MODEL DEVELOPMENT OF DEXTRAN SODIUM SULPHATE INDUCED ULCERATIVE COLITIS IN FEMALE BALB/C MICE

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ABSTRACT

Inflammatory bowel disease is the name of a group of disorders that cause the intestine to become inflamed. The inflammation last a long time and usually comes back over and over again. It is a complex multifactorial disease and commonly refers to ulceration colitis and crohn’s disease. Inflammatory bowel disease is common in developed countries with up to 1 to 200 of individuals in Northen Europian regions affected by these diseases. Colitis can occur from viral and bacterial infections, ischemic insult or autoimmune disorders; most notably Ulcerative colitis and crohn’s disease. Acute colitis may present with abdominal pain, distention, malabsortion, diarrhea, hematoschezia and mucus in the stool. We are beginning to understand the complex interactions between the environments, genetics factors.

Inflammatory bowel disease and animal model of colitis have been essential in advancing our understanding of the disease. Although the causes, events initiating and triggering inflammation, and the precise immune regulatory defects of IBD are still not known, investigations have provided a better understanding of the mechanisms of perpetuation of inflammation, genetic susceptibility, tissue injury, and symptoms. Ulcerative colitis and Crohn's disease are related disorders that probably share susceptibility genes and have similar nonspecific inflammatory mediator profiles. These diseases, however, almost certainly have different causes and respond to different antigenic stimuli. It is probable that both ulcerative colitis and Crohn's disease represent heterogenic groups of diseases that share similar mechanisms of tissue damage but have different initiating events and immunoregulatory abnormalities. Rodent models demonstrate that a wide variety of initial injuries or perturbations of immunoregulatory pathways can lead to similar phenotypes of
intestinal injury, and human studies show evidence of genetic heterogeneity. It is equally apparent from these models that initiating and perpetuating mechanisms are entirely distinct and that the intestine has a remarkable ability to heal.

**KEYWORDS:** Crohn's disease, Ulcerative colitis, Hematoschezia, Inflammatory bowels disease, Dysplasia, Regional enteritis.

**INTRODUCTION**

Inflammatory bowel disease is the name of a group of disorders that cause the intestine to become inflamed (red or swollen). The inflammation last a long time and usually comes back over and over again. It is a complex multifactorial disease and commonly refers to ulceration colitis and crohn’s disease. Inflammatory bowel disease is common in developed countries with up to 1 to 200 of individuals in Northen Europian regions affected by these diseases. In past decade dozens of different animal models of inflammatory bowel disease have been developed. These models can be broadly divided into spontaneous colitis models, inducible colitis models, genetically modified models and adoptive transfer model.

Chemically induced murine models of intestinal inflammation are one of the most commonly used models because are simple to induce, the onset, the duration and severity of inflammation is immediate and controllable. Both Dextron sodium sulfate and Trinitrosulfonic acid are used to induce colitis and are well established animal models of inflammation. The dextrin sodium sulfate induced colitis model has some advantages when compared to other animal model of colitis. For example: an acute, chronic or relapsing model can be produced easily by changing the concentration of administration of dextrin sodium sulfate (and cycle in rats and other strains of mice).

Moreover Dysplasia that resembles the clinical course of human ulcerative colitis occurs frequently in chronic phase of dextrin sodium sulfate induced colitis. DSS induced model for studying colitis associated carcinogenesis has been recently reviewed by others. Furthermore studies of that validated DSS model by using different therapeutic agents for human IBD show that model for the translation of mice data to human disease. There are two kinds of inflammatory bowel disease. They are crohn’s disease and ulcerative colitis.
**Crohn’s disease**

Crohn's disease, also known as regional enteritis, is a type of inflammatory bowel disease that may affect any part of the gastrointestinal tract from mouth to anus, causing a wide variety of symptoms. It primarily causes abdominal pain, diarrhea (which may be bloody if inflammation is at its worst), vomiting (can be continuous), or weight loss, but may also cause complications outside the gastrointestinal tract such as skin rashes, arthritis, inflammation of the eye, tiredness, and lack of concentration.

Crohn's disease is caused by interactions between environmental, immunological and bacterial factors in genetically susceptible individuals. These results in a chronic inflammatory disorder, in which the body's immune system attacks the gastrointestinal tract possibly directed at microbial antigens.

Crohn's disease has traditionally been described as an autoimmune disease, but recent investigators have described it as a disease of immune deficiency.

