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REVIEW

Diet, ageing and genetic factors in the pathogenesis of diverticular disease

Daniel Martin Commane, Ramesh Pulendran Arasaradnam, Sarah Mills, John Cummings Mathers, Mike Bradburn

Daniel Martin Commane, John Cummings Mathers, Human Nutrition Research Centre, School of Clinical Medical Sciences, University of Newcastle, NE1 8RU, United Kingdom
Ramesh Pulendran Arasaradnam, Clinical Sciences Research Institute, Medical School, University of Warwick, Coventry, CV2 2DX, United Kingdom and Human Nutrition Research Centre, School of Clinical Medical Sciences, University of Newcastle, NE1 8RU, United Kingdom
Sarah Mills, Mike Bradburn, Department of Surgery, Wansbeck General Hospital, Northumbria, NE63 9JJ, United Kingdom
Author contributions: All authors contributed equally to this manuscript.
Supported by Food Standards Agency, N12105 and Northumbria Colorectal Research Funds
Correspondence to: Ramesh Pulendran Arasaradnam, MB BCh BAO, C Clin Ed, PhD, MRCP, Clinical Sciences Research Institute, Medical School, University of Warwick, Coventry, CV2 2DX, United Kingdom. r.arasaradnam@warwick.ac.uk
Telephone: +44-2476-966087 Fax: +44-2476-966096
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Abstract

Diverticular disease (DD) is an age-related disorder of the large bowel which may affect half of the population over the age of 65 in the UK. This high prevalence ranks it as one of the most common bowel disorders in western nations. The majority of patients remain asymptomatic but there are associated life-threatening co-morbidities, which, given the large numbers of people with DD, translates into a considerable number of deaths per annum. Despite this public health burden, relatively little seems to be known about either the mechanisms of development or causality. In the 1970s, a model of DD formulated the concept that diverticula occur as a consequence of pressure-induced damage to the colon wall amongst those with a low intake of dietary fiber. In this review, we have examined the evidence regarding the influence of ageing, diet, inflammation and genetics on DD development. We argue that the evidence supporting the barotrauma hypothesis is largely anecdotal. We have also identified several gaps in the knowledge base which need to be filled before we can complete a model for the etiology of diverticular disease.

Key words: Diverticular disease; Dietary factors; Genetics; Colon; Inflammation

Peer reviewers: Frank Hoentjen, MD, PhD, Department of Gastroenterology, VU Medical Center, Sumatrastraat 16, 2022XL Haarlem, The Netherlands; Emiko Mizoguchi, MD, PhD, Department of Medicine, Gastrointestinal Unit, GRJ 702, Massachusetts General Hospital, Boston, MA 02114, United States

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INTRODUCTION

Diverticular disease (DD) is characterized by out-pouching in the wall of the colon; though generally benign, a minority of individuals develop associated morbidities, ranging from excessive flatulence and minor Irritable Bowel Syndrome (IBS)-like symptoms, through to inflammation of these out-pouchings (diverticulitis)[1]. Diverticulitis can lead to potentially life-threatening complications (i.e. abscess formation, colonic perforation, and bowel obstruction) in up to a quarter of sufferers[2] and one estimate puts European DD associated mortality at 23 600 deaths per annum[3].

EPIDEMIOLOGY AND PUBLIC HEALTH IMPACT

Necropsy-based studies implicate ageing as the primary risk factor for DD. Two studies in separate Northern European populations, dating from 1968 and 1979, indicate a prevalence of around 13% up to 54 years of age and rising to 40%-50% in individuals over 75 years old[4,5] (Figure 1A). Age-standardized mortality rates for DD in the UK have not changed considerably since 1979[6], so we can assume that these figures are a reasonable estimate of the current prevalence. As an age-related phenomenon we can expect the burden of DD upon society to rise with the continuing increases in life expectancy throughout the developed world (data from

