Social Inequalities and Cancer
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Diet and cancer: possible explanations for the higher risk of cancer in the poor

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Humans have always had to eat; diets have always contained the same nutrients and bioactive constituents. Therefore, some have argued, the present pattern of diseases and changes in that pattern cannot be causally linked to dietary intake. This argument, its naivety notwithstanding, raises some important issues for the way we think about the epidemiology of nutrition and disease. Current research on diet and specific diseases is based, obviously, on the premise that this argument is false. This chapter uses a broad brush to present the evidence for a significant and causal association between eating patterns and cancer. It shows that, far from being an implausible link, the relationship between dietary patterns and cancer is largely explained by the dependence of humans on their food supply – dependence not merely in the sense of providing energy to sustain life, but more related to evolutionarily adaptive patterns of food intake and contemporary aberrations in those patterns. The chapter also shows that it is plausible that at least part of the explanation for the higher risk of cancer among the poor in both rich countries and poor countries relates to the extent of the aberrations in food supply and eating patterns.

The starting point for this chapter is a diet to which humans are adapted. I note, especially, intakes of substances for which we are dependent on the environment and intakes of substances to which we have low or infrequent exposure. It is a diet with seasonal variability in total food intake and the availability of specific foods.

There are four types of aberrations in dietary patterns that could produce cancer and, perhaps, disease in general: an imbalance between energy intake and output; an alteration in the pattern of intake of either macro- or micronutrients or both; specific deficiencies – of nutrients and bioactive compounds; and the presence in the food supply, from time to time, of substances to which the organism has been almost never exposed and, therefore, to which there may not be the relevant metabolic responses.

Is there a diet to which we are well adapted?

Evoking a lost Golden Age to compare with current miseries has a long history: from Eden (where fruit-eating seems to have been part of the problem) through Rousseau's noble savage to discussions of the nature of palaeolithic diets (Eaton & Konner, 1985). We cannot know exactly the nature of diets to which humans are well adapted (although dentition, metabolic enzyme profiles, and the length and morphology of the gastrointestinal tract provide some clues). Nevertheless, is there some plausible description that can be presented of our early diet? If there is, we should also acknowledge that there must have been considerable variability in the details in the same way that there is extensive geographic variability in contemporary diets. Common features of our early diet must have included: a wide variety of foods – roots, nuts, seeds, leaves and fruit (grains have become a staple only in the last 10 to 15 thousand years but would have been gathered regularly in season); sporadic intake (despite the Tarzanist fantasies of many) of lean meat low in saturated fat (with a more secure and regular supply of fish and seafood for coastal dwellers); some intake of insects, larvae, bone marrow, and organ meats; very low intake of alcohol; low and irregular intake of eggs, milk, and milk products; little refining or fractionation of food into parts; and variability, by season, both of total amount of food available (and therefore body weight), and of kinds of foods available. Thus, there would also

have been variability in the availability of particular nutrients. Differences in this overall intake pattern (for example, diets higher in fat in extreme northern populations) would have been the result of climate and geography (as it varied over time and from place to place). However, in general, until very recently, saturated fat and alcohol intake would have been low, vegetable food (but not grain) intake high, and the kinds of plant food eaten highly varied.

An important argument in favour of human adaptation to specific eating patterns and food sources is that there are some nutrients for which we are known to be dependent upon the environment. This concept has some important implications for cancer etiology. The consequences of a variety of nutrient deficiencies are well described. But deficiency disorders can arise only if the organism is incapable of endogenous synthesis. This argues that there has been no selection pressure to develop (or maintain) such a capacity in the species and, therefore, that the essential substances are widely available in the environment. Perversely, then, because essential nutrients are widely available in naturally occurring human food, deficiencies are possible. Essential amino acids, essential fatty acids, microelements and vitamins are examples of substances that must be obtained from food. The fact that what is essential varies across species underlines the importance of the adaptation process.

The adaptation argument is as follows: essential nutrients – energy-bearing, micronutrient, and bioactive compounds – are widely available in nature; they have important functions in growth, development and reproduction; the organism is adapted to their ubiquity; and deficiencies impair growth, development and reproduction.

A plausible analogy exists in relation to substances that are necessary for the maintenance of the organism and this applies especially to substances that reduce the risk of carcinogenesis. This extension of the argument is that the normal function of cells is dependent on the presence of a variety of widespread dietary constituents probably including, but – importantly – not confined to, those necessary for growth and development. Without these substances, cells malfunction: the cells may become more susceptible to exposure to carcinogens; they may lose some specific protective mechanisms such as timely enzyme induction; or there may be an increase in replication rates as somatic cells seek to adapt to the new – deprived – conditions. Maintenance is a continuous function from birth almost to death, whereas growth, development and reproduction are confined to specific periods of life.

The converse of this argument applies to dietary constituents that are rare in nature. If the organism is exposed rarely (or not at all) to specific substances, then high intakes are likely to have untoward consequences. This is relevant both to rare exposures that result in acute toxicity and to hitherto unaccustomed levels of exposure that overwhelm the metabolic processes that normally handle lower levels. Plant, fungal and bacterial toxins are members of the first class of exposures; a Western-style high-fat/high-calorie intake that influences cholesterol and insulin metabolism, adipose storage, and sex steroid hormone production and transport is an example of the other type of exposure. Dietary patterns that are high in grains (common in agricultural communities) are often associated with a reduced intake of other plant foods; further, these diets include significant amounts of abrasive material that may result in tissue damage and reactive epithelial hyperplasia, particularly in the oesophagus. It is useful to consider that, in the same way that diets vary with geography, there may be differing degrees of adaptation in long-exposed versus relatively recently exposed populations.