There is a genetic association with Crohn's disease, primarily with variations of the NOD2 gene and its protein, which senses bacterial cell walls. Siblings of affected individuals are at higher risk.[8] Males and females are equally affected. Smokers are two times more likely to develop Crohn's disease than nonsmokers. Crohn's disease affects between 400,000 and 600,000 people in North America. Prevalence estimates for Northern Europe have ranged from 27-48 per 100,000. Crohn's disease tends to present initially in the teens and twenties, with another peak incidence in the fifties to seventies, although the disease can occur at any age.[112] There is no known pharmaceutical or surgical cure for Crohn's disease. Treatment options are restricted to controlling symptoms, maintaining remission, and preventing relapse.

The disease was named after American gastroenterologist Burrill Bernard Crohn, who, in 1932, together with two colleagues, described a series of patients with inflammation of the terminal ileum, the area most commonly affected by the illness.

Many people with Crohn's disease have symptoms for years prior to the diagnosis. The usual onset is between 15 and 30 years of age, but can occur at any age. Because of the 'patchy' nature of the gastrointestinal disease and the depth of tissue involvement, initial symptoms
can be more subtle than those of ulcerative colitis. People with Crohn's disease experience chronic recurring periods of flare-ups and remission.

Abdominal pain may be the initial symptom of Crohn's disease. It is often accompanied by diarrhea, especially in those who have had surgery. The diarrhea may or may not be bloody. People who have had surgery or multiple surgeries often end up with short bowel syndrome of the gastrointestinal tract. The nature of the diarrhea in Crohn's disease depends on the part of the small intestine or colon involved. Ileitis typically results in large-volume, watery feces. Colitis may result in a smaller volume of feces of higher frequency. Fecal consistency may range from solid to watery. In severe cases, an individual may have more than 20 bowel movements per day and may need to awaken at night to defecate. Visible bleeding in the feces is less common in Crohn's disease than in ulcerative colitis, but may be seen in the setting of Crohn's colitis. Bloody bowel movements are typically intermittent, and may be bright or dark red in color. In the setting of severe Crohn's colitis, bleeding may be copious. Flatulence and bloating may also add to the intestinal discomfort.

**Ulcerative colitis**

Ulcerative colitis is an inflammatory bowel disease that causes colon (a part of your large intestine) and rectum to become red and swollen. The redness and swelling can last for few weeks or for several months. Symptoms may come and go for up to a year. These occurrence are called Flare ups. Ulcers from where inflammation has killed the cells that usually line the colon. The most common symptoms are pain in the abdomen and bloody diarrhea. Other symptoms include anaemia, severe tiredness, weight loss, loss of apetite, bleeding from the rectum, sores on the skin and joint pains.

**CAUSES FOR ULCEERATIVE COLITIS**

The causes for ulcerative colitis are unknown. Ulcerative colitis is a form of inflammatory bowel disease. It is a form of colitis, a disease of the colon (large intestine) that includes characteristic ulcers or open sores. The main symptoms of active disease are usually unstant diarrhea mixed with blood, of gradual onset. IBD is often confused with irritable bowel syndrome (IBS), a troublesome, but much less serious condition. Ulcerative colitis has similarities to crohn’s disease another form of IBD. Ulcerative colitis is an intermittent disease, with periods that are relatively symptoms free. Although the symptoms of Ulcerative colitis can sometimes diminish on own, the disease usually requires treatment to go into remission. Although Ulcerative colitis has no known cause, there is a presumed genetic
component to susceptible person by environmental factors. Ulcerative colitis is treated as an autoimmune disease.

Comparison of Crohn’s disease with ulcerative colitis
MODEL DEVELOPMENT OF DEXTRAN SULFATE SODIUM INDUCED IN BALB/C MICE

Dextran is a complex polymer of glucose synthesized by certain bacteria, most commonly Leuconostoc species and Streptococcus spp, from sucrose (Bailey and Bourne 1961). It is made of straight and branched chains, with a highly variable molecular weight ranging from as low as 5000 to up to 1.4 million Da, DSS is a polyanionic derivative of Dextran. Its high purity and reproducible quality commend it for many applications in molecular biology and the health care sector.

The mechanism of Dextran sodium sulfate is presently unknown. However, the finding of crypt loss without proceeding or accompanying inflammation suggests that the initial insult is at the level of epithelial cell with inflammation being secondary phenomena. This may be a good model to study how early mucosal changes lead to inflammation and the biology of the colonic enterocyte. An ideal experimental model of inflammatory bowel disease (IBD) should mimic human inflammatory bowel disease (IBD) either Ulcerative colitis or Crohn’s disease quite closely. In addition, it should be simple to induce, not expensive and highly reproducible. Dextran sulfate sodium (DSS) model of colitis is widely perceived as a good model of experimental colitis because it has similarities to human IBD in etiology, pathology, pathogenesis, and therapeutic response. In addition induction is cheap and simple and may be acute or chronic. It is widely applicable to mice, rats, hamsters, guinea pigs. This review looks at the features, advantages, disadvantages of this model and suggests areas in which more research is required.