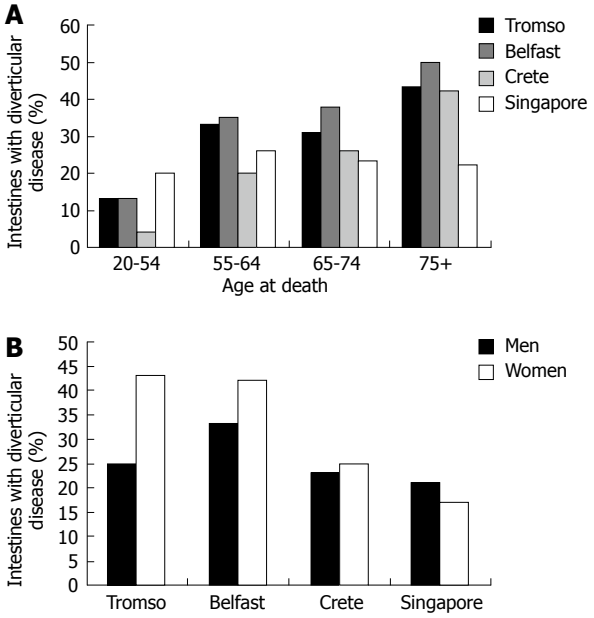

Figure 1 Prevalence of DD in intestines obtained at necropsy by age, gender and region. A: Increasing prevalence of DD with age in western populations. In contrast DD peaked amongst individuals in their late fifties and early sixties in Singapore. The Singapore study however is based on diverse ethnic populations which may be confounding these observations; B: Percentages of intestine shown to have DD present at necropsy by gender. Data obtained on individuals from the Trømso region of northern Norway between 1974 and 1976, Northern Irish subjects in 1968, Cretan subjects 1997-1999, and Singapore prior to 1986. Note: The data presented for the Cretan-, Belfast- and Singapore-based studies are adjusted for age groups used by the Norwegian study using slopes obtained from the published data. Figures adapted from reference[1-4].

the UK Office of National Statistics show continued increases in life expectancy in the UK[7]).

Diverticular disease has been described as a 20th century phenomenon[8], however there are cases in the European literature dating from well before 1900 as evidenced by Jun and Stollman[9]. In addition, evidence of an increase in the death rate from diverticulitis between 1923 and 1966 in England and Wales has been noted[10], and this probably reflects the increasing percentage of elderly people in the population over the same period[7]. The age-standardized mortality rates for DD in the UK have not changed considerably since 1979[3]; it follows that advances in medical practices coupled with increased lifespan may help explain in part the increased diagnosis of DD in the 20th century.

Necropsy data from Northern Europe, Southern Europe and Asia indicate wide geographic disparities in DD prevalence, i.e. it is more common in Northern Europe than in Crete or Singapore (Figure 1A). These studies also show an east-west divide in the nature of disease presentation, with right-sided diverticula being more prevalent in Asian populations; this hints at distinct etiologies[11]. Finally, the necropsy data also indicate that DD is more prevalent in women than men (Figure 1B). It is not yet clear as to whether this gender effect is related to hormonal or anthropometric risk factors, although Manousos *et al*[12] report a relationship with parity.

There have been several studies of DD risk in migrant populations. For example, "non western" immigrants showed a lower risk of DD-related hospital admissions and death but after adjusting for age, risk increased with years of residence in Sweden[13]. In contrast, other studies found no changes in DD incidence amongst migrant communities following periods of naturalization in countries with high or low risk DD in the native population. For example, evidence gathered from endoscopy reports suggests that the predominantly Turkish migrant community in the Zaanstreek region of the Netherlands have a significantly lower incidence of DD than the native Dutch population. Just 7.5% of 387 immigrants examined were shown to have DD, in contrast to 50% of the 5973 "native Dutch". Unfortunately, no information is available on the subjects' diet, how long they had been in the Netherlands or whether the subjects were first, second or third generation immigrants[14]. A UK study observed a lower incidence of DD amongst patients defined as "Indian subcontinent Asian males and females" compared with other ethnic groups. This study showed no difference in DD incidence between first and second generation Asians although numbers were limited[15]. In addition, an autopsy-based study of 1014 cadavers in Singapore showed a significantly higher risk of DD amongst the ethnically Chinese population when compared to the ethnically Malay and Indian populations[16]. The epidemiological data described suggests environmental and genetic components to DD etiology.

PATHOPHYSIOLOGY OF DIVERTICULAR DISEASE

DD presents as pockets within the colon wall, often around points of penetration of the vasa recta through to the luminal side of the muscularis propria[11], possibly because these sites are inherently weak. In western nations diverticula are most common in, though not confined to, the descending and sigmoid colon (left colon). This is in contrast to Asian nations where they occur primarily in the cecum and ascending colon (right colon)[17]. This difference suggests a role for genetic, environmental or lifestyle factors in the etiology of the condition.

At a functional level, the cecum and ascending colon are the primary sites of bacterial fermentation of carbohydrates and proteins which escape small bowel digestion. Microbial action, coupled with anti-peristaltic mixing, maintains a large digestive mass in this segment of the colon; thereby maintaining distention in the longitudinal and circular muscles of this region of the bowel for significant periods. In contrast, the descending colon serves primarily as a holding reservoir for fecal matter prior to excretion. Fecal matter reaching this stage of the colon is significantly reduced in bulk owing to the re-absorption of water and electrolytes, and the depletion of substrate for microbial activity. In addition, movement of bolus through this phase of the colon is subject to increasing voluntary control with variation in intra-luminal pressures throughout the length of the colon (Figure 2).

