The preoccupation with fat and slimming, especially in the U.S.A, has reached a stage of lipophobia. Yet, serum cholesterol is inversely associated with cancer. Serum lipids are not positively associated with cancer. Controlled trials of fat and cholesterol reduction failed to reduce cancer incidence, or even increase cancer mortality. So why do epidemiologists still allude to international comparisons of fat consumption, when inferences drawn from such studies are textbook examples of the ecological fallacy? And why are case–control studies, with relative risks of less than 2, used as "evidence", when such small elevations are accountable for by methodological biases?

There is no scientific justification for making specific recommendations for the whole population, such as, do not consume more than 30% of total calories as fat. No evidence is provided to show that people with a fat consumption of, say, 40% have shorter life expectancy (other things being equal) than people who consume only 25%. And why should 6–8% of the total energy intake be in the form of polyunsaturated fats? Which fats, *cis* or *trans*? In what foods? Is 10%, until very recently recommended by other committees as part of the "prudent diet", now wrong? On what evidence? Would 5% or 9% be harmful? It is disappointing that Miller and his colleagues support their quantitative recommendations only by reference to other consensus committees.

It is irrelevant to use dietary data from Uruguay, Japan or China for designing "optimal" European diet. Furthermore, there is something absurd in making blanket recommendations for hundreds of millions of people. For the young and the old, for the sedentary and the manual workers, for fat men and for pregnant women, for the healthy and for the sick, for those who live in hot climates and for those who live in warm climates. Food is not just a source of calories or of omega-3 fatty acids; eating is a social affair, a pleasure, a tradition of recipes, a culture of cuisine, a regional speciality appreciated by travellers. Should a fisherman in Iceland, eating smoked or salted guillemots, as generations of his ancestors did, now switch to a Mediterranean diet of pasta, garlic and wine? The authors are in two minds about the "Mediterranean" diet, since they don't like its main component– plenty of wine. They fear that this would lead to a "major increase in cancer in Central and Northern Europe". Conversely, it could lead to a dramatic decline in heart disease.

"Speculation as to the proportion of total cancer attributable to diet is so tenuous as to be almost frivolous" [3]. Yet Miller and his colleagues indicate that 66–98% of cancers are "potentially preventable", though these estimates are deemed "conservative"! Thus, the gap between unwarranted assumptions and foregone conclusions is finally bridged.

The authors recommend six servings of vegetable and fruit, and five servings of whole grain and cereal products a day. Is Europe to adopt the lifestyle of Seventh Day Adventists? From the age of 2? Why do the authors think that governments play into the hands of the industry if they provide full strength milk and cream "even to schools"?

There is an ethical dimension to the authors' proposals, which they do not discuss. Imputing causality without proof leads to victim-blaming among cancer sufferers who did not follow the "recommendations". The authors state that "the final evidence of disease causality will only come from a reduction in disease incidence following relevant action". In other words, a population experiment is required, yet the population is promised 66–98% of cancer reduction. If a healthy volunteer, or a patient, has a right to be fully informed about the risks and benefits of the trial in which he takes part, even more meticulous attention should be paid to the rights of a whole population of healthy people who are subjected to mass prevention programmes and intervention, however well meant [4].

Risks are not as far-fetched as they may seem. In many randomised controlled trials of multifactorial risk reduction, an increased mortality was observed, especially in the early phases of such trials, perhaps due to a sudden change in the body's homoeostasis. Abrupt changes in diet may result in mood changes, depression, violent behaviour or suicide. The change from eating as pleasure to eating as "healthy behaviour" has the potential to induce obsessive behaviour, hypochondriasis and, in young girls, anorexia.

I am reminded of Sancho Panza's opinion of Doctor Pedro Recio who boasted that he did not cure existing maladies but prevented them from arising. "And the remedies he uses," says Sancho Panza, "are diet, diet and still more diet. . . in short he is killing me".

1. Anon. Modern views of cancer. *Med Press* 1903, Dec 23, 700–701.
2. Freudenheim JL, Graham S. Towards a dietary prevention of cancer. *Epidemiol Rev* 1989, **11**, 229–235.
3. Anon. Diet and breast cancer. *Nature* 1992, **359**, 760.
4. Skrabanek P. Why is preventive medicine exempted from ethical constraints? *J Med Ethics* 1990, **16**, 187–190.

