*Let sleeping dogs lie; to leave the appendix at the time of Ladd's procedure.*

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## WHY IS THE APPENDIX USUALLY TAKEN AT THE TIME OF A LADD'S PROCEDURE?

Removal of the appendix has historically constituted formed part of the Ladd's procedure. The reason for appendicectomy is that the abnormal position of the caecum and appendix in a non-rotated bowel, post-Ladd's procedure, is thought make a diagnosis of acute appendicitis more difficult. A history of left sided abdominal pain associated with gastrointestinal symptoms might obscure the diagnostic process and delay definitive treatment.

In this article, we seek to question this conventional wisdom by considering the evidence from a number of different sources; from laparoscopy to colorectal cancer risks, to question whether current practice continues to be justified.

## BACKGROUND AND HISTORY

The Ladd's procedure for intestinal malrotation involves division of Ladd's bands and movement of the caecum to a new home in the upper left quadrant. According to William Ladd's original description [1], this does not involve removal of the appendix. Today, the Ladd's procedure is described in most textbooks of operative surgery to include an appendicectomy [2,3]; often by skeletalisation and inversion to minimize peritoneal contamination.

There are, to the authors' knowledge, no reported cases of a patient post-Ladd's procedure without appendicectomy, who then has gone on to develop appendicitis. This may be due to the widespread current practice. Modern surgical practice in both adults and children features a pivotal role of diagnostic imaging; almost all children will have an ultrasound and/or a CT in the case of equivocal examination findings [4]. Pain in the left side of the abdomen, without a reliable history from the parent or child of previous laparotomy or laparoscopy for Ladd's procedure, may not prompt a clinical diagnosis of acute appendicitis, but diagnostic imaging would then be performed, allowing the true anatomical position of the appendix to be revealed and the diagnosis reached.

The lifetime risk of developing appendicitis is approximately 7%. Although prophylactic appendicectomy is performed in some scenarios, e.g. before long-term visits to polar stations or extended space flights [5,6], and elective coincidental appendicectomy is performed alongside other abdominal operations, removal of a clinically silent appendix has been associated with complications and morbidity and remains a controversial issue [7–9]. One recent paper can be quoted "the practice of performing incidental appendectomy is an exercise in gambling."[10]

## WHY WOULD YOU WISH TO LEAVE AN APPENDIX DURING LADD'S PROCEDURE?

*1. Post-op complications*

Although infrequent, post-operative complications do occur following any negative appendectomy. These have been estimated at approximately 10%, and are comparable to those of removing an inflamed appendix [11]. Stump appendicitis is a rare late complication of appendectomy, with most cases present months to years following surgery for acute appendicitis. Cases of stump appendicitis after incidental appendectomy are very rare but they have been reported in children following incidental appendectomy [12]. The risk of complications following the appendicectomy often performed for a Ladd's procedure, i.e. by skeletalisation and inversion is probably lower but still present. Indeed, haemorrhagic complications following incidental appendectomy by entire inversion have been reported [13].

*2. Use of the appendix as a surgical conduit*

Admittedly, the proportion of patients having a Ladd's procedure who require a subsequent ACE or Mitrofanoff must be rather low, however malrotation is present in 12% of children with chronic dysmotility and intestinal dysfunction [14]. As such, a greater than expected proportion of these individuals may require a procedure to aid with continence; of which the antegrade continence enema (ACE) has proven to be the simplest and most popular. Paediatric surgeons and urologists may also wish to retain the appendix in the event of requiring a Mitrofanoff. For both an ACE and a Mitrofanoff, there are feasible alternatives to appendiceal mobilisation but these are deemed less desirable. Additionally, the appendix may be in the future used also for organ augmentation as demonstrated recently by successfully adopting decellularised appendices in a preclinical model for bladder augmentation [15].