A potent objection to any adaptation argument is that natural selection will be an influence only up to the age of reproduction; therefore, because chronic diseases, particularly cancers, are almost exclusively diseases of postreproductive years, dietary adaptation is an unnecessary postulate. There are four responses to this. The first is to argue that humans have a long period of juvenile dependence and that survival of parents in a healthy state is therefore likely to be selected for. The second response is based on consideration of the unit of selection. If the relevant issue is the survival of tribes, then those groups of protohumans and humans that had sufficient elders who knew how to respond to infrequent hazards (epidemic disease, food and water shortage, and natural hazards such as fire, earthquake or extreme weather) would have had a better chance of survival. Tribal wisdom maintained by the old would have facilitated survival of the whole group. Without elders and

without knowledge, tribes would be more likely to succumb to the vagaries of their habitat. Tribes in which longevity was selected for would survive to pass on their wisdom, their knowledge of the local ecology, their eating habits, their adapted metabolisms, and their genes in that fascinating blend of the heritability of both culture and biology that may mark the true distinction between humans and other animals.

Third, to argue that chronic diseases are a phenomenon of older age and therefore that resistance to them cannot have been selected for is to ignore the fact that these diseases do not occur at younger ages and that, therefore, some resistance (at least to the point of postponing them to older ages) has been selected for. Fourth, a diet that reduces risk of cancer and other chronic diseases may also improve reproductive success. A wide variety of substances are both teratogenic and carcinogenic and other substances, it is becoming increasingly clear, reduce risk of both teratogenesis and cancer (for example, folate); selection for improved reproductive success via an interaction between diet and metabolism could directly select for reduced cancer risk.

This chapter explores the evidence for the existence of unaccustomed exposures and protective dietary constituents, and for risks associated with both energy and nutrient imbalance. Possible biological mechanisms are considered briefly. In the absence of unequivocal evidence for a link between poverty and cancer via the quality/quantity of food consumed, what is known about dietary patterns and poverty is considered in the light of diet and cancer links.

Dietary exposure and cancer risk

I use the adaptation argument outlined above as a framework in the following discussion and show that some of the empirical relations that have been established in the epidemiological literature can be explained by four types of aberrations in dietary patterns: energy imbalance, nutrient imbalance, specific deficiency, and specific exposure. These are illustrated in relation to certain cancers, particularly breast, colon and pancreas.

Energy imbalance

Epidemiological evidence Energy imbalance is a massive topic and still not well understood in relation to cancer; only a few aspects are touched upon here. Three measures of energy balance (Pariza & Simopoulos, 1986) have been examined in etiological studies of cancer: total intake (Potter & McMichael, 1986; Lyon *et al.*, 1987; Willett & Stampfer, 1986), energy output (Garabrant *et al.*, 1984) and a variety of measures of growth (Micozzi, 1985) and obesity (Helmrich *et al.*, 1983; Paffenbarger *et al.*, 1980). There is no consistent relationship between these measures and all cancers; even for some specific cancers, the data are not clear. In addition, there are some paradoxes.

The present evidence suggests that higher physical activity is related to a lower risk of colon cancer (Garabrant *et al.*, 1984; Vena *et al.*, 1985; Gerhardsson *et al.*, 1986; Wu *et al.*, 1987; Paffenbarger *et al.*, 1987; Slattery *et al.*, 1988a; Potter *et al.*, 1993) but that obesity is probably not a risk factor (Potter & McMichael, 1986). For endometrial cancer (Elwood *et al.*, 1977; LaVecchia *et al.*, 1984; Folsom *et al.*, 1989) and postmenopausal breast cancer (Lew & Garfinkel, 1979; Helmrich *et al.*, 1983), however, obesity is a risk factor. For premenopausal breast cancer, obesity is associated with a reduced risk (Helmrich *et al.*, 1983; Paffenbarger *et al.*, 1980). Physical activity bears an uncertain but perhaps inverse relation to risk of breast cancer (Frisch *et al.*, 1985; Bernstein *et al.*, 1994). Total energy intake is an inconsistent risk factor for all three cancers. There are no established relationships of energy imbalance with other cancers but there is a general association between obesity and overall cancer risk (Lew & Garfinkel, 1979). Peripheral versus central adipose distribution as measured by ratios of waist and hip circumferences or fat folds has long been known to be related to risk of diabetes mellitus and coronary heart disease (Vague, 1956; Feldman *et al.*, 1969; Larsson *et al.*, 1984; Donahue *et al.*, 1987; Selby *et al.*, 1989). There is some evidence of a relationship with breast cancer that may be restricted to those with a family history of that cancer (Sellers *et al.*, 1992). Fat distribution does not appear to be related to risk of endometrial cancer (Folsom *et al.*, 1989).

Plausible mechanisms At least three mechanisms to explain the link between energy imbalance and cancer risk are plausible: mechanisms involving hormonal or mechanical processes or cellular workload. Peripheral adipose is the principal source of estrogens postmenopausally (Grodin *et al.*, 1973) via the conversion of adrenal androstenedione.

This provides a plausible explanation for the association with endometrial and postmenopausal breast cancer; both are associated with higher, cumulative lifetime estrogen exposures. The reason for the association between obesity and a lower risk of premenopausal breast cancer is yet to be established; it is not simply a matter of failing to detect cancerous lesions in large breasts (Willett *et al.*, 1985) but is possibly related to differences in the steroid receptor status of pre- and postmenopausal breast cancer (Potter *et al.*, 1994).

Physical activity may exert a protective effect against colon cancer by a mechanical effect – higher activity results in a shorter mouth-to-anus transit time, although this characteristic does not generally show an inverse association with colon cancer. Because obesity is not associated with an increased risk of colon cancer (while high calorie intake and low physical activity are), there may be metabolic differences between those who get colon cancer and those who do not. Additionally, the total amount of food passing through the large bowel may represent a measure of cellular work or epithelial damage and thereby influence rates of cell replication (Potter 1989, 1992a).

The complex relationships between dietary intake, obesity and physical activity, on the one hand, and cancer risk, on the other, will become clear only when the relevant intermediate metabolic steps are understood; these include effects on gut function, on cell turnover, and on hormone production. What remains, however, is the empirical observation that aspects of energy imbalance are related to risk of all cancers and to risk of cancers at specific sites.