Colitis can occur from viral and bacterial infections, ischemic insult or autoimmune disorders; most notably Ulcerative colitis and crohn’s disease. Acute colitis may present with
abdominal pain, distention, malabsorption, diarrhoea, hematoschezia and mucus in the stool. We are beginning to understand the complex interactions between the environments, genetics factors. Inflammatory bowel disease and animal model of colitis have been essential in advancing our understanding of the disease. One popular model involves supplementing the drinking water of BALb/c mice with low molecular weight DSS resulting in epithelial damage and a robust inflammatory response in the colon lasting several days. Variations of this approach can be used to model acute injury, acute injury followed by repair and repeated cycles of DSS interspread with modeling chronic inflammatory response. After the treatment of DSS in drinking water mice shows signs of acute colitis including weightloss, bloody stools and diarrhea.

In our experience with the acute murine DSS model of experimental colitis, we noted both interstrain and interanimal variations in daily water consumption. One might critically question whether observed difference in injuries are just a dose depending phenomenon reflecting variations in DSS intake. To clarify this important topic, we performed a dose and concentration depending study of DSS in BALb/c mice. Dextran sulfate sodium induced murine colitis represents an experimental model of human inflammatory bowel disease. The purpose of this study was to induce colitis in BALb/c mice by 7 days of oral DSS. Acute colitis was induced by 7 days of oral DSS in drinking water. In each experimental group, the entire colons were examined histologically and correlated with clinical symptoms.

METHODS: In Three groups (5 animals each group) different concentrations of Dextron sulfate sodium (4%, 5%) were given for 7 days and libitum. Mucosal injury of the entire colon was assessed and graded. This shows the weight loss, decrease in colon length, increase in colon weight, bloody stools and diarrhoea. This acute murine DSS colitis model is useful for studying the pathophysiological aspects of colonic inflammatory diseases as inflammatory bowel disease and for evaluating new potential therapeutic agents. The acute colitis was accompanied by elevated plasma levels of haptoglobin and increased colonic levels of IL-1alpha/beta, IL-6, IL-18, and granulocyte colony-stimulating factor. In summary, these data stress the effect of genetic background on the outcome of DSS provocation. We believe that the present protocol to induce acute colitis in BALB/C mice offers a robust model for validating future therapies for treatment of inflammatory bowel disease.
OBJECTIVE
Validation and model development of Dextran sulfate sodium (DSS) induced ulcerative colitis in BALb/c mice (female) MODEL.

LITERATURE REVIEW
Ulcerative colitis
Ulcerative colitis has been thoroughly reviewed clinically, but no pathologic investigation has been made recently, perhaps because the predominating manifestations are those of nonspecific inflammation. The importance of this condition demands that it be better understood. In the hope of advancing the fragmentary knowledge of its evolution, a series of 120 surgically treated and 60 autopsied cases of ulcerative colitis has been reviewed. All autopsies available and surgical cases from the 20-year period of 1927 to 1946 were included. The series comprised approximately two-thirds of all cases diagnosed as ulcerative colitis in this laboratory. Ulcerative colitis of specific etiology, such as tuberculosis, amoebic or bacillary dysentery, lymphopathic venereum, vitamin deficiency and uraemia, was excluded. Cases lacking sufficient histologic material for detailed analysis were discarded. A clinical classification of nonspecific ulcerative colitis has been provided by Bargenl: type i, or thrombo-ulcerative colitis, attributed to diplostreptococcal infection; type 2, or regional colitis, affecting mainly the right colon and type 3, or atypical ulcerative colitis, also termed idiopathic. These distinctions do not lend themselves to close pathologic correlation. In the course of study of our cases, two distinct pathogenetic processes were observed which lead to ulceration. They are termed type A (vasculitis) and type B (crypt abscess). Half the cases gave no clue as to their pathogenesis and are called indeterminate.