*3. Immune organ, microbiological and stem cell reservoir*

Charles Darwin in his *Descent of Man* comments on the appendix thus; "That this appendage is a rudiment, we may infer from its small size and from the evidence … of its variability in man…. (it) is useless….." [16]. However, this conclusion was reached on the basis of limited available data. A recent extensive consensus phylogenetic analysis of the presence and absence of the appendix in over 350 mammalian species arrived at the conclusion that the appendix has have evolved no fewer than 32 separate times in mammals, and has been lost six times [17,18]. These authors hypothesised that the appendix acts as a reservoir of beneficial microbiota, and that it is present in hominids because of the likely frequent diarrhoeal infections experienced during hominid evolution, in which a reservoir from which the intestine could rapidly recolonise with a beneficial microbiome would be an evolutionary advantage. Other evidence points towards the importance of the lymphoid tissue (gut associated lymphoid tissue; GALT) first recognised within the appendiceal mucosa over a century ago by Richard Berry[19]. The microbial reservoir / immune function of the appendix is given support by the findings that acute appendicitis is associated with improved hygiene in Western society [20,21], and that appendectomy increases the risk of recurrent *Clostridium difficile* infection [22–24]. Finally, various progenitors have been isolated from animal and human appendices. Mesenchymal stem cells, which tipically resides in bone marrow and fat have been isolated from human vermiform appendices [25]. More importantly, neural stem cells have been isolated from the appendix and they have been successfully differentiate into mature functional enteric neurons, similarly top neural stem cells derived from other sites of the gastrointestinal tract [26,27].

*4. Association of appendectomy with subsequent development of other pathologies*

Probably connected with the microbial reservoir function and lymphoid function of the appendix, appendectomy has been suggested to be associated with subsequent development of other pathologies, such as rheumatoid arthritis [28], colorectal cancer [29], gallstones [30] and even Parkinson's disease [31]. There is also a complex relationship between development of inflammatory bowel disease and appendectomy, with an apparently decreased risk of ulcerative colitis following appendectomy [32] but an increased risk of Crohn's disease [33,34], although this is a controversial area and it is difficult to dissect appendicitis from appendectomy, and to control for diagnostic uncertainty.

## Crohns' disease

An increased risk of Crohn's disease has been linked to the appendicectomy population. In a statistically high-powered, long-term follow-up study of over 200,000 patients post-appendicectomy, Andersson reports an increased risk of Crohn's disease which is maintained for 20 years after the operation [33]. They cite in this study, however, that their observed risks appear to be more prominent in cases of complicated appendicitis but did also pertain to non-appendicitis diagnoses. However, they also noted in fact that appendicectomy for clinically diagnosed appendicitis below the age of 10 was not associated with an increased risk of Crohn's.

While a number of studies demonstrating a link between the two conditions, there is reasonable argument to suggest that the correlation may be reversed; that appendicitis may be a harbinger of future Crohn's disease, as opposed to the appendicectomy itself being the cause.

## Colorectal cancer

The regulation of the intestinal microbiome that would appear likely to be at the core of purported risks of colorectal cancer among individuals who have had their appendix removed. Wu and colleagues completed a large population wide analysis [29], demonstrating an increased risk of colorectal cancer among appendicectomy patients – perhaps rather concerningly reporting a hazard ratio that was higher among the incidental appendicectomy population (HR=2.9 compared to control population). This group, and others, speculate the regulatory role of the appendix in the microbiome, citing the abundance of biofilms within the appendix and call into question the potential role of dysregulated growth of '*pathogenic*' species (such as *Fusobacterium spp.*)

## IMPROVING THE EVIDENCE BASE

Currently there is no evidence either for or against the removal of the appendix when operating on a child with intestinal malrotation. A recent published review of paediatric incidental appendicectomy has reasoned that the appendix should be removed but gives little evidence to support this recommendation [35]. A number of disparate sources support a beneficial role of the appendix; and it has become practice at the authors' centre to leave the appendix in situ for many years now. It is unlikely that a randomised trial of appendicectomy at Ladd's procedure would reach sufficient power to demonstrate an effect similar to the large-scale population follow-up studies cited here. However, based on the published evidenced discussed above, there are no benefits on performing a prophylactic appendectomy at the time of the Ladd's procedure.

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