

World Journal of *Gastroenterology*

Weekly Volume 31 Number 26 July 14, 2025



REVIEW

Zheng SH, Xue TY, Wang QY, Ye YA, Zhang P. Chinese medicine monomers for hepatocellular carcinoma: New ideas related to autophagy. *World J Gastroenterol* 2025; 31(26): 106113 [DOI: [10.3748/wjg.v31.i26.106113](https://doi.org/10.3748/wjg.v31.i26.106113)]

Lo RW, Bhatnagar G, Kutaiba N, Srinivasan AR. Evaluating luminal and post-operative Crohn's disease activity on magnetic resonance enterography: A review of radiological disease activity scores. *World J Gastroenterol* 2025; 31(26): 107419 [DOI: [10.3748/wjg.v31.i26.107419](https://doi.org/10.3748/wjg.v31.i26.107419)]

MINIREVIEWS

Pravda J. Ulcerative colitis: Timeline to a cure. *World J Gastroenterol* 2025; 31(26): 108375 [DOI: [10.3748/wjg.v31.i26.108375](https://doi.org/10.3748/wjg.v31.i26.108375)]

ORIGINAL ARTICLE**Retrospective Study**

Liu JY, Gao DL, Cao X. Risk factors and diagnostic biomarkers for asymptomatic immune checkpoint inhibitor-related myocarditis in patients with esophageal cancer after immunotherapy. *World J Gastroenterol* 2025; 31(26): 106509 [DOI: [10.3748/wjg.v31.i26.106509](https://doi.org/10.3748/wjg.v31.i26.106509)]

Clinical Trials Study

Zeng ZH, Liu JQ, Zhang M, Qiu CL, Xu ZY. Tenofovir amibufenamide in chronic hepatitis B: Lipid changes and 144-week safety with tenofovir disoproxil fumarate-to-tenofovir amibufenamide switch. *World J Gastroenterol* 2025; 31(26): 109285 [DOI: [10.3748/wjg.v31.i26.109285](https://doi.org/10.3748/wjg.v31.i26.109285)]

Observational Study

Ren S, Song LN, Zhao R, Tian Y, Wang ZQ. Serum exosomal hsa-let-7f-5p: A potential diagnostic biomarker for metastatic pancreatic cancer detection. *World J Gastroenterol* 2025; 31(26): 109500 [DOI: [10.3748/wjg.v31.i26.109500](https://doi.org/10.3748/wjg.v31.i26.109500)]

Basic Study

He XD, Li M, Zuo XD, Ni HY, Han YX, Hu YK, Yu J, Yang XX. Kushenol I combats ulcerative colitis via intestinal barrier preservation and gut microbiota optimization. *World J Gastroenterol* 2025; 31(26): 105656 [DOI: [10.3748/wjg.v31.i26.105656](https://doi.org/10.3748/wjg.v31.i26.105656)]

Bu XY, Tan HY, Wang AM, Wei MT, Pan S, Gao JZ, Li YH, Qian GX, Chen ZH, Ye C, Jia WD. Paneth cells inhibit intestinal stem cell proliferation through the bone morphogenic protein 7 pathway under rotavirus-mediated intestinal injury. *World J Gastroenterol* 2025; 31(26): 107044 [DOI: [10.3748/wjg.v31.i26.107044](https://doi.org/10.3748/wjg.v31.i26.107044)]

Nie HH, Yang XY, Zhou JK, Gao GL, Ding L, Hong YT, Yu YL, Qiu PS, Zeng ZY, Lai J, Zheng T, Wang HZ, Zhao Q, Wang F. Histone deacetylases 10 as a prognostic biomarker correlates with tumor microenvironment and therapy response in colorectal cancer. *World J Gastroenterol* 2025; 31(26): 108662 [DOI: [10.3748/wjg.v31.i26.108662](https://doi.org/10.3748/wjg.v31.i26.108662)]

LETTER TO THE EDITOR

Yang WQ, Xue LL, Wang JL. Metabolic dysfunction-associated steatotic liver disease: Mechanisms, metabolic reprogramming, and therapeutic insights. *World J Gastroenterol* 2025; 31(26): 108814 [DOI: [10.3748/wjg.v31.i26.108814](https://doi.org/10.3748/wjg.v31.i26.108814)]

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Neal Shahidi, MD, PhD, Assistant Professor, Department of Medicine, St Paul's Hospital, Division of Gastroenterology, Vancouver, British Columbia V6Z 1Y6, Canada. nshahidi@providencehealth.bc.ca

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2025 edition of Journal Citation Reports® cites the 2024 journal impact factor (JIF) for *WJG* as 5.4; Quartile: Q1. The *WJG*'s CiteScore for 2024 is 8.1.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Xu Guo*; Production Department Director: *Xiang Li*; Cover Editor: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF

Xian-Jun Yu, Jian-Gao Fan, Hou-Bao Liu

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

July 14, 2025

COPYRIGHT

© 2025 Baishideng Publishing Group Inc

PUBLISHING PARTNER

Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

POLICY OF CO-AUTHORS

<https://www.wjgnet.com/bpg/GerInfo/310>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

PUBLISHING PARTNER'S OFFICIAL WEBSITE

<https://www.shca.org.cn>
<https://www.zs-hospital.sh.cn>



Ulcerative colitis: Timeline to a cure

Jay Pravda

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade B, Grade B

Novelty: Grade A, Grade B, Grade C

Creativity or Innovation: Grade B, Grade B, Grade C

Scientific Significance: Grade B, Grade B, Grade B

P-Reviewer: Duan SL; Khan A

Received: April 12, 2025

Revised: May 1, 2025

Accepted: June 27, 2025

Published online: July 14, 2025

Processing time: 90 Days and 12 Hours



Jay Pravda, Department of Disease Pathogenesis, Inflammatory Disease Research Centre, Palm Beach Gardens, FL 33410, United States

Corresponding author: Jay Pravda, MD, MPH, MBE, Department of Disease Pathogenesis, Inflammatory Disease Research Centre, 4371 Northlake Blvd No. 247, Palm Beach Gardens, FL 33410, United States. jay.pravda@protonmail.com

Abstract

Ulcerative colitis has baffled researchers since the early 20th century. The prevailing explanation attributes the chronic recurring episodes of bloody diarrhea and abdominal pain to some form of immune abnormality, despite the lack of supporting evidence. This highlights the critical need for innovative research directions and methodologies to uncover the cause and develop a cure for this disease. By analyzing existing data from less than a dozen previously published studies, a novel, evidence-based pathogenesis was constructed, implicating colonic epithelial hydrogen peroxide as a causal factor in the development of this disease. This newly identified mechanism informed the creation of a groundbreaking class of therapeutics, known as reducing agents, which have demonstrated remarkable success in resolving colonic inflammation and restoring colonic health in patients with refractory ulcerative colitis. This paper outlines the timeline of these publications and reinterprets the findings within the context of contemporary biomedical science.

Key Words: Ulcerative colitis; Pathogenesis; Treatment; Hydrogen peroxide; Common pathway

©The Author(s) 2025. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Since the mid-20th century, research into the causes of ulcerative colitis has predominantly focused on the immune system and microbiome, overlooking the colonic epithelium's role in its pathogenesis. This conformation bias has delayed recognition of the causal role played by colonocyte hydrogen peroxide in the pathogenesis of this inflammatory bowel disease. Notably, fewer than a dozen studies since that time have laid the groundwork for this conclusion. This review critically examines these foundational studies through the lens of contemporary biomedical science, tracing their evolution toward the identification of a causal role for colonocyte hydrogen peroxide in the pathogenesis of ulcerative colitis.

INTRODUCTION

Ulcerative colitis (UC) is a major inflammatory bowel disease that leads to chronic episodes of relapsing and remitting bloody diarrhea and rectal bleeding lasting weeks, months or in some cases years. Typically manifesting during the second and third decades of life, the inflammation associated with UC originates within the colonic epithelium, where three distinct cell types converge. Neutrophils, the initial responding immune cells, migrate into the colonic epithelium, interacting with colonic epithelial cells and the microorganisms constituting the microbiome[1].

Research focused on the microbiome and immune system, spanning back to the early 20th century, has failed to clarify why neutrophils the most abundant innate immunocyte suddenly migrate *en masse* into the colonic epithelium of otherwise healthy young individuals in the prime of life. This has led to a default explanation of ‘immune dysregulation’ (and its various iterations) as a means to impart a sense of conceptual progress towards identifying the cause of this disease[2]. Just what is meant by ‘immune dysregulation’ is not clear. However, for as long as research has been ongoing to uncover the etiology of UC, no pathological organism or pre-existing immune vulnerability has been discovered to account for the development of this condition.

Nevertheless, in the mid-20th century, a third area of research emerged, focused on the colonic epithelium, which revealed an active causal involvement of colonic epithelial cells (colonocytes) in the pathogenesis of UC. By the early 21st century, cumulative experimental and clinical evidence converged into a coherent, evidence-based pathogenesis, substantiating the hypothesis about the pivotal role of the colonic epithelium in the development of this disease. This paper chronicles the significant paradigm shift in the perception of UC etiology, transitioning from a groundbreaking yet unconventional theory of the mid-20th century to its experimental validation over the course of five decades.