PATHOGENESIS OF ULCERATIVE COLITIS
The pathogenesis of ulcerative is still poorly understood. With the introduction of new culture-independent techniques the research on the intestinal microbiota has revealed an
important reduction of Bacteroidetes and Firmicutes leading to a reduced biodiversity and dysbiosis in these patients. Going in depth, the intestinal barrier is covered under physiologic conditions by a mostly sterile mucus layer. Besides a reduction of mucus thickness or an alteration in mucus composition hypothesized for human ulcerative colitis, new evidence coming from mouse models has introduced a novel concept based on cellular stress due to misfolded mucus-associated proteins opening a new research area for the epithelial cell lining. A dysregulated immune response involving the innate (e.g. toll-like receptors, dendritic cells, etc) and the adaptive immune system (e.g. effector T-cells, regulatory T-cells, eosinophils, neutrophils, etc) may follow or precede the macroscopic lesions. The immune response in ulcerative colitis is represented principally by secretion of interleukin-5 and -13 being the latter responsible for the direct cytotoxicity against the epithelial cells. In latter stages the role of interleukin-17 producing cells, apparently differently regulated compared with Crohn's disease, remains to be elucidated. Finally, human ulcerative colitis is characterized by the presence of various types of autoantibodies including pANCA, antibodies against goblet cells and the isoforms 1 and 5 of human tropomyosin. The pathogenic potential of these antibodies is still debated.
CYTOKINES IN THE PATHOGENESIS OF ULCERATIVE COLITIS

Its pathogenesis involves the breakdown of intestinal mucosal homeostasis due to a genetically determined miscommunication between commensally flora and the gut associated immune system. Cytokines are central components of the inflammatory pathways that take place during the active and chronic phases of ulcerative colitis. Recent research has identified several novel cytokine systems that are unregulated at the mucosa of patients with ulcerative colitis and started to unveil their functional importance for disease pathogenesis. The significance of Interleukin-13(IL-13), TNF-like cytokine IA (TL IIA) IL-13, and their receptors in ulcerative colitis is strongly supported by converging expression and functional data. These molecular systems may define subgroups of patients with uniform immunological profiles within these subpopulation such novel cytokine systems may serve as markers of biological activity of the disease. More importantly, they may offer unique therapeutic opportunities through the development of drugs that specifically target and neutralize well defined inflammatory pathways.

IMMUNO PHENOTYPE IN ULCERATIVE COLITIS

Cytokines are abundantly produced by the cells of the gut associated immune system. These small cell-signaling protein molecules act in a paracrine, autocrine or endocrine manner and affect the function of the immune system in a variety of ways. Accordingly, cytokines coordinate the communication between immune and non immune cells of the intestine compartment and modify acute and chronic inflammatory responses both at the local and systemic levels. Therefore, it is of no surprise that cytokines have been the main therapeutic targets in recent approaches for the management of ulcerative colitis.

Two decades ago a classification of immune responses has been proposed which was based on the cytokine profile that was prominent in different situations. The original scheme compromised of T helper1 (Th 1) vs T helper2 (Th 2) paradigm with the former being dominated by the production of interleukin-12 (IL-12) IFN-α are the latter by the secretion of IL-4, IL-5, and IL-13. A major shift in this archetype occurred following the identification of a third effector population, which is defined by high IL-17A secretion, hence its designation as the Th17 response. In addition, it has become recognized that differential CD4 lymphocytes may not only play an effector role but also a regulatory one, expressing suppressive activity, controlling effector pathway and dampening inflammatory responses.
These regulatory cells also comprise of different subgroups but typically act via the secretion of IL-10 and TGF-BETA1.

The application of this concept in mucosal immunology result in the characterization of ulcerative colitis as Th2- mediated condition. None the less, for several years this was mostly linked to the lack of increase IFN-GAMA expression rather than to the elevation of IL-4, the Th2-defining cytokine. In fact, the latter is not upregulated at the mucosal (tissue or cellular) in ulcerative colitis. Nevertheless, there is increased IL-5, hence the term “a typical Th2-condition” that was coined to ulcerative colitis.

**Th2 TYPE EFFECTOR PATHWAYS**

Although ulcerative colitis has been traditionally considered a Th2 mediated condition, it was only recently that research was directed away from IL-4 and towards alternative Th2-associated factors. This approach revealed the central role of IL-13 in the pathogenesis of ulcerative colitis. Earlier descriptive studies have already reported increased mRNA transcripts of IL-13 in the colon with ulcerative colitis. The authors subsequently showed that the critical cell population for IL-13 secretion was one of natural killer T (NKT) cells expressing surface CD161. These cells produced IL-13 in response to stimulation by antigen presenting cells expressing surface CD1d. based on the studies mentioned above, a pathogenetic scheme has been proposed for the involvement of IL-13 in ulcerative colitis.
pathogenesis. According to this theory, on identified stimuli, most probably commensal flora-derived microbial products stimulate a typical NKT cells to produce IL-13 in the colonic mucosa.

