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SPECIAL ISSUE

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Nutrition-toxicology: evolutionary aspects
Introduction

Introduction

To date, the subjects of nutrition and toxicology have developed independently in separate schools, colleges or university departments. Nutrition focuses on beneficial, whereas toxicology emphases negative effects on human health. Now there is increasing overlap of interests *[1]*. This is a summary of the proceedings of a conference dealing with evolutionary aspects of nutrition-toxicology held in June 1999 at the University of Ulster, Coleraine, Northern Ireland.

"Evolution is now widely perceived as the organising principle at all levels of life" *[2]*. The role of evolution in nutrition has long been a topic of considerable interest involving examples such as: a) modern versus Paleolithic diet; b) the role of diet in the evolution of the human brain; c) the evolution of human microflora; d) the evolution of the essential trace elements and nutrients.

Less well developed, but of growing importance, are examples on the toxicology and public health side: a) heavy use of pesticides and antibiotics has fostered the evolution of resistant pathogens and pests; b) phylogenies (the underpinnings of evolutionary theory) are used to track infectious disease; c) drug development makes use of "directed" evolution, using in vitro selection, mutation and evolution – some of nature's evolutionary mechanisms– to find molecules for specific tasks; d) bio-remediation exploits the evolution of specific functions in microbes to clean up toxic wastes *[2]*.

Key words Nutrition – toxicology – evolution – antioxidant defence – trace elements – n-3 fatty acids – gut flora

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The first session of the conference dealt with the combined influences of nutrition and toxicology on biochemical evolution. Perhaps the most important biochemical defence system to have developed over the long course of evolution of life on this planet is the cellular defence against oxygen. In the last two billion years, oxygen levels rose in the atmosphere to the current level of 21 %. The cells surviving this extended oxygen storm developed complex integrated genetic machinery both for the utilisation of oxygen and for protection against the reactive oxygen species produced during the process of oxidative metabolism. These antioxidant mechanisms include prevention of the production of reactive oxygen species and the removal of such species by enzymatic action, scavenging and quenching. It has been suggested that reactive oxygen species *per se* may play an important physiological role. Thus, antioxidant defence mechanisms are all the more important, if the cell is to make full use of oxygen metabolism (for a review, see Benzie, this volume).

The intake of plant food is now recognised as playing a major role in development of another major toxicological defence system in mammalian cells, the so-called drug metabolising enzymes *[3]*. The P-450 super-family of genes performs the first step or more commonly termed Phase I reaction. In this reaction, the P-450 enzymes introduce an atom of atmospheric oxygen into a wide variety of lipophilic foreign compounds, many of which are found in our diet. These reaction products are metabolically active and undergo phase II reaction to form water-soluble readily excretable conjugates with glucuronic acid, glutathione or similar hydrophilic endogenous substrates. Alternatively, the reaction product of Phase I can form stable adducts with proteins or nucleic acids, resulting in toxicity or even cancer. Thus, Phase I reactions may be either beneficial or deleterious to the survival of the cell. In general, it is believed that the beneficial aspects dominate the evo-

lutionary origins and development of these enzymes. In fact, Nebert and Gonzalez *[3]* have proposed that "several of the P-450 gene families have evolved and diverged in animals over their exposure to plant metabolites and decayed plant products during the last one billion years." They go on to claim that "there appears to be an evolutionary driving force for survival advantage in which the drug metabolising enzymes convert relatively hydrophobic substances to very hydrophilic innocuous excretable products. The phase I P-450 mediated mono-oxygenases supply only the first step and, without the conjugating enzymes, can be responsible for toxic, mutagenic and carcinogenic intermediates. Co-ordinately linked with the Phase II enzymes, P-450 mediated mono-oxygenation is a necessary and first step in the conversion of innumerable foreign chemicals to excretable products. Absence of all drug metabolising enzymes would probably be incompatible with life; the organism would accumulate hydrophobic foreign chemicals and ultimately die from immune-suppression and wasting disease."

The oxygen defence and p–450 drug metabolizing enzymes are examples of intrinsic drug resistance mechanisms found in most cells *[4]*. All organisms have to protect themselves against numerous forms of insults. Intrinsic resistance is an inherent and integral property that has arisen though the process of evolution. In addition to the two examples quoted above, resistance to toxic agents may involve changes in the structure of the cell envelope or membrane, transport proteins, the absence or presence of pathways of metabolism of foreign compounds, modifications in the structure of the target site(s), the expression of specific stress response proteins or high repair capacity.

