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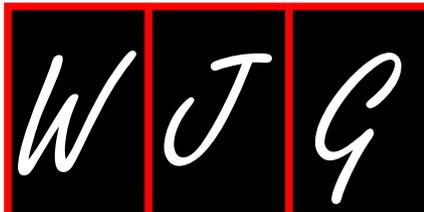
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## Montezuma's revenge - the sequel: The one-hundred year anniversary of the first description of "post-infectious" irritable bowel syndrome

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### Abstract

One-hundred years have passed since the original description of the commonly described phenomenon of persistent abdominal symptoms being triggered by an acute enteric infection. This first account was generated out of astute observations by Sir Arthur Hurst in World War I. Additional descriptions followed from military and non-military practitioners adding the evidence which has transitioned this recognized condition from association to causation. While mechanistic understanding is an area of active pursuit, this historical accounting of a centuries progress highlights important advances and contributions of military medicine and scientists to advances benefiting global populations.

**Key words:** Post-infectious irritable bowel syndrome; Medical history; Military medicine; Gastroenteritis; Travelers' diarrhea; Functional gastrointestinal disorder; Bacterial diarrhea

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**Core tip:** There are several reviews in the literature describing the clinical phenomenon of post-infectious irritable bowel syndrome including its history. However, this is the first review to consider the earliest description dating back nearly 100 years ago and describe the role of the individuals and context of discoveries that were

made, and the important contributions that military medicine has lent towards further understanding.

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## INTRODUCTION

"It takes good guts to be a good soldier"  
-Anonymous Civil War Observer

This reflection, though lost in attribution, transcends centuries where it was likely first remarked to describe the necessary qualities of nerve and grit required for military service in the 19<sup>th</sup> century<sup>[1]</sup>. However, it is possible the original intent was due to the fact that in the Civil War (and conflicts immemorial) the success in battle may well have depended on one's gastrointestinal constitution as much as bravery. Wars were once lost by the frequent alimentary casualties which rendered mass numbers of troops ineffectual and, before the advent of antibiotics and intravenous and oral rehydration, would kill by the thousands<sup>[2,3]</sup>.

But an even more transcendent meaning emerged decades later in 1918 where Sir Arthur Hurst first described the condition of frequently unexplainable chronic bowel problems well after a soldier's acute bout of dysentery had resolved<sup>[4]</sup>. Hurst, a British Physician and co-founder of the British Gastrointestinal Society, is recognized as a transformative and leading physician of the 20<sup>th</sup> century with an early career specializing in neurology where he made substantial contributions in understanding the etiology of War Neuroses during his appointment to the Royal Army Medical Corps in support of the Crimean War<sup>[5]</sup>. During duty assignments in Lemnos and Salonika, Hurst diagnosed and treated the broad range of ailments of ill and injured service members returning from the Gallipoli and Macedonia World War I battle fronts and methodically catalogued these observations in first and second editions of *Medical Diseases of War*<sup>[4]</sup>. In a section on Colitis and Irritability of the Colon following Dysentery of Chapter XII in the second edition, he recounts (p. 167):

"Patients who have recovered from an acute attack of dysentery frequently remain unfit for a considerable period, which may even extend to years. The symptoms are due to the chronic colitis, which may follow either amoebic or bacillary dysentery after the specific infection has died out...In most cases the patient suffers from alternating attacks of constipation and diarrhoea, the latter often being brought on by aperients taken for

the relief of the former, or it may follow an indiscretion in diet or exposure to cold...The diarrhoea may only last for a few hours, or it may continue for two or three days, the attacks being separated by intervals of several weeks or months...Sometimes the attacks of diarrhoea cease to occur, but intractable constipation remains and the general symptoms persist, though in a lessened degree."

One can imagine that he thought these observations of persistent abdominal symptoms after an acute bout of dysentery were unusual and shared such accounts with his colleagues who were treating similar patients. Dr. Hurst goes on further to relay accounts from his colleague, Thomas G Morehead of the Royal College of Physicians of Ireland who was treating patients in Egypt from the Gallipoli front and made similar observations as follows:

"...severe abdominal distension developed from four to eight months after the patient had apparently recovered from an attack of dysentery. They complained of a feeling of fullness in the abdomen, with dyspnea and general dyspeptic symptoms. The bowels were regular, and nothing abnormal was found except enormous tympanitic distension of the abdomen..."

These descriptions of non-ulcerative persistent abdominal symptoms spanning complaints of diarrhea, constipation, dyspepsia and bloating following an acute gastrointestinal infection are most likely the earliest written description of what we now regard to be post-infectious functional gastrointestinal disorders (FGD). This now expansively described phenomenon of incident FGDs after acute enteric infection has been detailed in a number of systematic reviews<sup>[6-8]</sup>. While there may have been alternative differential diagnoses including essential nutrient deficiencies, unmasking of organic bowel disease or chronic intestinal infections, the historical accounts from World War I indicate that patients with these symptoms were relatively common, had adequate intake of fresh fruits and vegetables (at least after returning home), lacked features of inflammatory bowel disease, and had cleared chronic infections (at least of amoeba). While the lack of detailed microbiological and endoscopic description leaves open the question of patho-etiology and association in Sir Arthur Hurst's account, the distinct characteristics of the "Post-dysenteric Irritable Colon Syndrome" describes features strikingly similar to the symptoms of PI FGD described today.