Operationally, the investigation into the potential causal agent of UC was refined by excluding the microbiome and immune system, as no evidence supported their involvement in the pathogenesis of disease. This process highlighted the colonic epithelium as the primary participant in the development of UC. Given that neutrophils are the initial responders into the colonic epithelium, attention turned to identifying a small, membrane-permeable, neutrophilic chemotactic factor originating in colonic epithelial cells. Subsequent research identified hydrogen peroxide (H₂O₂) as a viable candidate since all cells produce H₂O₂ during the course of cellular metabolism. H₂O₂ is both membrane permeable and a potent neutrophilic chemotactic agent. Colonocyte H₂O₂, when secreted into the extracellular space, would attract neutrophils into the colonic epithelium leading to colonic inflammation and UC. This was a biologically sound mechanism that satisfied the known histological data.

In contrast, the prevailing theory of immune dysregulation lacks evidence of immune vulnerability associated with UC. It also fails to offer specific clinical management strategies or curative therapeutic targets. An H₂O₂-based redox mechanism, however, provides a framework for targeted primary, secondary, and tertiary prevention, as well as potential curative approaches. Examples include mitigating oxidative stress (primary prevention), detecting excess H₂O₂ *via* stool analysis or during colonoscopy (secondary prevention), and eliminating excess H₂O₂ from the colonic lamina propria (tertiary prevention). Restoring normal H₂O₂ levels in colonic epithelial cells is a potential functional cure for UC.

Subsequent research identified environmental factors linked to UC as oxidative stressors that elevate cellular H₂O₂ production, facilitating its diffusion from colonocytes. Consistent with this mechanism, the predisposition to UC was attributed to an impaired ability to manage an acute H₂O₂ (oxidative) load. This understanding led to the development of therapeutic reducing agents aimed at enhancing cellular reductive capacity to address the underlying root cause of excessive H₂O₂. The lack of casual evidence for abnormalities of the immune system and microbiome coupled with the complete novelty of this H₂O₂-based mechanism made confirmation bias highly improbable. Notably, fewer than a dozen studies formed the foundational evidence implicating colonic epithelial H₂O₂ as the etiological agent of this debilitating disease. These pivotal studies are outlined below in chronological order, although their discovery followed a less direct path.

TIMELINE

1948

First report of fatal UC following the self-administration of a H₂O₂ enema[3]. The report prompts an important question: Why does H₂O₂ specifically induce UC rather than other forms of colitis, such as ischemic, collagenous, or lymphocytic colitis? What unique properties of H₂O₂ lead to UC upon interaction with the colonic mucosa? Crucially, could the unique properties of H₂O₂ offer insights into the mechanisms underlying the development of UC?

1949

This groundbreaking study offered the first empirical evidence highlighting the critical role of colonic epithelial cells in the pathogenesis of UC[4]. After reviewing nearly 200 colonic biopsies, two pathologists concluded that UC is caused by an unknown chemical secreted by colonic epithelial cells. This was a radical departure from current thinking at the time

and still is. The findings implied that colonic epithelial cells release a small membrane-permeable molecule with chemotactic properties for neutrophils—the first responder white blood cells entering the colon and leading to UC development. This study laid the foundational framework for a therapeutically actionable pathogenesis of disease. Unlike all other hypotheses proposed to explain UC, both historically and in subsequent research, this study represented direct empirical evidence establishing a causal role for the colonic epithelium in the pathogenesis of UC. More significantly, it provided a mechanism capable of accounting for all cases of the disease. This marked the first pivotal theoretical breakthrough in advancing our understanding of UC.

It is important to highlight that the authors of this study were pathologists rather than clinical practitioners directly involved in UC patient care. Clinical specialists had previously hypothesized several potential etiologies, including infection, psychogenic factors, allergies, autoimmune conditions, connective tissue abnormalities, cholinergic mechanisms, ischemia, and cytolytic enzymes, though none of these could be definitively established[5]. This underscores the value of approaching longstanding challenges from a fresh perspective. A new viewpoint can foster innovative thinking and generate creative solutions that have the potential to drive breakthroughs otherwise unattainable through conventional derivative approaches.

1951

Two cases of severe ulcerative proctosigmoiditis are documented following the administration of H₂O₂ enemas[6]. These findings suggest a mechanism beyond a generic chemical injury, as enemas typically reach up to the splenic flexure but the inflammation did not reach that high[7]. Additionally, it raises an important question regarding why the inflammation was limited to the rectum and sigmoid colon, mirroring the presentation of UC observed in many patients. This prompts consideration of whether the colon interacts with H₂O₂ differently from other chemicals and/or whether a gradient of protection against H₂O₂'s effects exists, increasing in more proximal regions of the colon. These observations emphasize the necessity of conducting a study to assess whether human UC can be reproduced in an animal model. This was addressed in the following study.

1960

Researchers successfully reproduce what they describe as acute and chronic UC by the administration of H₂O₂ enemas in rats[3]. This represented the first chemically-induced animal model replicating features found in the micro and macroscopic presentation of human UC. This raised further questions regarding how H₂O₂ enemas trigger UC in animals and humans. Additionally, it sparked inquiries into whether this phenomenon has a connection to naturally occurring human UC. Interest in H₂O₂ was further heightened by a review describing the histology of 14 chemicals causing colitis in which only H₂O₂ is described as being similar to UC[8]. This drew attention to H₂O₂, especially in view of the next study.

1970

Scientists discover that living cells generate H₂O₂[9]. This study marked the first biochemical evidence suggesting that H₂O₂ produced by colonic epithelial cells is the previously unidentified chemical secreted by colonic epithelial cells leading to the development of UC. Given that H₂O₂ is a well-known oxidizing agent, the findings highlighted the possibility that oxidative stress arising from excessive colonic epithelial H₂O₂ production plays a role in the pathogenesis of UC. This study served to focus inquiry on the biophysical and biochemical properties of H₂O₂, its cellular origins, and the ways in which environmental factors associated with UC may elevate intracellular H₂O₂ levels within colonic epithelial cells.

1979

An essential advancement in understanding emerged with the discovery that H₂O₂ is highly permeable through cell membranes[10]. Specific membrane aquaporin channels, known as peroxiporins, were subsequently identified as facilitators of H₂O₂ transmembrane permeability[11]. This finding established a mechanism by which H₂O₂ could exit colonic epithelial cells and engage with the innate immune system—an indispensable process if H₂O₂ is to play a role in the pathogenesis of UC. Peroxiporins are also found on mitochondrial membranes[12]. This allows diffusion of mitochondrial H₂O₂ throughout the cell to serve a messenger function but also provided a means for H₂O₂ to flood the cell during times of excess H₂O₂ production.

1987

5-aminosalicylic acid (5-ASA), the mainstay for the treatment of UC, is determined to be a reducing agent (antioxidant or radical scavenger)[13]. 5-ASA reacts efficiently with H₂O₂, during which 5-ASA undergoes oxidation to form the corresponding quinone-imine while simultaneously reducing H₂O₂ to water, as demonstrated in the following reaction (Figure 1).

The reaction proceeds spontaneously; however, its rate can be enhanced by peroxidases present in the inflammatory environment, such as neutrophilic myeloperoxidase, or by bacterial peroxidases located in the colonic lumen[14-16]. Significantly, 5-ASA exhibits therapeutic specificity for the inflammation associated with UC and does not function as a general anti-inflammatory agent[17]. Later studies demonstrated elevated colonic H₂O₂ in the uninvolved colonic epithelium in UC but not in Crohn's disease or healthy controls (detailed below). These observations lend further support to a causal role for H₂O₂ in the pathogenesis of UC.

5-ASA was first synthesized as the prodrug sulfasalazine in 1939 by combining the antibiotic sulfapyridine with salicylic acid[18]. In this compound, sulfapyridine is linked to carbon 5 of salicylic acid's aromatic ring *via* an azo bond (Figure 2).

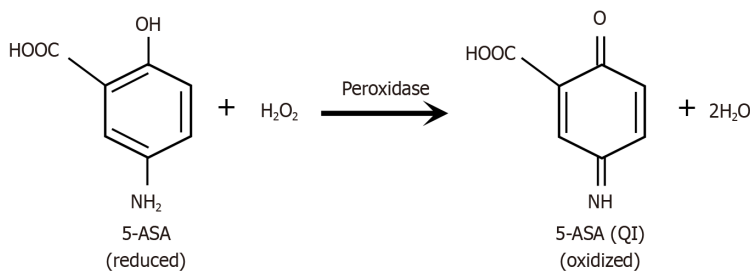


Figure 1 The redox-mediated reaction between 5-aminosalicylic acid, functioning as a reducing agent, and hydrogen peroxide, an oxidizing agent, involves the transfer of electrons. In this process, a single molecule of reduced 5-aminosalicylic acid (5-ASA) donates two electrons, accompanied by two protons, to reduce one molecule of hydrogen peroxide into two molecules of water. In the process, 5-ASA is oxidized to the corresponding 5-ASA quinone imine. The reaction is spontaneous but enhanced by peroxidase enzymes found in the inflammatory field or colonic bacteria. 5-ASA: 5-aminosalicylic acid; H₂O₂: Hydrogen peroxide; H₂O: Water; QI: Quinone imine.