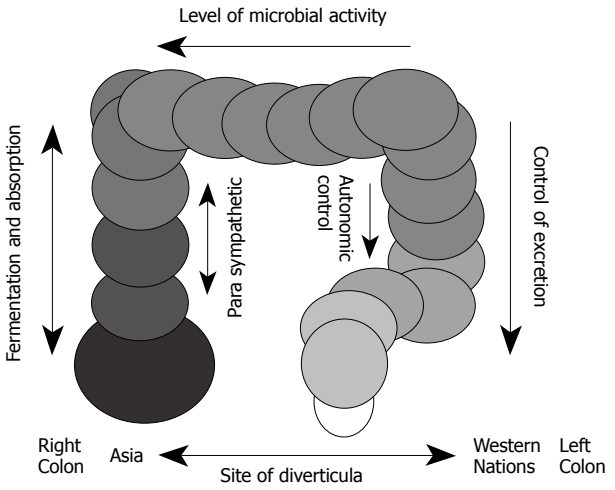

Figure 2 Physiological activity within the large bowel. Schematic of the human colon highlighting functional roles; the right colon is associated with high microbial activity, larger fecal volume and parasympathetic control. DD in the right colon is infrequently observed in western populations but commonly found in Asian populations. The left colon is the primary site of diverticula in western populations and has lower microbial activity, decreased fecal volume and is more responsive to voluntary control.

At a structural level, the mechanical characteristics of the bowel are maintained via circular and longitudinal muscle layers. The circular muscle thickens in regular bands of contraction (plicae circulares) which control peristalsis. The longitudinal muscle also condenses in thick bands (the teniae coli) which serve to pull the colon to a relatively short functional length. In DD, the circular muscle layer is thicker and the longitudinal muscle is shorter[1], although a similar thickening of the colon wall may be a natural feature of the normal ageing bowel[18] and seems to occur at an accelerated rate in inflammatory bowel disease (IBD)[19]. Comparing the DNA to nitrogen ratio in DD tissue confirms that the muscle thickening is not due to hypertrophy[20] whilst individual muscle fiber cells and their organelles appear normal on histological examination[18]. Instead, histological studies suggest that the accumulation and aberrant deposition of connective tissue fibers (elastin[18,21] and collagen[22]) underlie the altered muscle morphology. Furthermore, in diverticulitis the ratio of type I to type Ⅲ collagen is altered in both the serosa and sub-mucosa, indicative of scarring[23]. This effect may be attributable to aberrant activity of matrix metalloproteinases (MMPs) and tissue inhibitors of the matrix metalloproteinases (TIMPs). In one small DD study (11 cases, 6 of which were uncomplicated, *vs* 11 controls) increases in TIMP-1 and -2 expression were associated with disease severity i.e. expression was higher in symptomatic disease[24]. Separately, in a small study of patients with clinical diverticulitis (n = 13), Stumpf *et al*[23] found decreased expression of MMP1. In contrast, Rosemar *et al*[25] found an up-regulation of the expression of MMP1, in addition to increased expression of MMP2 and TIMP1, in DD affected tissues compared to unaffected bowel specimens from the same patients (who were undergoing sigmoid colectomy to treat complicated DD). Whether or not the MMPs and TIMPs play an important role in the tissue organisation observed in asymptomatic DD remains to be seen; the findings reported thus far may be due to acute inflammation rather than DD per se[26].

There have been a number of physiological studies of the diverticular diseased colon, focusing primarily on colonic transit times, intra-luminal pressure, colonic motility and electrophysiology. In the main, inference from these studies about DD specific events or processes is difficult because of the limited data on changes in normal colonic function with ageing, but they offer some insight into the disease process.

Colonic transit times

Studies of colonic transit times (performed by adding radiological markers to the diet) in DD, by both Evans *et al*[27] and Manousos *et al*[28], showed faster colonic transit in individuals with DD. This is perhaps in contrast to what we might expect, given that DD is an age-related phenomenon, and studies of transit time in the aged show either a slower rate of passage through the colon amongst the elderly[29-31], or no differences with ageing[27,32-34]. In addition, Evans *et al*[27] observed longer transit times in females, in whom the evidence points towards a higher risk for developing DD. We might question the potential confounding effects of habitual diet and physical activity in these studies. In particular, upon diagnosis, patients with DD are generally recommended a high fiber diet, which could account for accelerated transit time amongst cases. Nevertheless this interesting counter-intuitive observation is worthy of follow up.