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European Journal of Cancer Vol. 30A, No. 2, pp. 221–223, 1994

0959–8049/94 $6.00 + 0.00

0959-8049(93)E0017-K

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EPIDEMIOLOGISTS HAVE spent much time over the past three decades studying dietary factors in human cancer causation. The welter of results is becoming increasingly hard to digest — particularly since there have been rather few striking and consistent findings. Perhaps it is time to ask ourselves some more basic questions. Blow-by-blow reviews of this complex topic, such as is contained in the first half of the paper by Miller and colleagues, are increasingly unsatisfying, particularly if they lack contextual comment about the nature of the low-yield struggle between epidemiologists and diet-and-cancer research.

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Received 4 Aug. 1993; accepted 27 Sep. 1993.

In fact, the Miller paper touches on some of the methodological difficulties, research needs and limitations of the scientific evidence upon which public health nutrition policies currently depend. But we need more than ritual repentance and running repairs.

What conceptual framework has guided epidemiological research into diet and cancer? Have we been too influenced by laboratory models of carcinogenesis and by the early single-factor success stories of cancer epidemiology (e.g. smoking, ionising radiation and potent occupational exposures)? Maybe they are the exceptions, not the rule. Yet still we trawl through the human diet in an attempt to find lone carcinogenic culprits. Besides, much of the influence on adult risk of cancer may derive from early life, including perinatal experiences, as has been proposed for breast and testicular cancers [1, 2] and, more widely, by Barker and colleagues for cardiovascular and various other chronic non-communicable diseases [3]. We now know that in women exposed to ionising radiation, exogenous oestrogens and alcohol, their subsequent risk of breast cancer is markedly greater if exposure occurs at young age. Hence, by focusing on the adult age range, much of our exposure assessment of diet and body weight (and, by inference, of assorted hormones) may have been misdirected.

If genotoxic chemicals contained in, or deriving from, the diet are important causes of cancer, then stratifying study populations on relevant carcinogen metabolising phenotypes should be revealing. The standard epidemiological approach implies that individual humans (like sets of genetically identical rodents) are of equal susceptibility to dietary exposures. Meanwhile, some laboratory-assisted research is focusing, for example, on differences in colon cancer risk as an independent function of the individual's fast-slow 'acetylator' status [4]. We need to put together these exogenous and endogenous variables, to reveal interactive relationships which are otherwise submerged within the cross-strata averaging of risks. A compelling example of what might exist for many diet and cancer relationships is the recent report of a marked variation in the association of alcohol consumption with coronary heart disease between categories of a binary genotype (namely the Lewis blood group, which is presumably linked with some metabolically relevant gene)[5].

If epigenetic diet-related influences are more important than genotoxicity in carcinogenesis, then consideration of metabolic phenotypes may need to be redirected to a different class of mediating host characteristics. Various non-genotoxic mechanisms *do* seem to be important for some cancers. For example, animal evidence indicates that secondary bile acids play a 'promotional' role in colon carcinogenesis [6]. In humans, the shift in colon cancer risk within around 10 years of migration from low-risk to high-risk countries [7] accords with such an interpretation. The association of above average intakes of dietary energy or fat with cancers of breast and endometrium [6, 8] may be mediated by the stimulatory influences of increased sex hormone activity [9]. Since over-fed rodents and over-fed humans are generally at greater risks of cancer, perhaps there is a procarcinogenic effect of the increased metabolic load in overworked or hyperplastic tissues. The greater the number of cells or the greater their metabolic activity then the greater the exposure of that tissue to the reactive, potentially carcinogenic, 'free radical' progeny of oxygen. Here may lie the significance of dietary antioxidants in protecting against cancer [6, 10], by defending our DNA against an intrinsically hostile, oxidative, environment [11]. Indeed, there is recent evidence that the 'promotional' stages of carcinogenesis may actually entail an oxidative burst of free radicals and a molecular epidemic of DNA damage [12, 13].