Following this earliest description of chronic gastrointestinal consequences of the Great War, a young Surgeon-Lieutenant physician epidemiologist in the Royal Navy, Gordon T. Stewart, detailed nearly 500 cases of hospital admitted acute and chronic amoebic and bacillary dysentery in service members serving in World War II<sup>[9]</sup>. In Stewart's 1950 paper in the *British Medical Journal* acute and chronic diarrheal and dysentery cases were

characterized with specific etiologies identified, treatment recorded, and follow-up at three months and beyond with repeated assessments for infectious etiologies associated with recurrent symptoms. An important contribution of this report was the thorough culture and microscopic work-ups for infections in addition to sigmoidoscopy for those with persistent infections. Twenty-nine of the 228 (12.7%) admitted to the Combined Services Hospital and 49 of the 246 (19.9%) patients treated at the Liverpool Tropical Diseases Centre were identified as having persistent colitis symptoms despite appropriate treatment and no evidence of persistent infection. Among the 49 persistent diarrheal cases followed in Liverpool, sigmoidoscopy was conducted with 27 showing no signs of overt inflammation and these were classified as "Functional Post-Dysenteric Colitis". The remaining 22 had evidence of inflammation (some with ulceration and bleeding) and evidence of persistent infection mucosal scrapings and were labeled "Ulcerative Post-Dysenteric Colitis". Treatments, including large doses of soluble and insoluble sulphonamides, penicillin, and chiniofon retention enemas yielded eventual improvement in all but 4 patients, who persisted with "idiopathic ulcerative colitis". Among the functional cases, the authors noted that the patients had a tendency towards concomitant neurotic and anxiety features and generally resolved over time but continued to persist indefinitely in a few.

In the intervening years, while the "functional irritable colon" patient was recognized as not-infrequent diagnosis, little original research was conducted until 1962, when Chaudhary and Truelove reported on a large case series of 130 patients with the "Irritable Colon Syndrome" being cared for at the Radcliff Infirmary at Oxford<sup>[10]</sup>. They observed that the condition was more predominant in women and first diagnosis occurred between 20 and 59 years of age, and over 60% reported symptoms being present for over a year (and more than 10 years in 24%). From their detailed description of quality, quantity and location of pain and associated bowel movement patterns they further classified these patients into two distinct groups: (1) A spastic colon group characterized by colonic pain and variable bowel habits with periodic constipation or diarrhea or both alternating, and (2) a painless diarrhea group defined by patients without pain but who had chronic diarrhea. While lacking adequate study design, the authors did comment upon possible predisposing causes based on extensive patient histories. Most notable was the observation that in 26% of patients' symptoms clearly started after a proven or presumptive episode of dysentery. Among those with "post-infective" irritable colon syndrome, a majority (63%) had resolved compared to only 29% of those cases which were not ascribed to follow a bout of infectious dysentery, suggesting a more favorable prognosis. Psychological co-morbidities were important factors in both post-dysentery and "idiopathic" cases.

Interestingly, it would be another three decades before the first study on post-infectious irritable bowel

syndrome (PI-IBS) was published where an adequate control group was utilized to explore disease incidence and risk. In 1999, Rodríguez and Ruigómez utilized medical encounter data from the United Kingdom General Practice Research Database to conduct a retrospective cohort study among a population with a bacteriologically-confirmed gastroenteritis episode and a comparator population subsequently followed for incident irritable bowel syndrome<sup>[11]</sup>. Medical encounter data were augmented with practitioner case-diagnosis validation surveys. IBS was identified in 4% of subjects with bacterial gastroenteritis, 12-fold higher than the rate in the comparative population with no history of gastroenteritis in the preceding year.

In just the past 20 years, the scientific literature has greatly expanded with more than 30 independent studies in which exposed subjects with infectious gastroenteritis consistently demonstrate a 4-fold increase in the risk of IBS compared to unexposed subjects with the highest rates observed after protozoal infection (41.9%) compared to bacterial (13.9%) or viral etiologies (6.4%)<sup>[6]</sup>. Similar risk estimates have been reported after travelers' diarrhea<sup>[7]</sup>, and the first modern epidemiological study defining PI-IBS among military travelers was reported in 2011 following acute infectious diarrhea episodes among United States troops deployed to Egypt and Turkey<sup>[12]</sup>. Features which appear to increase the risk include more severe disease, longer disease, female gender and psychological comorbidities, though not entirely consistently across the multiple studies<sup>[6]</sup>. Additionally, the syndrome tends to be more commonly associated with the diarrhea-predominant IBS phenotype.