Intra-luminal pressure and colonic motility

Classically, researchers interested in colonic motility in DD performed endoscopy-based manometry studies to measure changes in luminal pressure in the evacuated colon. The main findings of these studies are that there are similar resting luminal pressures between DD cases and controls[35], but higher luminal pressures in segments of colon with diverticula in response to pharmaceutical stimulus[36,37] and an increase in post-prandial colonic motility[38]. Paradoxically, inflating a balloon in the colon of individuals with DD induces the musculature of the colonic wall to yield to the increasing luminal pressure more quickly than in controls[38,39]. In addition, these and later studies indicate increased colonic motility (as assessed by number and amplitude of bowel wall contractions) in the sigmoid colon of individuals with left-sided DD[40,41], and also in the ascending colon of patients with right-sided diverticulosis[42]. These classical studies were generally performed with low numbers and failed to account for age, gender, physical activity or body fat percentage; the physiological observations were made under artificial conditions, i.e. in the evacuated bowel during endoscopy. Furthermore, they were performed over one or two hours, with the subject at rest, whilst in reality one would expect variation in bowel pressures throughout the day. More recently however, Bassotti *et al*[41] made recordings over a 24 h period, and observed higher colonic motility in DD cases throughout the recording period than in a younger control group (cases

Table 1 Summary of electrophysiology studies in diverticular disease (DD)

Study material	Treatment	Response	Study details	Reference
Colonic longitudinal smooth muscle	Relaxative cannabinoid agonists	Decreased relaxation in specimens *vs* controls	Study performed on diverticulitis specimens *vs* colorectal cancer controls	Guagnini *et al*[46]
Colonic longitudinal smooth muscle	Nitroprusside, relaxative agent	Decreased relaxation in specimens *vs* controls	Study performed on 10 DD patients *vs* 10 colorectal cancer controls	Golder *et al*[21]
Colonic circular smooth muscle	Contractionary, cholinergic stimuli	Decreased induction of contractionary waves in cases *vs* earlier data on "normal" patients	Material obtained from 12 patients, 10 of whom exhibited 'abnormal responses' Multiple samples from the same patient showed site specific differences	Huizinga *et al*[103]
Left-sided colonic smooth muscle	Nitric oxide, relaxative agent	Decreased relaxation in cases *vs* controls	Left-sided DD 9 patients, *vs* 16 left-sided colon cancer controls	Tomita *et al*[52]
Colonic longitudinal and circular muscle	Contractory acetylcholine	Increased contractionary response in DD cases *vs* controls	20 subjects with rectal tumours, 10 cases and 10 controls	Golder *et al*[51]
	Contractory tachykinin receptor antagonists	Higher active and resting stress in DD cases		

42-65 mmHg, controls 37-55 mmHg). It is unclear whether or not failing to control for age confounds these studies; Firth and Prather[43] suggest that colonic motility is not altered in the normal ageing colon, but this warrants further investigation, ideally utilizing pressure-sensitive transducers which can be swallowed and allowed to pass through the GI tract to provide more representative measures of colonic physiology[44]. That said, the evidence described points towards a neuromuscular dysfunction in DD; although it remains uncertain whether this is a cause or effect of the condition.

Electrophysiology and neuromuscular dysfunction

Electrophysiological examinations of the bowel wall have been used to investigate neuromuscular dysfunction in DD in several studies. Shafik *et al*[45] identified two distinct types of neuromuscular dysfunction by transcutaneously measuring electrophysiological activity in the sigmoid colons of DD subjects and comparing with age- and sex-matched controls; (1) elevated electrophysiological activity in early stage diverticulosis, and (2) a silent or low electrophysiological tone in advanced DD. This finding is supported by the ex vivo observation of Guagnini *et al*[46] who failed to induce an electrical field twitch response in resected longitudinal muscle from 30% of DD patients, but observed similar responses to electrical field stimulation in the remaining 70% of the samples compared with resected smooth muscle from slightly younger colorectal cancer patients.

Similar *ex vivo* electrophysiological studies of this type on DD specimens are summarized in Table 1. Typically they also show aberrant responses to relaxatory and contractionary stimuli in colonic smooth muscle in DD. On a cautionary note, the weaknesses of these studies include: (1) a lack of power due to the small numbers of subjects; (2) the use of colorectal cancer patients as controls; (3) the focus on complicated/advanced DD specimens.

Evidence from recent histological studies of neurones in the ageing human gut suggests that there is a natural decrease in nerve density with ageing[47,48], a finding supported in animal models[49]. Age-related neurone loss is intuitively attractive as an explanation for the impaired colorectal motility in DD; however, data concerning this remains relatively sparse. An early study by Macbeth and Hawthorne[50] suggested the opposite, i.e. an increase in the number of intramural ganglia but with disorganized distribution of ganglia in DD tissues. Fortunately, recent studies contradict this finding[21], and this work may have been confounded by the morphological distortions associated with the colon shortening in DD. Golder *et al*[51] show histological evidence for decreased nerve content of longitudinal muscle in DD as evidenced by reduced prostaglandin immunoreactivity. They have also found that individual nerve fibers were smaller in cases *vs* controls and were less likely to stain positively for choline acetyltransferase[52] and NOS 1[51], suggestive of cholinergic and nitrergic denervation in these samples. Again the primary potential confounder to these studies is the fact that the colon shortens, and that the muscle layers become thicker (due to elastin and collagen deposition), in DD; it is not clear as to how the authors have controlled for this. In contrast, Bassotti *et al*[53] found no difference in the number of enteric nerves, but a significantly lower number of glial cells in DD. In an interesting take on the same principal, they also found a significant decrease in the number of interstitial cells of Cajal in the myenteric plexus, the sub-mucosa and within the muscle. These cells are emerging as potential colonic pacemaker cells and, like neural cells, their loss might explain poor bowel motility, but yet again we are left with a cause or effect type question. Simpson *et al*[54] have argued (though not evidenced) that nerve damage results from periods of acute inflammation which arise as a consequence of the presence of diverticulosis, whilst others argue that age-related nerve withdrawal induces smooth muscle dysfunction, which thus predisposes to diverticulosis formation[55].

