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LEADING ARTICLE

# Causation of human ulcerative colitis: A lead from an animal model that mirrors human disease

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**Key words**
causation of human ulcerative colitis, experimental colitis, hydrogen sulphide, nitric oxide, ulcerative colitis.

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## Abstract

Most models of experimental colitis do not replicate human ulcerative colitis and do not help in defining the causation of human ulcerative colitis. Inducing pantothenic acid deficiency in pigs produces an ideal model in terms of extent, histology, and chronicity of human ulcerative colitis. Comparing metabolic changes in human ulcerative colitis with metabolic changes in experimental colitis in pigs provided a guide for the search of initiating factors of human ulcerative colitis. Observations showed that bacterial nitric oxide with bacterial hydrogen sulphide reproduced the metabolic changes of human ulcerative colitis. Decreasing colon-produced nitric oxide and hydrogen sulphide by bacteria through diet and medication resulted in pronounced therapeutic improvement, both clinically and histologically, of human ulcerative colitis.

## Introduction

The causation of human ulcerative colitis is unknown. Observations from an ideal model of experimental colitis in pigs provided a lead toward causative agents in human ulcerative colitis.

A large number of models of colitis have been described in experimental animals.[1] Most of these models are produced by rectal instillation of acetic acid, ethanol, trinitrobenzene sulfonic acid, formalin, and hydrogen peroxide or by oral ingestion of sulphated polysaccharides. Histologically, these animal models of experimental colitis do not resemble human ulcerative colitis nor do they reflect the chronicity of the human disease.[2] On these grounds, animal models are not identical to human disease.[1]

## An ideal model of experimental colitis

A remark by August Krogh was that, for many research problems, there is an animal on which it can be most conveniently studied (the August Krogh principle).[3,4] Such an animal for ulcerative colitis was the pig, in which a model of experimental colitis could be induced by pantothenic acid (vitamin $B_5$) deficiency.[5] Pantothenic acid deficiency was induced by a diet free of pantothenic acid. Colitis developed 2–3 weeks after the pantothenic acid deficient diet was started. The colitis progressed from mild to moderate to severe and began at the rectum and progressed proximally. Maintaining a pantothenic acid-free diet eventually led to the death of the pigs. This model, histologically, very closely resembles human ulcerative colitis (Figs 1–3). It is an 'ideal' model in that, in distribution along the colon and chronicity, it reflects human ulcerative colitis.[5] Unfortunately, the model was reported in 1943, in a journal that has ceased publication and for which no electronic version is available. Consequently, the model has received only two citations since 1943, and these are prior to 1976. One purpose of this report is to republish the histological findings (Figs 1–5) and also to indicate that the model may be a lead to the causative factors of human ulcerative colitis.[6]

## Pantothenic acid (Vit $B_5$) deficiency

What is the role of pantothenic acid in tissues, and what does pantothenic acid deficiency result in? Worth noting is that pantothenic acid deficiency cannot be established in humans but is readily established in various animals.

Pantothenic acid is required in all tissues for the synthesis of coenzyme A,[7] a compound that is essential in the tissues of the body for chemical energy production, that is, adenosine triphosphate (ATP). One of the tissues is the lining epithelial cells, also referred to as colonocytes, of the colonic mucosa. A decrease in energy production by human colonocytes has been found in ulcerative colitis.[8,9]

Before proceeding, it is important to outline the substrate needs of colonocytes. Colonocytes in man and animals do not oxidize or produce energy from glucose but preferentially oxidize *n*-butyrate, which provides 70% of the energy for healthy colonocytes.[10,11] *n*-Butyrate is produced by the bacterial fermentation of dietary fiber in the colonic lumen. The oxidation of *n*-butyrate is referred to as beta-oxidation,[12] a metabolic pathway that requires four times more coenzyme A than the pathway of glucose oxidation.[12] Tissues highly reliant on coenzyme A would

