Diet and large bowel cancer

Colorectal cancer is the second most common cancer in Britain, affecting about 3% of men and women by the age of 75. Risks increase markedly with age, from 12 cases per 100 000 in men at age 40-45, to 419 per 100 000 at age 80-85[1]. It has been suggested that the aetiology of cancer of the colon is different from that of cancer of the rectum, but the two are treated as a single entity in this paper. The same chromosomal abnormalities have been found in both[2] and there are difficulties in determining the exact anatomical site of cancer of the recto-sigmoid area, where up to half of large bowel neoplasms may be found[1].

Within any one population, individual susceptibility to the disease is affected by genetic factors, which may be common to the sporadic form of colorectal cancer and the rare inherited susceptibility, familial polyposis coli[2]. However, several lines of evidence show that environment may overwhelm genetic factors in colorectal cancer at the population level. Firstly, there is at least a 15-fold range in age standardized incidence rates in different parts of the world[1]. Secondly, migrants from a low risk area adopt the incidence rates of a high risk host population within a single generation[3]. Thirdly, certain population groups have experienced striking changes in large bowel cancer risk with time. For example, colorectal cancer rates in Japan have more than doubled since 1960, and are fast approaching those recorded in Britain[1].

Of the possible environmental risk factors, diet, particularly meat and fat consumption, has been shown to be most strongly associated with colorectal cancer incidence rates[4]. As yet the mechanism by which diet may be involved in affecting risk is unknown, and this is likely to remain true until the molecular basis of colorectal cancer is established. Nevertheless, there are a number of hypotheses which relate dietary factors and bowel cancer, and many epidemiological studies have attempted to investigate them.

Cancer arises in general by a several-stage process of initiation and then promotion. The supposition that cancer initiators are formed in the lumen of the large gut has prompted the search for faecal mutagens and carcinogens, of which there are a number of candidates, including polycyclic hydrocarbons, phenols, and N-nitrosocompounds[5]. Recent attention has focused on the mutagenic heterocyclic amines which are formed in meat cooked at relatively low temperatures. These quinoline derivatives such as IQ, MeIQx MeIQ, result probably from Maillard reactions between a hexose such as glucose and an amino acid, with linkage of the resulting Strecker aldehyde to creatinine[6]. MeIQx forms covalent links with mouse DNA obtained from tissues including the large intestine[7]. MeIQ and IQ are damaging to mouse cells in vivo, and IQ induces large bowel tumours in mice[8]. Hayatsu et al. have shown an increase in faecal mutagenicity in human volunteers following a meal of 150 g fried beefburgers, but could not identify the major mutagenic component as MeIQx[9]. Other mutagens, the fecapentaenes, have not been shown to be carcinogenic in vivo and are not associated with increased risk of colon cancer in case

control studies[10,11]. Non-fecapentaene mutagenicity, possibly from heterocyclic amines, has however been associated with increased risk[12].

The presence of mutagens in cooked meat would offer a direct link with the epidemiological association of meat consumption and large bowel cancer. Both meat and fat consumptions are high in high risk areas, and the recent increases in bowel cancer rates in countries such as Japan and Greece have been accompanied by rapidly increasing consumption of meat[4,13,14].

However, other epidemiological support for the role of meat is inconsistent. Seventh Day Adventists, most of whom are vegetarian, have a reduced risk of cancer of the large bowel, but Mormons are also at low risk and they are not vegetarian[15,16]. Nineteen case control studies in various geographical locations have reported the risk of colorectal cancer with respect to meat[17]. The majority (12) of these studies yielded non-significant results, but in seven studies positive associations were found, relative risk increasing with increasing meat consumption. No study yielded inverse associations. Equivocal results are available from two prospective studies[18,19].