DIET AND LIFESTYLE IN DIVERTICULAR DISEASE

Evidence from man

Seminal papers by Painter and Burkitt[35,36,56] hypothesized

Table 2 Observational studies of dietary fiber consumption and DD risk in man

Design	Findings	Comments	Reference
Case control study comparing dietary fiber intake in 100 (symptomatic) DD cases *vs* 80 age and sex matched controls	Dietary fiber intake significantly higher amongst controls	Study participants were patients hospitalized due to diverticulosis; again symptoms may have influenced their diet	Manousos *et al*[12]
Prevalence of DD assessed by barium enema in 189 non-vegetarian volunteers *vs* 55 vegetarians	Diverticular disease was significantly higher in the non- vegetarian group	"Asymptomatic" volunteers recruited prior to diagnosis and grouped based on dietary choices. A potential confounder is a possible causative effect for meat	Gear *et al*[104]
Case control study comparing dietary fiber intake in 40 (symptomatic) DD cases *vs* 80 age and sex matched controls	Dietary fiber intake significantly higher amongst controls	Dietary fiber intake was "estimated" by dieticians. Symptomatic DD patients were studied so the symptoms may have influenced their diet	Brodribb *et al*[62]
"Prospective" case control study. As part of the Health professionals follow up study, 43 881 US men aged 40-75 followed over 6 years, for self reported diagnoses	Dietary fiber intake significantly lower in cases RR = 0.63	The largest and potentially most informative study. Crucially, the participants were not clinically examined for DD prior to the study. So we cannot rule out effects of DD on dietary choices	Aldoori *et al*[63]
Case control study comparing dietary fiber intake between 86 right-sided DD cases and 106 controls	No relationship between DD and fiber consumption	Only study on right-sided DD, negative finding may indicate either a different etiology or perhaps right-sided DD just has fewer effects that might influence diet choice	Lin *et al*[64]

RR: Relative risk.

that DD arises due to excessive luminal pressures which occur as a consequence of dietary fiber deficiency. This concept was based upon; (1) the apparent increase in DD incidence in western countries throughout the twentieth century, (2) an apparent decrease in dietary crude fiber consumption in western countries over the same period, and (3) an observed low prevalence of DD in Africa where crude fiber intakes were assumed to be higher. In particular, the authors made reference to necropsy studies in Africa which did not record any cases of DD, and to Burkitt's failure to observe any cases of DD whilst working as a clinician in Africa[56]. Subsequently, Painter and Burkitt[8] noted a comparable prevalence of DD amongst African Americans with the white American population.

There are several weaknesses in the evidence base underlying this hypothesis, particularly when one considers the populations being described; we have already evidenced the increasing lifespan of western populations throughout the 20th century which may parallel the increasing prevalence of DD. Life expectancy remains low on the African continent and the most recent World Health Organisation figures report a life expectancy of 51 years for both South Africa and Kenya (the African countries from which necropsy data were referenced by Painter and Burkitt)[57]. Thus there is a smaller percentage of people reaching old age in these countries which would lead to a lower prevalence of DD. Separately, let us consider the dietary fiber intake issue: the necropsy studies cited were performed in the 1950s and so the dietary patterns of the individuals studied would date back to the early half of the twentieth century, making it difficult to accurately determine dietary fiber intakes for these populations. The diet of present day sub-Saharan Africans differs regionally, with urbanization and social standing. For example, the Kenyan staple is the cereal-based "Ugali", fish is common around the coasts, and there are regional preferences for mutton or goat[58]. The average Kenyan diet whilst being relatively high in fiber is also considered, for much of the population, to be total

