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Epidemiologic Features of Appendicitis

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1. Introduction

Though appendicitis is common many important questions remain unanswered. When is the appendix normal and when is it the cause of abdominal pain? Why does appendicitis primarily affect older children and young adults? Why is appendicitis uncommon in those under five years of age and in those over sixty years of age? Why are boys affected more often than girls? Why does appendicitis appear to run in some families? Why is appendicitis more common in affluent parts of the world and rare in parts where poverty and poor hygiene are prevalent? The epidemiology of appendicitis is complex and its cause is not explained by any single factor. The peak incidence of appendicitis coincides with the age when the immune system is most efficient and the lymphoid follicles are at their maximum development. Could this implicate immunological factors in the pathogenesis and, therefore, the epidemiology of appendicitis?

Obstruction of the lumen of the appendix is believed to be the trigger initiating the processes that culminate in inflammation of the appendix. Fecaliths are a specific cause of appendicitis in about one-third of specimens (Mitros & Rubin, 2009) and are composed of fats (coprosterols), inorganic salts (calcium phosphate) and organic residue (vegetable fibres) in a proportion of 50%, 25% and 20%, respectively (Berg, RM., & Berg, HM., 1957). Their physical consistency varies from soft to hard concretions. The reported incidence of fecaliths depends on whether the data was obtained from intraoperative palpation of the organ, from histological analysis of operative specimens or from autopsy reports. It is suggested that vegetable matter entering the lumen of the appendix forms the nucleus around which glandular secretions in the lumen desiccate to form the calculi (Lowenberg, 1949). In the other two-thirds of instances where fecaliths are absent, the obstruction is thought to be caused by hypertrophy of mural lymphoid follicles in response to a host of causes that are discussed elsewhere in this book.

This chapter aims to understand the environmental, demographic, cultural and genetic factors that make the appendix susceptible to obstruction and inflammation. To understand the epidemiology of appendicitis is to look at the possibility of moving beyond treating it operatively to entertaining non-operative treatments and to foresee a future when some cases of appendicitis can be prevented.

2. What is a normal appendix ?

The histological features of pathological inflammation in most tissues are well defined. The inflammatory cell types encountered and the tissue architecture enable a precise diagnosis of

acute or chronic inflammation. For organs at the frontline of the fight against invasion by pathogens, however, a distinction has to be made between what is pathological and what is physiological. All would agree that transmural inflammation with edema, congestion and infiltration of polymorphs, intramural abscesses, mucosal ulceration, fibrinopurulent peritonitis and vascular thrombosis are pathological. When present these findings establish the diagnosis of appendicitis beyond doubt. However, when inflammation is confined to the mucosa, a finding that is reported in up to 35% of specimens (Day, et al., 2003), the question has to be asked whether this is early appendicitis or something entirely different. Likewise, reports of 'appendicitis' in specimens taken from well patients undergoing incidental appendectomies suggests that some histological 'appendicitis' might represent a normal physiological inflammatory response. The term 'sub-acute appendicitis' is used by some pathologists to circumvent this dilemma. Describing the appendix as either 'normal' or 'inflamed' may not sufficiently reflect the heterogeneity of the physio-pathological features of the appendix.

Wide differences in negative appendectomy rates are reported in the literature. Low rates are variously attributed to good clinical skills (repeated clinical examination by an experienced surgeon) (Lander 2007) or attributed to the higher specificity of diagnostic tests (Seetahal, et al., 2011). This section argues that some of this difference may be due to variation in the histological reporting of mild inflammation. For example, negative appendectomy rates vary from Spain (4.3%) to Nigeria (52.3%) and it has been hypothesised that these differences are unlikely to be due to difference in training, clinical skills or the availability of diagnostic technological accessories (Andreu-Ballester, et al., 2009; Uba, et al., 2006). This argument is supported by the observation that the diagnostic accuracy of appendicitis has largely been unaffected by technological innovations (Hale, et al., 1997; Gnanalingham, et al., 1997). Even in recent literature the negative appendectomy rate varies from as low as 3% (6/190) (Cleeve et al 2011) through 4% (Whisker, et al., 2009) to as high as 44 % (76/172) (Gopal and Jaffrey 2011). A large part of this variation in diagnostic rate may come from differences in clinical practice but some may come from variations in histological reporting. In departments where pathologists report superficial inflammation as "early appendicitis" there will be a lower negative appendectomy rates while others who regard it as a normal variant will report higher values.

In a 1961-study of 1000 consecutive appendectomy specimens in Ottawa, Canada, this problem was encountered and the authors concluded that appendicitis is an imprecise diagnosis (Campbell JS et al., 1961). The authors observed that 6.2% of specimens of primary appendectomies and 6.6% of specimens from incidental appendectomies showed evidence of superficial inflammation. In the same series during the year 1960, the authors encountered 40% (27/65) cases of superficial appendicitis from a total of 141 specimens after exclusion of 76 cases with diffuse inflammation of the appendix from primary appendectomy meeting the criteria for appendicitis. The same lesion was found in 35% (24/68) cases of incidental appendectomy. The findings in both periods of study suggested an almost equal incidence of superficial inflammation of the appendix in specimens from primary appendectomy as from incidental appendectomy. The authors wondered, "When is a superficial appendicitis responsible for symptoms and when is it not?" They were reproached by their clinical colleagues for "adding to the iatrogenic diseases produced in the laboratory". This same observation would be made in subsequent publications on incidental appendectomy by other workers.