One of the most extensively investigated hypotheses is that secondary bile acids are involved in bowel cancer. Originally bile acids were thought to be initiators via desaturation to 20-methyl cholanthrene, a polycyclic hydrocarbon[20] and more recently they have been proposed as promoters, via their damaging and cell proliferative effects on the colonic mucosa[21-23]. Bile acids alone however are unlikely to affect colorectal cancer risk because there is no difference in faecal bile acid output either between cases and healthy matched controls nor between individuals living in a high risk area and those living in a low risk area[24]. Nevertheless, the hypothesis that bile acids are important in colorectal cancer has yet to be entirely refuted, since it is possible that other factors, such as calcium and pH may be involved, reducing the solubility of free bile acids, at least in faecal water[25].

An increased output of bile acids due to a high fat diet, was a suggested explanation for the epidemiological association between high fat intake and high rates of bowel cancer[20]. The increase in colon cancer in Japan has been associated with an increase in total fat consumption[13] although not in Greece where the traditional diet is high in fat, from olive oil[14]. Experimental and epidemiological studies offer only limited support for a role for fat in bowel cancer, the majority of case control studies of diet and cancer (16 out of 25) having found no significant associations. In seven, risk was elevated with increased fat consumption, and in two, an inverse association was found[17].

Prospective studies of fat and bowel cancer have also yielded conflicting results. American nurses show mildly increased risk with higher fat intake[26] as do a vegetarian (Seventh Day Adventists) population[27] but an inverse association was seen in a Hawaii Japanese population[28]. Support for a role for saturated fat in bowel cancer could come from large prospective studies if they showed positive associations between risk and blood cholesterol. However, in the largest studies of more than 92 000 individuals in Sweden and California, blood cholesterol was positively related to large bowel cancer in one study[29] with no relation in the other[30]. Case control studies have not

established differences in the type of fat consumed, as judged by adipose tissue composition[31].

In animal studies of large bowel carcinogenesis induced with chemical carcinogens, recent work shows no overall effect of fat, nor saturated fat when standardized for total energy and for linoleic acid intake[32,33].

Alcohol, particularly beer consumption, has been linked for some time with large bowel cancer, especially rectal cancer. McMichael et al. in relating time trends in cancer mortality to changes in food supplies and alcohol consumption, found a positive association between beer consumption and rectal cancer[34]. Alcohol is not a direct acting carcinogen, but beer, wines and spirits contain at least 1200 different compounds, such as aldehydes, higher alcohols, phenols, amines etc. Acetaldehyde and urethane are known carcinogens, and acetaldehyde is a metabolic intermediate from alcohol in humans, particularly chronic consumers. A recent report found sufficient evidence to classify alcoholic beverages as carcinogenic to humans, but epidemiological studies were inconsistent for colon cancer, and only indicative for beer consumption in rectal cancer[35].

The hypothesis that lack of dietary fibre (NSP, non-starch polysaccharides) could account for high rates of large bowel cancer in western societies is by now familiar. In 1969 Burkitt suggested a mechanism for the protective action of dietary fibre in stating that 'with regard to bowel tumours ... with the Western diet, the greatly delayed transit time (most of the delay occurring in the distal colon), together with the concentration associated with diminished stool bulk, might enhance the action of any carcinogen by the multiple of these factors'[36]. Since that time, a number of studies have shown a reduction in faecal mutagenicity, probably by dilution, with bran in humans[37]. Bran, together with cellulose, also appears to have a consistently protective effect against chemical carcinogenesis induced in experimental animals[38].

There are however other aspects to the protective action of dietary fibre, in addition to its effect on stool bulk and transit time. Firstly, non-starch polysaccharides (fibre) are substrates for anaerobic fermentation by the flora of the large bowel. Secondly, recent research has shown that as much starch as non-starch polysaccharides may reach the large gut and be fermented by the flora[39]. The amount of 'resistant' starch that reaches the large bowel depends on cooking, processing, and ripeness of food[40] but in areas where starch remains the major contributor to energy supplies in human diets (and where fat intakes are low) substantial amounts of 'resistant' starch may reach the large gut.