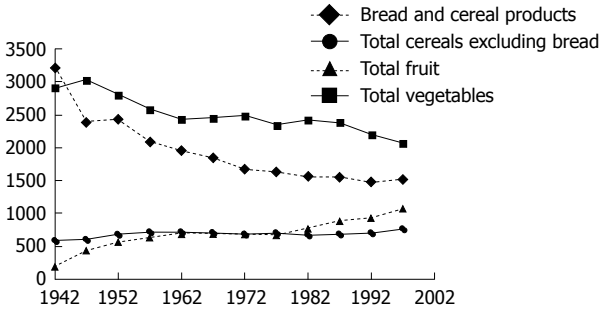

Figure 3 Consumption of major sources of dietary fiber in the UK in grams per person per week since 1942. Data shows a steadily decreasing consumption of dietary fiber-rich foods in the UK population since 1942. Adapted from data produced in the National Food Survey[64].

energy, macro and micronutrient deficient[59]. Similarly, the diet of poor urban South Africans may also be deficient in total energy and some macro and micronutrients, but in contrast to the Kenyan diet it is low in dietary fiber with an increasing emphasis on fat[60]. The point is that modern (and by inference non-traditional) African diets are highly variable; there is also evidence of a shift towards a western dietary pattern with corresponding clinical observations suggesting that DD prevalence may actually be on the rise[61]. However, this observation needs further detailed study and if confirmed, other non-dietary fiber variables should be considered. In the UK, the National Statistics Food Survey (NSFS) dates back to 1942; it shows a steady decrease in the consumption of fiber-rich foods throughout the latter half of the 20th century (Figure 3). However, there has been no great increase in age-adjusted mortality figures from DD in the UK over the last 30 years[3].

A small number of observational studies in man have since attempted to evaluate the dietary fiber/DD risk issue. These studies are summarized in Table 2 and in general support the dietary fiber hypothesis. Two of the three case-control studies[12,62] and the only prospective case-control study[63], found lower dietary fiber consumption amongst cases *vs* controls. In contrast,

one case-control study in an Asian cohort found no link between dietary fiber intake and DD risk (right-sided)[64]. We would argue that all these studies are methodologically flawed; low dietary fiber consumption amongst cases may simply reflect the patients attempt to ameliorate the effects of DD, i.e. excessive flatulence and disordered, possibly aberrant, colonic motility. This is also true of the prospective study[65] in which the volunteers were not clinically examined for DD at baseline, so the study team had no way of knowing whether diverticula were present prior to this. Further, from their cohort of 43 881 male volunteers, aged between 45 and 75, they identified 362 new cases of self-reported symptomatic disease. We would expect the true prevalence of undiagnosed DD in a western cohort (US) of this age and size to be several times that number (Figure 1). A further confounding factor to these studies may be co-linearity (and also inverse linearity) in intake of other nutrients and dietary constituents with fiber consumption. For example, dietary fiber consumption may be inversely related to total energy consumption and hence adiposity[66] and there are independent studies linking an increasing BMI to an elevated risk for complicated DD[65,67]. Unfortunately, there appears to be no published data on obesity and asymptomatic DD. Additional lifestyle risk factors emerging from the literature are: high red meat consumption[12,64], increasing socio-economic status in a Greek cohort[12], hypertension[65], parity[12] and low physical activity with increased symptomatic disease[63]. The evidence base for these risk factors is even less vigorous than it is for dietary fiber. Furthermore, there may be complex relationships between these variables. For instance, low physical activity might be related to obesity and hypertension; it may also be a consequence of symptomatic DD affecting the individual's mobility. Similarly a high socio-economic status in Greece might allow for a higher red meat contribution to the diet, which might itself be inversely correlated to fiber intake. In short, the evidence from studies in man suggests a relationship between diet/lifestyle and DD risk, but there remains a lack of robust definitive evidence. Long-term dietary intervention studies in man aimed at preventing the onset of diverticular disease are unfeasible; there have been intervention trials addressing the benefits of dietary fiber in preventing the complications of DD. These have had mixed success[68,69] and tell us little about disease etiology.

Evidence from animal models

Several investigators have induced the formation of diverticular-like entities in the intestines of rat models through extreme dietary manipulation practiced throughout the animals' natural life-span. Typically these diets were high in animal protein or fat and very low in fiber[70,71]. Increasing the fiber content of these basal diets reduced the DD incidence[72]. Indirectly, these rat models suggest a role for the intestinal flora in DD; Carlson and Hoezel[71] found that they were able to induce DD in rats fed Karaya gum as dietary fiber source, but not in rats where Psyllium seed husks or semi-fibrous cellulose flour was the dietary fiber source. The fundamental difference between these fiber sources may be that Karaya is not well-utilized by the gut microbiota[73]. Furthermore, a maternal high fiber diet throughout gestation in the rat was found to protect the animals' offspring from developing DD in later life[74]. Presumably, this was mediated through maternal colonization of the neonate with a protective microflora, although an epigenetic/imprinting type of effect might also be responsible.