In a study involving 90 pregnant women who were randomly assigned to undergo caesarean section alone or with prophylactic appendectomy three cases of "appendicitis"

were encountered that were not accompanied by symptoms, clinical signs or positive laboratory tests (Pearce, et al., 2008). In a more remarkable study comprising of 772 women in the state of Illinois undergoing laparoscopic examination for primary infertility who also underwent incidental appendectomy, 585 (75%) had histologic evidence of superficial appendicitis even though none of them presented with features that would suggest appendicitis preoperatively (Song, et al., 2009).

There are suggestions that this superficial inflammation of the appendix may be an extension of colitis caused by bacteria such as salmonella and campylobacter into the lumen of the appendix (Campbell LK et al., 2006; Chan, et al., 1983; Lau, et al., 2005).

Without agreement on the categorization of superficial appendicitis the basis for comparative epidemiological studies of appendicitis is shaky. The reported findings of inflamed appendices in specimens taken during incidental appendectomies will continue to be a nagging problem.

3. Etiologic hypotheses on appendicitis

Numerous hypotheses have been proposed to explain the etiology of appendicitis. Three of these have a measure of credibility and deserve discussion.

3.1 Mechanical hypothesis

The association between low-fibre diet and appendicitis was first proposed by Rendle Short in 1920 which was spurred by the observation of an upsurge of appendicitis in Britain at the beginning of the twentieth century (Short, 1920). He hypothesized a causal relationship with low cellulose content of imported food. About half a century later another British surgeon working in East and Southern Africa in the early 1970's, Denis Burkitt, built on this hypothesis by observing a low prevalence of diseases like appendicitis, diverticular disease, colon cancer and varicose veins among native Africans in comparison to the population he was used to back in Europe. He attributed this to the high fibre-content of the diet of Africans making for low transit time for gastrointestinal contents and softer consistency of stool which assuaged the need for straining at defecation (Burkitt, 1977a; 1977b; Burkitt, et al., 1979).

The mechanical hypothesis implicates two factors in the etiology of appendicitis: fecaliths and high intra-colonic pressure. In the first instance, Burkitt and his team demonstrated a significant difference in the incidence of fecaliths in appendicitis and in non-pathological specimens of the vermiform appendix in a comparative study of patients in Toronto and Johannesburg (Jones, et al., 1985). This study has been cited almost exclusively by many authors to defend the unproved claim that fecaliths in the appendix have a particular geographic distribution. On closer scrutiny, however, the publication is beset by a number of inadequacies that include; the small sample size, insensitive measurement (intraoperative palpation of the appendix to determine the presence of fecaliths) and inter-observer bias (one surgeon in Toronto and another in Johannesburg worked independently). Moreover, neither Toronto nor Johannesburg are representative of a North American and an African population, respectively.

The percentage of minorities (non-Aboriginal and non-Caucasian Canadians) in Toronto has been steadily rising and was estimated at 46.9% of the City's 2.5 million people in 2006 (Wikipedia Foundation Inc., 2011). In addition it is questioned whether the epidemiology of appendicitis and appendicular fecaliths in Aboriginal Canadians based on dietary habits resembled Caucasian Canadians at all. Similarly, Johannesburg during the period of study had a population that was not representative of the native African continent. The US Bureau of

Census estimated that as at 1992, 48% of all black South Africans lived in the ten nominally independent homelands under the segregation of the Apartheid system which limited their access to healthcare within urban Johannesburg (Byrnes, 1996). Thus, the conclusion drawn from this study is not from a representative sample reflecting racial or geographical characteristics. Another point of note is that, descriptively, the study showed a discordant mean age of the samples of the two populations. The African population were younger than their Canadian counterparts (with mean ages of 31 years versus 55 years, respectively) which may have skewed the observation to show a higher proportion of incidental fecaliths in Canadians since the prevalence of fecaliths in normal appendix specimens increases with age (*vide infra*). High intra-colonic pressure as the main cause of diverticulosis has an inverse relationship with diets high in fibre, typical for native Africans. Acquired diverticulosis is an age-dependent disease that is most noticeable after the third decade of life unlike appendicitis. While this explains the rarity of diverticulosis in rural Africans the role of high intra-colonic pressure in the pathogenesis cannot be deduced because of the differences in the peak age of incidence. A recent retrospective study claimed to have found an epidemiological similarity between appendicitis and diverticulitis in terms of low-fibre diets and better hygiene suggesting a common causal factor (Livingston, et al., 2011). The authors acknowledge that the peak incidence of the two diseases differ considerably. Fecaliths occupy the lumens of diverticuli as well as about a third of appendicitis specimens and that is where their etiologic similarities end. Even if a powerful cohort study or a case-control study finds a strong association, a causal relationship will be hard to sell simply because the diseases occupy opposite ends of the age spectrum. Why would the same causal factor produce appendicitis in the young and not in old and vice versa with diverticulosis?