During fermentation, bacterial cell mass and faecal weight are increased and the production of ammonia, amines and other precursor N-nitrosocompounds is altered. Short chain fatty acid production is also increased[39]. Butyrate is a well recognized differentiating and antiproliferative agent in cell culture lines, acting directly as an inhibitor of DNA synthesis and cell growth, mainly via inhibition of histone deacetylase. This may be a general mechanism for allowing access for DNA repair enzymes. The other short chain fatty acids, acetate and propionate, produced during fermentation are much less active than butyrate in this respect[41,42]. Interestingly, butyrate levels both in vitro and in vivo are enhanced when starch, rather than NSP, is the substrate for fermentation[43,44].

So far there has been little epidemiological testing of the protective effects of butyrate and none of resistant starch, although two small studies have shown lowered faecal butyrate in cases versus controls[45,46]. Intakes of resistant starch and NSP have not been measured in most dietary studies, but when all case control studies which have measured various indices of 'fibre' consumption are summarized, fibre is associated with a reduction in risk in 11 out of 22 studies, mainly due to lower vegetable consumption reported by cases than by controls[17]. In the largest study of 818 cases in Belgium, starch, fibre, cooked vegetables and raw vegetables were all protective factors with relative risks reduced to 0.82, 0.67, 0.71 and 0.37 respectively[47,48]. The association with vegetables may be due to the fact that they are the major sources of NSP in western diets, or that they contain micronutrients and pharmacologically active substances for which a general protective role in cancer has been described[49]. The problem of bias and misclassification in case control studies, particularly of diet and large bowel cancer, has been detailed elsewhere[50] and these findings require confirmation with large prospective and intervention trials using improved methods of dietary assessment.

At present, neither epidemiological studies nor experimental work supports an unequivocal role for fat in bowel cancer, and adequate explanations for the possible mechanisms of fat in carcinogenesis are lacking. Suggested mechanisms for the roles of meat and alcohol are interesting, but epidemiological studies as yet have failed to confirm their involvement. The 'bulking' theory to explain the protective role of dietary fibre is supported by a reduction in faecal mutagenicity with bran, and by animal carcinogenicity tests. The metabolic consequences of fermentation of resistant starch and NSP may be important in altering bacterial metabolism in the colon and stimulating butyrate production, but these protective aspects have yet to be tested epidemiologically and experimentally. Definitive assessments of risk must await the findings of large, well controlled and validated prospective and intervention trials of diet and cancer, coupled with specific testing of hypotheses in relation to molecular genetics. Meanwhile general dietary advice to restrict alcohol and fat consumption, and to increase the amount of vegetables, starch and non-starch polysaccharides in the diet will not increase risk of large bowel cancer and may be of benefit.

Sheila A Bingham
MRC Dunn Clinical Nutrition Centre
100 Tennis Court Road
Cambridge CB2 1QL

References
1 Muir C, Waterhouse J, Mack T, Powell J, Whelan S. Cancer incidence in five continents. V. Lyon: IARC, 1987:88
2 Solomon E, Voss R, Hall V, et al. Chromosome 5 allele loss in human colorectal carcinomas. Nature 1987; 328:616-19
3 Haenszel W, Kurihara M. Studies of Japanese migrants. Mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst 1968;40: 43-68
4 Armstrong B, Doll R. Environmental factors and cancer incidence in different countries, with special reference to dietary practices. Int J Cancer 1975;15:617-31

5 Bingham SA. Meat, starch and non-starch polysaccharides and large bowel cancer. *Am J Clin Nutr* 1988;**48**:762-7

6 Sjodin PB, Nyman ME, Nilsson L, Asp NG, Jagerstad MI. Binding of ^{14}C labelled food mutagens by dietary fibre in vivo. *J Food Sci* 1985;**50**:1-5

