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ABSTRACT John Rivers was a remarkable person, with enormous courage and a very generous spirit. He made a significant and long-lasting impact on the science of nutrition, disaster relief and the lives of those with whom he worked. His contribution to the understanding of the essential fatty acid requirements and metabolism in the cat while working at the Nuffield Institute of Comparative Medicine is described in this paper, together with background information on the polyunsaturated fatty acid research undertaken in the Biochemistry Department at the Institute. J. Nutr. 124: 2513S-2519S, 1994.

INDEXING KEY WORDS:
- polyunsaturated fatty acids
- cats
- arachidonic acid
- essential fatty acids
- linoleate

Mr. John Rivers (1945–1989) was a noted British nutritionist who left his mark in a number of areas in science and humanitarian causes. He made substantial contributions to teaching nutrition at the London School of Hygiene and Tropical Medicine where he was Head of the Centre for Human Nutrition and to research in protein and lipid metabolism in humans and animals. He was also very involved in relief work in natural disasters, particularly in East Pakistan, Somalia and Ethiopia. In 1971 he was one of the founding members of the London Technical Group, now known as the Relief and Development Institute. John Seaman, another founding member of the London Technical Group, described Rivers’ contribution in this area as outstanding in that he was instrumental in initiating changes in the way relief effort was given and was closely involved in the organization of an international conference on disaster relief and in establishing an international journal, Disasters, which is still running (Seaman and D’Souza 1989). Rivers was often involved in lobbying for improvements in international famine and refugee relief, including the United Nations High Commissioner for Refugees.

John Rivers also influenced the lives of many in the British Nutrition Society where he played a stimulating and provocative role as a member and, later, as the first Editor of Nutrition News and Notes (the newsletter of the Nutrition Society). For many members, the newsletter became priority reading after Rivers became the editor. His style is epitomized by the following reflection he made in his second issue: “My first experiences of occupying the editorial chair of this newsletter have been somewhat mixed. When I took the job, I saw it as little more than editing a parish magazine, a view confirmed not least by the fact that the editorial chair itself is on temporary loan from my kitchen to the editorial offices in my middle room. It has come as a surprise, therefore to find how seriously some people take it. Not that our circulation of 1,500 has excited either Robert Maxwell or Rupert Murdoch to put in a bid, so page 3 remains unadorned. But the British Museum has asked for its statutory free copies, seemingly determined to keep this news-sheet for posterity somewhere amongst its collection of mummies, and other people’s artefacts. So have the other copyright libraries in these islands, given the profusion of which, I think that there is a risk that the number of copies on file for generations yet unborn may well exceed the number that are being read.”

Few members of the British Nutrition Society can fail to have been influenced by his contributions to the Society and nutrition as a whole, whereas many would have been moved into action by his contribution to debate on a wide variety of topics, as can be judged from the titles of some of his more important papers:

1 Presented as part of the Waltham Symposium on the Nutrition of Companion Animals in association with the 15th International Congress of Nutrition, at Adelaide, SA, Australia, on September 23–25, 1993. Guest editors for this symposium were Kay Earle, John Mercer and D’Ann Finley.

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"Between the combine harvester and the ribosome" [Rivers 1975], "The inability of the cat to desaturate essential fatty acids" [Rivers et al. 1975], "The protein myth" [Rivers and Crawford 1976], "The profession of nutrition—an historical perspective" [Rivers 1979], "Why eating should carry a government health warning" [Rivers and Payne 1979] and "Allometric considerations in the nutrition of dogs and cats" [Rivers and Burger 1989]. He was a remarkable and unique person and inspired those who knew him. He was noted particularly for his courage, his generosity toward others, his fine sense of humor (and the ridiculous) and his quick and incisive wit.

In this address, the first in a series of memorial lectures, I would like to highlight the contribution that John Rivers made to research on polyunsaturated fatty acid (PUFA) metabolism and requirements of cats. This work was initiated at The Nuffield Institute of Comparative Medicine (NICM) at the Zoological Society of London. I am honored to have been invited by Dr. Ivan Burger of the Waltham Centre for Pet Nutrition to give this address. I believe that this series of lectures will pay tribute to the contribution of John Rivers to the science of nutrition.