3.2 Infection hypothesis

Specific infections with viruses, bacteria and parasites have been linked to appendicitis prompting the suggestion that local invasion could trigger appendicitis. Dengue, Influenza, Epstein-Barr, Rota and Cytomegaloviruses has been linked to appendicitis (Alder, et al., 2010; Boon-Siang, et al., 2006; Livingston, et al., 2007; Thalayasingam, 1985). Similarly, bacteria such as *Campylobacter*, *Brucella* and *Salmonella* (Campbell LK et al., 2006; Chan, et al., 1983; Lau, et al., 2005; Pourbagher, et al., 2006) as well as parasites like *Entameba histolytica*, *Schistosoma mansoni/japonicum*, and *Enterobius vermicularis* (Andrade, et al., 2007; Elazary, et al. 2005; Gali, et al., 2008; Gotohda, et al., 2000; Isik, et al., 2007; McCarthy, et al., 2002; Sah & Bhadani, 2006; Terada, 2009) have been isolated in specimens or indirectly implicated in the pathogenesis of appendicitis. These pathogens are thought to cause appendicitis by invading the lamina propria and inciting edema to cause obstruction of the narrow lumen of the appendix to result in appendicitis.

If infectious agents have a causal relationship with appendicitis, then infections by airborne viruses with known seasonal variations might show a temporal pattern coincident with that of appendicitis. This issue was studied in two recent publications that showed a decreasing incidence of non-perforated appendicitis (but not perforated appendicitis) in the 10-19 years age-group from 1970 to 1995 coincident with a decreasing incidence of influenza infections in the United States (Livingston, et al., 2007; Alder, et al., 2010). These studies also observed a falling rate of negative appendectomy after 1995 which they attributed to CT scanning and laparoscopy. Consequently the authors made a distinction between perforated and non-perforated appendicitis by suggesting that they may be etiologically distinct implying that viruses like influenza may be causally related to the latter but not the former (Livingston, et

al. 2007, 2011). A critique of one of these papers (Alder, et al., 2010) observed that hospital discharge records fail to take note of the fact that patients with appendicitis will require admission but most people with influenza will not and that while appendicitis is predominantly a disease of the young, influenza is a disease of the old (Britt, 2010). Similarly, enteric viruses (rotavirus) and outbreaks of entero-invasive bacteria like some strains of *Escherichia* and *Shigella* should show similarity to outbreaks of appendicitis.

Lymphotropic viruses like Epstein-Barr and Cytomegaloviruses should show an epidemiological pattern that mimics the seasonal variation of appendicitis. Evidence for an association with these pathogens is scant. It is suggested that because of the latency period from infection with these viruses to induction of appendicitis the link between the two is missed because we do not routinely perform studies to determine recent infections with these viruses (Thalayasingam, 1985; Dzabic, et al., 2008).

The infection hypothesis may explain why some patients with a good history and signs of appendicitis recover spontaneously without operation and may be the explanation for the finding of fibrosis in the submucosa of the appendix showing that previous inflammation had occurred. To this end, florid mesenteric lymphadenitis with an unimpressive appearance of the appendix on the one hand and gangrene or perforation of the appendix on the other may represent extremes of the pathological spectrum of appendicitis. The difference between what is appendicitis and what is not maybe dependent in part on the temporal stage of the illness and the pathological diagnostic criteria used.

The relationship between childhood appendicitis/appendectomy and subsequent low incidence of ulcerative colitis is intriguing and is the subject of a recent large population-based study in Sweden and Denmark (Frisch, et al., 2009). The study confirmed the reported observation that people who underwent appendectomy in childhood had a lower incidence of ulcerative colitis as adults than those who did not. The authors concluded that appendicitis and mesenteric lymphadenitis in childhood, and not appendectomy, accounts for the lower incidence of ulcerative colitis in later adulthood.

The infection hypothesis outlined above is closely related to the hygiene hypothesis below.

3.3 Hygiene hypothesis

At the beginning of the 1980s another British physician with past clinical experience in East Africa, David Barker, sought to elucidate the link between diet and certain diseases. He published a cross-sectional study with team members at the Medical Research Council's Environmental Epidemiology Unit of the University of Southampton on the incidence of appendicitis in England and Wales. They found that despite similar dietary habits the distribution of appendicitis did not follow other diseases associated with low-fibre consumption (Barker & Liggins, 1981). In a subsequent case-control study they concluded that infection and familial predisposition, rather than the fibre-content of the diet, may enhance susceptibility to appendicitis (Nelson, et al., 1984, 1986). Barker followed this by proposing an alternative hypothesis commonly referred to as the hygiene hypothesis in which he looked at historical data that showed a steep increase in appendicitis in Britain from 1895 through 1930 before declining. He declared that "*...dietary changes do not explain the time trends in appendicitis and that the epidemiology of the disease is more readily explained by a primary infectious aetiology*" (Barker, 1985). In subsequent publications, Barker and his team suggested that the observed increase in the incidence of appendicitis at the end of the 19th century was a consequence of the adoption of a housing policy in Britain and Ireland which enforced the provision of safe-drinking water and sanitary measures like sewage and waste disposal (Barker, et al. 1982, 1988a; Morris, et al.,

1987). In another paper they proclaimed *“We conclude that our findings support the hypothesis that appendicitis is primarily caused by Western housing rather than by Western diet. This would explain the international distribution of the disease which is one of industrialized communities. It explains the rarity of the disease in blacks in South Africa despite their adoption of aspects of Western lifestyle, including low consumption of fiber. It predicts that communities in which children still grow up in conditions of Third World hygiene will experience outbreaks of appendicitis when housing improves”* (Barker, et al. 1988b). With this, Barker and his team offered an attractive hypothesis by hinting that the immune system may be induced by prevailing circumstances to reach a compromise with gut pathogens and commensals through adaptation.

