

It has been said that he was in some ways "not well cast as an administrator"[3]; but he brought to this highly responsible post the qualities of a statesman—sagacity, far-sightedness and skill in the management of practical affairs—in unusual measure; he deputed to the professional administrator those matters which could safely be entrusted to him. It was characteristic that on one occasion he denied that the Council had a policy in financing research workers except "to find the right men and back them in every way possible"[4]. He often said that the recruitment of first-class administrators was an easy matter compared with securing men of the best type for medical research; such men are, he said, "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". Such men, he recognized, 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"[5]. While he stoutly maintained that the supply of the right type of man was the basis of success in medical research, he defined the main function of the Medical Research Council 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"[6].

On the many occasions when he gave important named lectures he drove home with telling examples the benefits to mankind in the past hundred years of the application of the discoveries in medical science. It is fifteen years ago since he opened his Rede Lecture with the words: "Probably at no time in the world's history has the average citizen of this and most other civilized communities felt so insecure against death by violence. At no time in the world's history has the same citizen had reason to feel so secure against death by disease". Concluding this Lecture, he claimed that "medical science and its instrument, medical research, have indeed justified themselves. For every problem—social and economic . . . 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!"[7].

One principle that he returned to time and again was the difference in effectiveness in research of the experimental method over observation: "Where", he said, quoting Lord Moulton, "we are reduced to observation, science crawls. Where and in proportion as you can use experiment, science advances rapidly"[5]. He recognized, however, "the enormous difficulties of the experimental method in biological investigation due to the complexity of the inter-acting materials"[8]. "Long experience has taught me", he said in his Harveian Oration, "that it is seldom in the facts of discovery, but rather in the interpretation, especially the first interpretation, that mistakes are made"[4].

In his personal work, Mellanby considered himself fortunate to have come as a medical student in 1902 in the scientific care of Hopkins, in whose laboratory he later spent two years (1905–7) as a research worker. Mellanby published his first paper in the *Journal of Physiology* in 1908 on creatine and creatinine. Even at this time he had begun to pry into the effects of disease, in this case liver damage, carcinoma and other conditions likely to affect creatine metabolism, and his broad biological interest was also already manifest in that he examined the creatine content of various animals and its occurrence in the course of development of several of these in an attempt to discover whether from ontogeny and phylogeny light might be cast on the evolution of vertebrate animals. An incidental observation in the course of this work—that creatine is destroyed by bacterial action—led him in later papers to examine the problem of the effects of the bacteria from the alimentary canal on various substances. One outcome of this work was the discovery that an organism in the alimentary canal could convert histidine into histamine, a substance now of great biological importance. He continued the study of creatine with reference to the metabolism of lactating women, which was the subject of his first communication—presented by Hopkins—to the Royal Society early in 1913. Next he published the results of an attempt to discover the relationship between the formation and absorption of histamine and diarrhœa and vomiting in infants[9]. Thus there was already evidence of his interest in the interaction between clinical and experimental work in the laboratory, the theme of a book published in 1934, "Nutrition and Disease", based on the Croonian Lectures delivered to the Royal College of Physicians in 1933. By 1918 he had begun to publish the results of his investigations on the production of experimental rickets. This investigation arose out of a plan drawn up by the original Medical Research Committee in 1913. Rickets was included in a list of major disabling diseases besetting Great Britain at that time. Mellanby was asked to investigate the part processes of oxidation might play in the etiology of the disease.

His experiments soon demonstrated that serious bone abnormalities result from faulty diet, and this oriented the work towards the hypothesis that the diet might well be a primary factor in the etiology of the disease. From that time onwards investigations became more and more along dietetic and nutritional lines, as seen in "A Story of Nutritional Research", his Abraham Flexner Lectures published in 1950[10]. One result of this work is that whereas at one time "stunted children with bandy legs were so common as either to pass unnoticed or be a source of amusement", nowadays if we saw them "we would be angry, because we would realise they were the products of ignorance or negligence"[8].

It was his involvement in this investigation of rickets that decided Mellanby not to return to Cambridge when invited to by Hopkins when the latter became, in 1920, the first professor of biochemistry at Cambridge. It was, he has said, a crucial decision and probably a wrong one, and hereafter he felt he could no longer be regarded as a biochemist. By this time the index to his publications had been once through the alphabet; before his death the alphabet was to be exhausted more than twice again.

There is space here to deal with only a few of the main themes of Mellanby's research since that time. One was the presence in food of substances having specific harmful effects, an inquiry which arose out of the work on effects of cereals on bones. Evidence was obtained of the presence in some foods of an anti-calcifying substance, later identified as phytic acid[10]. There was, he demonstrated, antagonism between phytate and vitamin D, the former trying to expel calcium from the body, the latter promoting its absorption and retention. This anti-calcifying factor he included in a group of substances which he called toxamins, now more widely known as anti-metabolites.