Is it helpful to think about diet and cancer within a wider evolutionary framework? Oxygen, predominantly a waste product of photosynthesis, has built up in the atmosphere during the latter part of the Earth's life. For 'modern' aerobic organisms, such as *Homo sapiens*, oxygen is a double-edged sword. Its reactive energy powers aerobic respiration in the cell's mitochondrial engine room. (Those mitochondria are the descendants of ancient oxygen-using bacteria that parasitised pre-eukaryotic cells 2–3 billion years ago, and imported into those evolving cells their own mechanisms for coping with potentially lethal oxygen [14].) However, there is some leakage of free radicals into the cell nucleus and cytoplasm and these reactive oxygen-centred radicals, such as superoxide, hydroxyl and peroxyl radicals, damage cellular DNA and other important macromolecules [15]. That leakage appears to increase with age.

Terrestrial plants, which evolved from aquatic plants in the last 10% of the Earth's history, have acquired various essential antioxidant defences against this ambient oxidative assault. These defences depend on certain elements (e.g. selenium) and the synthesis of complex molecules [e.g. carotene (pre-vitamin A), vitamins C and E]. Unsurprisingly, many of these micronutrients have become, again, through natural selection, the 'passive' antioxidant defences of the terrestrial animals that eat those same plants. Leaves and fruits (which are metabolically active parts of the plant) contain high levels of antioxidant vitamins. Seeds, however, comprise dormant genetic material and stored energy, and so have much lower concentrations of antioxidant vitamins (although they have high concentrations of selenium). The evolutionarily formative diet of apes and hominids was mostly a diet of fruit and vegetables and was, therefore, high in antioxidant intake [16]. Thus, human metabolism and the molecular machinery of cells should function optimally with a diet high in antioxidants. However, in modern agriculture-based (i.e. predominantly seed-eating) populations, with a much reduced reliance upon fresh fruits and vegetables, the oxidative assault of the terrestrial environment is probably less well countered. The consequent increase in molecular oxidative damage may be important in carcinogenesis [11, 15].

Parts of the paper by Miller and colleagues display a certain restlessness — an awareness that epidemiologists may be missing much of 'the truth' about diet and cancer, and a recognition that there is a need for new research approaches. Increased interdisciplinary contacts between epidemiologists and biologists, toxicologists and other laboratory scientists will help the evolution of our conceptual framework for studying diet in the causation of human cancer. As Rose has recently argued, epidemiologists will learn best about the causation of disease "by studying the interaction between the internal defects (mechanisms) and the external agents or modifiers (causes)" [17]. The food on our plate tells only part of the story.

1. Prener A, Hsieh C-C, Engholm G, Trichopoulos D, Jensen OM. Birth order and risk of testicular cancer. *Cancer Causes and Control* 1992, **3**, 265–272.
2. Trichopoulos D. Hypothesis: does breast cancer originate in utero? *Lancet* 1990, **335**,939–940.
3. Barker DJP, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. *Lancet* 1993, **341**, 938–941.
4. Minchin RF, Kadlubar FF, Ilett KF. Role of acetylation in colorectal cancer. *Mutation Res*, in press.

5. Hein HO, Sorensen H, Suadicani P, Gyntelberg F. Alcohol consumption, Lewis phenotype, and risk of ischaemic heart disease. *Lancet* 1993, **341**, 392–396.
6. Willett W. The search for the causes of breast and colon cancer. *Nature* 1989, **338**, 389–394.
7. McMichael AJ, McCall MG, Hartshorne JM, Woodings TL. Patterns of gastro-intestinal cancer in European migrants to Australia: the role of dietary change. *Int J Cancer* 1980, **25**, 431–437.
8. Potischman N, Swanson CA, Brinton LA, *et al.* Dietary associations ina case-control study of endometrial cancer. *Cancer Causes Control* 1993, **4**, 239–250.
9. Parazinni F, La Vecchia C, Bocciolone L, Franceschi S. The epidemiology of endometrial cancer. *Gynecol Oncol* 1991, **41**, 1–16.
10. Steinmetz KA, Potter JD. Vegetables, fruit and cancer. I. Epidemiology (Review). *Cancer Causes and Control* 1991, **2**, 325–357.
11. Bruyninckz WJ, Mason HS, Morse SA. Are physiological oxygen concentrations mutagenic? *Nature* 1978, **274**, 606.
12. Ji C, Marnett LJ. Oxygen radical-dependent epoxidation of (7S,8S)-dihydroxy-7, 8-dihydro[a]pyrene in mouse skin *in vivo*. *J Biol Chem* 1992 **267**, 17842–17848.
13. Frenkel K. Carcinogen-mediated oxidant formation and oxidative DNA damage. *Pharmacol Ther* 1992, **53**, 127–166.
14. Margulis L, Fester R. *Symbiosis as a Source of Evolutionary Innovation*. London, MIT Press, 1991.
15. Ames BN, Gold LS. Endogenous mutagens and the causes of aging and cancer. *Mutation Res* 1991, **250**, 3–16.
16. Steinmetz KA, Potter JD. Vegetables, fruit and cancer. II. Mechanisms. *Cancer Causes and Control* 1991, **2**, 427–442.
17. Rose G. Reflections on the changing times. *Br Med J* 1990, **301**, 683–687.