If appendicitis is simply a disease that results from the obstruction its lumen, akin to obstruction of the common bile duct or the ureters by calculi, we should expect that the mere presence of a calculus in its lumen is sufficient to trigger appendicitis. However it does not always cause it. The appendix, with a lumen estimated at 1-2 mm in diameter when compared to the supra-duodenal portion of the common bile duct (6mm) and the middle third of the ureters (3-4mm), is small. Unlike the calcular diseases of the common bile duct and the ureter, appendicitis shows a population distribution not easily explained by the prevalence of luminal calculi alone. While the lumens of the ureters and the CBD tend to dilate proximally in response to obstruction by stones the only time they narrow is during peristaltic movements to aid the downward movement of their contents. The lumen of the appendix, on the other hand, will become narrow when the lymphoid follicles become hypertrophic in response to remote or local infection.

Autopsy studies show that the prevalence of asymptomatic fecoliths in the elderly exceeds what should be expected in surgically resected specimens in younger populations on the basis of the prevalence of appendicitis in the general population (Andreou, et al., 1990). Unlike the appendix where calculi can remain silent, silent calcular diseases of the ureters and the common bile duct are a rarity. This would suggest that the presence of calculi does not trigger appendicitis per se. A recent follow up study of the finding of incidental appendicoliths on pelvic CT scans in patients younger than 18 years at the Children’s Medical Center of the University of Utah, found that of 75 patients who met the inclusion criteria, only 16 patients (21%) subsequently developed clinical symptoms and signs suggestive of appendicitis and of these only 6 patients (8%) had histological evidence of appendicitis (Rollins, et al., 2010).

This perspective may offer an explanation as to why the incidence of appendicitis is low not only in Africa but also in other developing countries in Latin America, the Middle East and Southeast Asia. The prediction of an increase in the incidence of appendicitis in emerging economies with rapid industrialization, urbanization and higher standards of living maybe the explanation for the recent observation of a high incidence of appendicitis in South Korea with 227 cases per 100,000 people (Lee JH, et al. 2010). This figure is more than 12 times the rate in Ghana (Ohene-Yeboah & Abantanga, 2009). Saudi Arabia, another country that is attaining rapid improvement in health indices, maybe showing this trend as a post-hoc analysis of the data in our study shows that in the city of Hail with a population of around 356,000 an estimated average of 526 cases of appendicitis were recorded annually from 2000 to 2006 giving an incidence rate of 147/100,000 people; a figure that is similar to figures obtainable from European countries and higher than figures from sub-Saharan Africa by as much as a factor of 10 (Sanda, et al., 2008). This observation fits in with the hypothesis offering an explanation for the propensity of appendicitis in the age group with the most developed immune system and, conversely, explains its rarity at the extremes of age.

4. Comparative incidence and temporal trends of appendicitis

The epidemiology of appendicitis is best studied by comparing national incident rates from different regions of the world with low and high incidences of appendicitis. Fidelity of medical databases and accurate population counts at multiple points in time are necessary to calculate incidence rates and trend. Ideally this should be based on age-specific annual rates but since the peak incidence of appendicitis appears to vary slightly from one region of the world to another, a crude rate using all cases is an acceptable alternative. Because of the variable negative appendectomy rates it is ideal to compare rates of histologically confirmed cases. These data are unfortunately not frequently reported in various publications. A search of the literature from around the world using the standardized annual incidence rates shows a wide range of estimates of the incidence of appendicitis.

Importantly, most publications reporting incidence rates do not differentiate between calcular appendicitis and the non-calicular variety. Table 1 shows a comparison of annual incidence rates from around the world in the last 25 years. What can possibly account for the huge difference in the annual incidence rates of appendicitis between European and African countries as represented by Ireland (174/100,000) and Ghana (18/100,000) ? (Morris, et al., 1987; Ohene-Yeboah & Abantanga, 2009). Why is the incidence rate higher for white South African children (215-395 per 100,000) in comparison to black children (5-19 per 100,000) in the same country (Walker, et al. 1989)? Why does appendicitis run in families? (Basta, et al., 1990; Brender, et al., 1985) Why is the rate lower in girls compared to age-matched boys? (Hale, et al., 1997; Humes & Simpson, 2006)

5. Innate immunity insights

5.1 Toll-like receptors

For over a century after the discovery of phagocytes and endotoxin by Ilya Mechnikov and Richard Pfeifer, respectively, research in immunology focused on adaptive immunity to the neglect of innate immunity. Perceived as an archaic, passive, non-discriminatory pathway, the importance of innate immunity was under-appreciated until recently. The insight derived contributed to our understanding of the hygiene hypothesis as proposed by Barker and his team.

Charles Janeway led the way in this renewed interest in innate immunity just over two decades ago (Janeway Jr., 1989). He postulated that the cells of the first line of defence such as those of the gastrointestinal tract possessed molecules he termed "pattern recognition receptors" (PRRs) and the ligands on the surfaces of those pathogens that they are capable of reading as "pathogen-associated molecular patterns" (PAMPs). Inspired by earlier work on the *Drosophila* Toll antigen in regards to the dorsal-ventral polarity in the embryo of that species (Anderson, et al, 1985), Janeway's team identified the product of the human homologue of this gene calling it "the Toll-like receptor" (TLR) and characterized it as a trans-membrane protein that replicates the functions of the PRRs in adaptive immunity (Medzhitov, et al., 1997). Through these molecules the innate and the adaptive arms of the immune system are able to share information and collaborate in defence. They ensure that when pathogens breach the first line of defence they are eliminated or contained to minimize further invasion and harm. This collaboration ensures that the inflammatory response mounted against invading pathogens is appropriate and proportionate so as to minimize collateral damage from immunological over reaction.