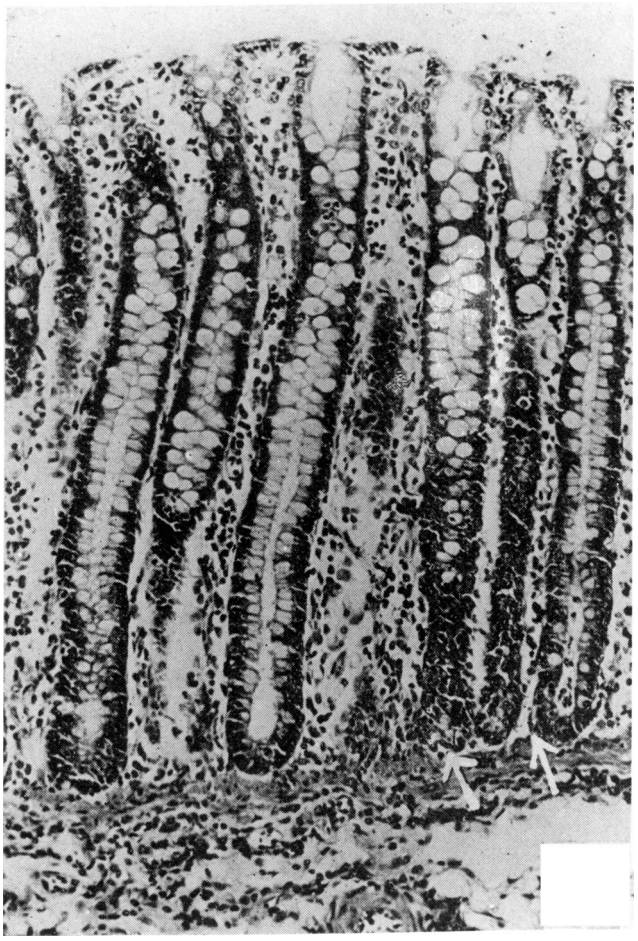

**Figure 1** Histopathology of the pig colon with pantothenic acid deficiency. Magnification 125×. Features resemble human ulcerative colitis. (reprinted from reference[5] with permission from Johns Hopkins University Press).

therefore be most prone to cell damage in pantothenic acid deficiency.

## Beta oxidation in colonocytes of human ulcerative colitis

The inhibition of beta oxidation of *n*-butyrate can be experimentally induced either acutely in rats over 4 days[13] or more chronically in pigs over several days.[5,14] Colitis due to the inhibition of beta oxidation, either acutely or chronically, produces histological features not unlike human ulcerative colitis.[5,13]

Inhibition of beta oxidation in colonocytes of acute and chronic human ulcerative colitis was reported in 1980[8] and was subsequently confirmed in humans, in vivo, by several researchers.[15,16] Consequently, a prolonged search[6] was carried out for the agents causing inhibition of beta oxidation in humans. Two agents, nitric oxide and sulphide, acting together, were found to inhibit beta oxidation and lower coenzyme A levels in healthy human colonocytes.[17] Nitric oxide in colonocytes would react with the thiol group of coenzyme A. The resultant product

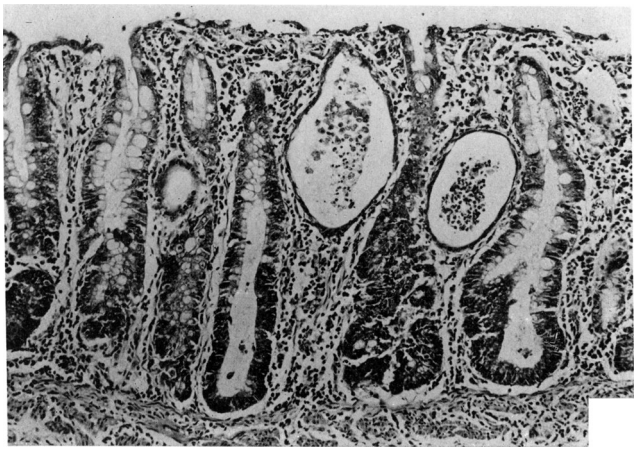

**Figure 2** Histopathology of the pig colon with pantothenic acid deficiency. Magnification 125×. Crypt abscesses and crypt branching as in human ulcerative colitis. (reprinted from reference[5] with permission from Johns Hopkins University Press).