Adaptation It was argued above that the human organism is adapted to extensive variability in food intake. It is able to make rapid use of increases in food supply in order to survive through lean times. This is the 'thrifty gene' hypothesis originally proposed to explain the survival advantage of the predisposition to diabetes and obesity (Neel, 1969). However, a high intake of food as a regular, rather than occasional, phenomenon will 'jam open' more than insulin responses; it will also increase adipose production of estrogen, a factor perhaps originally associated with reproductive success – sufficient body fat, as well as hormonal support, to carry a child to term. Is this related to the fact that obesity is associated with a reduced risk of premenopausal breast cancer and a liability only later in life? Intriguingly, higher abdominal fat in prepregnancy (as measured by waist-to-hip ratio) is associated with significantly larger infants at delivery (Brown *et al.*, 1996).

In fasting animals, the structure of the intestinal epithelium is simple with a low cell replication rate (Stragand & Hagemann, 1977). Following refeeding, the replication rate increases, as does the complexity and the total area of the epithelial surface. This appears to be a highly adaptive response to variable food availability – a rapid cell turnover and a large absorptive surface during feasting, but low activity during fasting, which thus conserves energy. With high intake as a regular phenomenon, however, rapid cell turnover and maximal epithelial surface provide an environment that increases the probability of cancer. Our original observation that increased meal frequency increased the risk of colon but not rectal cancer (Potter & McMichael, 1986) has now been confirmed in several other studies (LaVecchia *et al.*, 1988a; Young & Wolf, 1988; Potter *et al.*, 1993) – additional evidence that there is a cost for more frequent food intake.

Therefore, although prolonged obesity was probably uncommon in our ancestors, the ability to assimilate and store energy rapidly when it was available has probably been selected for. Inheriting this kind of metabolism in societies where food is widely available and consumed *ad libitum* appears to have consequences for cancer risk. It remains to be seen if the tendency for variation in body fat distribution (as measured for example by waist-to-hip ratio) – an established risk factor for several chronic diseases – is a marker for particular metabolic differences.

Imbalance of food/nutritional intake

Epidemiological evidence Currently, dietary epidemiological studies of cancer are frequently focused on the role of intakes of macronutrients, particularly fat and alcohol.

Fat is of uncertain relevance in the etiology of breast cancer but the association with alcohol is surprisingly consistent. Subpopulations with intakes of animal fat and protein that are lower than those of the general community, such as vegetarian nuns (Kinlen, 1982) and Seventh-day Adventists (Phillips *et al.*, 1980), show little evidence of a lower risk of breast cancer. In both these groups, the reproductive

rate is lower than in comparison populations but these studies certainly do not provide strong evidence for a role for ingested fat in breast carcinogenesis.

There have been at least 11 case–control studies on the relationship between meat or fat consumption and breast cancer (Phillips, 1975; Miller *et al.*, 1978; Lubin *et al.*, 1981; Graham *et al.*, 1982; Talamini *et al.*, 1984; Howe, 1985; Hirohata *et al.*, 1985; Le *et al.*, 1986; Lubin *et al.*, 1986; Katsouyanni *et al.*, 1986; Shun-Zhang *et al.*, 1990). The study of Lubin *et al.* (1981) – the only study showing a significant increase in risk in association with consumption of fat – was based on frequency of consumption of just eight food items. Two of three studies (Talamini *et al.*, 1984 and Le *et al.*, 1986 versus Katsouyanni *et al.*, 1986) reporting on dairy product consumption found positive associations with risk.

Of the cohort studies (Willett *et al.*, 1987, 1992; Hirayama, 1978; Phillips & Snowdon, 1983; Kushi *et al.*, 1992; van den Brandt, 1993), only that of Hirayama (1978) found an association with daily consumption of meat and risk of breast cancer after age 54 years. This finding was based on just 14 cases in this category.

In contrast, meat, protein and fat intake are consistently, almost universally, positively related to risk of colon cancer. Of the 16 studies that have reported on the association of colon cancer with fat and protein, 13 have shown an increased risk. Only the studies of Macquart-Moulin *et al.* (1986) in France and Tuyns *et al.* (1988) in Belgium failed to find an association; sugar was the only nutrient associated with increased risk in this latter study. [One study (Stemmermann *et al.*, 1984), using a 24-hour recall, found an inverse association with fat in a Hawaiian Japanese cohort.] Sixteen of 27 studies have reported an increase in risk associated with higher meat consumption (see Potter *et al.*, 1993); only Hirayama (1981), using a three-item questionnaire in a very large cohort study in Japan, found an inverse association. Of the 10 studies, both case–control and cohort, with at least 100 cases, with a food frequency questionnaire of at least 50 items, and a response rate among cases (case–control studies only) of at least 60%, eight showed a positive association with meat intake. Five studies have noted a positive association with eggs; four have shown an inverse association with fish or seafood (for a detailed review, see Potter *et al.*, 1993).

Pancreas cancer shows an even more consistent relationship with meat and fat intake. Almost all the reported studies show an increased risk in association with higher consumption of meat, fat or fried foods (for a detailed review, see Anderson *et al.*, 1994)

Alcohol consumption has been shown in ecological studies to be related to rectal and colon cancer (Potter *et al.*, 1982) and to cancers of the oesophagus and larynx (McMichael, 1979). In analytical studies, there is a very consistent but not strong relationship with breast cancer and a somewhat less consistent association with cancers of the colon and rectum. Alcohol may interact with estrogen replacement therapy to increase further the risk of breast cancer (Gapstur *et al.*, 1992; Colditz *et al.*, 1990). The evidence for a causal association with pancreas cancer is weak (Velema *et al.*, 1986). However, alcohol is extensively implicated in cancers of the upper digestive and respiratory tracts; it is regarded by the International Agency for Research on Cancer as an established human carcinogen for this association in particular (IARC, 1988).

High-grain-consuming areas are at higher risk of oesophageal and stomach cancer. van Rensberg (1981) has shown that there is a consistently higher risk for oesophageal cancer among populations with high corn and wheat consumption compared with those where sorghum, millet, cassava, yams or peanuts are staples. It is worth noting that a lower risk of colon cancer in high-risk areas (for example, the United States of America (USA), western Europe and Australia) is much more consistently found with high vegetable rather than high cereal intake, although cereal-eating communities are, in general, at lower risk of cancer of the bowel.