It is possible that inflammatory bowel disease (ulcerative colitis and Crohn’s disease) is a consequence of an inappropriate and excessive immune response to pathogens that are mildly harmful or harmless to the host.

Country	Incidence per 100,000	Year or Period	Data Scope	Author(s)	Observation/Remarks
Italy	570	1955	National	Basoli, et al., 1993	Decline in incidence from two-point incidence rates.
	370	1987			
Finland	340	1987-2007	National	Ilves, et al., 2011	32% decline over 21 years.
Ethiopia	307 (M)	1971-1988	Provincial	Horntrich & Schneider, 1990	46% decline between 1971 and 1988.
	327 (F)				
South Korea	227	2005-2007	National	Lee JH, et al., 2010	No change in rate
United States	97	1979-1981	Provincial (South Carolina)	Sugimoto & Edwards, 1987.	Noted a high incidental appendectomy with 75 NNT at a cost of \$20 million.
	233	1979-1984	National	Addiss, et al., 1990.	14.6% decline in rate.
Australia	180	1986-1990	Provincial (NSW)	Close, et al., 1995.	Decline from 1986 to 1990.
Germany	130		West Germany	Haussler, et al., 1989.	
	165		National	Sahm, et al., 2011	
Greece	652 (70)	1970-1999	National	Papadopoulos, et al., 2008	75% decline in incidence rate over 30 years.
	164 (99)				
Turkey	149.8	2004-2007	National	Sulu, et al., 2010.	Decline attributed to better quality of data.
Norway	140	1977-1978	National	Soreide, 1984	
	84	1989-1993	Provincial (Rogaland)	Korner, et al., 1997.	Covered period of introduction of laparoscopic appendectomy
	117	1990-2001	National	Bakken, et al., 2003.	
Spain	79.6	2000	Provincial	Osta et al., 1991	Difference not significant.
	117.5			Andreu-Ballester, et al., 2009.	
Sweden	132.1	2003	Meta-analysis	Andersson, et al., 1994.	Data from meta-analysis of six studies.
Canada	116	1984-1989		Al-Omran, et al., 2003	
	75	1991-1998	Provincial (Ontario)	To & Langer, 2010.	Noted decreasing incidence rate with increasing perforation rate.
Poland	93.2	1993-2000	Provincial (Ontario)	Freud, et al., 1988.	Data calculated exclusively for appendicitis in children younger than 19 years.
Israel	61.6	1989-1998	Provincial (Cracow)	Anielski, et al., 2001.	Authors noted a decreasing incidence rate.
	37.5	1973-1983	Provincial (Negev)	Freud, et al., 1988.	Higher incidence in Jewish versus Israeli Arabs. Noted seasonal variation related to humidity as well as viral/bacterial infections.
Papua New Guinea	39		Provincial (North Solomons)	Foster & Webb, 1989.	The figures were derived from rural population.
Thailand	32 & 37		Meta-analysis	Chatbanchai, et al., 1989	
South Africa	5-19 (Black) 215-395 (White)	1985-1987	Provincial (Free State, North West)	Walker, et al., 1989a	Authors also noted a decline in dietary fibre in blacks without a rising incidence.
Central African Republic	36.5	1991	Provincial (Bangui)	Zoquereh, et al., 2001	Rising incidence was claimed
Ghana	18	2000-2005	Provincial (Ashanti)	Ohene-Yeboah & Abantanga, 2009	
Madagascar	77		Hospital	Langenscheidt, et al., 1999.	Negative appendectomy rate of 85%by histological assessment.

NNT = Number Needed to Treat; NSW = New South Wales.

Table 1. Comparison of annual incidence rates of appendicitis from around the world.

Ten subtypes of TLRs have been identified in man with TLRs1, 2, 4, 5, and 6 known to be present on the cell membrane surface and recognize microbial components such as lipids, lipoproteins and proteins. They function to identify bacterial lipopolysaccharide (LPS) in Gram-negative bacteria, peptidoglycans, lipoprotein and lipoteichoic acid in Gram-positive bacteria. TLRs 4, 5 and 6 identify HSP60, flagellin and diacyllipopeptides in chlamydia, bacteria and mycoplasma, respectively. In addition TLR4 recognizes respiratory syncytial virus fusion proteins. On the other hand, TLRs 3, 7, 8, and 9 appear to be confined to the intracellular compartment where they recognize microbial nucleic acid. TLRs 3, 7 and 8, identify single-stranded RNA viruses. The function of TLR10 is still unclear (Yoon, 2010).

5.2 Nucleotide-binding oligomerization domain-containing proteins

Another group of molecules thought to work intimately with the TLRs are the intracellular Nucleotide-binding Oligomerization Domain-containing proteins 1/2 (NOD1/NOD2). NOD1 mediates innate immunity by recognizing bacterial molecules containing the D-glutamyl-meso-diaminopimelic acid (iE-DAP) moiety while NOD2 recognizing muramyl dipeptide (MDP) found on the surfaces of certain bacteria. Signals transduced by these two groups of molecules trigger a response from the cells of the innate immune system such as macrophages, monocytes and dendritic cells (DCs). This response produces cytokines which initiate inflammation, phagocytosis of bacteria and subsequent presentation of the antigens to CD4+T cells or, in the case of viruses, switching off the mechanism of induction of protein synthesis or apoptosis of the infected cell (Damgaard & Gyrd-Hansen, 2011; Le Bourhis, et al., 2007; Kawai & Akira, 2009).

