

## *From the editors*

This year's issue of EIR contains eight scientific articles, six of which are concerned with Exercise Immunology itself while the last two have a decidedly clinical orientation. We would love to see this latter part increase a bit in future issues of EIR. It must however be acknowledged that all of the "nonclinical" articles carry substantial general implications for health beyond competitive exercise.

The first three articles by D. Freidenreich et al., by G. Paulson et al., and by G. Zhou et al. are solid, conventional reviews, focusing on resistance exercise, muscle damage and regeneration or effects of exercise intensity on Th<sub>1</sub>/Th<sub>2</sub> balance.

The next three articles present novel results from three studies, two in humans, one in mice. A new role for IL-17 is discussed in the study by K. Sugama et al., linking it to post-exercise muscle damage. The next by A. Berg et al. elucidates effects of soy based supplements, linking them to metabolic but not inflammatory effects. The third by N. Pervaiz et al. defines differences between central and peripheral compartments concerning the cytokine response to exercise, in the mouse model.

The last two articles comprise the "clinical" compartment of this issue. The first article by J. Goh et al. is a review elucidating the role of tumour associated macrophages (TAMs) in the context of exercise. While TAMs of subtype M<sub>2</sub> are often referred to as bad guys, exercise, although also associated with M<sub>2</sub> formation, is known to be beneficial in several tumour entities. This apparent paradox of the M<sub>2</sub> subtype may be a suitable topic for future research in our field. The last paper is an extension of a previously published study (EIR 16 - 2010) reporting the *ex vivo* reaction of immune cells from solid organ transplant recipients to bacterial stimuli – before and after strenuous exercise. Obviously, strenuous and high performance exercise is possible with an entirely curbed inflammatory response. While extending our general knowledge on exercise immunology, the findings may also serve to make patients in this condition more aware of possible risks of high performance exercise.

Finally, Lindy Castell honours the outstanding personality and great scientific achievements of Eric Newsholme who passed away in March 2011.

For the editors

*Hinnak Northoff*

## ***Obituary for Professor Eric Arthur Newsholme, MA, DSc, (PhD, ScD Camb)***

Eric Newsholme died peacefully in hospital from heart failure a few hours after slipping into a coma on 17<sup>th</sup> March 2011. Although those of us who were close to him were well aware of his heart and circulation problems over several years, it was nevertheless a shock and, as many have observed, untimely.

He had not completed his final project, which was a book on the scientific basis for outstanding physical performance in football. Football was a very appropriate topic for Eric, since he was born in Liverpool, England in May 1935 and was a lifelong devotee of Liverpool Football Club. He used to express surprise that so many premier league football clubs showed little, if any, interest in therapeutic nutrition when an expensive player was hors d'combat. Those of us who acted as occasional amanuenses, due to Eric's intense distrust of computers, were aware of his current interests. Eric would request reprints which we could obtain via Pubmed: he initially tried his hand at the vernacular, asking one of us to achieve this by "surfing the internet, or whatever it is that you do!"

Eric read Natural Science at Cambridge and this was followed by a PhD in Biochemistry. In 1964 he moved to Oxford University to work with Sir Hans Krebs: he became a Fellow of Merton College and a Lecturer at the Department of Biochemistry in 1973. Eric was a rare example of a talented researcher who was also an outstanding teacher. He certainly captured the attention of undergraduates. The usual trend is for numbers to decline during a term's series of lectures: Eric's lectures were exceptional, in that the reverse occurred, and numbers of students attending actually increased as word got round. Dr Chris Milne (Australasian College of Sports Physicians) who encountered him as a visiting lecturer in London says:

"I was fortunate to be exposed to Eric's superb teaching whilst completing the Diploma Course in Sports Medicine at the London Hospital Medical College in the 1980s.

"I had experienced some teaching from exercise physiologists during my undergraduate and postgraduate years, but none from an exercise biochemist. It was great to hear about the Krebs cycle from someone who had worked alongside Hans Krebs himself. For most of us, a study of the Krebs cycle is only palatable following a small libation with C<sub>2</sub>H<sub>5</sub>OH, but Eric made it possible without any such premedication! He had the knack of making complex scientific ideas simple to understand and, in my view, was second only to the famous science fiction (and fact) writer Isaac Asimov in that regard.

"On hearing of Eric's untimely death, I pulled out an article he co-wrote with Tony Leech entitled 'Fatigue Stops Play' (New Scientist, 22 September 1988 p39 43). It is a masterpiece in communication of complex scientific principles in layman's terms, such that coaches can make good use of the material. It even anticipates some aspects of Tim Noakes' 'Central Governor' model by several years."

