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IMMUNE FUNCTIONS OF THE VERMIFORM APPENDIX

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KEY WORDS

Mucosal immunology, gut-associated lymphoid tissues, immunocompetence, appendix (human and rabbit), appendectomy, neoplasm, vestigial organs.

ABSTRACT

The vermiform appendix is purported to be the classic example of a vestigial organ, yet for nearly a century it has been known to be a specialized organ highly infiltrated with lymphoid tissue. This lymphoid tissue may help protect against local gut infections. As the vertebrate taxonomic scale increases, the lymphoid tissue of the large bowel tends to be concentrated in a specific region of the gut: the cecal apex or vermiform appendix. The rabbit appendix has the greatest relative lymphoid development. Neonatal appendectomy in rabbits results in decreased total lymphocyte counts and lower antibody response to immune challenges relative to sham-operated controls. Appendectomy in young adult rabbits subject to whole body irradiation also depresses immunocompetence. The ultrastructure of the rabbit and human appendix mirrors that of Peyer's patches and the avian bursa of Fabricius. The appendix shares secondary functions of the avian bursa: it transports antigens from the intestinal lumen to the lamina propria; these antigens stimulate B cell proliferation, dissemination throughout the gut-associated lymphoid tissues, and differentiation into antibody secreting cells. In vitro studies indicate the human appendix contains immunocompetent B cells, T cells and natural killer cells. It is also a major site of IgA induction. Several epidemiologic studies suggest a correlation between appendectomy and cancer risk but these findings are inconclusive. Incidental appendectomy is often practiced by physicians despite the growing evidence that the appendix may be an important component of the immune system.

INTRODUCTION

Since the turn of the century it has been well documented that the human appendix is a specialized region of the gut containing considerable lymphoid tissue. Hence it has been called the "abdominal tonsil" [8]. Yet even today the appendix is probably the most commonly cited example of a vestigial organ [7]. This assertion is supported by a critique of 1991 editions of biology textbooks which were adopted by the state of Texas [31]. Textbooks selected by Texas and California typically set the national standard because of the large numbers of textbooks they purchase. In the chapters pertaining to evolution, the appendix was used as an example of a vestigial organ more than any other structure.

According to macroevolutionary theory, the appendix is a useless remnant of a large cecum which was important for digestion by hominoid ancestors [7]. This evolutionary bias has likely influenced investigators to neglect examining this organ and persuaded physicians to remove it incidentally. Specific immune functions of the human appendix have only been discovered within the last ten years. This paper reviews historical and current studies of the appendix in humans and animals. These studies are organized according to three categories: comparative anatomy of the appendix and its homologous structures, immunology of the rabbit and human appendix, and epidemiology of appendectomy and cancer.

COMPARATIVE ANATOMY

The vermiform appendix refers to a worm-like extension of the cecum also called the vermiform process of the cecum [12]. In humans and rabbits it is approximately 9 cm long. The cecum is one of the most variable digestive organs among vertebrates. Found in every vertebrate class, it ranges in size from a small pouch in man to an elongated sac twice the body length in the woolly lemur [40]. In mammals this diverticulum of the colon is located

at the proximal end of the large intestine. It functions not only in fermentation of polysaccharides, but also in absorption of water and nutrients, and recycling of wastes [11]. Relatively few species have a cecum with a vermiform process. The most well known examples are the lagomorphs, great apes, and man [8]; it is also reportedly found in some monkeys and civets [46] and in the wombat [47]. The cecum in most vertebrates contains abruptly more lymphoid tissue than other sections of the colon.

Although birds do not have a vermiform appendix, they do have paired colonic ceca, some of which appear worm-like. The avian cecal lymphoid tissue is more concentrated in species with short as opposed to long ceca [8]. The small ceca of the pigeon, for example, is infiltrated with masses of lymphoid tissue especially near the junction of the colon. Regardless of length, the lymphoid tissue is more prominent in the avian ceca than in other regions of the gut. Many piscivores birds (e.g. penguins and gannets) and some carnivorous birds (e.g. hawks and eagles) allegedly have "vestigial" ceca [29]. Although these diminutive ceca do not appear to have a digestive role, they may function immunologically. Such a function should be investigated considering the high proportion of lymphoid tissue typically found in short avian ceca.

