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Invited commentary

Molecular biology and nutrition: the quest for integration

Biology has been the major science for much of the latter half of the 20th century, gradually replacing the earlier pre-eminence of physics and of chemistry. Within the biological sciences the field of molecular biology has become dominant. Indeed, molecular biology now represents a remarkable intellectual edifice which has spawned a whole new biotechnology. This has led to major changes in the way in which academic science is conducted, particularly in relation to the sharing of information, commercialization, and the development of the concept of 'intellectual property'. Although originally there was much debate as to whether or not molecular biology was a distinct discipline, or simply a part of mainstream biochemistry, it has come increasingly to be seen as a discipline in its own right. This reflects, of course, the strong tendency of biologists to create new specialities, the negative effect of which is to fragment the subject with a consequent loss of coherence.

The triumph of molecular biology is such that the concepts and techniques that it represents have permeated deeply into most other areas of biology. This is true of fields as diverse as ecology and epidemiology, as well as the central biological disciplines of physiology and of biochemistry itself. Even the solving of crimes has been revolutionized through DNA fingerprinting. Many would argue, however, that nutrition has been somewhat slow in embracing the opportunities provided by the developments in molecular biology. This may be partly because nutrition is segmented to a substantial extent by an emphasis on species – man, farm animal, or laboratory animal – and by the level of focus – public health, community nutrition, whole-body physiology, biochemistry, etc.

At the simplest level it has for some years been possible to examine the effects of nutrients on the expression of specific genes, whether they encode enzymes, receptors, transporters, carrier proteins or hormones, and much work of this type is increasingly undertaken. This means that one can construct a picture of dietary interactions from the level of body composition and whole-body physiology, to substrate flux through metabolic pathways, to the amount and activity of critical enzymes, and on down to effects on gene expression. For example, the switch from a low-fat–high-carbohydrate diet to a high-fat–low-carbohydrate diet may impact on body composition, respiratory quotient, the rates of lipogenesis and gluconeogenesis, the level of lipogenic enzymes, and the expression of the genes encoding those enzymes and allied proteins.

Molecular biology also enables novel genes and gene products to be identified which may be important in a nutritional context. Examples of this include the recent identification of CART (cocaine- and amphetamine-regulated transcript) and the orexins, which are neuropeptides involved in the central control of food intake. The localization of mutant genes, by approaches such as positional cloning, again can lead to the discovery of novel proteins and new physiological systems of importance to nutrition. A potent example of this comes from the identification of the mutant gene in *ob/ob* mice, the encoded protein leptin being a critical signalling molecule in the regulation of energy balance.

Other opportunities offered by molecular biology and molecular genetics include the application of transgenics, with the development of transgenic animals for assessing the physiological significance of particular proteins. There are a number of examples of this in the context of nutritional science, including knockout animals for GLUT4 (the facilitative glucose transporter), metallothionein, uncoupling protein-1 and neuropeptide-Y. The application of molecular genetics should also enable issues such as variations in nutrient responses in relation to individual genetic makeup to be assessed. For example, polymorphisms in specific genes encoding particular enzymes, receptors or transporters might impact on the handling of dietary components. This in turn offers the long-term potential for developing individualized dietary advice based on genetic profiling.

The extent of the contribution that molecular biology can provide to areas within nutrition is particularly well-illustrated in the review of John Hesketh and colleagues (Hesketh *et al*. 1998) in this issue of the *British Journal of Nutrition*. The authors provide a completely fresh perspective, addressing the role of mRNA stability, translation and localization (i.e. post-transcriptional control) on the interaction between nutrients and the expression of particular genes. They conclude that nutrients can influence the expression of genes through the regulatory signals in the untranslated regions of mRNA. In turn, the post-transcriptional regulation of gene expression by such mechanisms can influence nutritional requirements. Several examples of this are evident, including the regulation of selenoprotein synthesis in response to altered selenium supply, and lipoprotein lipase gene expression and the tissue-specific handling of lipid. Overall, a new perspective on nutritional science is offered by such an analysis.

In focusing on the general significance of molecular biology for nutrition it is important to highlight a major caveat and concern. Nutrition is an integrative science which must seek to understand, at multiple levels, the interaction between man and other animals and that component of the environment represented by food. This ranges from the population, sub-groups, whole-body, organ, cellular, subcellular and molecular levels, i.e. across traditional subject disciplines, these disciplines usually being defined by the focus on a particular level of organization.

Each needs to be integrated, and none stands on its own. Molecular biology will, of course, represent a critical approach to understanding biological systems for the foreseeable future, but it will undoubtedly be followed by other emphases – perhaps neuropsychology and behaviour. It would therefore be somewhat naïve to take a view that ‘in the end it all comes down to molecules’.

Molecular biology is at its most valuable when it is used to explain how whole animals or human subjects and animal or human systems work. As with all areas of science we must be acutely aware of the tendency of ‘discovering more and more about less and less’ as we tunnel down into finer and finer detail. Nutritional scientists, whilst encompassing molecular biology, need to emphasize continually the power and centrality of genuine integrative biology. Integrative biology is at the core of nutrition, and the best nutrition centres have invariably been multidisciplinary and holistic, rather than simply taking a narrow view of the subject.

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