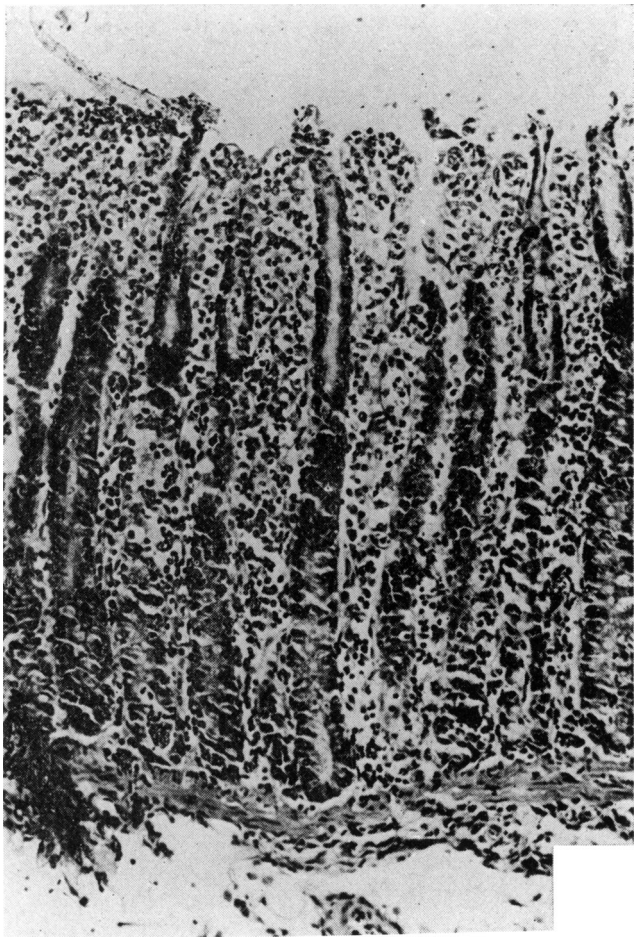

**Figure 3** Histopathology of the pig colon with pantothenic acid deficiency. Magnification 125×. Increased interstitial cell infiltrate and atrophy of superficial colonocytes. (reprinted from reference[5] with permission from Johns Hopkins University Press).

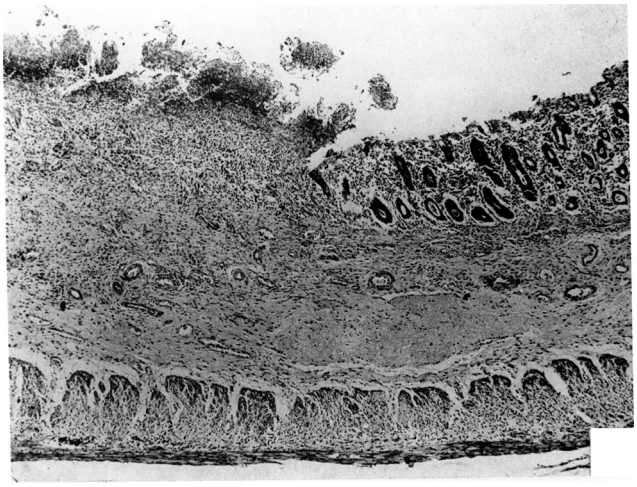

**Figure 4** Histopathology of the pig colon with pantothenic acid deficiency. Magnification 50×. Edge of ulcer with loss of colonic epithelial cells. (reprinted from reference[5] with permission from Johns Hopkins University Press).

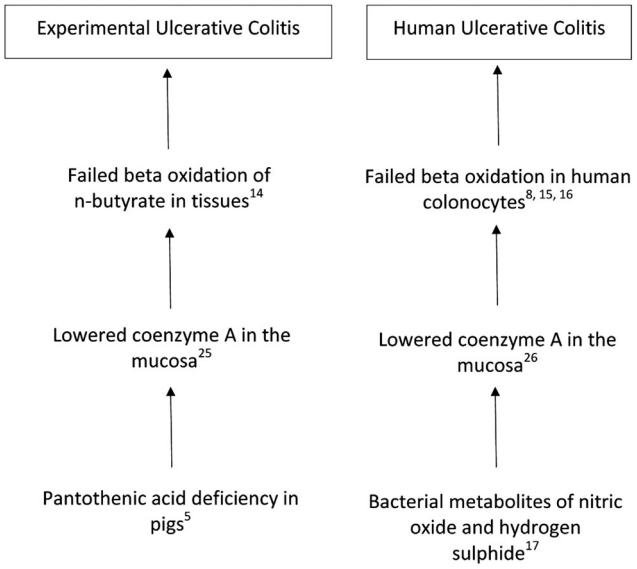


**Figure 5** Parallelism between an ideal model of experimental colitis[5] and human ulcerative colitis.

is a "nitrosothiol" that, in human ulcerative colitis, was found to be elevated.[18]

The two agents, nitric oxide and hydrogen sulphide, are bacterial metabolites. Production of these metabolites, particularly sulphide, depends on a high intake of meat[19] or sulfur amino acids. Reducing sulfur amino acid intake in the diet[20] or reducing sulphide production of colonic bacteria with 5-aminosalicylic acid,[21,22] the active therapeutic moiety of salazopyrin,[23] leads to amelioration of active ulcerative colitis. Attacks of active ulcerative colitis are often preceded by a diet high in meat content,[24] which, as mentioned above, raises the sulphide content in the colon.

## Parallelism between experimental and human ulcerative colitis

A close parallel between human ulcerative colitis and the ideal model of experimental ulcerative colitis can be drawn (Fig. 5). The steps outlined in the human and animal diseases are congruous and have been biochemically validated as indicted by the references shown in Figure 5. Metabolic changes in the colonic mucosa of human disease and animal colitis are correlated.

## Conclusions

An ideal model of experimental colitis in pigs has long been disregarded and "lost," yet it provides a guide to the causation of human ulcerative colitis. Removing the causative factors of human ulcerative colitis, that is, bacterially produced nitric oxide and hydrogen sulphide, provides a therapeutic gain. Both experimental colitis and human ulcerative colitis are reversible diseases by removing the causative factors. What remains to be done is to identify which bacteria, and their metabolic activity in the microbiome, produce the causative factors leading to human ulcerative colitis.

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