In mammals the greatest concentration of colonic lymphoid tissue lies either at the apex or the vermiform process of the cecum (if these structures are present) [8]. The cecal apex is a small sac distinguished from the body of the cecum by a slight constriction. It is found in many rodents such as mice and rats and in some carnivores as in domestic cats. In mammals possessing a cecal apex or vermiform process, nearly all the cecal lymphoid tissues is confined there. Comparative anatomy suggests that the cecal apex and vermiform appendix are homologous structures adapted for immune roles as opposed to rudimentary remnants of a longer cecum. Berry, who has performed what may be the most extensive comparative study of the vermiform appendix and its homologous structures concluded,

The vermiform appendix of Man (sic) is not, therefore, a vestigial structure. On the contrary, it is a specialised (sic) part of the alimentary canal [8, p. 98].

If the human appendix is a useless vestige of a large cecum, then why does a rabbit have a similar appendix in addition to a large cecum? The lengthy cecum (> 30 cm) of the rabbit is an indispensable digestive organ which acts as a fermentation chamber [40]. But if the appendix is excised at birth, the developing rabbits do not appear to be handicapped nutritionally since weight gain and serum protein levels remain normal [37]. The primary function of the rabbit appendix is immunologic rather than digestive as described in the following section.

The structure and development of the human and rabbit appendix are similar. Hence the rabbit appendix has been used as a model in numerous experiments. Anatomical examinations indicate they both are well developed lymphoid organs containing numerous follicles [12,18]. The lymphoid follicles are composed of an apical dome, a germinal center in the basal nodule, and thymus dependent areas on the periphery [12]. The human and rabbit appendix are about the same length but only in the rabbit is it the largest lymphoid organ. The appendix of both typically contain fewer T than B lymphocytes. Percentages of T lymphocytes in the rabbit appendix vary from 7-40% [20]; human appendiceal T cells vary from 30-50% [25,32]. Lymphoid development begins a few days after birth and peaks in adolescence or young adulthood [3,10,12]. In humans after the age of 30, the lymphoid tissue begins to atrophy significantly [10].

IMMUNOLOGIC STUDIES

The rabbit and human appendix share secondary functions of the bursa of Fabricius, a central lymphoid organ controlling the development of B cells in peripheral lymphoid tissues of birds [5]. Although the appendix has not been shown to induce B cell differentiation from pluripotent stem cells, it does perform other functions of the bursa. It is a site of high B cell proliferation and seeding to peripheral lymphoid tissues. It may act as a B cell pool holding antibody producing precursors which upon antigenic stimulation disseminate to gut-associated lymphoid tissues (GALT) and differentiate into antibody secreting (plasma) cells.

The appendix is also anatomically similar to the avian bursa. The human and rabbit appendix, mouse Peyer's patches, and chicken bursa of Fabricius all contain a follicle-associated epithelium (FAE) which is identical in ultrastructure [13]. Tests with rabbits show that the FAE transports electron-opaque tracers from the lumen to the lamina propria. Bockman and Cooper suggested the FAE contains a pinocytotic channel through which antigens stimulate B cell proliferation and seeding throughout GALT. Most of the lymphocytes are transported by lymph from the appendix through the spleen and lymph nodes to the lamina propria throughout the gut. Many of the B cells complete their differentiation by becoming IgA secreting cells. Stimulation also occurs by macrophage processing and presentation of microbial antigens. In the germinal centers and domes, Bockman observed numerous macrophages which phagocytize bacteria from the lumen [12].

Lymphoid development of the appendix is largely dependent upon antigenic stimulation. If the appendix is ligated during neonatal development to isolate it from the intestinal contents but not the blood supply, growth of the appendiceal lymphoid follicles is significantly reduced [12]. Bockman concluded,

The appendix is a prominent example of gut associated lymphoepithelial tissue, whose function is to react to the wide variety of antigens present in the gastrointestinal tract [12, p. 271].

It is strategically located near the junction of the small and large intestines to perform such a function. It can sample the first contents of the colon and mount a specific immune response.

The appendix is one of many peripheral lymphoid organs; others include the spleen, tonsils, Peyer's patches, and lymph nodes. Does its extirpation affect immunocompetence or do other peripheral lymphoid tissues compensate for its loss? Experiments with rabbits reveals appendectomy in neonates markedly impairs immunocompetence several weeks later relative to sham-operated controls (sham surgery involves making an abdominal incision and externalizing the bowel). Antibody responses and total lymphocyte counts have been reduced significantly in five to eight week-old rabbits appendectomized at birth [3,37]. In fact neonatal appendectomy has depressed primary antibody response as much as thymectomy alone. Cell mediated responses, however, have not been affected by appendectomy as tested by delayed hypersensitivity to old tuberculin and rejection of skin homografts.