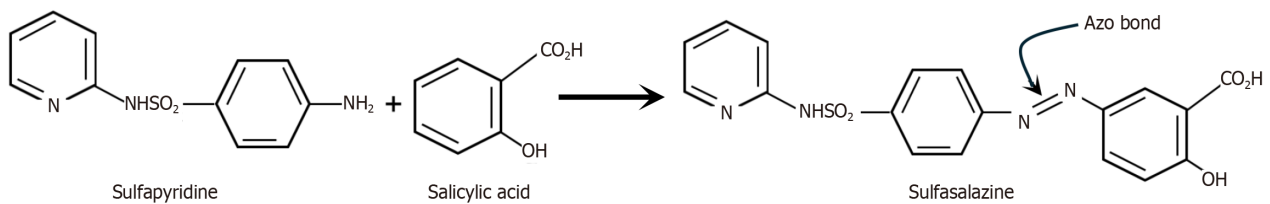


Figure 2 The reaction of the antibiotic sulfapyridine with salicylic acid to create sulfasalazine. The sulfonamide antibiotic sulfapyridine was chemically combined with salicylic acid to synthesize the prodrug sulfasalazine. This synthesis involved the formation of an azo bond, which linked the two molecules into a single compound, sulfasalazine. Synthesis of the larger molecule sulfasalazine, and the incorporation of the azo bond proved to be pivotal in ensuring the clinical efficacy of sulfasalazine in the treatment of ulcerative colitis.

After ingestion, 5-ASA is released from sulfasalazine (along with sulfapyridine) when acted upon by bacterial azo reductase in the colon (Figure 3). A total of 4 electrons are donated by azo reductase to reduce the azo bond[19]. Two electrons are added to generate the reduced form of 5-ASA while two remain with sulfapyridine. The reduction of the azo bond introduces an amino group at the aromatic-ring's 5th carbon of salicylic acid, a compound devoid of therapeutic activity in UC or H₂O₂ reducing capacity. This process transforms salicylic acid into 5-ASA, a H₂O₂ reducing agent with targeted efficacy in treating UC. The two electrons added by bacterial azo reductase to create 5-ASA facilitates its function as a reducing agent. This transformation suggests a key therapeutic role for the newly acquired reductive capacity of 5-ASA.

This supports a mechanism whereby 5-ASA induces remission by acting as a topical reductive sink for neutrophil generated H₂O₂. This eliminates the H₂O₂-dependent chemotactic signal that attracts additional neutrophils into the colonic lamina propria. 5-ASA can maintain remission by continuing to serve as a reductive sink for H₂O₂ diffusing from colonic epithelial cells, thereby preventing relapse. The capacity of 5-ASA to act as a reducing agent and interact with H₂O₂ further reinforces the evidence supporting H₂O₂'s causal role in the pathogenesis of UC.

1994

This study identified abnormal cellular metabolism in colonic biopsies from individuals with UC in remission. Specifically, it demonstrated the inhibition of beta-oxidation of n-butyrate, a short-chain fatty acid that serves as a primary energy source for colonic epithelial cells[20]. This finding holds substantial significance as beta-oxidation takes place in the mitochondria, the primary site of cellular H₂O₂ generation. Notably, the inhibition of beta-oxidation was observed weeks prior to relapse supporting the notion of a colonic epithelial abnormality preceding disease recurrence [21]. It further suggests the possibility that the inhibition of beta-oxidation might result from an initial accumulation of H₂O₂, which subsequently exits the cell, initiating the development of UC. These findings provide biochemical evidence highlighting a critical role of the colonic epithelium in the pathogenesis of UC.

H₂O₂ was subsequently demonstrated to inhibit beta-oxidation (discussed further below). This progression suggested that the initial accumulation of H₂O₂ within mitochondria resulted in the inhibition of beta-oxidation. This was followed by relapse weeks later as mitochondrial H₂O₂ diffused into the cytoplasm and, ultimately, into the extracellular space.

1996

H₂O₂ is shown to be highly chemotactic for neutrophils[22]. This was another critical piece of the puzzle. This phenomenon explains why H₂O₂ introduced into the colons of mice and humans (inadvertently during colonoscopy) can lead to the onset of UC. H₂O₂ is one of the few molecules that are capable of attracting neutrophils, which are the first responding cells in UC. Given that H₂O₂ is bio-membrane permeable, it indicated that excess H₂O₂, when present in the colonocyte, could easily diffuse through the colonocyte cell membrane into the lamina propria, where blood vessels

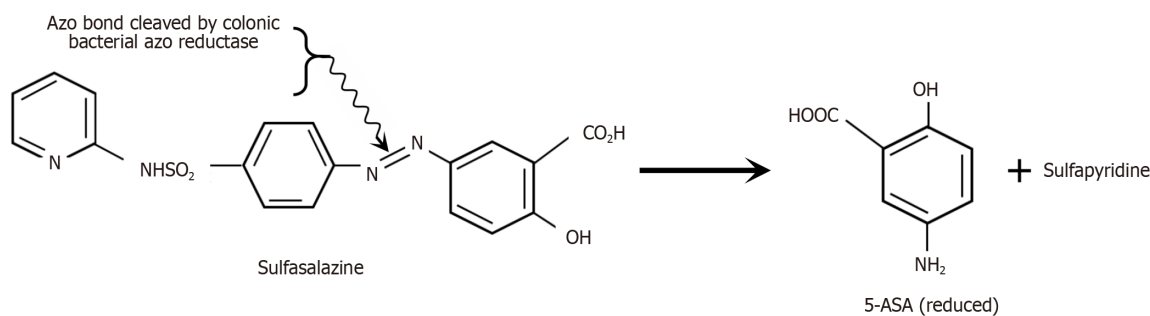


Figure 3 The reduction of the azo bond in sulfasalazine produces 5-aminosalicylic acid and sulfapyridine. While unconjugated 5-aminosalicylic acid (5-ASA) is predominantly absorbed in the small intestine before it can reach the colon, sulfasalazine largely remains unabsorbed during its transit through the small intestine. Upon reaching the colon, bacterial azo reductases reduce the azo bond, releasing free reduced 5-ASA and sulfapyridine. This reduction reaction introduces an amino group to the No. 5 carbon in the aromatic ring of salicylic acid, resulting in the formation of reduced 5-ASA. Reduction of the azo bond enhances the electron density of the resulting 5-ASA, enabling it to function as a reducing agent and effectively neutralize hydrogen peroxide in the colonic lumen. 5-ASA: 5-aminosalicylic acid.

reside. Once in the lamina propria, H₂O₂ would initiate the directed migration of neutrophils from the blood vessels, *via* diapedesis, into the colonic epithelium and subsequently the development of UC. The precise mechanism by which H₂O₂ attracts neutrophils was elucidated in 2021[23].

Up until now we know that H₂O₂ is produced intracellularly and is a biomembrane permeable neutrophilic chemotactic agent that is capable of causing UC when introduced into the colon. This observation suggested that UC may originate from the primary accumulation of H₂O₂ within colonic epithelial cells. The remaining critical question is: Can colonic epithelial cells generate sufficient levels of H₂O₂ to initiate UC? The next study provided the missing evidence and addressed this pivotal gap in knowledge.

2001

Glutathione peroxidase knockout mice, which lack the ability to neutralize H₂O₂, develop colitis that closely resembles human UC[24]. This finding represents a pivotal piece of evidence, demonstrating that colonic epithelial cells are capable of producing sufficient H₂O₂ to induce UC. This study further substantiated the causal role of the colonic epithelium in the pathogenesis of UC. It also confirmed prior hypotheses that an accumulation of excess H₂O₂ within colonic epithelial cells is the underlying cause of this disease.

2006

This study demonstrated that the distal large intestine (rectum) has the lowest reductive capacity of the entire large intestine[25]. This observation provides a biologically sound explanation for the long-standing question of why UC originates in the rectum and progresses proximally. The reduced reductive capacity results in the rectum becoming the initial site for H₂O₂ accumulation. As H₂O₂ diffuses into the colonic epithelial extracellular space, it attracts neutrophils, leading to the development of UC. The observed decline in reductive (antioxidant) capacity from the proximal to distal colon aligns seamlessly with H₂O₂ playing a causal role in the pathogenesis of UC. To date, no alternative explanation has adequately addressed why UC begins in the rectum and advances proximally. This finding adds to the cumulative evidence supporting an etiological role for H₂O₂ in UC pathogenesis. This observation contributes to the growing body of evidence that supports H₂O₂ as a causal factor in the pathogenesis of UC.

2007

This study was the first to report significantly elevated levels of H₂O₂ production in colonic biopsies from individuals with UC in remission, compared to those with Crohn's disease or healthy controls[26]. This discovery provides compelling evidence supporting the role of colonic epithelial H₂O₂ as the etiological agent in the development of UC. Moreover, the detection of elevated H₂O₂ levels in colonic epithelial cells prior to the onset of colitis fulfills the absolute criterion of temporality required to establish a cause-and-effect relationship between H₂O₂ (the cause), which must be present before UC (the effect).