There are some data to suggest that a high intake of simple carbohydrate is associated with increased risk of colorectal cancer (Bristol *et al.*, 1985; Tuyns *et al.*, 1988; Bostick *et al.*, 1994).

Plausible mechanisms A variety of mechanisms have been proposed to account for an association between cancer and dietary fat. Intriguingly, the explanations have been most prolific for breast cancer, for which the empirical evidence from analytical studies is weakest. Both direct and indirect mechanisms have been proposed.

The proposed direct mechanisms are, first, via effects of unsaturated fatty acids on cell membrane

structure and function (Welsch & Aylsworth, 1983), epithelial proliferation (Kidwell *et al.*, 1982), immune responsiveness (Vitale & Broitman, 1981) and cell–cell communication (Welsch & Aylsworth, 1983); and, second, via effects of fatty acid and cholesterol metabolites (epoxides and peroxides) on promotion of transformed cells (Petrakis *et al.*, 1980; Gruenke *et al.*, 1987).

The postulated indirect mechanisms are, first, via the effects of fat on hormone receptors (Welsch & Aylsworth, 1983), on prolactin production (Hill *et al.*, 1980) or on bowel flora (Hill *et al.*, 1971), which may either alter the bioavailability of estrogens through effects on steroid deconjugation (Gorbach, 1984), or alter the bacterial production of specific anticarcinogenic agents (Adlercreutz *et al.*, 1982; Adlercreutz, 1984, 1991); and, second, via the effects of higher food intake on age at menarche (Frisch & McArthur, 1974), age at menopause (de Waard *et al.*, 1964), and the accumulation of adipose tissue, already noted as the site in the body where adrenal androstenedione is converted to estrone (Grodin *et al.*, 1973).

Although many of these proposed mechanisms may be conceptually attractive, their large number is itself a problem. Breast cancer, like all other cancers, is undoubtedly of multifactorial origin, so that a sizeable list of potential etiological pathways is not an insurmountable problem. However, there is currently no clear understanding of human breast carcinogenesis, no unequivocal precursor lesion, and no known biochemical marker. Accordingly, it is inappropriate to search for a mechanism in the absence both of an understanding of the intermediate steps and of data establishing that a high-fat diet is indeed a risk factor for mammary tumorigenesis.

For colon cancer, the dominant hypothesis has long been derived from the relationship between dietary fat intake and bile acid metabolism. Fat intake, it is proposed, increases the amount or concentration of bile acids secreted into the small bowel; bacteria present in the large bowel metabolize the primary acids to secondary acids and these, it is suggested, have greater toxicity, cocarcinogenic or promotional activity, and trophic effects. There is a considerable amount of corroborative human metabolic and animal experimental evidence for this hypothesis; the body of evidence is, however, not totally coherent (McMichael & Potter, 1985, 1986). Other roles for fat have been proposed, including direct toxic action on the bowel wall (Bruce, 1987).

Arylamines, produced when meat is cooked, have been proposed as specific colon carcinogens (Sugimura & Sato, 1983) and there is a growing literature on the role of these compounds (Sugimura, 1985) and their metabolism, including, especially, genetically variable acetylator (NAT2) status (Weber, 1987; Turesky *et al.*, 1991; Kadlubar *et al.*, 1992).

McMichael (1981) has argued that gastrointestinal hormones have trophic and hyperplastic effects on the exocrine pancreas and could act as mediators of known or suspected dietary (and other) risk factors. Gastrin and cholecystokinin are potent stimulators of pancreatic hyperplasia (Johnson, 1981). Cholecystokinin has been shown, in animal models, to be a significant promotor of pancreatic neoplasia (Howatson & Carter, 1985). More recently, Anderson *et al.* (1992) have shown that the pancreas is capable of metabolizing arylamines (found in both cooked meat and tobacco smoke, the major risk factors for pancreas cancer), thus suggesting another potential pathway from diet to cancer.

For the relationship between alcohol and breast cancer, there have been no major advances in relation to biological mechanisms beyond the mechanism originally postulated by Williams (1976) – namely, stimulation of prolactin secretion. It is also possible, as a number of workers have pointed out, that because alcohol is a significant energy source, the mechanism could be related to those postulated for obesity or caloric intake in general. Finally, it appears plausible that DNA damage could result following formation of acetaldehyde adducts; acetaldehyde is a highly reactive compound formed as the first step in the oxidative metabolism of alcohol. For colon and rectal cancer, the evidence suggests that the effect of alcohol on bile acid metabolism is rather like that of fat (McMichael & Potter, 1985, 1986). Several mechanisms have been postulated to account for the causal association of alcohol with cancers of the larynx and oesophagus (IARC, 1988). These include acting as a chronic irritant and inducing excess cell replication, acting as a solvent for direct-acting carcinogens (particularly those in cigarette smoke), being associated with specific nutrient deficiencies, and being a vehicle for other compounds present in alcoholic drinks.

Possible mechanisms for the association between grain consumption and higher risks of upper

digestive tract cancer include traumatic effects of silicaceous fibres and resultant high epithelial cellular turnover, and reduced intake of other plant foods, which results in deficiencies either of micronutrients (van Rensberg, 1981) or specific bioactive substances (see below).

Adaptation The argument for adaptation in relation to these exposures is more than a general affirmation of a human incapacity to handle a high-fat or a high-alcohol intake but, nonetheless, remains rather speculative and possibly circular. The primary premise is that high-fat, high-alcohol or high-grain intakes were not part of the regular dietary patterns of early humans. An intermittent high intake of food (a feast–fast economy) produced rapid short-term adaptive responses – increased gut epithelial cell proliferation, increased secretion of appropriate hormones (both trophic and secretory-control hormones) and bile acids, and so on. These, as an energy-conserving mechanism, then subsided when food became scarce; high metabolic and cellular activity is a cost to the organism that is not a good investment in the presence of reduced food availability. This capacity for rapid response (an extension of the thrifty gene hypothesis) becomes non-adaptive in the presence of consistent high intake, leading not only to alcoholism and obesity but also to chronic high gut hormone levels and elevated epithelial proliferation rates. High intakes of abrasive fibres result in higher upper digestive tract proliferation rates and an elevated risk of carcinogenesis, particularly in the oesophagus.

