John Rivers (1945–1989): His Contribution to Research on Polyunsaturated Fatty Acids in Cats[1]

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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:

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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 dedicated to John Rivers established by the Waltham Centre for Pet Nutrition, I would like to highlight the contribution that John Rivers made to research on polyunsaturated fatty acid (PUFA)[3] 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, Glynne 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 (phoshopholipids 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

[3] Abbreviations: AA, arachidonic acid; ALA, α-linolenic acid; DHA, docosahexaenoic acid; EFA, essential fatty acids; LCP, long-chain polyunsaturated fatty acids; NICM, Nuffield Institute of Comparative Medicine; PUFA, polyunsaturated fatty acids; SBOL, soybean oil and linseed oil; SSO, safflower seed oil.

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 ω-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 ω-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 ω-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 intakes of people in Ethiopia (Miller and Rivers 1971, Rivers et al. 1974) and an inquiring mind. Within weeks of his arrival, he and Michael Crawford were having animated and wildly exciting discussions on a range of topics, which sometimes ended with John saying "That's nonsense, Michael" and Michael would smile broadly and reply optomistically "You'll see, John, you'll see." Rivers' first task was to devise a semipurified diet that cats would eat. He was advised that this was an impossible task, which immediately presented him with the sort of challenge he enjoyed. Soon, the basement of the Institute was humming with activity and a variety of bakery-like smells permeated throughout the building. The initial experiments proved that it was possible to make the food into a biscuit that the cats would eat without crumbling into a powder. Three semipurified diets were made that differed in the type of oil used, either a mixture of soybean and linseed oil (SBOL) to provide linoleic and linolenic acids and designed to be a control diet, safflower oil (SSO) to provide only linoleic acid (ω-3 PUFA–deficient diet) or hydrogenated coconut oil (EFA-deficient diet). A fourth diet, consisting of commercial canned cat food, was also used. In the first experiments, cats were maintained for ~15 mo on the SBOL and SSO diets and the commercial cat diet, after which time the plasma and red blood cell were analyzed by packed-column gas liquid chromatography. The data were very confusing because it appeared that there were almost no LCP in the samples from the cats on the semipurified diets compared with the commercial cat diet (0.3–0.9% LCP in the plasma phospholipid fatty acids vs. 29.2% in control plasma) (Rivers et al. 1975). It was concluded that there was a substantial block in the conversion of linoleic acid and ALA to the LCP and that the block was likely to be at the Δ^6 desaturase stage, the first step in the conversion to the LCP. This was an exciting result because it confirmed Crawford's hypothesis that the cat might be the first species to show a requirement for the LCP. It was also reported in this paper that the animals fed the experimental diets were listless, had dry staring coats and severe dandruff. The livers were infiltrated with fat and the animals became behaviorally infertile. Although it was tempting to conclude that these changes were the result of a deficiency of LCP, such as AA and DHA, in the tissues, this could not be claimed with any certainty because there was no true control diet containing LCP. It was noted in this paper that one animal was returned to the commercial cat food diet (containing LCP) and this was associated with an improvement of the clinical symptoms within ~1 mo, followed by successful birth and rearing of four kittens.

This work led to a series of studies published by John Rivers and his colleagues (Frankel and Rivers 1978, Hassam et al. 1977, Rivers 1982, Rivers and Frankel 1979, Rivers and Frankel 1980, Rivers and

Frankel 1981, Rivers et al. 1976a, Rivers et al. 1976b, Rivers et al. 1976c), including research by Theresa Frankel, who gained her Ph.D. in studies on the EFA requirements of cats under the supervision of John Rivers (Frankel 1980). Based on this research, which was the first to demonstrate a requirement for EFA for cats, Rivers and colleagues showed that an EFA deficiency syndrome could be induced in the cat by feeding a diet based on hydrogenated coconut oil as the fat source. The clinical picture described by this group showed a close similarity to the usual signs of EFA deficiency as described in the rat (Holman 1968). Their findings also showed that animals in the three groups fed the semipurified diets coconut oil (EFA deficient), SSO (linoleic acid only) and SBOL (linoleic and linolenic acids) developed the same syndrome, with more severe symptoms observed in the group fed the EFA-deficient diet. Because the initial studies predated studies that led to clarification of many nutrient requirements of the cat (MacDonald et al. 1984a), Rivers and Frankel acknowledged there were inadequacies with their diets (Rivers 1982, Rivers and Frankel 1980), including a lack of taurine, an excessive amount of vitamin D and the possibility of a low vitamin E 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-deficiency syndrome they reported (Frankel 1980, Rivers and Frankel 1980). Nonetheless, Rivers and Frankel accepted that their "case control" approach had limitations. 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 laboratories 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 degeneration 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 linoleate met the requirements for spermatogenesis in males (possibly due to the ability of the testes to synthesize some AA) but that dietary AA was essential for adequate reproduction in female cats (MacDonald et al. 1984b). The AA was provided either as pure ethyl arachidonate (100 mg/d) or in minute amounts from chicken fat or unbleached beef tallow (AA at 0.1% total fatty acids in the animal fat, providing ~25 mg AA/d), which led to relatively small increases in tissue AA levels compared with the values on control commercial cat diets (MacDonald et al. 1983a, MacDonald et al. 1984b).