7 Alldrick AJ, Lutz WK. Covalent binding of MeIQx to mouse DNA in vivo. *Carcinogenesis* 1989;**10**:1419-23

8 Sugimura T. Carcinogenicity of mutagenic heterocyclic amines. *Mutat Res* 1985;**150**:33-41

9 Hayatsu H, Hayatsu T, Wataya Y. Use of blue cotton for detection of mutagenicity in human feces excreted after ingestion of cooked meat. *Environ Health Perspect* 1986;**67**:31-4

10 Schiffman MH. Diet and faecal genotoxicity. *Cancer Surv* 1987;**6**:653-72

11 Ward JM, Anjo T, Ohannesian L, et al. Inactivity of fecapentaene-12 as a rodent carcinogen or tumor initiator. *Cancer Lett* 1988;**42**:49-59

12 Schiffman MH, Andrews AW, Van Tassell RL, et al. Case control study of colorectal cancer and fecal mutagenicity. *Cancer Res* 1989;**49**:3420-4

13 Minowa M, Bingham S, Cummings JH. Dietary fibre intake in Japan. *Hum Nutr* 1983;**37A**:113-19

14 Trichopolou A, Mossalios E. Changing dietary habits in the population: the experience of the Mediterranean countries of Europe. *Proc Belgium Cancer Soc* 1990 (in press)

15 Phillips RL, Snowdon DA. Association of meat and coffee use with cancer of the large bowel, breast and prostate among Seventh Day Adventists. *Cancer Res* 1983; **43**(Suppl):2403S-8S

16 Lyon JL, Gardner JW, West DW. Cancer among Mormons 1967-1975. In: Cairns J, Lyon JL, Skolnick M, eds. *Cancer incidence in defined populations*. Banbury Report 4. New York: Cold Spring Harbor Laboratory, 1980:3-27

17 Bingham S. Evidence relating dietary fibre (NSP) and starch to protection against large bowel cancer. *Proc Nutr Soc* 1990 (in press)

18 Phillips RL, Snowdon DA. Dietary relationships with colorectal cancer among Seventh Day Adventists. *J Natl Cancer Inst* 1985;**74**:307-17

19 Hirayama T. A large scale cohort study on the relationship between diet and selected cancer of digestive organs. In: Bruce WB, Correa P, Lipkin M, Tannenbaum SR, Wilkin TD, eds. *Gastrointestinal cancer: endogenous factors*. Banbury Report 7. New York: Cold Spring Harbor Laboratory, 1981:409-29

20 Hill MJ, Drasar BS, Aries V, Crowther JS, Hawksworth G, Williams O. Bacteria and aetiology of cancer of the large bowel. *Lancet* 1971;**i**:95-100

21 Fitzer CJ, O'Brian CA, Guillem JG, Weinstein IB. The regulation of protein kinase C by chenodeoxycholate, deoxycholate and several structurally related bile acids. *Carcinogenesis* 1987;**8**:217-20

22 Thornton JR. High colonic pH promotes colorectal cancer. *Lancet* 1981;**i**:1081-3

23 De Rubertis FR, Craven PA, Saito R. Bile salt stimulation of colonic epithelial proliferation. *J Clin Invest* 1984;**74**:1614-24

24 Setchell KDR, Street JM, Sjovall J. Faecal bile acids. In: Setchell KDR, Kritchevsky D, Nair PP, eds. *The bile acids*. New York: Plenum, 1987:441-571

25 Bruce WR. Recent hypotheses for the origin of colon cancer. *Cancer Res* 1987;**47**:4237-42

26 Stampfer MJ, Willet WC, Colditz GA, Rosner B, Hennekens C, Speizer F. A prospective study of diet and colon cancer in a cohort of women. *Fedn Proc* 1987; **46**:883(Abs)

27 Morgan JW, Frazer GE, Phillips RL, Andrews MH. Dietary factors and colon cancer incidence among Seventh Day Adventists. *Am J Epidemiol* 1988; **128**:918(Abs)

Stemmerman GN, Nomura AMY, Heilbrun LK. Dietary fat and the risk of colorectal cancer. *Cancer Res* 1984;**44**:4633-7