Running almost in parallel with the work on the hardening of bones was his study of the shaping and modelling of bones—work which began with an observation made in the study of rickets that in vitamin A-deficient animals damage to the nerves of the animal occurred, with the development of severe ataxia and loss of sensation of various kinds resulting in deafness, blindness and anosmia. Mellanby was ultimately able to show that, in his own words, "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"[10]. Despite the growth of knowledge of the effect of vitamin A on the body to which he had largely contributed, Mellanby continued to be dissatisfied because so little was known about the site and the mechanism of its action. He determined to examine the direct effect of the vitamin on the tissue by tissue-culture techniques, and after preliminary exploration of the problem he sought the collaboration of Dr. Honor Fell. They found among a number of other interesting results one exciting effect on tissues of plasma with a high vitamin A content, namely, that chick ectoderm develops not into normal skin, but into more highly developed mucus-secreting ciliated respiratory epithelium. Returned to normal plasma, such tissue reverts to normal skin. Likewise in culture in high vitamin A plasma, corneal epithelium becomes hyperplastic, like the conjunctiva. Clearly, since metaplasia is most prominently seen in cancer, this discovery has a bearing on this outstanding unsolved medical problem. He also thought that a similar type of approach may well be rewarded in the study of other unsolved problems of disease involving degenerative and other structural changes due to altered metabolism.

Another recent discovery, and again an extension of earlier research, is the experimental proof that agenized flour is toxic to dogs and other animals. The substance formed by the action of agene (nitrogen trichloride) on a wheat protein has been identified as methionine sulphoximine. The mechanism of the biological action of this substance is still unknown. This discovery has had far-reaching effects in emphasizing the need for attention to be given to the effects of the chemical manipulation of food. Recently steps have been taken to secure international action in this field. Commenting in his Sanderson-Wells Lecture on the increased incidence in the past fifty years of certain morbid conditions, Mellanby said that he found it "difficult to avoid the conclusion that some at least of these increases in disease are due to errors in living recently introduced or greatly expanded in modern times", and that the effects of chemical manipulation of foods provide "at least a subject worthy of enquiry" and one which "might well be considered whenever a disease commonly found in countries which use these methods has resisted all efforts of the investigator to find a satisfactory ætiological basis"[11].

These examples by no means exhaust the topics of Mellanby's published researches, which also include studies on alcoholism and disease of the thyroid gland, ergotism, the metabolism and transmission of cancer, the control of infections, especially puerperal sepsis and maternal mortality. Nor does it include new probings into some major problems in disease which were in hand at the time of his death. His declared aim was to open up new fields of research, especially of a physiological nature. This was a deliberate attempt to secure relatively more attention for biological objectives in research. He restricted his own interests in the biochemical and chemical aspects of problems he was studying, as he felt that biochemistry was developing rapidly into a special branch of chemistry only too rarely with any direct relation to biological function.

In his book, "Nutrition and Disease"[12], Sir Edward had outlined a plan for combining research in the clinical and laboratory fields; his success in applying his plan on a national scale will, it is hoped, be evident from the foregoing incomplete survey. His success is the more remarkable when it is realized that not only was there a substantial volume of peace-time research initiated and sponsored by the Medical Research Council, but also an enormously increased activity on numerous war-time problems in civilian matters and in all branches of the Fighting Services. The last two reports of the Medical Research Council published while Sir Edward Mellanby was still its secretary contain admirable accounts of these activities.

In nutrition, Mellanby's chosen field of special interest and research, he early achieved international prominence, and in the early 'thirties he was made chairman of the League of Nations International Technical Commission on Nutrition. He was an active member of the Accessory Food Factors Committee of the Medical Research Council since its inception and its chairman for many years. He contributed in this and other ways to the improvement of health through better nutrition. As a member of the Scientific Food Policy Committee of the War Cabinet and later of the Chief Medical Officer's Committee of the Ministry of Health, he exercised a powerful influence on the medical aspects of food policy in Great Britain. As chairman of the Food Rationing (Special Diets) Advisory Committee he took an important part in the difficult task of deciding how war-time rations should be modified or supplemented for persons with certain diseases.

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. In all these countries he had many friends. He took an active interest in the work of the British Council and was chairman of the advisory Medical Panel from its formation in 1942, and he gave unstinting help and encouragement to the Council's medical work; his interest in the *British Medical Bulletin* never flagged, and it was his abiding concern to ensure that this journal conformed to its main purpose of presenting to overseas readers the many aspects of medical research in which British workers have excelled. For many years he was active in the development of medical research in Colonial territories and was chairman of the Colonial Medical Research Committee. Not only did he recognize the great need for the application of medical science, but he also foresaw what has only recently been widely recognized 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, biological in nature, and the sooner this fact is recognized the sooner will these difficulties be controlled or dispersed . . . and we can only pray," he said, "that there is sufficient wisdom left among us to use the fruits of science properly"[7].