To describe his contribution to research on PUFA and cats, I need first to set the scene of research at NICM in the years before his arrival there, the early 1970s. At the Institute, headed by Dr. Len Goodwin, there were a number of departments each of which had a small nucleus of scientists. The departments included Biochemistry (Head, Dr. Michael Crawford), Haematology (Dr. Christine Hawkey), Pathology (Mr. Richard Fiennes) and Immunology (Dr. Richard Smith). The Biochemistry Department was interested in comparative aspects of fatty acid metabolism and the significance of long-chain polyunsaturated fatty acids (LCP) in brain development. It was staffed by Michael Crawford, Glyyne Williams [Senior Technical Officer], Carmel Lloyd, Lyn Springett, Pamela Stevens [Technical Assistants] and myself as Research Fellow. Others also joined the Department later on, including Cathy Alderson, Duncan Moore, Bruce Davidson, Barbara Hall and Ahmed Hassam. Michael Crawford was the driving force of this team and he was fascinated by the diversity in brain development in different species and the significance of higher development of the brain as a driving force in evolutionary terms. As a result, he turned his attention to the chemicals that made up the brain and to lipids, in particular, because structural lipids (phospholipids and cholesterol) constitute a very high proportion (=50%) of dry matter in this tissue (O'Brien 1986). Michael Crawford had made the remarkable discovery that there was a constant pattern of PUFA in mammalian brains from a wide variety of different mammalian species [Crawford and Sinclair 1972a]. In the brain grey matter phospholipids, two ω-6 PUFA [arachidonic acid (AA) and docosatetraenoic acid] and one ω-3 PUFA [docosahexaenoic acid (DHA)] were the only PUFA present in significant quantities in all species examined. In contrast, examination of the liver and muscle phospholipids from the same species showed that a wide range of PUFA were present in varying amounts between species [Crawford et al. 1976].

This discovery had several interesting dimensions to it. First, it highlighted the importance of the ω-3 PUFA because, up until that time, there was a widely held view that the only important PUFA for mammals were the ω-6 PUFA. Second, it raised important questions about the rates of synthesis of AA and DHA in vivo (from the parent essential fatty acids, linoleic and linolenic acids, respectively) compared with the direct incorporation of the preformed LCP (AA and DHA) from food into tissues such as liver and brain.

After the discovery of the essential fatty acids (EFA) [Burr and Burr 1930], it was shown that linoleic acid was more effective than α-linolenic acid (ALA) in curing the common clinical signs of EFA deficiency in the rat, including scaly skin, hair loss and reduced growth rate, this observation was subsequently extended to other vertebrate species of terrestrial origin including humans [Aaes-Jorgensen 1961]. The discovery that polyunsaturated oils (linoleic acid–rich oils) were associated with the lowering of plasma cholesterol levels in humans may also have played an important role in their widespread use throughout the food industry. A possible reason why oils containing significant quantities of ALA (linseed oil, walnut oil, soybean oil) have not been widely used for margarines and vegetable cooking oils is that ALA oxidizes more readily than linoleic acid, leading to undesirable flavors and odors in foods. There are two types of ω-3 PUFA: plants are the major source of ALA, which is an 18 carbon ω-3 fatty acid whereas fish and other marine products are the main source of eicosapentaenoic acid and DHA, which are 20 and 22 carbon [long-chain] ω-3 PUFA, respectively. As a result of the above observations, it was generally felt that linoleic acid was the main EFA for terrestrial mammals including humans and that the ω-3 PUFA were more likely to be important as the EFA for animals in the marine environment [Holman 1968].

The constant PUFA composition of the brain and particularly the high concentration of LCP, including AA and the ω-3 PUFA, DHA, suggested to Crawford that this was evidence of an important role for LCP in general and also for the ω-3 family of fatty acids in human development. It was subsequently shown that the retinal phospholipid fatty acids also displayed a...
constant PUFA pattern, being particularly rich in DHA (Fleisler and Anderson 1983). Crawford argued that because the brain was rich in lipid and LCP (AA and DHA) and brain growth took place pre- and immediately postnatally, the AA and DHA in human milk may make a contribution to the brain PUFA. He also argued that it would be unsound to feed infants on formulas that were rich in linoleic acid and relatively deficient in \(\omega-3\) PUFA at a time when the brain is laying down DHA. It should be noted that at this time many infant formulae were manufactured using linoleic acid–rich vegetable oils that were also almost completely deficient in \(\omega-3\) PUFA (Sinclair 1975a). Thus, Crawford and his group became involved in a series of studies examining the developmental changes in PUFA accumulation in the mammalian brain (Sinclair and Crawford 1972), the significance of \(\omega-3\) PUFA as EFA for mammals (Crawford and Sinclair 1972b; Fiennes et al. 1973), the rate of incorporation of linoleic acid and ALA into liver and brain vs. the rate of incorporation of preformed derivatives (AA and DHA) (Hassam et al. 1975, Sinclair 1975b), the importance of LCP in human milk (Crawford et al. 1973) and the terrestrial food chain (Crawford and Sinclair 1972a, Crawford et al. 1976). This work was conducted in the period from 1970 to 1974 and by the time John Rivers joined the NICM in 1973, it was clear to Crawford and his team that dietary sources of LCP were very efficiently taken up by tissues when compared with endogenous synthesis of the LCP in vivo from linoleic acid and ALA. In other words, the data suggested that the small quantities of AA and DHA in human milk (0.2–1% of total fatty acids, or up to 400 mg LCP/d per infant) may have been an important source or reservoir of LCP for tissue growth and that dietary linoleic acid and ALA on their own may not have been sufficient to sustain similar tissue accretions of LCP.