Metallic ions may have been the first catalysts to initiate the evolution of life on this planet *[5]*. Certainly, metals are essential components of the earliest cells in the evolutionary chain. It has been argued that those metals present at the higher concentrations in the Archaean ocean became the metals now regarded as "essential" to life *[6]*. As in the case of oxygen, the evolutionary process made use of potentially toxic metals to perform various essential functions in the cell, such as maintaining osmotic balance, stabilising tertiary structure of both catalytic and structural proteins as well as facilitating the processes of nucleic acid replication and expression. It has also been proposed that metals at the lower concentrations in the Archaean oceans were not utilised by evolving life.

Their role today is that of non-essential but potentially toxic metals. Changes in the importance of essential metals may have taken place over the course of evolution. For example, nickel and cobalt were better catalysts in the reducing environment where life began but are now replaced by copper, iron and zinc in the electron-poor environment of today.

An interesting example of natural selection is the role of copper, vanadium or iron in oxidation-reduction systems and in carrying oxygen. Primitive organisms such as worms used iron and eventually evolved into vertebrates including humans. Organisms using the less efficient copper or vanadium failed to advance in the evolutionary competition.

An important development in natural selection was the appearance of homeostatic mechanisms for the essential metals. The need to maintain a well-defined internal milieu became critical as life moved from sea to land. This transition resulted in moving from an aquatic environment, where metals were evenly distributed, to one in which there would be uneven distribution resulting in over abundance or deficiency. These homeostatic mechanisms involve control over absorption or excretion or the storage of metals in inert sites.

The evolutionary history of metals has important consequences relating to interactions among metals in the diet. The gastro-intestinal absorption of metals such as lead and cadmium is reduced by the presence in the diet of divalent essential metals such as calcium, ferrous iron, and zinc.

Competition for common membrane carriers or target enzymes may also explain the toxic action of many of the non-essential metals. For example, lead inhibits a key enzyme in the synthesis of porphyrins by displacement of the essential metal, zinc. Many of the toxic actions of lead in the nervous system probably occur though competition with calcium [6].

The second session dealt with the influence of nutrition and toxicology on evolutionary changes at the whole animal and human level. The role of fish consumption is of special interest, both in terms of the evolutionary development of the human brain and in attenuating the toxic effects of a number of environmental pollutants occurring in fish. Specifically, an adequate dietary supply of members of the family of long chain polyunsaturated fatty acids (LCPUFA), especially docosahexaenoic acid, is essential for brain growth and development. It is argued that the explosive development in size of the primate brain observed in East African fossils was owing to a plentiful supply of fresh water fish. The fact that early human communities tended to live in coastal and riverine regions lends further support to the importance of fish consumption in human development *[8]*. The developing brain is also vulnerable to deficiencies in essential elements, zinc, copper and iodine for which fish in the diet offer a plentiful supply *[9]*.

Many persistent neurotoxic environmental pollutants are accumulated in the aquatic food chain. Mercury released to the environment from both human and natural sources is subject to methylation by micro-organisms present in both freshwater and ocean sediments. The resulting methyl mercury compounds readily diffuse into plankton to begin their journey ascending the aquatic food chain to attain the highest concentration in long-lived predatory fish. Human consumption of fish highly contaminated with methyl mercury has caused two outbreaks in Japan of severe poisoning. However, these outbreaks were because of man-made release of methyl mercury. The question re-

mains open on health risks from methyl mercury naturally bio-accumulated in fish. The most recent study of people having high daily consumption of ocean fish reveals no adverse effects on child development. Indeed, fish consumption appears to be beneficial, despite levels of methyl mercury some ten times higher than in low fish consumers. The authors of this study have suggested that the beneficial effect of nutrients in fish, especially LCPUFA, more than compensate for any toxic effects from methyl mercury *[10].*

Several speakers discussed the potential consequences to human health from the change in dietary patterns over the past million years. Our diet has changed dramatically from Paleolithic times but our genome has changed little. Thus, genetically, humans remain stoneagers adapted for a Paleolithic dietary regimen but not necessarily for modern diets. Is modern degenerative disease a consequence of changes from Paleolithic diets rich in fruit and vegetables to the low fibre, high fat of the modern diet? Does modern evolutionary theory support such a causal connection? Should we modify our dietary patterns towards an evolutionarily earlier period in human and mammalian history?

Paleolithic man developed a greater bone mass and experienced less age-related bone loss than do modern humans *[11]*. It is argued that greater intakes of calcium in the diet and/or diminished urinary excretion were contributing factors. Fruit and vegetables were a major source of carbohydrate in the Paleolithic period as opposed to cereals, refined sugars and dairy products of the modern era. Evolutionary considerations, together with epidemiological evidence indicate that fruit and vegetables are protective against neoplastic disease (Eaton BS and Eaton BS III, this volume).