The appendix plays a significant immunologic role in young adult rabbits as well [5,38]. Recovery of antibody-forming potential after irradiation is dependent upon the appendix. Sussdorf measured the hemolysin response to sheep erythrocytes in rabbits exposed to whole or partial body irradiation in which the appendix was protected by a lead shield [42]. The antibody response was near normal in the shielded rabbits but significantly lower in the whole body irradiated animals. Nieuwenhuis et al. found a significantly greater antibody response to paratyphoid vaccine ten days after irradiation in rabbits whose appendices were left intact versus appendectomy [35]. Sussdorf and Nieuwenhuis also demonstrated regeneration of splenic lymphoid follicles (white pulp) was aided by lymphocyte migration from the appendix [35,41]. Sussdorf attributed the preserved hemolysin response in the shielded rabbits to the rapid restoration of splenic white pulp derived from the appendix. Subsequently, Ozer and Waksman found the bone marrow and appendix worked synergistically to restore splenic antibody response to sheep erythrocytes [36]. In combination the two produced 5 to 10 times more antibody than either alone or in summation. Splenic antibody response could be restored if the bone marrow was shielded during irradiation and appendiceal cells injected after radiation treatment.

With humans, no study has tested the effect of appendectomy on immunocompetence in vivo has not been documented. In vitro studies, however, do demonstrate the immunocompetence of adult appendiceal cells. Kawanishi found isolated B cells from the appendix produced mostly IgA antibodies without mitogen stimulation [25]. With stimulation, production of IgG, IgM and IgA was amplified. Suppressor T cells, if present, were not activated, but appendiceal helper T cells initiated and maintained B cell reactivity against immune challenges. Kawanishi concluded the appendix played a primary role in GALT responsiveness to foreign stimuli. He also found the appendiceal lymphocytes contained small subpopulations possessing natural killer (NK) markers and NK activity. NK cells are a subset of lymphocytes known to lyse certain tumor and virus-infected cells without specific antigenic stimulation [1]. They are the principle mediators of antibody-dependent cell-mediated cytotoxicity (ADCC). ADCC enables NK cells to increase their specificity as their target cells become coated with antibodies (IgG). These antibodies assist NK cell binding to their target which is followed by cytotoxicity.

Other studies indicate the human appendix is a major site of IgA induction. Benson et al. has cloned T cells from the appendix which stimulate both IgM B cell conversion to IgA (i.e. isotype switching) and IgA synthesis [6]. IgA is the major antibody found in intestinal secretions [34]. It is secreted exclusively by mucosal epithelium and is the only antibody which can be selectively transported across mucosal barriers into the gut lumen [1]. In the lumen, it helps control pathogenic microbes and infectious protozoans and tapeworms [9].

Fujihasher et al. [17] reported the appendix may be an enriched source of IgA B cells (especially IgA₂ subclass) containing abundant interleukin-6 receptors (IL-6R). Among other functions, IL-6, a T cell derived cytokine secreted in response to local inflammation, induces B cells to form plasma cells. In the appendix, human recombinant IL-6 preferentially stimulates B cells to differentiate into IgA plasma cells. They postulate the appendix may be a major source of IgA₂ B cell precursors that migrate to mucosal tissues. The appendix is the only known human lymphoid tissue with B cells expressing IL-6R endogenously unlike the spleen, tonsils or peripheral blood mononuclear cells (PBMC) which only express IL-6R when stimulated by a mitogen. Furthermore, the B cells of the appendix produce more IgA₂ in response to IL-6 than the tonsils, PBMC, and spleen [17,28].

Since human and animal studies clearly demonstrate the appendix functions immunologically, the question arises whether loss of the appendix increases susceptibility to diseases such as cancer.

EPIDEMIOLOGIC STUDIES OF APPENDECTOMY AND CANCER

Numerous epidemiologic studies have investigated an association between appendectomy and cancer [10,16,19,22,23,24,26,30,33,43,44,48]. These studies are divided in showing or failing to show a positive correlation with appendectomy and all types of cancer, especially colorectal. Epidemiologic studies often give conflicting results because of the difficulty in identifying confounding variables, selecting matched control groups, and using reliable means of data collection [27]. For instance, selecting a matched control group for diet is important since a low fiber diet has been associated with both appendicitis and colon cancer [14,16]. The strong correlation between these two diseases and the weaker association between appendectomy and colon cancer may indicate it is the low fiber intake not the appendectomy which predisposes to colon cancer. A thorough review of the literature has failed to find an appendectomy-cancer study which selected matched control groups for fiber intake.

