Animal studies: summary, gaps, and future research 1-3

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ABSTRACT Animal models are essential in cancer research but investigators should recognize the limits of the models they use. Because there is no ideal animal model, researchers should use the biological and biochemical diversity among the models to experimental advantage. The differences can tell us as much as the similarities. Fatty acid metabolism seems to play a role in hormone-dependent and hormone-independent cancers, and cell culture experiments have yielded much information on possible mechanisms. However, a knowledge gap exists between these studies and a full understanding of mechanisms in vivo. Mechanisms must be understood before the possible relevance of the findings to humans can be confidently assessed. There is little evidence to suggest that either trans fatty acids or oleic acid has any specific effect on carcinogenesis and it is unlikely that further study will reveal something important but heretofore overlooked. By contrast, there appear to be notable gaps in our understanding of n-3 fatty acids, linoleic acid, and conjugated linoleic acid in relation to possible effects on cancer in humans. The major knowledge gap, and our greatest challenge, is relating promising data from animal models and cell culture studies to the prevention of cancer in humans. Am J Clin Nutr 1997;66(suppl):1539S-40S.

KEY WORDS Cancer, fatty acids, animal models, linoleic acid, conjugated linoleic acid, n-3 fatty acids

Ten years ago the International Life Sciences Institute (ILSI) sponsored a symposium entitled “Calories and Energy Expenditure in Carcinogenesis” (1). The National Research Council report Diet, Nutrition and Cancer (2) had appeared just 4 years earlier and one of its major conclusions—that dietary fat per se was causally associated with some human cancers—was being widely quoted despite the reservations of many scientists and epidemiologists (3). The ILSI symposium was the first major scientific forum in which this putative causal link was openly challenged. It is clear now, from the data presented at this ILSI symposium on individual fatty acids and cancer, that what we have learned in the past decade reinforces the skepticism voiced at that first ILSI conference.

Birt (4) opened the discourse in this section of the supplement by emphasizing that animal models are essential in cancer research but that investigators should recognize the limits of the models they use. There is no ideal animal model. Hence, rather than being unduly concerned about the lack of consistency that sometimes occurs among animal cancer models, researchers should strive to use the biological and biochemical diversity among the models to experimental advantage. The differences can tell us as much as the similarities.

Although diversity among models can work to advantage, indifference to unjustified diversity in the diets fed to experimental animals may present difficulties. Carcinogenesis is an extremely complex process that is influenced by many dietary factors in addition to fat. Accordingly, it is essential that the diets fed to experimental animals be appropriately standardized to ensure that results are reproducible and properly interpreted.

Another factor that can influence experimental outcome is the practice of ad libitum feeding. Virtually all carcinogenesis experiments are conducted under ad libitum feeding conditions, yet we know that this induces abnormal changes in hormone balance (5). Hence, investigators should be mindful of possible complications from the practice.

Rose (6) discussed the possible role of fatty acid metabolism in hormone-dependent cancers. A key fatty acid in this regard is linoleic acid (18:2n-6), the only fatty acid clearly shown to enhance carcinogenesis in some animal models (7). There are also intriguing findings regarding the possible anticarcinogenic effects of n-3 fatty acids, which are found principally in fish oils. Cell culture experiments have yielded much information regarding the possible mechanisms of these effects. However, a knowledge gap exists between these studies and a full understanding of mechanisms in vivo. This is particularly evident when models yield opposing results—the same fatty acid enhancing carcinogenesis in one model while inhibiting carcinogenesis in another model—as also pointed out by Birt (4). The mechanisms of both effects must be understood before the possible relevance of either to humans can be confidently assessed.

Ip (8) summarized the extensive in vivo carcinogenesis database for several fatty acids: trans fatty acids, oleic acid (18:1), n-3 fatty acids, and conjugated linoleic acid (CLA). There is little evidence to suggest that either trans fatty acids or 18:1 has any specific effect on carcinogenesis and it is unlikely that further study will reveal something important but heretofore overlooked. By contrast, there appear to be notable gaps in our understanding of n-3 fatty acids, 18:2n-6, and CLA in relation to possible effects on cancer in humans.

During this symposium n-3 fatty acids were revisited many times. There is a considerable database on these interesting

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dietary components that has come from investigations involving cell cultures, animals, and humans (from both epidemiology and clinical trials). Studies in this area span more than a decade. There was divided opinion about the potential importance of n-3 fatty acids in preventing human cancer, with some attendees arguing that the potential benefits could be large. This area clearly deserves further scrutiny.

The research base on CLA is much more recent and has been derived almost exclusively from animal models. Ip (8) pointed out that in the rat mammary cancer model few anticarcinogens, and certainly no other known fatty acids, are as effective as CLA in inhibiting carcinogenesis. The potent anticancer effect of CLA may be due partly to its effect on body composition; highly significant reductions in body fat, often accompanied by increases in lean body mass, are seen in mice, rats, and chickens fed diets containing CLA (9). Energy intake and expenditure exert major effects on carcinogenesis in experimental animals by influencing hormone balance (5). Accordingly, CLA represents a frontier area for research on fatty acids and cancer risk in humans.

It was noted that 18:2n-6, n-3 fatty acids, and CLA may all act at least in part by influencing prostaglandin metabolism. Prostaglandin inhibitors (eg, aspirin) also inhibit colon carcinogenesis in animal models and there is encouraging evidence from human clinical trials as well (10).

This discussion was followed logically by the presentation by Klurfeld and Bull (11) on the possible roles of fatty acids in colon carcinogenesis. As in other cancer models, energy intake and retention (as body fat) and the effects of certain fatty acids on prostaglandin metabolism are important considerations. In addition, regarding the colon, direct effects of fatty acids, bile acids, and fat oxidation products, as well as related dietary factors (eg, fiber), are important considerations. In summary, the major knowledge gap, and our greatest challenge, is relating promising data from animal models and cell culture studies to the prevention of cancer in humans.

REFERENCES