It was therefore reasonable to ask the question whether there were any species of animals in which the rates of conversion of EFA to LCP were so slow that there was a dietary requirement for the LCP. Based on his knowledge of the fatty acid composition of the terrestrial food chain, Crawford proposed that the cat would be the most likely candidate and upon joining the Institute it was John Rivers’ task to examine the EFA requirements of this species. The rationale for Crawford’s thesis was that the cat, being an obligate carnivore, evolved consuming a diet of meat and other animal products, which were the main sources of LCP in the terrestrial food chain (Crawford and Sinclair 1972a, Crawford et al. 1976).

John Rivers joins the Nuffield Institute of Comparative Medicine

John Rivers brought to the Institute a wealth of knowledge in nutrition, a vast experience of food in-
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uj-3 LCP) (Frankel 1980, Rivers and Frankel 1980).

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similar to those reported by Rivers et al. (severe fatty degen
eration of the liver, excessive fat in the kidneys, mineralization of the adrenal glands, degeneration of the
testes and hyperkeratosis of the skin). These signs were
prevented by including safflower oil in the diet at a
level to provide 6.7% dietary energy as linoleic acid
(MacDonald et al. 1983a). These results suggested an
important role for linoleic acid as an EFA in its own
right because of the negligible conversion of linoleate
to arachidonate. Subsequently, this group went on to
investigate the role of linoleic acid and AA as EFA,
showing that linoleic acid could prevent reduced feed
efficiency (in male cats), high rates of transepidermal
water loss, poor skin and coat condition and fatty liver
(MacDonald et al. 1983b). They also showed that lin-
oleate met the requirements for spermatogenesis in
males (possibly due to the ability of the testes to syn-
thesize some AA) but that dietary AA was essential
deficiency as described in the rat (Holman 1968).

level relative to the linoleic acid intake. Studies by
this research group, which addressed these dietary
problems, could not provide evidence that the other
dietary inadequacies were related to the EFA-defi-
ciency syndrome they reported (Frankel 1980, Rivers
and Frankel 1980). Nonetheless, Rivers and Frankel
accepted that their “case control” approach had lim-
itations. At that time, they were unable to feed a fourth
semipurified control diet containing both EFA and
LCP, because there was no readily available source of
AA, and therefore they had to rely on the commercial
cat food as the control diet. Rivers and Frankel argued
that the disease they had described was due to the lipid
moiety of the diet, because later studies by this group
showed improvements in the clinical picture after the
addition of evening primrose oil (a source of linoleic
acid and γ-linolenic acid) or cod liver oil (a source of
ω-3 LCP) (Frankel 1980, Rivers and Frankel 1980).

Research on the requirements and metabolism of
EFA in cats was also investigated in two other labor-
atories in the 1980s. Quinton Rogers and colleagues
described the effect of feeding diets deficient in EFA,
diets containing linoleic acid and diets containing
both linoleic acid and AA (MacDonald et al. 1983a,
MacDonald et al. 1983b, MacDonald et al. 1984b).
Cats fed the EFA-deficient diet developed signs similar
to those reported by Rivers et al. (severe fatty degen-
eration of the liver, excessive fat in the kidneys, min-
eralization of the adrenal glands, degeneration of the
testes and hyperkeratosis of the skin). These signs were
prevented by including safflower oil in the diet at a
level to provide 6.7% dietary energy as linoleic acid
(MacDonald et al. 1983a). These results suggested an
important role for linoleic acid as an EFA in its own
status of the cats, as suggested by Rivers (1982). For example, variations in the levels of other nutrients may have altered the already limited capacity of the cat to synthesize AA. Although the EFA requirements of cats have not been precisely determined, MacDonald et al. (1983a, 1983b, 1984b) have shown that linoleate at 6.7% energy is more than adequate for growth and normal skin condition. With linoleate at 4.8% of dietary energy and arachidonate at 0.04%, reproductive performance was essentially normal. This level of arachidonate can be met by the inclusion of animal products in the diet (Rivers and Frankel 1980).

None of the above experiments were able to provide evidence of a requirement by cats for ω-3 PUFA, although Monger (1986) reports that refeeding EFA-deficient cats with a diet containing linseed oil as the sole source of fat led to a deterioration of the cats’ condition (coat and reproductive performance) compared with refeeding with safflower oil. This would be consistent with the ALA in the linseed oil interfering with the metabolism of linoleate to AA.