More than 50 PhD students and a similar number of postdoctoral scientists received research training in Eric's lab. He was regarded by them as a gifted and

inspirational supervisor. As one of his former DPhil students said: “Eric was an excellent supervisor who taught me how to be a scientist, always probing and questioning and never rushing, always stressing the importance of paying attention to detail. These are qualities I am trying to pass on to my students, both undergraduate and postgraduate.” A frequent tribute to Eric from graduate students and colleagues alike was his kindness and courtesy. He would spend time discussing an individual’s research ideas regardless of the quality: equally, he enjoyed coming into the lab and saying to whoever was around “I have this crazy idea....!” to prompt what he hoped would be a lively discussion, involving challenges to his concepts.

He frequently advised us on, and tried to adhere to, the principle which Krebs instilled in him, viz. that you should only make one point per sentence. We were not always successful! His use of red pen on first, second, third and more of his and our drafts was legendary. In pre-computer days, his secretary (upon presenting him with a 5<sup>th</sup> draft of a paper) said: “You can read it but sit on your hands!” It says much for his teaching that, out of more than 40 Oxford DPhil theses which he supervised, there was only one referral.

Eric published over 300 research papers and reviews: his textbooks (*Regulation in Metabolism* by Newsholme & Start (1973) and *Biochemistry for the Medical Sciences* by Newsholme & Leech (1983) provided many biochemists with much knowledge of intermediary metabolism and metabolic control. In particular, Newsholme & Start (1973) was regarded by many as a classic. Eric recently updated his 1983 textbook to become ‘*Functional Biochemistry in Health and Disease*’ with Tony Leech (2010).

His first full paper (with his PhD supervisor, Sir Philip Randle, in *Biochem. J.* 1961) was on the regulation of glucose uptake by muscle. Four of his papers on muscle metabolism of fatty acids, ketone bodies, glucose and pyruvate, (two of which were in *Nature*) expanded on the “glucose-fatty acid cycle” data first published by Randle, Garland, Hales and Newsholme in the *Lancet* (1963). About 20 of the 100 papers that Eric published in the *Biochemical Journal* are recognized as seminal papers by the research community.

Eric took up marathon running in his mid-30s and successfully completed around 40 marathons: this gave him a considerable appreciation of energy metabolism in exercise. However, his work on the biochemistry of exercise and potential nutritional therapy initially stemmed from an unusual occurrence: his 6-yr-old daughter suffered from a particularly aggressive form of Guillain-Barre syndrome (inflammatory demyelinating polyneuropathy), and was paralysed for 6 months. She rapidly recovered to full health after receiving daily doses of sunflower seed oil and home-based physiotherapy. Eric recognized that, in order to understand the possible mechanisms for this outcome, he would need to “get his feet wet in immunology”. He was fortunate to receive advice and generous help with facilities from immunologists Simon Hunt and Siamon Gordon at the Dunn School of Pathology in Oxford.

Work in the late 70s, early 80s with a DPhil student, MSM Ardawi, resulted in the discovery (among others) that the amino acid, glutamine, was used as a fuel at a surprisingly high level in resting, unstimulated lymphocytes. In vitro work in Eric’s lab by another student, Mark Parry Billings, demonstrated that, despite the presence of all other essential nutritional components in cell culture medium,

only when glutamine was decreased did a decrease in the proliferative ability of lymphocytes occur. Philip Newsholme (Eric's son) and, later, Philip Calder (also students) showed that glutamine was essential for macrophage function. On becoming aware of a decrease in some key immune cell numbers after prolonged, exhaustive exercise, Eric hypothesized that a lack of glutamine might be responsible.

Glutamine is a metabolic fuel for many cells and a nitrogen donor for purine and pyrimidine nucleotide synthesis, and thus for DNA synthesis: there is an extensive literature on the role of glutamine in clinical situations, to which Eric's group has contributed, showing that burns and major trauma are associated with very low glutamine levels in the blood. Several field studies confirmed that the plasma concentration of glutamine was indeed low (by 20-25%) in endurance runners after an event, as well as in overtrained athletes at rest. Subsequent studies on more than 150 marathon runners showed that the provision of glutamine within the recovery period reduced self-reported illness (mostly upper respiratory tract infections) by around 43% compared with placebo. Five other published studies unequivocally show similar decreases.

Disappointingly, it has not so far been possible to demonstrate which aspects of the immune system are affected by restoring plasma glutamine to normal physiological levels. However, this situation is similar to some other, more recent studies which have looked at different supplements and self-reported illness.

Eric's work in the biochemistry of exercise extended to the central fatigue hypothesis, fatigue emanating from the brain rather than from muscle. This is based upon the effects of a surge of unbound tryptophan, uniquely splitting from albumin in the blood, crossing the blood-brain barrier (in competition with branched chain amino acids, BCAA) to increase the synthesis of the neurotransmitter 5-HT which is involved in fatigue. Eric suggested that the provision of BCAA might combat the surge in tryptophan (a precursor for 5-HT, also known as serotonin) and thus reduce premature fatigue. Some studies with BCAA vs placebo have shown some effect on physical performance, others have not. Several central fatigue studies have shown an increase in mental performance. Most of the studies showing no effect of BCAA did not measure mental performance: this is an unfortunate omission, since the mental component required to maintain a given power output is clearly of considerable importance.