5.3 Role of dendritic cells and other immune effectors in the induction of tolerance

TLR signals and the immune effector responses to them contribute to the well-being of the gut ecosystem and the integrity of the intestinal epithelial barrier which confers tolerance to commensals. NOD2 signalling contributes to this by exerting antimicrobial activity and prevents pathogenic invasion (Cario, 2005). The pathogenesis of both Crohn's disease and Blau syndrome have been linked to mutations in the genes coding for NOD2 and the resulting imbalance of these groups of molecules produces the chronic mucosal inflammation that characterize these two diseases. (Blau syndrome is a rare autosomal dominant granulomatous polyarthritis with panuveitis, cranial neuropathies, and exanthema with Crohn's disease seen in 30%.) TLRs are thought to be constitutively expressed and inducible throughout the gastrointestinal tract by absorptive enterocytes, Paneth cells, goblet cells, neuroendocrine cells, myofibroblasts, as well as in immune cells such as monocytes, macrophages, DCs, and CD4+ T cells in response to the load of commensal and pathogenic cell wall antigens (Cario, 2010). It has been observed that the pattern of TLR expression by some of these cells is variable in different anatomic sites. While DCs may develop from a number of distinct precursors, most of them go through distinct maturation stages that are shaped by the local conditions of the tissues in which they reside or migrate through. The two subsets of DCs are plasmacytoid (pDCs) and conventional myeloid DCs (cDCs). The key features of pDCs are their expression of TLR7 which binds ssRNA in endosomes and TLR9 which binds unmethylated Cytosine-phosphate-Guanine (CpG) regions of the DNA as well as their production of interferon-1 (INF-1). Both pDCs and cDCs localize to intestine immune inductive and effector sites. The microbiota in combination with CD8+ T cells cooperate to regulate systemic numbers of pDCs (Garrett et al., 2010) When differentiating into immature dendritic cells, monocytes progressively lose

the expression of some TLRs, but gain the expression of others (Visintin, et al., 2001). Bone-marrow derived CD11c⁺ DCs express TLR4 to pathogens but, in contrast, CD11c⁺ DCs in the lamina propria do not express TLR4 to LPS. Thus, the gut responds to the presence of different commensal and pathogenic ligands by modulating its immune response against real threats and ignoring low level ones by mounting mild attack responses. Host innate and adaptive immunity thus cooperate to limit bacterial overgrowth and to prevent mucosal penetration by pathogens. They do this by the elaboration of α -defensins from Paneth cells and the induction of IgA secretion coordinated by regulatory T lymphocytes. In this way both arms of the immune system collaborate to maintain the luminal ecosystem for the mutual benefit of the host and the commensals (Cerovic, et al., 2009; Uematsu, et al., 2006; Yanagawa, et al., 2007)

5.4 Response to endemicity of gut commensals and pathogens

It can be hypothesised that in communities with poor levels of hygiene through poor waste disposal and perpetual exposure to gut pathogens from contaminated water that the maturing immune system of growing children and young adults has the capability to adapt and avoid further damage to the gut by limiting the severity of the immune response. This is the postulated role of T-reg cells in adaptive immunity. In genetically susceptible individuals it is thought that this process is compromised and may be the underlying mechanism by which pathogens cause IBD (Matricon et al, 2010; Fava & Danese, 2011). The immune response to the ubiquitous enteric pathogens such as viruses (rota, hepatitis and polio), bacteria (Salmonella, Shigella, and Escherichia) and protozoans (Entamoeba and Giardia) have to be kept in check to limit the inflammatory reaction to the minimum necessary to prevent invasion. The immune response of long-term residents in these parts of the world may be controlled to attain balance between letting these organisms invade the individual and the individual succumbing to excess immune response. It is increasingly recognized that during early childhood and early adulthood gut bacteria shape the tissues, cells and the molecular profile of the gastrointestinal immune system. This partnership was forged over thousands of years of coevolution based on molecular exchange involving bacterial signals that are recognised by host receptors to mediate beneficial outcomes to both commensals and humans and are tolerated (Lee YK & Mazmanian, 2010; Round & Mazmanian, 2010; Round et al., 2011).

This is the premise by which it is being suggested that the gut of people living in areas with low standards of hygiene eventually attain a level of tolerance to gut commensals that results in a controlled reaction to the presence of pathogens and commensals. In the case of the appendix this means that its lumen is not at the risk of occlusion by lymphoid hyperplasia in response to common local or remote infections in people living under conditions of low hygiene and may explain the low incidence of appendicitis in the Third World.

5.5 Gene polymorphism and severity of appendicitis

It is tantalizing to attempt to detect differences in the susceptibility of individuals to infections by studying the differences in the levels of gene products that are elaborated in response to localized inflammation like appendicitis. In a study involving 56 patients with pathologically-confirmed appendicitis of whom 85% of the patients met the criteria for systemic inflammatory response syndrome, the authors compared the levels of soluble pro- and anti-inflammatory cytokines in the serum and peritoneal fluids of the patients. The pattern of the soluble cytokines and the effect of the plasma on monocyte activation by LPS

led the authors to conclude that a difference exists in the elaboration of these cytokines between mild localized infections in comparison to the severe form of the disease (Rivera-Chavez, et al., 2003). In a subsequent publication, the authors studied the relationship of the severity of local inflammation in appendicitis with the occurrence of single nucleotide polymorphism that account for microbial recognition and local inflammation in the innate response. They demonstrated polymorphism in the IL-6 gene was associated with the severity of acute appendicitis even after adjustment for duration of symptoms (Rivera-Chavez, et al., 2004). The suggestion that the human response to a local infection, such as appendicitis, is influenced by inherited differences in innate immunity genes such as IL-6 supports the hypothesis that children growing up in environments that predispose them to rampant and sustained exposure to gastrointestinal pathogens as is common in developing countries, may have their innate immune effectors subject to regulation to modify their responses to gut pathogens to a point that makes for less likelihood of their lymphoid follicles to hypertrophy and occlude the lumen of the organ and cause appendicitis. This would both explain the rarity of appendicitis in developing countries and the higher incidence rates in developed nations with higher standards of public health.