**Metabolism of EFA in cats**

In the initial study by Rivers et al. (1975), it was suggested that cats lacked the Δ⁶ desaturase; however, there was no impairment in the chain elongation process. This was confirmed independently by more detailed studies by Hassam et al. (1977) and Sinclair et al. (1979) in the domestic cat and supportive evidence was also presented for a lack of Δ⁶ desaturase in the lion (Rivers et al. 1976b). It was not known whether the other PUFA desaturases (Δ⁶, Δ⁸) were operative in cats; however, in a study aimed at determining the structural identity of one of the unknown fatty acids that appeared in the cats fed diets rich in linoleate, it was revealed that cats possessed an active Δ⁵ desaturase. This result accounted for the appearance of a novel fatty acid in tissues of linoleate-fed cats, identified as 20:3 (5, 11, 14) [Fig. 1]. The likely derivation of this fatty acid was from linoleate by chain elongation to 20:2 (11, 14) followed by Δ⁵ desaturation to 20:3 (5, 11, 14) [Sinclair et al. 1979]. The presence of this enzyme was also confirmed by the increase in AA [20:4 (5, 8, 11, 14)] after the feeding of cats with evening primrose oil (a source of γ-linolenic acid) that effectively by-passed the missing Δ⁶ desaturase (see Fig. 1) and by the appearance of label in PUFA with four double bonds after dosing of cats with C¹⁴-20:3 [8, 11, 14] [Sinclair et al. 1979]. AA could be synthesised from 20:3 (5, 11, 14) by the action of a Δ⁸ desaturase (Fig. 1); however, Hassam et al. (1977) suggested that the cat lacked both Δ⁸ and Δ⁶ desaturases because there was no evidence of significant conversion of C¹⁴-linoleate to AA. This evidence does not exclude the possibility that there may be a limited amount of synthesis of AA in particular tissues by the normal pathway (involving the Δ⁵) or by that involving the Δ⁸ desaturase. McDonald et al. (1983b) have suggested that this may occur in the testes on the basis of high levels of AA in the testes of cats fed diets containing linoleate, a concept that would be supported by the report of the occurrence of a Δ⁶ desaturase in rat testes (Albert and Coniglio 1977).

In cats fed diets deficient in EFA, Sinclair et al. (1981) and Rivers and Frankel (1981) showed that there was the production of small quantities (relative to the rat) of 20:3 (5, 8, 11) [20:3ω-9]. Sinclair et al. (1981) suggested that this was evidence that the cat would be able to synthesise small quantities of AA, because these two fatty acids are produced by the same pathway. Whether AA can be produced in the cat is an important question, because McDonald et al. (1984b) showed that a very small quantity of dietary AA (0.01–0.04% energy, ≈25 mg/d) was sufficient to allow normal reproduction. The data available suggest that on diets containing linoleic acid, the cat cannot synthesise sufficient quantities of AA to maintain tissue AA levels comparable with that found when the cat’s diet contains small quantities of AA.

This research initiated by Michael Crawford and John Rivers has been of considerable significance for the following reasons. First, it has stimulated research into the nutrition of the domestic cat and has provided new information about the EFA requirements of this species. Second, and in a more general sense, it has highlighted the fact that the rate of the Δ⁶ desaturase activity can vary between species. This has quite important implications because much of the research on PUFA has been conducted in the rat, which is a species with a very efficient Δ⁶ desaturase enzyme. Until the publication of these data, it had been generally assumed that all species had the same high rate of desaturation. The significance of these results is that for species with high rates of Δ⁶ desaturase activity, linoleate is the main ω-6 EFA because it provides adequate tissue AA levels. In contrast, in species with low/negligible Δ⁶ desaturase activities, it is likely that there would be a dietary requirement for AA. Species with
low or negligible desaturase activities include the cat, the turbot, Scophthalmus maximus, L., a carnivorous fish (Owen et al. 1975); the guinea pig and humans (Willis 1981).

The interest in ω-3 PUFA and LCP in human nutrition has expanded considerably since the early research of Crawford and his research group. Interested readers are referred to review articles in the Proceedings of the Third International Congress on Essential Fatty Acids and Eicosanoids held in 1992 (Sinclair and Gibson 1993) for an update on the effects of ω-3 deficiency in animals and humans [including alterations in visual function and behavior], the role of DHA in biological membranes, the significance of LCP in human milk, a new pathway for the synthesis of DHA in the rat and the role of ω-3 PUFA in regulating events involved in occlusive vascular disease and inflammatory diseases.

**LITERATURE CITED**