There is an additional aspect to the adaptation argument that is particularly related to the internal ecology of the large gut. The large bowel can be regarded as a complex ecosystem in which the colonic contents act as a culture medium for both bacterial and upper-crypt colonic cells (McMichael & Potter, 1986; Potter, 1989, 1992a). The culture medium in turn is influenced extensively by both host conditions (including a variety of hormones) and ingested foods and alcohol. This complex ecosystem may be one of the most flexible parts of the human–environment interaction. It is argued, however, that its flexibility is finite and that sufficient disturbance of its homeostasis has consequences for carcinogenesis (McMichael & Potter, 1986; Potter, 1989, 1992a).

Specific deficiencies – nutrients and bioactive compounds

Epidemiological evidence The most obvious specific deficiencies are those of micronutrients. It is important to note that, in relation to β-carotene, retinol and ascorbate, higher risks of particular cancers have been reported in individuals with lower intakes or blood levels but these have largely been within the normal range (Wald *et al.*, 1980; Kark *et al.*, 1981; Peto *et al.*, 1981). There are several cancers that have a probable relationship with micronutrient deficiencies – notably lung cancer and cervical cancer (Peto *et al.*, 1981; Ziegler, 1989) with reduced intakes or lower levels of vitamin A. Other squamous epithelial cancers (for example, skin) may be related to lower β-carotene or retinol levels. Lower dietary ascorbate levels have been associated with a higher risk of rectal cancer (Bjelke, 1973; Potter & McMichael, 1986). Minerals, such as calcium, and trace elements, such as selenium, have also been examined for their possible role in cancer etiology (Bruce, 1987; Willett *et al.*, 1983; Slattery *et al.*, 1988b). It is worth noting, however, that supplementation with β-carotene does not reduce risk of lung cancer (the risk may even be elevated) (The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, 1994) or metachronous polyp formation (Greenberg *et al.*, 1994).

Of most interest, and, until recently, not clearly identified as the most consistent finding in the dietary etiology of cancer, is the more general relationship between a higher intake of vegetables and a lower risk of cancer at a wide variety of sites including mouth and pharynx, lung, stomach, pancreas, colon and rectum (for comprehensive reviews of data and mechanisms see: Potter, 1990; Steinmetz & Potter 1991a, 1991b).

Of the 28 studies of colon cancer that have discussed findings for vegetables, 23 reported an inverse association. Inverse associations with fruit are much less common. Of the nine studies, both case–control and cohort, that have reported on vegetables, with at least 100 cases, with a dietary questionnaire of at least 50 items, and a response rate among cases (case–control studies only) of at least 60%, only the study of Peters *et al.* (1992) failed to find a reduced risk in association with higher intake of one or more measures of vegetable intake. Four other similar studies, lacking only data on response rates, showed comparable findings.

The related finding that foods high in fibre (often a measure of vegetable as well as grain intake) are protective also has been noted in 10 of 16 studies and 6 of 11 of the larger, better-conducted studies as defined above. Three of four other studies, again lacking only data on response rates, reported similar findings (for more detail, see Potter *et al.*, 1993). Howe *et al.* (1992) have recently completed a formal meta-analysis of 13 case–control studies using the original data and found that there is a consistently lower risk in association with higher overall fibre intake, with odds ratios of 1.0, 0.79, 0.69, 0.63 and 0.53 for each quintile of consumption from lowest to highest (P for trend < 0.0001). However, in those populations where cereal consumption is high – southern Europe and Asia, particularly – there is a puzzling observation that risk is higher in association with higher consumption of rice (Japanese) (Wynder *et al.*, 1969) or pasta and rice (southern Europeans) (Macquart-Moulin *et al.*, 1986; LaVecchia *et al.*, 1988a). Of the studies of pancreas cancer, all have reported a lower risk in association with a higher intake of vegetables or fruit or both (see Anderson *et al.*, 1994 for more detail). Recent studies of prostate (Oishi *et al.*, 1988), mouth and pharynx (McLaughlin *et al.*, 1988), lung (Byers *et al.*, 1987; Koo, 1988), cervix (LaVecchia *et al.*, 1988b; Brock *et al.*, 1988) and stomach (You *et al.*, 1988; LaVecchia *et al.*, 1987) cancer show similar findings for vegetables or fruit or both.

The obvious question is whether these data are merely providing less specific support for the association between high intakes of defined micronutrients such as β-carotene and ascorbate and lower risk of cancers or whether additional factors are at work. The failure of some of the specific supplement trials to reduce cancer risk, and data from animal and *in vitro* studies, suggest that this is a broader and more interesting phenomenon related to more than the commonly cited specific vitamins (but, importantly, not excluding them).

Vegetables contain a wide variety of substances that have been shown to have anticarcinogenic properties, such as phenols, isothiocyanates, flavonoids, indoles and lignans (Wattenberg, 1985; Steinmetz & Potter, 1991b), fermentable fibre, and, of course, vitamins and trace elements. A recent nested case–control study found serum lycopene levels to be markedly different between cases of pancreas cancer and controls (relative risk for low versus high tertile = 5.40). Lycopene is a carotenoid without retinoid activity (Burney *et al.*, 1989). Higher folate intake is associated with lower risk of colon adenomatous polyps (Giovanucci *et al.*, 1993) and colon cancer (W.C. Willett, pers. commun.).

At present, we are not able to provide a summary estimate of the intakes of most of the bioactive substances – food tables do not provide the data, most of the relevant food analysis has not been done, and it is probable that whole classes of these constituents, and certainly individual constituents, remain to be identified.

Plausible mechanisms Several roles have been identified (Wattenberg, 1985) for the known bioactive components of plant foods in reducing cancer risk, and some of these are summarized in the following list.