6. Distribution and variation of appendicitis in populations

6.1 Age distribution

Appendicitis is overwhelmingly a disease of childhood and early adulthood. This is a consistent finding in almost all publications on the subject regardless of the population studied (Hale, et al., 1997; Lee JH, et al., 2010; Smink, et al., 2005; Uba, et al., 2006). As discussed earlier, the lymphoid follicles are most developed in this age group. The presence of local infections probably stimulates the lymphoid follicles to hypertrophy and occlude the lumen of the appendix more commonly in this age group. The efficiency of the immune system in this age group is also a plausible explanation for the tendency for remote agents like air-pollution and sandstorms to be associated with significant variations in the incidence of appendicitis (Kaplan, et al., 2009; Sanda, et al., 2008). On the other hand the immaturity of the immune system before the age of five years and immunosenescence as well as the atrophy of the wall and obliteration of the lumen of the appendix as seen intra-operatively or at autopsy in aged individuals may explain why appendicitis is less common in these age groups.

6.2 Sex distribution

The consistent observation of a slight preponderance of appendicitis in boys is not explained by a difference in fecalith formation. Since the peak incidence of appendicitis coincides with sexual maturity with the sex hormones being most active, it maybe that they play a role in the pathogenesis of appendicitis. Whether this has any relationship to the high incidence of autoimmune diseases like systemic lupus erythematosus, Grave's disease, multiple sclerosis and myasthenia gravis being predominant in women in this age group is not clear. Since the 17-ketosteroids estrogen and progesterone have been implicated in the modulation of the immunosuppressive state of pregnancy, it maybe that different levels of estrogens and androgens between boys and girls may be responsible for this observed difference in incidence (Ben-Hur, et al., 1995; Jara, et al., 2006; Zen, et al., 2010). Furthermore, antigen-presenting cells which play key roles in innate and adaptive immunity as well as tolerance have been found to express estrogen receptors on their surface implying that their functions

may be modulated by sex hormones and would explain the purported immunological dimorphism between genders (Bouman, et al., 2005; Kovats & Carreras, 2008). One study suggests that the better prognosis in females following infectious challenge may be due to gender-specific differences in LPS-induced TNF- α and IL-1 β but not IL-6 and suggests that the underlying mechanism may be due to alterations in mitogen-activated protein kinase phosphorylation (Imahara, et al., 2005).

6.3 Familial appendicitis

Appendicitis runs in some families (Andersson et al., 1979; Basta et al., 1990; Ergul, 2007). A very neat prospective study noted a significant familial relationship when comparing three groups of children aged 2-19 years admitted to a single large center whose family histories were taken at admission over a 52-month period (Gauderer, et al., 2001). Group A (n=166) comprised of children who underwent appendectomy, group B (n=117) comprised of children who presented with an acute abdomen and with a tentative diagnosis of appendicitis but did not undergo appendectomy due to resolution of symptoms, and group C (n=141) was made of children who were seen in the same hospital over the same period for unrelated complaints. A positive parental history was obtained from 59 patients (36%) in group A, 24 patients (21%) in group B, and 20 patients (14%) in group C. The odds ratios (OR) were 2.0 ($p=0.035$), and 2.9 ($p<0.001$) for groups A versus B and A versus C, respectively. Of the 13 patients whose sibling had had acute appendicitis, 9 were in group A while 2 each were in groups B and C. The OR for any family history (siblings, parents) in groups A versus B was 1.9 ($p=0.028$) and for groups A versus C was 2.9 ($p<0.001$). The authors concluded that children with appendicitis are three times more likely to have a positive family history of appendicitis in first degree relatives than controls. Similar observations had been made in smaller studies earlier (Andersson, et al., 1979; Brender, et al., 1985; Basta, et al., 1990). These familial associations, however, do not prove a genetic component since members of families often share similar environments.

6.4 Twin studies

Twin studies have attributed both genetic and environmental factors in the predisposition to appendicitis. The evidence suggests that environmental and genetic factors may account for about 70% and 30% of the predisposition to appendicitis, respectively. The ratio attributable to genetic factors appears to be consistent (Basta, et al., 1990; Duffy, et al., 1990; Oldmeadow, et al., 2009; Sadr-Azodi, et al., 2009). An interesting observation linked the incidence of appendicitis to cigarette smoking in 3808 pairs of Australian twins after controlling for sex, age and year of birth. This was not affected by socioeconomic status or the father's occupation and the effect was stronger in females (Oldmeadow, et al., 2008).