Jock McLean, Andrew Sinclair and colleagues also conducted studies into the EFA requirements of cats (Monger 1986, McLean and Monger 1989, Sinclair et al. 1979, Sinclair et al. 1981). They showed that cats maintained for up to 8 years on diets containing safflower oil as the sole source of lipid (5% by weight in diet) did not suffer from the severe symptoms reported by Rivers et al. (1975), but appeared normal except for slight dulling of the coat and generally an inability of the females to produce more than two viable litters. At postmortem, the major change evident was an accumulation of lipid in the liver.

To summarize then, EFA deficiency does develop in the cat when deprived of linoleic acid; however, there is not complete agreement among the three laboratories on the consequences of addition of linoleic acid (as safflower oil). Rivers reported that a diet containing safflower oil as the sole source of fat at 15% by weight was ineffective in completely preventing clinical signs of EFA deficiency, including failure to reproduce (Rivers 1982, Rivers and Frankel 1980, Rivers et al. 1975). MacDonald et al. (1983a, 1983b, 1984b) reported that a diet containing 5% safflower oil plus 30% hydrogenated beef tallow prevented all clinical signs and was effective in all respects except that it did not allow reproduction in female cats. McLean reported that a diet containing 5% safflower oil did not allow normal reproduction beyond two litters (Monger 1986, McLean and Monger 1989). The failure of the safflower oil diet to completely reverse all the clinical signs of EFA deficiency in the experiments of Rivers has not been adequately explained, apart from the suggestions of MacDonald et al. (1984a) that these diets contained inadequate levels of several nutrients. Because it appears that very small quantities of dietary AA are sufficient to allow for adequate reproduction (MacDonald et al. 1984b), it is possible that for, as yet unexplained reasons, the different diets used by the above groups led to variations in the AA

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 Δ^6 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 Δ^6 desaturase in the lion (Rivers et al. 1976b). It was not known whether the other PUFA desaturases (Δ^5, Δ^4) 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 Δ^5 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 Δ^5 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 Δ^6 desaturase (see Fig. 1) and by the appearance of label in PUFA with four double bonds after dosing of cats with C^{14}-20:3 (8, 11, 14) (Sinclair et al. 1979). AA could be synthesised from 20:3 (5, 11, 14) by the action of a Δ^8 desaturase (Fig. 1); however, Hassam et al. (1977) suggested that the cat lacked both Δ^6 and Δ^8 desaturases because there was no evidence of significant conversion of C^{14}-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 Δ^6) or by that involving the Δ^8 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 Δ^8 desaturase in rat testes (Albert and Coniglio 1977).

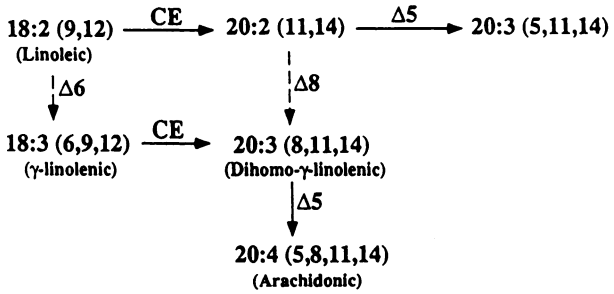

FIGURE 1 Pathways of metabolism of linoleic acid in the cat. Desaturation steps are indicated by vertical arrows (Δ^6 = 6–7 desaturation, etc.) and chain elongation by horizontal arrows. Interested readers should refer to Voss et al. (1991) for details of a new pathway for the synthesis of 22-carbon PUFA.

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 synthesize 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 Δ^6 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 Δ^6 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 Δ^6 desaturase activity, linoleate is the main ω-6 EFA because it provides adequate tissue AA levels. In contrast, in species with low/negligible Δ^6 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; *Scopthalamus 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.

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