29 Tornberg SA, Ham LE, Cartensen JM, Eklung CTA, Odunt D. Risk of cancer of the colon and rectum in relation to serum cholesterol. *N Engl J Med* 1986; **315**:1629-33

30 Klatsky AL, Armstrong MA, Friedman GD, Hiatt RA. The relation of alcoholic beverage use to colon and rectal cancer. *Am J Epidemiol* 1988;**128**:1007-15

31 Berry EM, Zimmerman J, Peder M, et al. Dietary fat, adipose tissue composition and development of carcinoma of the colon. *J Natl Cancer Inst* 1986; **77**:93-7

32 Clinton SK, Visek WJ. The macronutrients in experimental carcinogenesis of the breast, colon and pancreas. *Progress in Clinical and Biological Research in Dietary Fat and Cancer*, Vol. 222. New York: Alan R Liss, 1986:377-401

33 Newberne PM, Nauss KM. Dietary fat and colon cancer: variable results in animal models. *Progress in Clinical and Biological Research in Dietary Fat and Cancer*, Vol. 222. New York: Alan R Liss, 1986:311-30

34 McMichael AJ, Potter JD, Hetzel BS. Time trends in colorectal cancer mortality in relation to food and alcohol consumption. *Int J Epidemiol* 1979;**8**:295-303

35 IARC. Monograph on the evaluation of carcinogenic risks to humans. *Alcohol drinking*, vol. 44. Lyon: IARC 1988

36 Burkitt DP. Related disease - related cause. *Lancet* 1969;**ii**:1229-31

37 Venitt S. Mutagens in human faeces and cancer of the large bowel. In: Rowland IR, ed. *Role of the gut flora in toxicity v. cancer*. London: Academic Press, 1988: 399-460

38 Pilch S, ed. *Physiological effects and health consequences of dietary fiber*. Bethesda: FASEB 1987

39 Cummings JH, Bingham SA. Dietary fibre, fermentation and large bowel cancer. *Cancer Surv* 1987;**6**: 601-21

40 Englyst HN, Cummings JH. Resistant starch, a 'new' food component: a classification of starch for nutritional purposes. In: Morton ID, ed. *Cereals in a European context*. Chichester: Ellis Horwood, 1987:221-33

41 Kruh J. Effects of sodium butyrate, a new pharmacological agent, on cells in culture. *Mol Cell Biochem* 1982;**42**:65-82

42 Smith PJ. n-Butyrate alters chromatin accessibility to DNA repair enzymes. *Carcinogenesis* 1986;**7**: 423-9

43 Macfarlane GT, Cummings JH, Allison C. Protein degradation by human intestinal bacteria. *J Gen Microbiol* 1986;**132**:1647-56

44 Scheppach W, Fabian C, Sachs M, Kasper H. Effect of starch malabsorption on fecal SCFA excretion in man. *Scand J Gastroenterol* 1988;**23**:755-9

45 Vernia P, Ciarniello P, Cittadini M, et al. Stool pH and SCFA in colorectal cancer and polyps. *Gastroenterology* 1988;**96**:A528

46 Bonnen H, Clausen MR, Mortensen PB. Colonic concentration and production of butyrate from dietary fibre is decreased in patients with adenomas in colon. *Gastroenterology* 1989;**96**:A51

47 Tuyns AJ, Haelterman M, Kaaks R. Colorectal cancer and the intakes of nutrients: a case-control study in Belgium. *Nutr Cancer* 1987;**10**:181-6

48 Tuyns AJ, Kaaks R, Haelterman M. Colorectal cancer and the consumption of foods: a case-control study in Belgium. *Nutr Cancer* 1988;**11**:189-204

49 Wattenberg LW. Chemo prevention of cancer. *Cancer Res* 1985;**45**:1-8

50 Bingham S. The dietary assessment of individuals; methods, accuracy, new techniques and recommendations. *Nutr Abs Rev* 1987;**57**:705-42