Those who have known Sir Edward Mellanby and his work can easily add further tributes from their knowledge of other contributions of this great man to the quantity and quality of the life and living of mankind. The illustrations given speak, out of his own mind, of the man, his work, character, ideals and objectives in ways which need no elucidation; indeed, any attempt to do so would be unjustifiable presumption. It is a sign of his influence and calibre that those who knew him best are united in their profound respect and affection for him. Our appreciation of the contribution of his constant partner, Lady Mellanby, must be one of gratitude; and we trust that she, with us, will find comfort in contemplation of his magnificent record of achievement.

B. S. Platt

[1] Mellanby, E., The Hopkins Memorial Lecture, *J. Chem. Soc.*, 713 (May 1948).
[2] Medical Research Council Minute, February 18, 1955.
[3] *Lancet*, p. 309 (February 5, 1955).
[4] Mellanby, E., The Harveian Oration, *Lancet*, ii, 929 (1939).
[5] Mellanby, E., The Huxley Lecture, pp. 12 and 7 (1935).
[6] Medical Research Council Report 1945–8, p. 37.
[7] Mellanby, E., Rede Lecture, pp. 5, 62 and 59 (Camb. Univ. Press, 1939).
[8] Mellanby, E., 13th Stephen Paget Memorial Lecture, "The Fight Against Disease", **27**, pp. 5, 4, 2 (1939).
[9] Mellanby, E., *Quart. J. Med.*, **9**, No. 35 (1916).
[10] Mellanby, E., "A Story of Nutritional Research", pp. 430 and 431 (Williams and Hopkins, Baltimore, 1950).
[11] Mellanby, E., *Brit. Med. J.*, ii, 863 (1951).
[12] Mellanby, E., "Nutrition and Disease" (Oliver and Boyd, Edinburgh, 1934).

Prof. J. K. Parnas

News has been received recently of the death of J. K. Parnas, formerly professor of physiological chemistry in the University of Lwów (Lemberg), known internationally for his fundamental researches in the biochemistry of muscle.

Jakób Karol Parnas was born in Eastern Poland on January 17, 1884, and as a boy was educated in Lwów. He then entered upon an academic career as a student of chemistry, at the Technische Hochschule of Berlin-Charlottenburg. In 1905 he joined the laboratory of Richard Willstätter in Zurich, where as a subject for his Ph.D. dissertation he was allotted the tedious task of preparing the so-called third (or 'amphi') naphthoquinone. It was much to the pupil's credit, and to his teacher's delight, when two years later, after numerous trials with a wide range of metallic oxides, he succeeded in preparing the crystals of this long-sought-after labile compound. Years later this achievement brought him warm praise from Willstätter, who in his autobiography records also the accident which occurred in the course of Parnas's experiments, when a preparation of gold oxide freshly removed from the desiccator exploded in contact with a spatula, and countless particles of gold became lodged in the young experimenter's eye. Although some of the larger particles were removed surgically, smaller ones stayed in the cornea permanently, fortunately without discomfort to the bearer, who in his later years was ever ready to exhibit them to his students and accompany this with a suitable reference to the physiological inertness of gold as a 'noble' metal.

Having thus obtained his doctorate, Parnas removed to Hofmeister's laboratory in Strassburg, where he worked until the outbreak of war in 1914, except for short periods spent on research at the Stazione Zoologica in Naples and in the Physiological Laboratory in Cambridge. The years which he spent with Hofmeister, first as 'assistant' and later as 'dozent', remained in Parnas's memory as his happiest ones, and for Hofmeister himself he preserved lasting devotion and admiration. His first scientific contribution from this laboratory, which he submitted to the *Biochemische Zeitschrift* in 1906, was on the purification, properties and composition of brain cephalin, a subject of which he was very fond but on which he worked only for a few more years.

Soon afterwards, Parnas's interest turned to the intermediary metabolism of animal tissues—more specifically, the physiological significance of the Cannizaro reaction. In 1910 he demonstrated that this reaction, in which two molecules of aldehyde interact to produce one molecule of acid and one of alcohol, is catalysed in the liver by a soluble enzyme which he named 'aldehyde mutase'. The study of this enzyme formed an introduction to Parnas's further work on enzymic processes underlying the intermediary carbohydrate metabolism of tissues, particularly that of muscles. Among his other contributions made at Strassburg, three deserve specific mention: (i) the recognition of the fact that of the two optical isomers of lactic acid, one, namely, L(+) lactic acid, is metabolized in the animal body in preference to the D(−) isomer; (ii) the elaboration of energy requirements for smooth and skeletal muscles, both when resting and during contraction; and (iii) a quantitative study—one of the earliest of its kind—of the relationship between the disappearance of glycogen and the formation of lactic acid in isolated, contracting frog muscles. In the last-