(1) Inhibition of formation of direct-acting carcinogens. Ascorbate is effective in blocking the formation of *N*-nitrosamines *in vivo* from precursor nitrates and amines (Mirvish, 1981; Bartsch *et al.*, 1988).
(2) Prevention of reaction of agents with target tissues. There are a variety of ways in which this may occur (see Wattenberg, 1985). Non-nutrient compounds, such as phenols, found in plant foods (Wood *et al.*, 1982) can react with active carcinogens.
(3) Induction of enzymes that detoxify or conjugate carcinogenic compounds. A variety of plant-related substances have been shown to have this effect (Wattenberg, 1977, 1983).
(4) Inhibition of carcinogenesis even when delivered after known carcinogen exposure in animals. Carotenoids and selenium are included in this category but the mechanisms are unclear (Wattenberg, 1985).
(5) Reduction or prevention of hyperplasia in a variety of epithelial tissues.

More generally, the steps from procarcinogen exposure to cell transformation can be considered as follows: the procarcinogen is activated to the ultimate carcinogen (each of these may be solubilized and excreted); the carcinogen passes through membranes; the carcinogen interacts with DNA – perhaps forming adducts and/or producing mutations; DNA synthesis and replication (or DNA

repair) occur; repair may have varying degrees of fidelity; and cell replication with abnormal DNA and subsequent abnormal protein synthesis result (or cell differentiation occurs). At almost every one of these steps, specific known phytochemicals can alter the likelihood of carcinogenesis, occasionally in a way that enhances risk, but usually in a favourable direction. For example, substances such as glucosinolates and indoles, isothiocyanates and thiocyanates, phenols and coumarins can induce a multiplicity of solubilizing and (usually) inactivating enzymes; ascorbate and phenols block the formation of carcinogens such as nitrosamines; flavonoids and carotenoids can act as antioxidants; lipid-soluble compounds such as carotenoids and sterols may alter membrane integrity; some sulphur-containing compounds can suppress DNA and protein synthesis; and carotenoids suppress DNA synthesis and enhance differentiation (Steinmetz & Potter, 1991b; Wattenberg, 1992).

Adaptation It is here that the adaptation argument has its most interesting implications (and perhaps significant testability). There are known to be substances, including vitamins and trace elements, without which the organism cannot grow, be maintained, or reproduce optimally. The consequences of low levels (dietary or tissue) of these substances may include carcinogenesis. It is argued here that we are equally dependent on the environment to provide other substances that have specific anti-carcinogenic properties. In the absence of these substances, humans (perhaps all vertebrates) are at higher risk of cancers at a number of sites, particularly those where epithelial surfaces are more exposed to the environment – lung, digestive tract, and cervix. It is argued that these compounds supplied by the diet act to induce detoxifying enzymes, to block activation, and so on, and that the organism is reliant on them to do so.

As is clear from this whole chapter, the adaptation hypothesis can be related to each of the four dietary phenomena associated with increased cancer risk. However, there are more problems in testing the notion that humans are exposed to 'unaccustomed levels' of total energy or specific nutrients than in testing whether specific deficiencies or specific exposures are carcinogenic. There is no way to modify unaccustomed levels of one factor in a controlled trial that does not also modify others: for example, any attempt to decrease fat will result in decreased calories or increased levels of other nutrients; similarly, weight modification changes nutrient intakes, energy intake, energy expenditure, or all three. In contrast, addition of either specific compounds to the diet or modification of vegetable intake provides tests both of the protective hypothesis (and perhaps of their 'essential nutrient' status) and of possible public health strategies. There are also ways to test the adaptation argument with *in vitro* studies.

Specific exposures

Epidemiological evidence The mostly widely accepted theory of carcinogenesis implicates specific damage (either physical or chemical) to cellular DNA and now, more specifically, to proto-oncogenes and tumour suppressor genes. The diet contains a number of naturally occurring substances that have been shown to be carcinogenic – for example, aflatoxins and *N*-nitroso compounds – but there are very few human cancers for which a specific dietary carcinogen has been identified unequivocally [primary hepatocellular cancer, where aflatoxins are strongly implicated, is the major exception (IARC, 1976; Peers *et al.*, 1987)]. While DNA-interacting carcinogens are a major focus of animal experiments, most human studies to date have identified promoters or cocarcinogens, such as alcohol, or host phenomena, such as obesity, as discussed above. There is also, however, evidence for the importance of arylamines in colon cancer (and perhaps *N*-nitroso compounds in upper digestive tract cancers) and it may still be the case that specific dietary carcinogens will be identified for other epithelial cancers.

Plausible mechanisms The mechanisms of action of DNA-damaging carcinogens in general (Pitot, 1986), and aflatoxins (IARC, 1976), *N*-nitroso compounds (Bartsch *et al.*, 1982) and arylamines (Sugimura, 1985) in particular, have been well reviewed elsewhere.

Adaptation The adaptation argument in relation to specific exposures has four facets. First, we appear not to have developed specific mechanisms to detoxify certain carcinogens. (It is equally clear that there are mechanisms to detoxify some (Chasseaud, 1979) and to activate others.) Second, there are differences in the population distribution of specific

detoxifying enzymes (for example, approximately 40% of the population lacks one component subset (M1) of the glutathione *S*-transferase enzymes). Third, the mechanisms may become overloaded at high exposures. Fourth, the specific enzymes may not be lacking but exposure to the agents themselves is relatively uncommon and induction of the detoxifying enzyme(s) is normally achieved by other ubiquitous substances; it seems likely that this is the nature of the relationship that we have with a wide variety of the bioactive compounds. There are areas of the world where cancer has been attributed both to reduced intakes of specific nutrients and to exposure to specific dietary carcinogens: for example, China, where oesophageal cancer may be associated with *N*-nitroso compounds (Yang, 1980) and low intakes and blood levels of a variety of vitamins and trace elements (Thurnham *et al.*, 1985). To this point, supplementation with the missing nutrients has been disappointingly ineffective in reducing risk (Muñoz *et al.*, 1985; Wahrendorf *et al.*, 1988; Li *et al.*, 1993). This may suggest that what are missing are not the obvious micronutrients (these may be just markers for the real deficiencies) but specific compounds that keep the detoxifying enzymes 'tuned'. The experiment that follows from this hypothesis is obvious – either add a variety of fruits and vegetables to the diet or add some specific non-nutrient enzyme inducers, blocking agents, and so on. The advantage of studying oesophageal cancer is that there is an identified precursor lesion. Assessing precursor lesions allows more rapid tests of a variety of strategies on relatively small populations over shorter time periods than studies of the cancers themselves. Similar arguments apply to testing the role of vegetables in the prevention of recurrence of adenomatous polyps in addition to existing studies of single likely preventive agents (Bertram *et al.*, 1987). Such studies are now being undertaken in a number of settings.