In their book, Vestigial Organs are Fully Functional, Bergman and Howe [7] cite a 1968 study by Bierman [10] which found the incidence of leukemia, Hodgkin's disease, colon cancer, ovarian cancer and cancer in general was markedly greater in people who had appendectomies versus a control group without appendectomy. This study along with an earlier one by McVay [30] was criticized for relying on autopsy records [33]. Such records do not indicate whether the appendix was removed prior to cancer onslaught or whether it was removed during an operation for intestinal neoplasms, the latter being a common procedure. The data are unreliable since the number of appendectomies is skewed in the cancer group. Since McVay's and Bierman's study, other studies of the appendectomy-cancer association have obtained better data through hospital records or interviews. After reviewing several of these studies, an epidemiologist concluded that their results raised more questions than they answered and emphasized the need for controlled experiments in animal models,

Clearly, further investigation into the structure and immune function of the vermiform appendix is needed. Studies assessing immune regulation and competency, pre-and post-appendectomy, in a suitable animal model are the next logical step. If appendectomy were found to affect immunocompetency adversely in animals, it would lend credence to the possibility of an appendectomy-cancer association in man particularly in view of the high incidence of neoplasia in immunosuppressed individuals [23, p. 394].

It is possible that both a low fiber diet and appendectomy contribute to the risk of colorectal cancer; the two may even have a synergistic effect. If appendectomy does impair the immune system, then examining the interaction between immunodeficiency and cancer may illuminate questions regarding an appendectomy-cancer association. Data from the Immunodeficiency Cancer Registry (ICR) established by the World Health Organization reveals children with a genetic immunodeficiency disease are a hundred times more likely to develop cancer than the average child. [15,39]. Of the cases reported in the ICR, gastrointestinal (GI) cancers were the number one neoplasm associated with selective IgA deficiency. Other studies have shown selective IgA deficiency is more frequent in GI cancer patients than normal individuals [21]. IgA deficiency is the most common primary immunodeficiency syndrome.

Elevated levels of circulating immune complexes (CIC) in the sera of cancer patients provides further evidence of the possible protective role of antibodies against neoplasia. CIC are antigen-antibody complexes which can be monitored clinically to determine the degree of tumor burden or prognosis of cancer patients [45]. IgA immune complexes have been found to be significantly higher ($p < .001$) in colon cancer patients versus normal or benign surgery controls [4]. These studies implicate IgA may bind malignant tumor antigens and help protect against cancer. The contribution of the appendix may be particularly important in protecting against GI malignancy since it may be an enriched source of IgA B cell precursors.

CONCLUSION

It is unfortunate that the appendix is still commonly considered vestigial by textbooks, instructors, and medical doctors despite the wealth of evidence to the contrary. On the positive side, the author has never found this claim made by a researcher who has published a firsthand investigation of the anatomy and/or physiology of the appendix. Rather, those who have studied this organ have described it as a specialized lymphoid structure. This lymphoid organ has distinct immune functions as well as immune functions similar to that of other peripheral lymphoid tissues such as the Peyer's patches and tonsils. Immunologic research on the appendix has lagged behind that of other lymphoid organs. The critical question remains: Does appendectomy impair the immune system? It would not be difficult to answer this question by testing immunocompetence in patients undergoing appendectomy.

Investigating the function of the appendix may not only benefit creation science but also health care. It would benefit the patient rather than a physician who considers the primary function of the appendix as financial support of his or her profession. Incidental appendectomy remains a common practice. In the United States, 36 incidental appendectomies are performed for every case of appendicitis; yet the lifetime risk of appendicitis is low (8.6% for males and 6.7% for females) and may be reduced by a high fiber diet [2,14]. One medical doctor quipped,

The vermiform appendix, a dangling vestige of our evolutionary development, has been considered singularly devoid of any useful function, and the privilege of its amputation has rewarded many a fledgling physician for his patient pulling of retractors [33, p. 549].

Doctors who view the appendix as vestigial are reminded of the change in surgical practices regarding the criteria for performing tonsillectomy. In the 1930s, most children had their tonsils and adenoids removed [7]. Today doctors are reluctant to perform tonsillectomies unless serious infection occurs. Tonsils are believed to protect against oral infection even though the epidemiologic evidence is tenuous [27]. If appendectomy is shown to affect immunocompetence adversely, the medical profession may be more apt to consider it the "abdominal tonsil" and avoid removing it unless it is pathologic.

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