6.5 Racial variation

Racial variation in the incidence of appendicitis is difficult to investigate. Poverty and low levels of public hygiene are difficult to separate for many peoples of African, Hispanic or Asian ancestry. One study from the USA comparing the incidence of appendicitis in various ethnic groups concluded that the rate was lower in Negroes and Asians in comparison to Caucasians and Hispanics (Luckmann & Davis, 1991). A case-control study from Brazil comparing the people of that country on the basis of skin colour claimed that race was a factor in the incidence of appendicitis. After excluding native Indians the study found a

significantly lower incidence of appendicitis in Negroes in comparison to Caucasians (Petroianu, et al., 2004). This finding has to be interpreted in the context of social differences and genetic variables between black and white Brazilians. Figures showing comparative economic indices of Brazilians among its races are hard to find. A study on phenotypes as an indicator of genotypes in the same country concluded: "Our data suggest that in Brazil, at an individual level, color, as determined by physical evaluation, is a poor predictor of genomic African ancestry, estimated by molecular markers" (Parra, et al., 2003). From the Republic of South Africa, another multiracial society, some publications suggest that appendicitis has racial associations. The incidence of appendicitis in Black children was estimated at 8.2 per 100,000 which is 10-20 times less than the incidence in their White compatriots (Walker, et al. 1989a, 1989b, Walker & Segal, 1995). It should be remembered that the Apartheid political system in the country at the time left the native Africans economically and social disenfranchised with a standard of living that was not comparable to their White counterparts. What these studies share is the inability to separate race from poverty.

6.6 Geographic distribution

The different incidences found across geographic regions are possibly explained by economic and public health factors rather than by environmental factors. As table 1 shows the incidence of appendicitis increases with the level of sophistication of the health system across nations (Barker, et al., 1988a & 1988b). That appendicitis is less common in sub-Saharan Africa and Asia may have more to do with shared poverty and underdevelopment and less to do with geography.

6.7 Seasonal variation

Seasonal variations in appendicitis are reported in several studies across many regions. Most studies report a summer peak with a winter nadir; USA (Luckmann & Davis, 1991), Canada (Al-Omran, et al., 2003), Italy (Gallerani, et al., 2006), Israel (Freud, et al., 1988) and Russia (Khaavel & Birkenfeldt, 1978). Our own study in northern Saudi Arabia showed a winter low but a spring peak which coincides with the sandstorm season characterized by rise in infections and allergic conditions of the upper respiratory tract which concur with earlier studies on the spread of allergens during this season in Saudi Arabia (Kwaasi, et al., 1992a, 1992b, 1993, 1998; Sanda, et al., 2008). A similar seasonal variation to ours was reported four decades earlier in Britain (Ashley, 1967). Our observation of an association between appendicitis and air pollution was corroborated by a study from Western Canada (Kaplan, et al., 2009). The significance of these observations is underscored by pathological studies linking appendicitis to eosinophilic degranulation (Santosh & Aravindan, 2008; Aravindan, et al., 2010). Seasonal variation of appendicitis with its peak associated with a season characterized by high ambient pollen and other phyto-allergens or sandstorm is an observation that can neither be explained by diet nor fecaliths but may have a bearing on immune modulation playing a role.

7. Conclusion

The epidemiology of appendicitis is important but ill understood. We can study the incidence of appendicectomies but this is not to say we are studying appendicitis. To measure the incidence of appendicitis a definition of the disease is required and a

confidence that all cases are ascertained. These criteria are not well met. Finding mucosal inflammation in the appendix in a significant portion of incidental appendectomies challenges the definition of a “normal appendix”. Furthermore variation in histopathological reporting may account for some of the variation in negative appendectomy rates. Finding fibrous adhesions around the appendix in unrelated operations and at autopsy proves that appendicitis does not always run an inevitable course to perforation and surgery.

It is difficult to deduce the causes of appendicitis from the associations but we can make hypotheses. Fecaliths accompany appendicitis in only a third of cases suggesting that they are only one risk factor. It is also important to note that not all obstructed appendices develop appendicitis that ends in an appendectomy.

A temporal relationship between some viral infections and non-perforated appendicitis gives credence to the belief that some infections can cause a luminal appendiceal obstruction leading to appendicitis. However, an inverse relationship between the incidence of appendicitis and the prevalence of some enteric infections exists and may be explained by an adaptive immunological response. A mechanism for this may involve the TLRs and T-reg Lymphocytes. A better understanding of these two phenomena may lead to novel non-operative treatments for a subset of cases of appendicitis.

8. References

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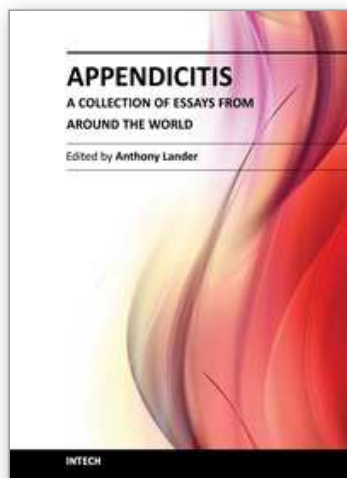
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This book is a collection of essays and papers from around the world, written by surgeons who look after patients of all ages with abdominal pain, many of whom have appendicitis. All general surgeons maintain a fascination with this important condition because it is so common and yet so easy to miss. All surgeons have a view on the literature and any gathering of surgeons embraces a spectrum of opinion on management options. Many aspects of the disease and its presentation and management remain controversial. This book does not answer those controversies, but should prove food for thought. The reflections of these surgeons are presented in many cases with novel data. The chapters encourage us to consider new epidemiological views and explore clinical scoring systems and the literature on imaging. Appendicitis is discussed in patients of all ages and in all manner of presentations.

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