These results also resolved the long-standing question of why the inhibition of colonic epithelial cell beta-oxidation is followed, after several weeks, by disease relapse[21]. As mitochondrial H₂O₂ levels continue to rise, it first inhibits mitochondrial thiolase leading to impaired beta-oxidation after which H₂O₂ exits the mitochondrion and enters the cytoplasm. Subsequently, it diffuses through the cell membrane into the colonic epithelial extracellular space, where it attracts neutrophils to the colon, ultimately leading to the development of UC. The entire interval can span several weeks (discussed below).

This approach highlights the critical importance of analyzing pre-existing experimental data to develop a biologically coherent model of pathogenesis, subsequently validated through laboratory experimentation. The practical result is the formulation of an innovative therapeutic strategy for the treatment of UC. This novel intervention targets the colonic epithelium by supplying the deficient reducing equivalents necessary to neutralize excess H₂O₂, thereby re-establishing and maintaining redox homeostasis.

By eliminating the H₂O₂-induced immunologic chemotactic signal that attracts neutrophils into the colonic epithelium, this approach resolves colonic inflammation and leads to the complete resolution of UC[27]. In other words, achieving colonocyte redox homeostasis prevents the diffusion of H₂O₂ into the extracellular environment, halting neutrophilic infiltration and recurrent episodes of UC. This is the same mechanism used naturally by the colonocyte to prevent extracellular diffusion of H₂O₂. Ultimately, this outcome represents a functional cure.

At this point, we have come full circle, showcasing the classic bench-to-bedside application of experimental evidence to establish a causal role for colonic epithelial H₂O₂ in the pathogenesis of UC. This breakthrough has led to an effective new treatment approach and holds promise for a potential cure for this chronic, debilitating disease.

DISCUSSION

H₂O₂ generation

All cells generate H₂O₂ as consequence of cellular metabolism. The production of H₂O₂ is not static and is influenced by the fluctuating nature of metabolic activity in the cell at any given time. To maintain redox homeostasis and prevent the buildup of H₂O₂ cells must adjust their reductive (antioxidant) capacity in response to these fluctuations. This involves modulating the synthesis of reducing equivalents, such as glutathione and thioredoxin, to prevent the harmful accumulation of H₂O₂ within the cell. Such adaptive mechanisms enable cells to enhance their metabolic activity in response to external stimuli without adverse effects from excess intracellular H₂O₂. However, if H₂O₂ production surpasses the reductive capacity of the colonocyte, intracellular H₂O₂ can accumulate and diffuse through the cell membrane into the extracellular microenvironment. This diffusion triggers the recruitment of intravascular neutrophils to the colonic epithelium, ultimately leading to the development of UC (Figure 4)[28-30].

Loss of redox homeostasis

Thus, external (to the cell) stimuli are transduced to the cell interior as a change in metabolic activity, which can translate into higher H₂O₂ levels. Various external factors can enhance H₂O₂ production through alterations in cellular metabolism. A good example is the metabolism of soluble fiber in the colon to form n-butyrate, a short chain fatty acid that provides most of the energy used by the colonic epithelial cell. Normally, ingested soluble fiber is fermented by colonic bacteria to generate n-butyrate and other short chain fatty acids. N-butyrate is absorbed by colonic epithelial cells and provides 70%-80% of the energy used by colonic epithelial cells[31]. Luminal soluble fiber is the beginning of a sequential bioenergetic pathway that includes colonic bacteria, butyrate, beta-oxidation and acetyl CoA. A deficiency of any one of these elements can usher in metabolic changes, leading to a loss of redox homeostasis and the accumulation of cellular H₂O₂. This can raise the risk of relapse or developing UC as illustrated in Figure 5A[32-34].

Other cellular sources become significant generators of H₂O₂ when exposed to specific oxidative stressors. Thus, mitochondria (smoking cessation), high fat diet (peroxisomes), drug metabolism (smooth endoplasmic reticulum), monoamine oxidase (stress) all known risk factors for UC can increase cellular H₂O₂ (Figure 5B)[35-38]. These processes establish a clear link between environmental factors that drive H₂O₂ production and the development of UC. This implies that H₂O₂ serves as the final common pathway through which environmental factors contribute to the pathogenesis of UC.

Oxidative stress

By definition, external stimuli that generate H₂O₂ are known as oxidative stressors. Exposure to these environmental oxidative stressors significantly increases the risk of developing or worsening UC. H₂O₂ is a potent cell membrane permeable neutrophilic chemotactic agent whose intracellular production is increased by exposure to environmental oxidative stressors. These characteristics establish H₂O₂ as both a necessary and sufficient causal factor in UC. Given that the final common pathway for all oxidative stressors in UC is H₂O₂, exposure to multiple contemporaneous sources of oxidative stress is cumulative over the short term. Cumulative exposure to oxidative stress can overwhelm cellular reductive capacity leading to UC.

New classification of UC

From an immunological perspective, H₂O₂ is an immune signaling agent that is inappropriately secreted by the colonic epithelium. However, the colonic epithelium is also capable of secreting other neutrophilic chemotactic agents that contribute to a histological presentation consistent with UC. This is exemplified by a documented case of UC arising in the context of disseminated candidiasis, which was successfully treated with anakinra, an interleukin (IL)-1 receptor antagonist[39]. In this case, IL-1 produced by activated macrophages induced colonic epithelial cells to secrete IL-8, which is a strong neutrophil chemotactic agent. Antagonism of colonic epithelial cell IL-1 receptors with anakinra prevented IL-8 secretion thereby resolving the colitis. These findings suggest that UC may be classified based on the specific chemotactic agent driving its pathogenesis, with H₂O₂ being the most prevalent. This further implies that the use of reducing agents to neutralize H₂O₂ could serve both diagnostic and therapeutic purposes. A positive therapeutic response would confirm a causal role for H₂O₂, whereas a lack of response would indicate involvement of an alternative chemotactic agent. Partial responses might signify a combined presence of H₂O₂ and other oxidative stressors, such as infection.

Recognizing environmental oxidative stressors entails probing the lived experience of patients with UC. Multiple jobs, school, work, sleep deprivation, dietary history, medication use, recent relocation, smoking cessation, lifestyle, *etc.*, can

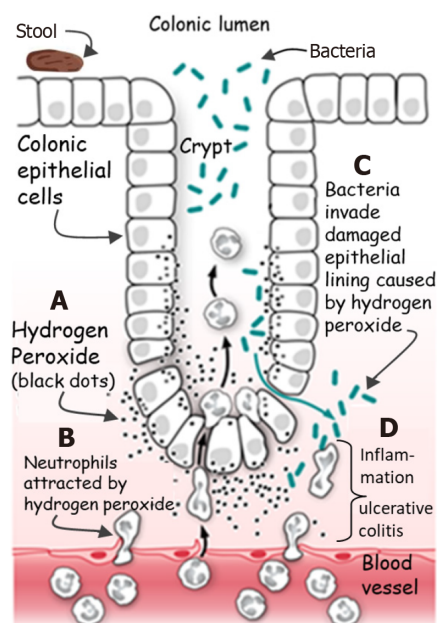


Figure 4 Evidence-based pathogenesis of ulcerative colitis. A: Hydrogen peroxide (H₂O₂) diffuses from colonic epithelial cells into the extracellular space and lamina propria; B: The neutrophilic chemotactic effect of H₂O₂ attracts neutrophils into the colonic epithelium; C: H₂O₂ disintegration of tight junctional proteins facilitates bacterial invasion into the sub-epithelial tissues; D: The ensuing mucosal inflammation leads to ulcerative colitis.

provide clues to identify the source of oxidative stress that can be targeted for mitigation. It can also provide clues to the cellular source of excess H₂O₂ as indicated above.

H₂O₂ explains the entire pathogenesis of UC

The evidence supporting a causal role for colonic epithelial cell H₂O₂ in the pathogenesis of UC is compelling. Patients with refractory UC have achieved histologic remission through the use of reducing agents, which neutralize excess colonic H₂O₂ by providing the reducing equivalents required by the colonic epithelium. This is supported by cessation of rectal bleeding within 1-2 weeks after initiation of treatment in addition to colonic biopsy results showing histologic remission in a case series of 36 patients with refractory UC[40]. Unsolicited feedback was received from one patient with a 30 + year history of refractory UC who was treated in 2007. His colonoscopy and biopsy performed 12 years later in 2019 was completely normal. The patient continues asymptomatic as of the date of this publication[41].

The use of reducing agents such as sodium thiosulfate (STS) and R-dihydrolipoic acid (RDLA) to induce and maintain remission, respectively, in UC is based on the evidence indicating that H₂O₂ plays a causal role in the pathogenesis (development) and pathophysiology (mucosal inflammation) of this inflammatory bowel disease. STS is an orally administered, water soluble extracellular reducing agent that is thought to neutralize H₂O₂ in the colonic lamina propria. This action abrogates the H₂O₂-induced chemotactic signal attracting neutrophils into the colonic epithelium, which induces remission. RDLA is a lipid soluble intracellular reducing agent that can normalize colonic epithelial cell H₂O₂, which maintains remission indefinitely as long as H₂O₂ does not exist the cell. Both have favorable safety profiles[42,27].