Diet and social class

Clear evidence that diet contributes to the higher risk of cancer associated with lower social class is lacking but, based on the above view of dietary carcinogenesis, some important circumstantial evidence exists. This evidence particularly shows that there are unequal distributions of dietary and related risk factors across the social class spectrum in the developed world and that such a pattern may be even more pronounced in the developing world. The most obvious specific risk factors with evidence of differences by social class are fat, meat and alcohol intake and intake of vegetables and fruit. However, not all of these differences are in a direction consistent with these as agents that explain the social class gradient for cancer.

Specific evidence of a poorer-quality diet in lower social classes comes from a variety of studies in different parts of the world. In the USA, Davis *et al.* (1990) have shown, using data from the Nationwide Food Consumption Survey, that living alone, a lower income, a reduced expenditure on food, and unemployment are statistically independent (although clearly sociologically interrelated) predictors of a poorer-quality diet among those over 55 years of age. In this study, quality of diet was measured on the basis of the intake of a number of vitamins and minerals, some of which – for example, vitamin C, calcium and vitamin A – are known to be related to cancer risk.

Data from the Second National Health and Nutrition Examination Survey (NHANES II), and particularly from the Continuing Survey of Food Intake of Individuals (CSFII), were used by Block and Abrams (1993) to show that income has a major influence on the dietary intake and nutritional status of women between 15 and 44 years. They showed that poverty is associated with, among other things, lower intakes of folate, 'carotene', vitamins C and E, and calcium. They further showed that among poorer women (the criterion used, somewhat obscurely, was earning ≤131% of the official USA poverty level) only 53.7% reported consuming vegetables at least once in four non-consecutive 24-hour periods. In contrast, among women with incomes over 300% of the USA poverty level, 82.0% reported such consumption. For fruit and juice, the proportions were 67.4% and 87.4%, respectively. Murphy *et al.* (1992) have shown that among young males (19–24 years) in the USA poverty is associated with a poorer diet, again as assessed by intakes of specific micronutrients.

In common with the poor in the developing world, there is sometimes an overall shortage of food among those dependent on government assistance programs (Taren *et al.*, 1990) and other very poor members of USA society. This applies particularly to the elderly, single-parent families,

and children (Food and Research Action Committee, 1984, 1985; Physician Task Force on Hunger in America, 1985, 1986, 1987).

The 1989 baseline survey of the New York State Health Heart Project showed that beef and whole-milk (and possibly egg) intakes were inversely related to social class as measured by educational attainment (Shea *et al.*, 1993) – although somewhat paradoxically, this is probably explained in part by the relatively inexpensive nature and abundance of animal food in the USA, and the constant marketing of these products via the media. The opposite was true for vegetable and fruit consumption (Shea *et al.*, 1993). Subar *et al.* (1992) also reported that vegetable intake was lower in the less educated and lower in Blacks and Hispanics than in Whites, but that intakes of fruit and juices were not markedly different by ethnic status. Education was inversely related to fat consumption in the Minnesota Heart Survey in the early 1980s (Kushi *et al.*, 1988). These data could suggest that poverty and lower educational achievement in postindustrial societies, at least, may lead to a complex mix of poverty of information and skills, a distorted view of 'status foods', and an approach to dietary priorities typical of the 1940s, which was then much more focused on protein and calories.

Similar data on the quality of diets among the poor and individuals of lower socioeconomic status are available for other developed countries. A number of surveys in the United Kingdom show lower intakes of fibre, vitamin C, calcium and, among some groups, total calories in individuals of lower socioeconomic status than among the population at large (Braddon *et al.*, 1988; Gregory *et al.*, 1990; Cade *et al.*, 1992). The homeless (Cade *et al.*, 1992) and unemployed (Braddon *et al.*, 1988) seem particularly at risk. Cade *et al.* (1992) also reported on the very high rates (around 70%) of smoking that prevail among those living in shared public housing (a group that is essentially a subset of the homeless).

In Australia, there is important evidence that cost of food and social status (as defined by occupational status, education and income) are determinants of diet quality. Individuals of higher socioeconomic status have diets lower in fat and refined sugar and higher in fibre (this again suggests that access to information on diet and health shows significant social class differences), although such individuals also consume more alcohol (Smith & Baghurst, 1992). When food groups rather than nutrients are considered, groups of higher socioeconomic status consume more whole-grain cereals, more low-fat milk, and more fruit. Finally, these Australian data, however, also show that individuals of higher socioeconomic status consume more meat and cheese. Very similar data were reported for Australia by Steele *et al.* (1991) and Baghurst *et al.* (1990).

Data for Canada in the 1970s showed that folate and vitamin C were strongly related to income (Myers & Kroetsch, 1978). They also showed that intakes of calcium and, in pregnant women, vitamin A were low in the poorest groups. Vegetable and fruit intake were consistently inversely related to income in most age groups and both sexes (Myers & Kroetsch, 1978).

Finnish data showed that social class was a determinant of a variety of health-related habits in the 1970s and 1980s. Blue-collar males smoked more, drank more heavily though less frequently, were less physically active, and consumed diets less well matched to official dietary recommendations than white-collar males. Women showed similar but less marked social class differences (Aro *et al.*, 1986). The reported dietary differences particularly focused on intakes of butter and whole milk, both of which were higher among males of lower socioeconomic status, particularly (Aro *et al.*, 1986).