The third major aspect of Eric's input into exercise biochemistry concerns fatty acids and the immune system. This work was carried out largely with his former student, Philip Calder, whose excellent research in this area is widely reported and has certainly made an impact on exercise nutrition. It is hoped that their contribution to sports science in this area will be reviewed elsewhere.

Eric's book with Tony Leech and Glenda Duester (Eric's daughter) "*Keep on Running*" (1994) included his hypotheses. It is an extremely practical book, including running schedules from Bruce Tulloh and high carbohydrate/low fat recipes for athletes (not just runners), but the biochemistry is also there if the reader is interested.

Eric's key contributions almost certainly emanated from his desire to provide quantitative descriptions of complex metabolic pathways, and to consider whole body metabolism, not just the cell or tissue in which the study was con-

ducted. All students and members of the Newsholme laboratory were made familiar with this approach! Another principle which he liked to instil in us was: “you can never prove or disprove a hypothesis: you can only add to the evidence for or against it.” A senior academic colleague from the 1980s recalls “He was such a stalwart seeker after truth, and possessed an inspiringly independent mind”.

What is unquestionable is that many scientists, all over the world, have worked on Eric’s novel ideas for years, adding to the evidence for or against the hypotheses. This is true not just of past members of the Newsholme group, who now have their own successful laboratories in the UK, Europe, North America, South America, Asia and Australia.

Eric was also a man of integrity and never expected nor received royalties from firms producing the amino acids on which he worked. He did receive research funding from pharmaceutical companies (there are few who do not!) but, true to form, always maintained an intransigent view about independence.

Eric was once described to me (by an innovator in sports science) as being “the greatest metabolist this country has ever produced”. In an earlier appreciation of his work (*The Biochemist*, 2006) it was said: “Throughout the 1970s and 1980s, the University of Oxford was the base of...key researchers [who] have shaped our understanding of the regulation of energy metabolism in health and diseases. Hans Krebs, Philip Randle, Derek Williamson and Eric Newsholme all pursued their own research within areas they each considered to be the most important aspects of metabolic regulation...Of all these great names, Eric arguably has had the most impact at ‘grassroots’ level...”

It seems fitting to close with Eric’s own words, speaking of his retirement, as part of a message to the inaugural meeting of the revised Metabolic Discussion Group this March:

“...I find biochemistry and especially Metabolism impossible to neglect, and I am delighted that recently it seems to be close to being restored to a central core of Biochemistry, at least in relation to research related to clinical problems and medicine!” [*EAN*, 7 March 2011]

Eric passed on his enthusiasm for running marathons to his wife, Pauline, who completed even more than he did, including the New York marathon to celebrate her 60th birthday! He is survived by Pauline, whom he met while undertaking his National Service and married in 1959; his son Philip, daughters Glenda and Clare; six grandchildren and one great-grandchild.

*[The material on Eric’s publications is reproduced in part from Past Times (by Philip Newsholme, John Challiss and Greg Cooney; published in The Biochemist (2006). I am grateful to Chris Milne, Simon Hunt and Elizabeth Opara for permission to use their tributes, and to Philip Newsholme for commenting on this obituary. Lindy Castell, April 2011]*

## **Instructions for authors of EIR**

EIR usually solicits papers from authors with acknowledged expertise in the field to be covered. Unsolicited papers will be considered and can also be accepted. All papers are subject to a peer review process.

Usually the manuscripts will fit into one of two major categories: i. a review which thoroughly covers the area indicated in the heading and includes structuring and critical discussion of existing knowledge and, if possible, the ideas of the authors about potential practical consequences and future developments. Mere mentioning and listing of existing literature is not considered to be a good review. The review can be long, if necessary, or short, if the field covered by the heading is relatively new or very focussed. ii. a paper showing original data accompanied by an extended, review-type discussion.

The general format of the review is somewhat flexible. A review must however have an abstract, an introduction and a conclusion around the main sections. Reviews with three or more sections should list the headings of the sections in form of a bullet point table at the end of the introduction. Longer sections should also give a short interim summary at their end.

If substantial amounts of the authors' own new data are to be shown, a section on methods and on results must be included. Data will only be accepted, if methods are stated clearly and appropriate statistical evaluation of results is given.

Other types of papers, eg true meta-analyses of a circumscribed sector of literature or papers focussing on new ideas or hypotheses may also be considered. Interested authors, please contact the editorial board.

For reference style use the one as applied by *J. Appl. Physiol.*, with references listed in alphabetical order. In text use ref. numbers in brackets. When giving more than 1 reference in one bracket, use numerical order.

A short running head should appear after the title, followed by the authors and their respective affiliations. The full address of correspondence should include an e-mail address of the correspondent author. Up to five key words should be added after the abstract.

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