Evidence indicates that UC can be cured

Based on the available evidence, treatment with reducing agents represents a cure for UC in the same way that vitamin C is a cure for scurvy. This implies that relapse cannot occur as long as colonic redox homeostasis is maintained, which prevents the extracellular diffusion of colonic epithelial cell H₂O₂, thereby precluding the recruitment of neutrophils into the colonic epithelium. In contrast, nearly 25% of patients with UC do not respond to biologics and almost 60% of patients eventually lose their response[43]. Additionally, biologics (an immunosuppressive agent) neither offer a cure for UC nor significantly reduce the risk of surgical intervention in cases of moderate to severely active UC[44]. Furthermore, studies report that 66%-88.5% of patients with UC receiving Janus kinase (JAK) inhibitors (another immunosuppressive agent) fail to achieve clinical remission with 34%-52% maintaining clinical remission at one year[45]. Notably, even induction rates for emerging therapeutic agents remain stagnated, at approximately 20%-30% in clinical trials[46].

Tweaking a study to orchestrate significance helps profits, not patients

Numerous strategies have been proposed to enhance the response rates to immunosuppressive agents[46], including: (1) Excluding refractory patients from clinical trials; (2) Administering multiple immunosuppressive agents to individual patients; (3) Reducing placebo response rates by employing central reading to achieve statistical significance; (4) Replacing human central reading with automated systems; (5) Developing new scoring systems that are better suited to the limitations of immunosuppressive agents; (6) Implementing stricter exclusion criteria to identify trial participants who are using other medications (e.g., steroids); (7) Establishing new endpoints to evaluate therapeutic response; (8) Employing innovative clinical trial designs; and (9) Introducing standardized biopsy sampling procedures.

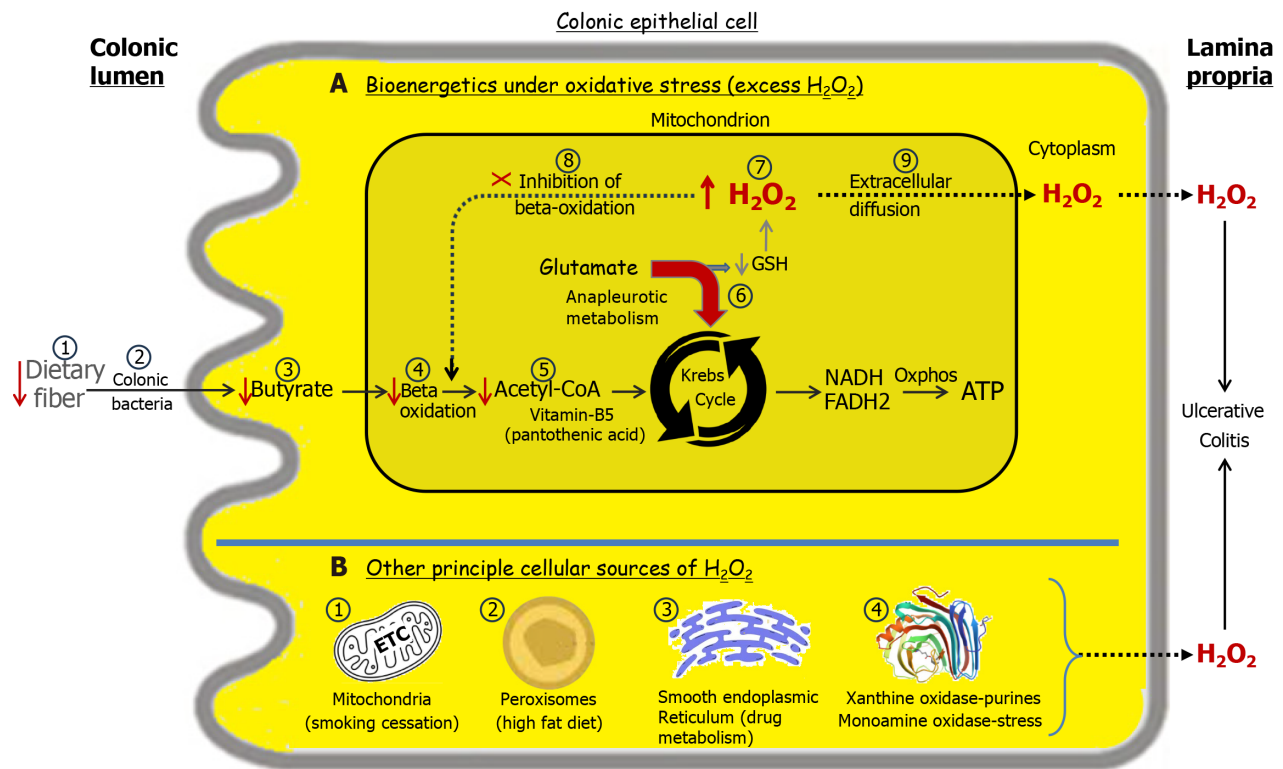


Figure 5 Transduction of environmental stimuli increases cellular hydrogen peroxide levels, elevating the risk of ulcerative colitis[27].

Normal energy flux in the colon begins with luminal soluble fiber, which is fermented by bacteria into *n*-butyrate, a key short-chain fatty acid. Butyrate is absorbed by colonic epithelial cells, where it undergoes beta-oxidation, generating acetyl-CoA. Subsequently, acetyl-CoA enters the Krebs cycle, producing the reducing equivalents NADH, nicotinamide adenine dinucleotide (reduced form) and FADH₂, flavin adenine dinucleotide (reduced form) that drive oxidative phosphorylation to generate ATP, adenosine triphosphate. Panel A: Bioenergetics under oxidative stress. A deficiency in dietary soluble fiber (A1) results in inadequate butyrate production (A3) and reduced acetyl-CoA levels (A5). To offset the energy shortfall, the Krebs cycle engages in anaplerotic metabolism of glutamate (A6)[32,33]. This redirection of glutamate for energy production compromises glutathione synthesis required for hydrogen peroxide (H₂O₂) neutralization leading to elevated cellular H₂O₂ levels (A7). With sufficient accumulation, mitochondrial H₂O₂ can diffuse into the cytoplasm and across the cell membrane into the lamina propria, contributing to the development of ulcerative colitis (UC) (A9). A reduction in acetyl-CoA due to deficiencies in any factors involved in its synthesis, starting with luminal fiber, can lead to elevated cellular H₂O₂ levels, increasing the risk of UC. This is exemplified by a deficiency of vitamin B5, required for the synthesis of coenzyme A, which leads to a colitis in pigs analogous to human UC[34]. Initially, H₂O₂ accumulates within mitochondria, impairing beta oxidation, and is followed by relapse weeks later [21]. This delay reflects the time needed for mitochondrial H₂O₂ to establish a sufficient concentration gradient for cytoplasmic and extracellular diffusion. This explains why butyrate enemas are ineffective in resolving UC as H₂O₂ inhibits beta oxidation (A8)[26]. Sufficient damage to the colonic microbiota (A2) may increase the risk of developing or exacerbating UC. Panel B: The source of H₂O₂ production is influenced by the nature of the environmental stimuli[27]. B1: Disinhibition of the mitochondrial electron transport chain following smoking cessation can result in elevated H₂O₂ production, contributing to the development of ulcerative colitis[35]. B2: A diet rich in fats promotes increased peroxisomal beta-oxidation of long-chain fatty acids, leading to heightened H₂O₂ production, which predisposes individuals to UC. B3: The metabolism of certain drugs, such as nonsteroidal anti-inflammatory drugs, *via* cytochrome P450 enzymes in the smooth endoplasmic reticulum generates H₂O₂[36], which may contribute to the onset or relapse of UC. B4: Xanthine oxidase metabolizes purines found in red meat, producing significant amounts of H₂O₂[37]. Monoamine oxidase-A metabolizes serotonin released by enterochromaffin cells in the colon under stress, generating significant amounts of H₂O₂[38]. Oxidative stressors are stimuli that increase H₂O₂ in the body. More than one can be present simultaneously and contribute to UC development or relapse. H₂O₂: Hydrogen peroxide; NADH: Nicotinamide adenine dinucleotide (reduced); FADH₂: Flavin adenine dinucleotide (reduced); ATP: Adenosine triphosphate; GSH: Glutathione.

These methodological modifications are designed to increase statistical significance of clinical trials in order to secure regulatory approval by compensating for the inherent limitations of immunosuppressive agents, which do not address the underlying cause of UC. While such optimizations to trial design may succeed in gaining approval for additional immunosuppressive therapies, allowing pharmaceutical companies to claim their share of the insurance market, they do nothing to genuinely benefit patients with UC and instead contribute to escalating healthcare costs. An alternative and potentially transformative solution lies in addressing confirmation bias, which perpetuates an exclusive focus on immune dysregulation and ineffective immunosuppressive therapies.