A Danish nutritional survey, undertaken in 1985 with the specific purpose of understanding the social distribution of diet-related disease risk, showed that intake of a number of foods varied extensively by social class (Haraldsdottir *et al.*, 1987). Fat intake was much higher in the lowest social class than in the highest social class among men, although the variability among women was much less marked. Intake of potatoes showed a similar pattern, but the gradient for intake of other vegetables was reversed and particularly so among women. The pattern of fruit intake was similar to that for vegetables and, again, the social class gradient was more marked among women. Bread intake showed a positive social class gradient in women but an inverse pattern among men. Beer also showed this difference by sex: intake among men in the highest social class was twice that of men in the lowest social class, but the opposite pattern was seen among women. Wine consumption showed a positive social class gradient in both sexes.

A crucial additional social class difference involves tobacco consumption – considered in detail in the chapter in this book by Stellman and Resnicow. One important observation that is relevant here is that in the developed world there is a higher prevalence of smoking among individuals of lower socioeconomic status, and that, generally, individuals who smoke have diets poorer in quality, particularly characterized by lower intake of vegetables and fruits. Perversely, smokers have a greater need (given the intake of toxic and carcinogenic compounds) of the micronurients that such foods provide. It may be, therefore, that the poorer members of society are at significantly elevated risk of cancer – both because of the interactive nature of the poor-diet–smoking combination and because of the large numbers of cancers that are related to both exposures.

Dietary differences around the world are much greater than those seen within countries. The developing world, as a broad generalization, shows patterns of intake that are much lower in meat and fat and much higher in abrasive cereals than the industrialized world but intakes of specific micronutrients are often marginal among the poor in these countries. Many of the studies that have been undertaken in the developing world have focused on nutrition among mothers, children and pregnant women, largely because this is perceived as the group at most risk of nutritional deprivation. It is likely, however, that the poor of both sexes and all ages are generally malnourished and that this is a significant contributor to cancer risk.

Intakes of a number of micronutrients – including folate, calcium, and vitamins D and C – are lower in Asian populations, for instance; but not all differences appear to be in a deleterious direction (Newman *et al.*, 1991). In some populations, intakes of fruit (Zeitlin *et al.*, 1992) or vegetables and fruit (Mele *et al.*, 1991) are lower among poor women and children.

The relationship between specific nutritional and food deficiencies has been discussed extensively in the first part of this chapter. More generalized malnutrition, however, is likely to have a complex relation to carcinogenesis with some steps in the process being enhanced and others inhibited (Deo, 1981).

In only a few studies have diet and cancer data been examined to establish whether socioeconomic indicators might explain dietary associations. For instance, LaVecchia *et al.* (1987) noted that including socioeconomic status in models reduced the strength of the positive association between pasta and rice and risk of stomach cancer in a northern Italian population but did not modify the relationship with other dietary risk factors. In an analysis of all cancer incidence in the Iowa Women's Health Study, however, socioeconomic status, as measured by educational status, remained predictive in models that also contain vegetable intake (Potter *et al.*, unpublished). Smith and Baghurst (1992) made the point that although there are social class differences in the Australian diet, these do not appear to be large enough to explain the social class gradient observed, particularly for coronary heart disease. What proportion of the socioeconomic-status-related variation in cancer is explained by diet remains unknown. Given the extent of misclassification of both diet and social class, there could be a considerable degree of confounding between the two kinds of variables that remains uncontrolled when both kinds of variables are used in analytical models.

In his preface to the second edition of *Poverty and Health* (Kosa & Zola, 1975), Zola notes that the 'social sciences discovered illness in the 1950s and rediscovered poverty almost a decade later'. Epidemiology, from its earliest days, clearly knew about poverty; John Snow's discussion of cholera (Snow, 1855) includes the following potent reminder to those who remember only the removal of the Broad Street pump handle:

> It is in the families of the poor that cholera is often observed to pass from one individual to another, while in cleanly dwellings, where the hand-basin and towel are in constant use, and where the rooms for cooking, eating, and sleeping are distinct from each other, the communication of cholera from person to person is rarely observed. In the houses of the poor also, the disease is hardly ever contracted by medical, clerical, and other visitors, who do not eat or drink in the sick room, while it often fares differently with the social visitor, who comes either to see the patient or attend his funeral.

Perhaps in the 1990s, nutrition and epidemiology, too, can rediscover poverty and appreciate this

as a fundamental and preventable determinant of cancer risk.

Summary

There are a variety of ways in which diet may influence the development of human cancers. What is proposed here (and elsewhere – see Potter, 1992b) is a theoretical framework and an argument, with the features summarized below.

(1) There is a dietary pattern to which humans are well adapted – an 'original diet'.
(2) This original dietary pattern had specific features, which included regular exposure to a variety of substances that are required for human metabolism but that are not usually explicitly labelled as 'essential nutrients'.
(3) The original dietary pattern was low in highly abrasive cereal products (consumption of large amounts of grains is a relatively recent phenomenon), with less resultant damage and frequent cell repair, particularly to the upper gastrointestinal tract.
(4) The original dietary pattern involved variability in intake, which resulted in variability in cell replication rates particularly in the gastrointestinal tract, and little risk of obesity.
(5) The original dietary pattern involved almost no intake of alcohol and therefore little capacity for its solvent and chronic cell damage capacities.
(6) Abandonment of each of these aspects of dietary adaptation has consequences for carcinogenesis. Most notable is the reduction of intake of vegetables and fruit with subsequent loss of appropriate enzyme 'tuning' and so on, and a generally increased susceptibility to cancer at a number of sites. A high intake of fat, of grains, and of alcohol, and increased obesity, are each associated with recognizable patterns of cancers.
(7) The higher risk of cancer that exists among the poor, in both the developed and developing world, is to some, as yet unknown, degree related to the fact that the amount of variation from the diet to which we are well adapted is greater in that portion of the population who have less access to the world's goods and services. This is particularly true regarding the intake of fresh vegetables and fruit, almost universally consumed in smaller quantities among the poor in most parts of the world. Some diet-related cancers, particularly breast cancer, run counter to the general trend towards higher risks in poorer people; it is probable that social class differences in other risk factors, particularly reproductive history, explains this discrepancy, at least in part.

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