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European Journal of Cancer Vol. 30A, No. 2, pp. 223–224, 1994

0959–8049/94 $6.00 + 0.00

0959-8049(93)E0018-L

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In Doll and Peto's 1981 report to the U.S. Congress on the causes of avoidable cancer [1], the proportion of cancer deaths attributable to dietary problems was estimated at 35% with a range of acceptable estimates from 10 to 70%. The width of this range reflected, quite properly, the uncertainty of the state of knowledge at that time.

The reader of the review of diet in the aetiology of cancer by Miller and co-authors in this issue might be forgiven for feeling pessimistic about the likely success of future work after comparing our current state of knowledge according to Miller and his colleagues with Doll and Peto's report. The epidemiological literature is still contradictory and confusing. While this must reflect to some degree the varying quality of the research conducted over the intervening 12 years, the main message to emerge must surely be that the problem is too complicated to be completely solved by the relatively simplistic approach of gathering dietary data, consulting food tables, and comparing the nutrient intakes of cancer cases with appropriately chosen subjects free of the disease of interest. The tools for such studies: dietary questionnaires, food tables, computers and statistical methodology have only be generally available for one or two decades, and it was right and proper that they be applied to the problem of human cancer. But in the final analysis, it would seem that no single nutrient (macro or micro), not even fat, has yet been *unequivocally* implicated in the aetiology of any cancer. As the reviewers point out, the weight of evidence against high fat and energy intakes continues to increase, but there are still many contradictory findings.

Research in all disciplines is bounded by the information and tools currently available. Epidemiological studies of diet and cancer have concentrated heavily on the nutrients for which food composition tables are available. In some cases, associations between a nutrient and a cancer have been over enthusiastically interpreted as causal, when in fact the association can indicate no more than that the foods from which the study populations derive their greatest contributions of that particular nutrient (not necessarily the foods with the highest content!) are associated with the risk of disease within that population. The real dangers/benefits associated with certain foodstuffs may, therefore, involve mechanisms which are completely unrelated to the nutrient through which the food items were initially identified. (The reviewers appear to flirt dangerously with this approach with an initial discussion of fat, and separate discussions of vitamin C and beta-carotene, but retreat from the brink in a slightly illogical ordering with a generalised discussion of this very problem under a separate paragraph heading of 'other dietary factors'.)

So, 12 years down the track from Doll and Peto, is the most we have to offer, a broad recommendation to eat less fat and more fruit and vegetables? What happened to wholegrain breads and cereals? Evidently, one author of this review, who also co-authored a recent meta-analysis [2] of studies looking at fibre and colon cancer, was insufficiently convinced by the outcome to make any recommendation about increasing intakes of the richest sources of fibre. Perhaps he was concerned by the ambiguities of the health benefits of a nutrient which increases cell proliferation in the colonic mucosa [3]. Experimental studies (both animal and human) looking at the effects of fibre on the circulating levels of steroid hormones implicated in breast and prostate cancer [4] are still in their infancy, but it is a pity that they were not given a passing reference.

Once a nutrient has been implicated in the aetiology of a disease, we can reasonably prudently recommend to the target population that it should modify its consumption of foods contributing most of that particular nutrient, pending further evidence of a more direct and convincing nature. This evidence is most likely to be provided by an intervention study. However, the difficulties, both ethical and practical, of intervening in human populations require that the majority of intervention studies are either performed with laboratory animals, or in humans, but with some measure (a biomarker) other than clinical disease as the endpoint. With our current state of

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Received 4 Aug. 1993; accepted 27 Sep. 1993.