Dependence isn't accidental

Reflecting on the patient's journey with a chronic disease such as UC, the cycle of ethical concern revolves around the interplay between learned helplessness and the erosion of personal agency. When individuals are led to believe their condition is incurable, a sense of futility takes hold, fostering dependence and diminishing autonomy. This gives rise to a learned helplessness, reinforced by reliance on long-term, expensive and potentially harmful immunosuppressive medications, creating a feedback loop. The prolonged dependence perpetuates the feelings of helplessness, discouraging individuals from exploring alternative solutions or taking control of their own health. Confined to a system that offers no

cure, individuals normalize their illness as a coping mechanism, unaware that they are both patients and victims of the very system from which they seek help. Breaking this cycle necessitates not only empowering individuals to reclaim agency but also challenging established narratives about disease pathogenesis and management.

Research diversity is essential for finding cures

A critical element in disrupting this cycle is fostering research diversity. By encouraging exploration of innovative approaches to disease pathogenesis, we can open doors to new understandings and perspectives that may contradict the prevailing narratives of incurability. Diverse research efforts allow for the examination of novel biological, environmental, and social factors that could reshape our understanding of how diseases develop and progress. Research diversity in inflammatory bowel disease is essential for uncovering the root causes of disease, enabling targeted solutions that address these causes directly rather than relying on symptom management with immunosuppressive agents. This diversity is vital in paving the way for groundbreaking discoveries that challenge entrenched medical dogmas and offer new solutions that restore the public trust in medical research, which is at an all-time low[47].

CONCLUSION

The evidence indicates that UC is a metabolic disease characterized by impaired colonic redox homeostasis leading to excess H₂O₂, a condition that cannot be effectively treated or cured with immunosuppressive agents. There are approximately 1.9 million individuals living with UC in the United States according to the NHANES 2009-2010 United States inflammatory bowel disease diagnosed prevalence[48]. The continued long-term reliance on immunosuppressive therapies has resulted in a generation of predominantly young individuals with chronic UC who face significant life-long challenges, including an uncertain future, financial insecurity, and persistent emotional distress. These issues are compounded by the narrow focus on developing new and largely ineffective, immunosuppressing drugs. This approach not only jeopardizes the well-being of many young lives but also places an unsustainable financial strain on the healthcare system. The cost of these immunosuppressive agents is reported to range between 50000 Dollars and 75000 Dollars *per patient* annually in 2021[49]. This represents a lifetime total cost for the prevalent 2016 UC population in the United States of 377 billion Dollars, or 508 billion Dollars when adjusted for inflation in 2025[50]. And that's just one disease. If the United States government wants to save its healthcare system and preserve sustainability for future generations, it is imperative for United States policymakers to mandate that therapeutic approaches are grounded in an evidence-based understanding of pathogenesis, starting with a thorough evaluation of the current treatment strategies for UC.

The treatment of UC with immunosuppressive therapies including biologics, JAK inhibitors, and small molecules, *etc.* has reached a therapeutic plateau[51,52]. These interventions are fundamentally limited in their effectiveness, as none address the underlying etiology of UC. Consequently, the therapeutic ceiling can never be overcome, as the efficacy of one immunosuppressive agent is just about as good or bad as the other[53]. As a result, the management of UC has devolved into an unpredictable trial-and-error process—essentially a speculative attempt to determine which, and how many, of the 16 currently approved immunosuppressive drugs a patient can tolerate[54]. This often continues until physicians resort to recommending a total colectomy. These practices amount to unconsented post-marketing human experimentation under the guise of medical care. This is the future for the approximately 30% of the 1.9 million individuals in the United States diagnosed with UC including nearly 600000 children, adolescents, and young adults who are projected to become refractory to all immunosuppressive therapies, ultimately requiring surgical removal of their entire large intestine[55-58].

From 2000 to 2021, nearly 7400 individuals with UC succumbed to their disease, including 440 deaths in 2021 alone [59]. This was accompanied by an increase in the UC mortality rate and the number of annual deaths attributable to UC. Despite the availability of “advanced therapy” immunosuppressive agents (biologics, Janus kinase inhibitors, *etc.*), mortality rates have shown an upward trend. These therapies do not target the underlying cause of UC and are not curative. This is reflected in the progressive nature of this disease, which often results in severe outcomes, including surgery or death, for many patients. Unfortunately, there is no indication that this ominous trend will improve as long as highly profitable immunosuppressive agents are prioritized as long-term treatments, to the exclusion of innovative therapeutic approaches and alternative perspectives regarding disease pathogenesis. This dire prognosis, coupled with documented reports of undisclosed harms to patients with UC participating in induction and maintenance clinical trials [60,61], underscores profound ethical concerns within the continuum of UC drug approval and patient care. Such practices are not only exploitative but raise serious ethical concerns regarding how these immunosuppressive agents have been able to dominate the entire global therapeutic landscape of inflammatory bowel disease to the exclusion of new ideas or innovative therapies that might lead to a cure and save many lives.

Given the lack of a guiding pathogenesis and the dominance of highly lucrative (but largely ineffective) immunosuppressive drugs, a collective descent into a normalization of deviance within this field appears to have been inevitable. This issue is further exacerbated by the overconfidence on internal expertise, fostering an insular environment perpetuated by uniformity of thought and limited external perspectives, ultimately resulting in a culture deeply resistant to change. The factors contributing to the ethical drift within the field of inflammatory bowel disease are beyond the scope of this review. Nevertheless, they warrant thorough investigation to identify the underlying causes of this decline, so they can be replaced with a research environment that prioritizes and incentivizes creativity and innovation in pathogenesis and therapeutics, thereby maximizing the potential for discovering cures. The optimal achievement of immunosuppressive therapy, including biologics and Jak inhibitors (“advanced therapy”), has been the transformation of

UC from a highly fatal disease in the early 20th century to its current status as a progressive condition[62,63]. It is now crucial to move forward and embrace emerging evidence that holds the potential to advance toward a cure.

The pioneering gastroenterologist Sydney Truelove[64] (1913-2002) asserted “The ideal way to treat any disease is based on a thorough knowledge of the aetiology so that the root causes can be attacked directly”. We have the opportunity to apply this principle to UC and potentially achieve a cure. However, without a unified and dedicated effort from leaders in the field to rigorously evaluate the existing evidence, the prospects of alleviating the lifelong suffering and avoiding disfiguring surgeries and heightened risk of death for the millions afflicted by this disease remain unattainable. This was true for peptic ulcer in the past and continues to be relevant for inflammatory bowel disease today.

FOOTNOTES

Author contributions: Pravda J is the sole author of this manuscript and solely responsible for its content; Pravda J performed all the research, collected, analyzed, and interpreted all the data, conceived of and developed the hydrogen peroxide-based pathogenesis of ulcerative colitis, prepared and wrote the manuscript and performed all critical revisions, certifies that this manuscript is the product of his original research and has overall responsibility for this manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Open Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country of origin: United States

ORCID number: Jay Pravda 0000-0001-5737-5506.