There are an estimated 100 trillion organisms in the intestinal tract of the average human. They comprise some 400–500 different species and their potential total metabolic activity is probably of the same order as that of the liver. The gut flora has the potential to enhance the beneficial effect of nutrients in the diet, to protect against cancer and to attenuate the adverse effects of certain toxicants in our diet. The developing metabolic activity in the early days after birth may explain susceptibility to certain toxic agents in the very young. The role of evolution in determining the current role of the gut microflora is still not well understood. The metabolism of plant-derived chemicals is clearly important, for example the gut flora's role in phytoestrogens, flavonoids and lignins *[12]*. The metabolism of steroids, perhaps one of the oldest biochemical structures, is important for handling both dietary steroids as well as the bile salts.

The human gut flora are also adapted to high fibre diets, as evidenced by recent comparative studies with diets of other primates *[13].* Fibre intakes are associated with beneficial effects, such as reduced coronary heart disease *[14].*

Microflora can metabolise foreign compounds and can sometimes play a protective role. For example, a key step in the elimination of methyl mercury from the body is its conversion to inorganic mercury by gut flora followed by the faecal excretion of the poorly absorbed inorganic species *[15]*. Without this key step, fish eating populations may not be able to survive the daily intake of methyl mercury. If indeed the human species developed as a result of fish consumption at a critical stage of evolution, it is possible that the gut flora played a key role in protecting against methyl mercury intake, as this form of mercury was certainly present in the aquatic food chain from the very beginning of life.

On the other hand, the gut flora can result in pathological effects and even cancer in humans. Perhaps, as a result of our modern diet, rich in fat and meat and our exposure to synthetic chemicals recently arriving in our diet in the industrial era, the gut flora can produce compounds capable of mutagenic and carcinogenic activity *[12].*

The toxicity testing of new chemicals has now become an established procedure in the protection of public health. Typically, animals are exposed in their diet or drinking water to carefully prescribed levels of the chemical under test and, thereby, the lowest toxic level is determined. Little attention was paid to the diet or even the energy intake, both food and water being available "ad libitum". In recent years, it has been found that diet is a key factor – influencing response to toxic agents and chemical carcinogens. Test animals on a restricted energy intake are more resistant to toxicity and exhibit fewer carcinogenic responses *[16].* Future toxicological testing will have to include careful attention to diet.

The third and final section of the workshop was devoted to consideration of the health consequences of the interaction between nutrients and toxicants. Dietary exposure over the period of human and animal evolution has probably played a major role in determining our tolerance or susceptibility to the chemicals we are exposed to today, both in the work place and in the environment.

As Hayes & Wolf *[4]* have noted, the intrinsic resistance to toxic agents involves all cells and was developed by evolutionary mechanisms. The characteristic that bestows resistance will have evolved through selection pressures that are entirely independent of the chemical agent against which resistance is observed. Examples might be resistance to plant toxins acquired via the diet that now appears as an intrinsic resistance to today's drugs or new synthetic chemicals.

A recent Toxicology Society Symposium *[16]* on diet noted that "Animal toxicology and safety evaluation studies have shown that, in addition to exacerbation of spontaneous diseases (e. g. cancer, nephropathy, cardiovascular disease), caloric overfeeding and over-nutrition can modulate the response to chemicals and pharmaceutical agents in toxicity and carcinogenicity studies."

Minerals in the diet may be either essential for life or toxic depending on the absorbed dose. This presents a challenge to those persons concerned with regulating levels of

perceived toxic substances in our diet. Certain compounds of chromium are potent human carcinogens yet chromium is an essential trace element. To follow the normal regulatory practice of setting limits to carcinogens in our diet would reduce chromium to such a level as to cause deficiency problems. The challenge is to weigh the balance of risks from deficiency on the one hand versus toxicity and even carcinogenesis on the other.

A similar challenge is faced when the toxic agent is present in a highly nutritious form of food. For example, the predominant if not sole medium of exposure to methyl mercury, polychlorinated biphenyls and certain other lipophilic pesticides, is via fish and seafood. To over-restrict the intake of these toxic chemicals might, at the same time, restrict intake of fish and seafood. Again the regulator is faced with balancing the potential toxic effects of contaminants versus the well-established benefits of fish consumption.

Those concerned with health risk assessment from chemicals and with the subsequent promulgation of regulations must now take into account the added dimension of dietary influences, not only directly on the results of animal testing but also interpreting the results of epidemiological investigations. In an example referred to earlier, the effects of methyl mercury and other neurotoxicants in fish may not have their expected toxic potency because the beneficial effects of nutrients in fish tissue dominate the overall biological response. This and other myriad intreractions between nutrition and toxicology were emphasised through an evaluation of the evolutionary aspects of nutrition and toxicology at the aforementioned conference, selected papers of which are published in this volume.

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