Though the historical readings behind the centenary description of the origins of PI-IBS and studies of recent times may be of interest, we focus on the nature and challenges remaining in developing our understanding of etiology in the "functional" diseases as well as the sometimes limiting paradigm of Koch's postulates in ascertaining disease causality. Traditionally, Koch's postulates proved effective at establishing disease-pathogen relationships for acute illness but often falls short with more complex associations beyond one-pathogen, one-disease models<sup>[13,14]</sup>. An alternative paradigm is considered in Hill's criteria which includes strength of association, consistency of effect, specificity of effect, temporality, biological gradient or dose response, and biological plausibility to form the basis of an argument for causation<sup>[15]</sup>. For PI-IBS, strength, consistency, specificity, temporality and biological gradient are clearly evident. Where the field is focused and uncertainty remains, is in the area of biological plausibility. While intensive studies have explored the patho-etiological underpinning post-infectious IBS, unfortunately a unifying mechanism has not emerged. Rather there appears to be multiple mechanisms to disease progression including low-grade inflammation<sup>[16,17]</sup>, microbiome dysbiosis<sup>[18]</sup>, epithelial barrier dysfunction<sup>[19]</sup>, and auto-immunity<sup>[20]</sup>, bringing added complexity to potential treatment and preventive

solutions. Thus, while much as been learned over the 100 years since Hurst made his first observations, we are presently improved only in our ability to provide symptomatic therapies and an ability to put a name to the symptoms of an often frustrated patient. We remain without a diagnostic test, preventative or cure.

Finally, the appending of another contribution to the list of important discoveries and medical advancements by military medicine and science is noteworthy. Whether it be through the contributions of British Navy Captain James Lind in treating and preventing scurvy<sup>[21]</sup>, advancements of anesthesia during the Civil War<sup>[22]</sup>, development and use of mobile X-ray diagnostics in World War I by Marie Curie<sup>[23]</sup>, use of intramedullary nails to help heal fractures by the German military medical services during World War II<sup>[24]</sup>, pioneering contributions by Robert Phillips in the advancement of oral rehydration therapy after World War II<sup>[25]</sup>, advances in use of frozen blood products<sup>[26]</sup> during the Viet Nam war which are currently used today in saving countless lives around the world, or the early aggressive use of trauma management techniques in Iraq and Afghanistan<sup>[27]</sup>, many lives have been and continue to be saved throughout the world from these military lead medical advances. While the incalculable wastage of life and well-being that is attributed to armed conflict cannot be compared to the value of innovation that is often born out of necessity to retain dominance, the efforts to save and preserve life and limb by the many dedicated clinicians and researchers to their uniformed patients are laudable. Sir Arthur Hurst's astute inquiry and tireless dedication to his patients is also recognized and clearly led to further interest, investigation and advancement of understanding by those he mentored and taught.

## CONCLUSION

As legend would tell, Montezuma II, was the 9<sup>th</sup> Aztec Emperor between 1502 to 1520 when the Spanish, led by Hernan Cortés, began the conquest of modern day Mexico in the early 16<sup>th</sup> century<sup>[28]</sup>. Montezuma, who had perhaps observed the powerful Spanish forces with guns and cannons and crossbows and knew that his forces would be a poor match, attempted strategic diplomacy and appeasement to the invading Conquistadors and invited them into the city-capitol, Tenochtitlan, to negotiate. However, relations would quickly sour with skirmishes between arriving Spanish reinforcements and accusations of betrayal eventually led to Cortés taking Montezuma prisoner. Plunder and chaos in Tenochtitlan ensued and in an effort by to quell the masses, Cortés had Montezuma address the crowds from the palace roof to which he was met with hurled stones and spears from his own people and died three days later of his wounds (though some claim that Cortés had him strangled). Reinforcements would arrive, and smallpox disease spread throughout the susceptible native population assuring the fall of the

Aztec Empire in a few short months.

According to the tenets of Aztec religion, the soul went to one of three places after death: the sun, the underworld, or the lower sky<sup>[29]</sup>. Interestingly, souls of fallen warriors and women that died in childbirth would transform into hummingbirds that followed the sun on its journey through the sky. Aztec religion ascribed the emperors (called tlatoani, translated "Great Speaker") unique supernatural powers such as shape shifting, foreseeing the future, and even immortality where they were thought to take up life in the afterworld with abilities to have impact of the world they left. While there is no written documentation of any edict of revenge, a belief is held by some that Montezuma lives on and awaits the opportunity to come back to life to banish the invaders and rescue his loyal people<sup>[30]</sup>. Others attribute the persistent scourge of acute travelers' diarrhea among those visiting the lands of the Aztec as an enduring message sent by Montezuma to those visiting from other countries to think twice about ideas of colonization of foreign lands. While previously ascribed to the acute watery diarrhea so frequently encountered, perhaps Montezuma's full plan for revenge was designed to have some such visitors develop an enduring reminder that might live in their bowels for years after. Then again, this could all be a myth.

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