We should, however, consider the validity of the rat model; the rat does not normally develop diverticular diseases and the diets required to induce them were extremely low in fiber. The rat bowel is anatomically distinct from the human; it does not contain teniae coli[74] which have been shown to be abnormal in DD in man. The diverticula observed in the rat model were restricted to the cecum and its proximity, which may be more representative of the Asian phenomenon than the left-sided DD seen in the West. On the other hand, the rat cecal diverticula did show certain similarities to those found in the human in that the muscle wall was thickened with increased deposition of elastic tissue[70] and altered collagen deposition[75]. The rabbit colon does contain teniae and Hodgson[76] induced diverticula in a rabbit model with a long term low residue diet. But again we should consider the validity of the model. The rabbits' natural diet is herbage and they engage in coprophagy to utilize the microbial fermentation products of this rich fiber source. The low fiber diet in this study failed to meet the nutritional needs of the animals and they began to show deficiency type symptoms in addition to developing diverticula. Both models indicate a protective effect for dietary fiber; however in each animal the experimental diets necessarily involve the replacement of dietary fiber with another food constituent; and one could argue that the replacement (fat, carbohydrates and meat protein) components of these diets may be causative of DD in these systems. In line with the studies in man, the animal models suggest that dietary fiber may protect against diverticula development, possibly mediated through the intestinal microflora. Collectively, however, the evidence is poor and the role of other dietary and lifestyle factors remains unexplored.

INFLAMMATION AND DD

It is tempting to postulate that inflammation plays a role in the etiology of DD for several reasons; (1) An increase in plasma inflammatory markers correlates with ageing in man and rats[77,78] as does the prevalence of DD; (2) Bowel wall thickness increases in both IBD[19] and DD[1]; (3) Inflammation could explain neuronal cell death in DD[54]; (4) In a small minority of DD cases the bowel becomes acutely inflamed; (5) Narayan and Floch observed non-specific inflammation in biopsy specimens from non-inflamed DD cases *vs* controls[79]; (6) Kealy observed significantly higher numbers of lymph nodes in disease-free portions of necropsied colon from subjects with DD *vs* controls[80]; (7) Inflammation could be a common factor linking diet and DD.

In contrast, Pezzilli *et al*[81] did not observe differences in fecal calprotectin concentrations between subjects with DD *vs* controls, though the study size was rather small (17 cases). More importantly, recent case-control studies of IBD suggest that chronic acute inflammation actually protects against DD[82,83]. The mechanisms by which this protection occurs are not yet understood, but may involve alterations to the luminal bolus, i.e. the loose watery stool associated with IBD may lower luminal pressures and help prevent DD, or through the impact of intestinal inflammation on the colonic flora. In either case, these findings do not rule out a role for mild non-acute inflammation, with a less pronounced effect on the fecal stream, in DD etiology. However, any mild non-specific inflammation in DD remains poorly evidenced.

THE ROLE OF GENETICS IN DD

Clinical observations associate a number of rare genetic disorders with a strong predisposition towards diverticula formation. Notably, patients with Ehlers-Danlos syndrome[84,85], Williams-Beuren syndrome[86], polycystic kidney disease[87] and Coffin-Lowry syndrome[88] are often afflicted with diverticula of the colon and other internal organs. The etiology of diverticula formation in these syndromes may be unrelated to sporadic age-related DD, but they may offer insight into mechanisms of disease in that at least three of these syndromes are associated with a connective tissue disorder. Ehlers-Danlos syndrome is an inherited connective tissue disorder arising through mutations in either the COL5A1 or COL5A2 genes encoding part of the type V collagen protein or through mutations in the gene for the extra cellular matrix (ECM) protein, tenascin-X[89]. Williams-Beuren syndrome affects 1:10 000 of the population and is due to a deletion of about 20 genes on chromosome 7. Although the genetic basis of this syndrome has not been elucidated fully, it appears to result in elastin haplo-insufficiency[90]. Coffin-Lowry syndrome is a maternally inheritable disorder that may also be related to disrupted collagen metabolism[88]. Scheff *et al*[91] observed colonic diverticulae in 83% of patients with end stage polycystic kidney disease (PKD). PKD is due to mutations in the PKD1 or PKD2 genes coding for the cell membrane-bound polycystin proteins. Whilst the function of these proteins is uncertain, it has been suggested that they interact with the ECM and with extra-cellular signaling pathways regulating cell migration and differentiation[92]. Collectively, these syndromes linked by an ECM defect might suggest that the accumulation of collagen and elastin in the smooth muscle of sporadic DD specimens[20,21] is a prerequisite to diverticula formation.

Separately, clinical observations of poor colonic motility also feature in a significant subset of individuals with mitochondrial diseases[93]. Perez-Atayde *et al*[94] observed a duodenal diverticulum in a 14-year-old with mitochondrial neurogastrointestinal encephalomyopathy which suggests that mitochondrial neuromuscular dysfunction may be associated with DD.