S-Editor: Fan M

L-Editor: A

P-Editor: Zheng XM

REFERENCES

- Porter RJ, Kalla R, Ho GT. Ulcerative colitis: Recent advances in the understanding of disease pathogenesis. *F1000Res* 2020; **9**: F1000 Faculty Rev-F1000 Faculty 294 [PMID: 32399194 DOI: 10.12688/f1000research.20805.1] [FullText]
- Kirsner JB. The historical basis of the idiopathic inflammatory bowel diseases. *Inflamm Bowel Dis* 1995; **1**: 2-26 [DOI: 10.1002/ibd.3780010103] [FullText]
- Sheehan JF, Brynjolfsson G. Ulcerative colitis following hydrogen peroxide enema: case report and experimental production with transient emphysema of colonic wall and gas embolism. *Lab Invest* 1960; **9**: 150-168 [PMID: 14445720] [FullText]
- Warren S, Sommers SC. Pathogenesis of ulcerative colitis. *Am J Pathol* 1949; **25**: 657-679 [PMID: 18152861] [FullText]
- Kirsner JB. Historical aspects of inflammatory bowel disease. *J Clin Gastroenterol* 1988; **10**: 286-297 [PMID: 2980764 DOI: 10.1097/00004836-198806000-00012] [FullText]
- Pumphrey RE. Hydrogen peroxide proctitis. *Am J Surg* 1951; **81**: 60-62 [PMID: 14799687 DOI: 10.1016/0002-9610(51)90181-x] [FullText]
- Chapman NJ, Brown ML, Phillips SF, Tremaine WJ, Schroeder KW, Dewanjee MK, Zinsmeister AR. Distribution of mesalamine enemas in patients with active distal ulcerative colitis. *Mayo Clin Proc* 1992; **67**: 245-248 [PMID: 1545592 DOI: 10.1016/s0025-6196(12)60100-1] [FullText]
- Sheibani S, Gerson LB. Chemical colitis. *J Clin Gastroenterol* 2008; **42**: 115-121 [PMID: 18209577 DOI: 10.1097/MCG.0b013e318151470e] [FullText]
- Sies H, Chance B. The steady state level of catalase compound I in isolated hemoglobin-free perfused rat liver. *FEBS Lett* 1970; **11**: 172-176 [PMID: 11945479 DOI: 10.1016/0014-5793(70)80521-x] [FullText]
- Chance B, Sies H, Boveris A. Hydroperoxide metabolism in mammalian organs. *Physiol Rev* 1979; **59**: 527-605 [PMID: 37532 DOI: 10.1152/physrev.1979.59.3.527] [FullText]
- Bienert GP, Möller AL, Kristiansen KA, Schulz A, Möller IM, Schjoerring JK, Jahn TP. Specific aquaporins facilitate the diffusion of hydrogen peroxide across membranes. *J Biol Chem* 2007; **282**: 1183-1192 [PMID: 17105724 DOI: 10.1074/jbc.M603761200] [FullText]
- da Silva IV, Mlinarić M, Lourenço AR, Pérez-García O, Čipak Gašparović A, Soveral G. Peroxiporins and Oxidative Stress: Promising Targets to Tackle Inflammation and Cancer. *Int J Mol Sci* 2024; **25**: 8381 [PMID: 39125952 DOI: 10.3390/ijms25158381] [FullText]
- Ahnfelt-Rønne I, Nielsen OH. The anti-inflammatory moiety of sulfasalazine, 5-aminosalicylic acid, is a radical scavenger. *Agents Actions* 1987; **21**: 191-194 [PMID: 2888280 DOI: 10.1007/BF01974941] [FullText]
- El Zein R, Ispas-Szabo P, Jafari M, Siaj M, Mateescu MA. Oxidation of Mesalamine under Phenoloxidase- or Peroxidase-like Enzyme Catalysis. *Molecules* 2023; **28**: 8105 [PMID: 38138595 DOI: 10.3390/molecules28248105] [FullText]
- Abdel-Hamid I, Ivnitki D, Atanasov P, Wilkins E. Fast Amperometric Assay for E. coli O157:H7 Using Partially Immersed Immuno-electrodes. *Electroanalysis* 1998; **10**: 758-763 [DOI: 10.1002/(sici)1521-4109(199809)10:11<758::aid-elan758>3.0.co;2-5] [FullText]
- Carlin G, Djursäter R, Smedegård G, Gerdin B. Effect of anti-inflammatory drugs on xanthine oxidase and xanthine oxidase induced depolymerization of hyaluronic acid. *Agents Actions* 1985; **16**: 377-384 [PMID: 3840323 DOI: 10.1007/BF01982876] [FullText]

- 17 **Hauso Ø**, Martinsen TC, Waldum H. 5-Aminosalicylic acid, a specific drug for ulcerative colitis. *Scand J Gastroenterol* 2015; **50**: 933-941 [PMID: 25733192 DOI: 10.3109/00365521.2015.1018937] [FullText]
- 18 **Svartz N**. Sulfasalazine: II. Some notes on the discovery and development of salazopyrin. *Am J Gastroenterol* 1988; **83**: 497-503 [PMID: 2896459] [FullText]
- 19 **Ryan A**. Azoreductases in drug metabolism. *Br J Pharmacol* 2017; **174**: 2161-2173 [PMID: 27487252 DOI: 10.1111/bph.13571] [FullText]
- 20 **Chapman MA**, Grahn MF, Boyle MA, Hutton M, Rogers J, Williams NS. Butyrate oxidation is impaired in the colonic mucosa of sufferers of quiescent ulcerative colitis. *Gut* 1994; **35**: 73-76 [PMID: 8307454 DOI: 10.1136/gut.35.1.73] [FullText]
- 21 **Den Hond E**, Hiele M, Evenepoel P, Peeters M, Ghooys Y, Rutgeerts P. In vivo butyrate metabolism and colonic permeability in extensive ulcerative colitis. *Gastroenterology* 1998; **115**: 584-590 [PMID: 9721155 DOI: 10.1016/s0016-5085(98)70137-4] [FullText]
- 22 **Klyubin IV**, Kirpichnikova KM, Gamaley IA. Hydrogen peroxide-induced chemotaxis of mouse peritoneal neutrophils. *Eur J Cell Biol* 1996; **70**: 347-351 [PMID: 8864663] [FullText]
- 23 **Morad H**, Luqman S, Tan CH, Swann V, McNaughton PA. TRPM2 ion channels steer neutrophils towards a source of hydrogen peroxide. *Sci Rep* 2021; **11**: 9339 [PMID: 33927223 DOI: 10.1038/s41598-021-88224-5] [FullText]
- 24 **Esworthy RS**, Aranda R, Martín MG, Doroshow JH, Binder SW, Chu FF. Mice with combined disruption of Gpx1 and Gpx2 genes have colitis. *Am J Physiol Gastrointest Liver Physiol* 2001; **281**: G848-G855 [PMID: 11518697 DOI: 10.1152/ajpgi.2001.281.3.G848] [FullText]
- 25 **Hoensch H**, Peters WH, Roelofs HM, Kirch W. Expression of the glutathione enzyme system of human colon mucosa by localisation, gender and age. *Curr Med Res Opin* 2006; **22**: 1075-1083 [PMID: 16846540 DOI: 10.1185/030079906X112480] [FullText]
- 26 **Santhanam S**, Venkatraman A, Ramakrishna BS. Impairment of mitochondrial acetoacetyl CoA thiolase activity in the colonic mucosa of patients with ulcerative colitis. *Gut* 2007; **56**: 1543-1549 [PMID: 17483192 DOI: 10.1136/gut.2006.108449] [FullText]
- 27 **Pravda J**. Evidence-based pathogenesis and treatment of ulcerative colitis: A causal role for colonic epithelial hydrogen peroxide. *World J Gastroenterol* 2022; **28**: 4263-4298 [PMID: 36159014 DOI: 10.3748/wjg.v28.i31.4263] [FullText]
- 28 **Rao RK**, Baker RD, Baker SS, Gupta A, Holycross M. Oxidant-induced disruption of intestinal epithelial barrier function: role of protein tyrosine phosphorylation. *Am J Physiol* 1997; **273**: G812-G823 [PMID: 9357822 DOI: 10.1152/ajpgi.1997.273.4.G812] [FullText]
- 29 **Seth A**, Yan F, Polk DB, Rao RK. Probiotics ameliorate the hydrogen peroxide-induced epithelial barrier disruption by a PKC- and MAP kinase-dependent mechanism. *Am J Physiol Gastrointest Liver Physiol* 2008; **294**: G1060-G1069 [PMID: 18292183 DOI: 10.1152/ajpgi.00202.2007] [FullText]
- 30 **Sasaki M**, Klapproth JM. The role of bacteria in the pathogenesis of ulcerative colitis. *J Signal Transduct* 2012; **2012**: 704953 [PMID: 22619714 DOI: 10.1155/2012/704953] [FullText]
- 31 **Gasaly N**, Hermoso MA, Gotteland M. Butyrate and the Fine-Tuning of Colonic Homeostasis: Implication for Inflammatory Bowel Diseases. *Int J Mol Sci* 2021; **22**: 3061 [PMID: 33802759 DOI: 10.3390/ijms22063061] [FullText]
- 32 **Kim MH**, Kim H. The Roles of Glutamine in the Intestine and Its Implication in Intestinal Diseases. *Int J Mol Sci* 2017; **18**: 1051 [PMID: 28498331 DOI: 10.3390/ijms18051051] [FullText]
- 33 **Blachier F**, Boutry C, Bos C, Tomé D. Metabolism and functions of L-glutamate in the epithelial cells of the small and large intestines. *Am J Clin Nutr* 2009; **90**: 814S-821S [PMID: 19571215 DOI: 10.3945/ajcn.2009.27462S] [FullText]
- 34 **CABI**. Pantothenic acid deficiency in swine. [cited June 23, 2025]. Available from: <https://www.cabidigitallibrary.org/doi/full/10.5555/19442201802>
- 35 **Pryor WA**, Arbour NC, Upham B, Church DF. The inhibitory effect of extracts of cigarette tar on electron transport of mitochondria and submitochondrial particles. *Free Radic Biol Med* 1992; **12**: 365-372 [PMID: 1317324 DOI: 10.1016/0891-5849(92)90085-u] [FullText]
- 36 **Gómez-Tabales J**, García-Martín E, Agúndez JAG, Gutierrez-Merino C. Modulation of CYP2C9 activity and hydrogen peroxide production by cytochrome b(5). *Sci Rep* 2020; **10**: 15571 [PMID: 32968106 DOI: 10.1038/s41598-020-72284-0] [FullText]
- 37 **Kelley EE**, Khoo NK, Hundley NJ, Malik UZ, Freeman BA, Tarpey MM. Hydrogen peroxide is the major oxidant product of xanthine oxidase. *Free Radic Biol Med* 2010; **48**: 493-498 [PMID: 19941951 DOI: 10.1016/j.freeradbiomed.2009.11.012] [FullText]
- 38 **Prah A**, Purg M, Stare J, Vianello R, Mavri J. How Monoamine Oxidase A Decomposes Serotonin: An Empirical Valence Bond Simulation of the Reactive Step. *J Phys Chem B* 2020; **124**: 8259-8265 [PMID: 32845149 DOI: 10.1021/acs.jpcc.0c06502] [FullText]
- 39 **Truyens M**, Hoste L, Geldof J, Hoorens A, Haerynck F, Huis In 't Veld D, Lobatón T. Successful treatment of ulcerative colitis with anakinra: a case report. *Acta Gastroenterol Belg* 2023; **86**: 573-576 [PMID: 38240554 DOI: 10.51821/86.4.11246] [FullText]
- 40 **Pravda J**, Weickert MJ, Wruble LD. Novel Combination Therapy Induced Histological Remission in Patients with Refractory Ulcerative Colitis. *J Inflamm Bowel Dis Disor* 2019; **4**: 1-9 [DOI: 10.4172/2476-1958.1000130] [FullText]
- 41 **Pravda J**, Gordon R, Sylvestre P. Sustained Histologic Remission (Complete Mucosal Healing) 12 Years after One-Time Treatment of Refractory Ulcerative Colitis with Novel Combination Therapy: A Case Report. *J Inflamm Bowel Dis Disorder* 2020; **5**: 1-5 [DOI: 10.37421/JIBDD.2020.5.132] [FullText]
- 42 **AlBugami MM**, Wilson JA, Clarke JR, Soroka SD. Oral sodium thiosulfate as maintenance therapy for calcific uremic arteriolopathy: a case series. *Am J Nephrol* 2013; **37**: 104-109 [PMID: 23363879 DOI: 10.1159/000346410] [FullText]
- 43 **Koo HM**, Jun YK, Choi Y, Shin CM, Park YS, Kim N, Lee DH, Shin YK, Yoon H. 10 years of biologic use patterns in patients with inflammatory bowel disease: treatment persistence, switching and dose intensification - a nationwide population-based study. *Therap Adv Gastroenterol* 2023; **16**: 17562848231201728 [PMID: 37786473 DOI: 10.1177/17562848231201728] [FullText]
- 44 **Yokoyama Y**, Ohta Y, Ogasawara S, Kato J, Arai R, Koseki H, Saito M, Kaneko T, Tokunaga M, Oura H, Oike T, Imai Y, Kanayama K, Akizue N, Kumagai J, Taida T, Okimoto K, Saito K, Ooka Y, Matsumura T, Nakagawa T, Arai M, Katsuno T, Fukuda Y, Kitsukawa Y, Kato N. The long-term effect of biologics in patients with ulcerative colitis emerging from a large Japanese cohort. *Sci Rep* 2022; **12**: 21060 [PMID: 36473879 DOI: 10.1038/s41598-022-25218-x] [FullText]
- 45 **Honap S**, Agorogianni A, Colwill MJ, Mehta SK, Donovan F, Pollok R, Poullis A, Patel K. JAK inhibitors for inflammatory bowel disease: recent advances. *Frontline Gastroenterol* 2024; **15**: 59-69 [PMID: 38487554 DOI: 10.1136/flgastro-2023-102400] [FullText]
- 46 **Alsoud D**, Verstockt B, Fiocchi C, Vermeire S. Breaking the therapeutic ceiling in drug development in ulcerative colitis. *Lancet Gastroenterol Hepatol* 2021; **6**: 589-595 [PMID: 34019798 DOI: 10.1016/S2468-1253(21)00065-0] [FullText]
- 47 **Blendon RJ**, Benson JM. Trust in Medicine, the Health System & Public Health. *Daedalus* 2022; **151**: 67-82 [DOI: 10.1162/daed_a_01944] [FullText]
- 48 **Weisman MH**, Oleg Stens, Seok Kim H, Hou JK, Miller FW, Dillon CF. Inflammatory Bowel Disease Prevalence: Surveillance data from the U.S. National Health and Nutrition Examination Survey. *Prev Med Rep* 2023; **33**: 102173 [PMID: 37223580 DOI: 10.1016/j.pmr.2023.102173] [FullText]

- 10.1016/j.pmedr.2023.102173] [FullText]
- 49 **Schultz BG**, Diakite I, Carter JA, Snedecor SJ, Turpin R. Cost-effectiveness of intravenous vedolizumab vs subcutaneous adalimumab for moderately to severely active ulcerative colitis. *J Manag Care Spec Pharm* 2021; **27**: 1592-1600 [PMID: 34714104 DOI: 10.18553/jmcp.2021.27.11.1592] [FullText]
- 50 **Lichtenstein GR**, Shahabi A, Seabury SA, Lakdawalla DN, Espinosa OD, Green S, Brauer M, Baldassano RN. Lifetime Economic Burden of Crohn's Disease and Ulcerative Colitis by Age at Diagnosis. *Clin Gastroenterol Hepatol* 2020; **18**: 889-897.e10 [PMID: 31326606 DOI: 10.1016/j.cgh.2019.07.022] [FullText]
- 51 **Raine T**, Danese S. Breaking Through the Therapeutic Ceiling: What Will It Take? *Gastroenterology* 2022; **162**: 1507-1511 [PMID: 34995533 DOI: 10.1053/j.gastro.2021.09.078] [FullText]
- 52 **Solitano V**, Hanžel J, Estevinho MM, Sedano R, Massimino L, Ungaro F, Jairath V. Reaching the therapeutic ceiling in IBD: Can Advanced Combination Treatment (ACT) offer a solution? *Best Pract Res Clin Ga* 2025 [DOI: 10.1016/j.bpg.2025.101981] [FullText]
- 53 **Jairath V**, Raine T, Leahy TP, Potluri R, Wosik K, Gruben D, Cappelleri JC, Hur P, Bartolome L. Efficacy and safety of advanced therapies for moderately to severely active ulcerative colitis in induction and maintenance: systematic literature review and Bayesian network meta-analysis. *J Comp Eff Res* 2025; **14**: e240225 [PMID: 40095567 DOI: 10.57264/cer-2024-0225] [FullText]
- 54 **Vieujean S**, Jairath V, Peyrin-Biroulet L, Dubinsky M, Iacucci M, Magro F, Danese S. Understanding the therapeutic toolkit for inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* 2025; **22**: 371-394 [PMID: 39891014 DOI: 10.1038/s41575-024-01035-7] [FullText]
- 55 **Wong DJ**, Roth EM, Feuerstein JD, Poylin VY. Surgery in the age of biologics. *Gastroenterol Rep (Oxf)* 2019; **7**: 77-90 [PMID: 30976420 DOI: 10.1093/gastro/goz004] [FullText]
- 56 **Liu S**, Eisenstein S. State-of-the-art surgery for ulcerative colitis. *Langenbecks Arch Surg* 2021; **406**: 1751-1761 [PMID: 34453611 DOI: 10.1007/s00423-021-02295-6] [FullText]
- 57 **DeLeon MF**, Stocchi L. Elective and Emergent Surgery in the Ulcerative Colitis Patient. *Clin Colon Rectal Surg* 2022; **35**: 437-444 [PMID: 36591393 DOI: 10.1055/s-0042-1758134] [FullText]
- 58 **Lee KE**, Faye AS, Vermeire S, Shen B. Perioperative Management of Ulcerative Colitis: A Systematic Review. *Dis Colon Rectum* 2022; **65**: S5-S19 [PMID: 36007165 DOI: 10.1097/DCR.0000000000002588] [FullText]
- 59 **Merza N**, Ahmed Z, Nawras M, Dar SH, Itani MI, Al-Hillan A, Zafar Y, Naguib T, Kobeissy AA, Hassan M, Islam A, Alastal Y. S946 Ulcerative Colitis Mortality Rate Trends the United States: Two-Decade Analysis Based on US Death Certificates. *Am J Gastroenterol* 2023; **118**: S709-S710 [DOI: 10.14309/01.ajg.0000953424.54975.0f] [FullText]
- 60 **Din S**, Segal J, Blackwell J, Gros B, Black CJ, Ford AC. Harms with placebo in trials of biological therapies and small molecules as induction therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2024; **9**: 1020-1029 [PMID: 39307145 DOI: 10.1016/S2468-1253(24)00264-4] [FullText]
- 61 **Gros B**, Blackwell J, Segal J, Black CJ, Ford AC, Din S. Harms with placebo in trials of biological therapies and small molecules as maintenance therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2024; **9**: 1030-1040 [PMID: 39307146 DOI: 10.1016/S2468-1253(24)00233-4] [FullText]
- 62 **Krugliak Cleveland N**, Torres J, Rubin DT. What Does Disease Progression Look Like in Ulcerative Colitis, and How Might It Be Prevented? *Gastroenterology* 2022; **162**: 1396-1408 [PMID: 35101421 DOI: 10.1053/j.gastro.2022.01.023] [FullText]
- 63 **Torres J**, Billioud V, Sachar DB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis as a progressive disease: the forgotten evidence. *Inflamm Bowel Dis* 2012; **18**: 1356-1363 [PMID: 22162423 DOI: 10.1002/ibd.22839] [FullText]
- 64 **Truelove SC**. Medical management of ulcerative colitis. *Br Med J* 1968; **2**: 605-607 [PMID: 5694768 DOI: 10.1136/bmj.2.5605.605] [FullText]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