On a different note, clinical case reports hint at familial risk factors for DD in the general population; Schlotthauer reported DD in seven American brothers (aged 40-70), but not in their two sisters (ages not given)[95]; Omojola and Mangete[96] observed DD in three siblings in a Nigerian population with a traditionally low incidence of DD and Claassen *et al*[97] observed DD in two teenage siblings in Holland, in whom they also noted joint hypermobility, perhaps indicating a collagen disorder. Siblings share similar environmental exposure which may help explain familial clustering of DD but does not account for observations in populations where the prevalence is low or in the very young. These observations may simply be statistical anomalies, but taken together with the ethnic variations in both the site and age of onset of DD (Figure 1) they do suggest a genetic component. Unfortunately there is no published literature on attempts to quantify the hereditary component of this condition. Of note, our own preliminary epigenetic data have shown unusual DNA methylation patterns in the colonic mucosa of patients with DD[98,99].

CONCLUSION

A number of questions still remain regarding the biology and etiology of DD. Perhaps the most pressing amongst these relate to the role of diet and lifestyle, as these factors offer strategies for prevention. The two approaches which have been most successful in illuminating the role of diet and lifestyle in DD prevalence thus far are epidemiology and observational studies in man. The epidemiological approach is currently confounded by the lack of available up-to-date data on DD prevalence in different populations. A priority for future research should therefore be the collection of recent necropsy data to indicate current regional prevalence.

There have been no true prospective case-control cohort studies into DD and diet performed to date. For validity, any such study would require a prospective colonic examination to exclude DD patients at baseline, a follow up period of some years and a subsequent exam; this may be unfeasible given the time taken for diverticula to develop and demands on research budgets. In considering a low budget approach, it could be possible to append this type of study to the back of any new prospective colorectal cancer cohorts or to future polyp recurrence trials.

Other clinical and biological questions concern the mechanisms underlying the disease process. Gaps in the knowledge base on the natural changes in bowel physiology, inflammation and composition with ageing impede our understanding of DD. Less invasive methods for measuring physiological activity in the GI tract are under development[44], which may allow for the measurement of colonic motility under more natural physiological conditions and could be employed to study the effects of diet and ageing on normal bowel function and specifically changes related to DD.

Diverticulosis is ultimately a disease of ageing; recent studies show increasing mitochondrial dysfunction in the

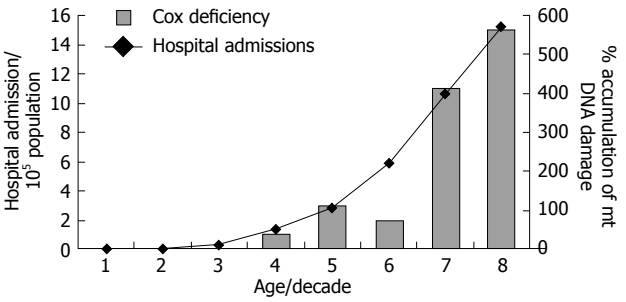

Figure 4 Graph showing the relationship of age with mitochondrial DNA damage and risk of hospital admissions for DD. Graph showing the correlation between the percentage accumulation mitochondrial (mt) DNA damage in the colonic mucosa - right hand y axis whilst left hand y axis shows hospital admissions for DD/10^5 in the UK. Ageing is expressed on the x axis in decades. The incidence of asymptomatic disease is considerably higher but the rate of hospital admissions may mirror DD incidence in the population as a whole. Mitochondrial DNA mutations are inferred from level of deficiency/inactivity in the respiratory chain mitochondrial protein Cytochrome C oxidase[102].

ageing colonic epithelia and this data correlates well with DD prevalence (Figure 4)[100]. We have been conducting preliminary investigations into the accumulation of mitochondrial deficiencies in the colonic epithelia in DD[101], Studies of mitochondrial deficiency or other age-associated changes in the colonic muscle might further illuminate the pathology of this condition. Similarly, we should further examine what phenomenon (if apparently not inflammation) drives excess ECM deposition in ageing and DD.

Animal models of DD hint at a role for the colonic microflora in the disease process, especially when one considers the differences in microflora composition between high and low risk populations[60,102]. A direct comparison of the fecal and colonic mucosal flora between cases and controls might simply reveal differences associated with the altered luminal environment; a better approach would be to characterize the microflora of volunteers prior to any prospective study.

Finally, it remains to be established as to whether right- and left-sided DD have different etiologies and to what extent genetics, environmental and lifestyle factors contribute to this difference. Ageing is the primary risk factor in DD, but the condition is not an inevitable consequence of the ageing process. It seems probable that dietary or environmental factors protect against diverticula formation but further evidence is needed to fully define these factors. The high prevalence of DD within our increasingly elderly population translates into significant morbidity. We feel therefore that the investment of research funds in this area is justified.

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