**TL1A/DR3/DCR3 PATHWAYS**

TNF- Like cytokine 1A (TL1A) is a novel member of the TNF superfamily of proteins (TNFSF). TL1A (designated as TNFSF 15) has the ability to bind to two receptors of the TNF receptor superfamily (TNFRSF), which display opposing functions. In particular DR3 (Death domain containing receptor3, TNFRSF25) is a functional receptor and TL1A/DR3 association provides co-stimulatory signals for activated lymphocytes, leading to cell proliferation and cytokine secretion and amplifying pro-inflammatory pathways.

**IL-33/ST2 PATHWAYS**

IL-33 (formerly known as IL1 F11) is the latest identified members of the IL-1 family of cytokines. Like other IL-1 family of IL-33 may exists as precursor molecule or as a smaller bioactive structure that is obtained after cleavage by caspases, although contrasting results have been reported. The receptor for IL-33 is ST2 which occurs in both transmembrane and soluble forms. Binding of IL-33 to membrane bound ST2 leading to functional signaling, whereas the soluble proteins have been long recognized as important inflammatory mediators.
in several immune-mediated disorders, including IBD, the involvement of IL-33 in gut homeostasis and inflammatory has been examined.

**GENETIC FACTORS**

- A genetic component to the aetiology of ulcerative colitis can be hypothesized based on the following
  - Aggregation of ulcerative colitis in families.
  - Identical twin concordance rate of 10% and dizygotic twin concordance rate of 3%
  - Ethnic differences in incidence
  - Genetic markers and linkages

There are 12 regions of the genome that may be linked to ulcerative colitis, including, in the order of their discovery, chromosomes 16, 12, 6, 14, 5, 19, 1, and 3, but none of these loci has been consistently shown to be at fault, suggesting that the disorder arises from the combination of multiple genes. For example, chromosome band 1p36 is one such region thought to be linked to inflammatory bowel disease. Some of the putative regions encode transporter proteins such as OCTN1 and OCTN2. Other potential regions involve cell scaffolding proteins such as the MAGUK family. There may even be human leukocyte antigen associations at work. In fact, this linkage on chromosome 6 may be the most convincing and consistent of the genetic candidates.

Multiple autoimmune disorders have been recorded with the neurovisceral and cutaneous genetic porphyrias including ulcerative colitis, Crohn's disease, celiac disease, dermatitis herpetiformis, diabetes, systemic and discoid lupus, rheumatoid arthritis, ankylosing spondylitis, scleroderma, Sjogren's disease and scleritis. Physicians should be on high alert for porphyrias in families withautoimmune disorders and care must be taken with potential porphyrinogenic drugs, including sulfasalazine.

**ENVIRONMENTAL FACTORS**

**Cigarette smoking**

There are several environmental clues to the susceptibility and development of ulcerative colitis. The long-standing finding that cigarette smoking protects against the development of ulcerative colitis has withstood the test of time. Indeed, case series continue to demonstrate a protective effect of smoking on both the development and course of ulcerative colitis. Smoking accounts for much of the discordance between ulcerative colitis and Crohn's disease.
within families or siblings - in families with siblings affected by either ulcerative colitis or Crohn's disease, cigarette smoking continues to demonstrate a protective role against ulcerative colitis. Although smokers are less likely to develop ulcerative colitis, however, ex-smokers are more likely to develop extensive or severe colitis. I, and others, believe that ex-smokers account for the preponderance of the second age peak for ulcerative colitis in patients over the age of 40 years (J Tuvlin and J Cho, personal communication).

The protective effect of smoking also extends to the extra-intestinal manifestations and post-surgical complications of ulcerative colitis. For example, smoking protects against the development of PSC, and I speculate that smoking, or non-smoking, accounts for the differing incidence of PSC associated with ulcerative colitis and Crohn's disease (personal observation).

**Appendectomy**

Another consistent epidemiologic clue to the pathogenesis of ulcerative colitis is the observation that appendectomy, particularly at a younger age, both reduces the likelihood of developing ulcerative colitis and is associated with a less severe disease course. The impact of appendectomy seems to be an additive protective factor to cigarette smoking against the development of ulcerative colitis. In contrast to ulcerative colitis, prior appendectomy does not seem to be protective against the development of PSC. This pathogenic clue pertains to animal models of colitis for which appendectomy at an early age prevents the spontaneous development of colitis in T-cell-receptor- knockout mutant mice or after exposure to dextran sulfate.

**Bacteria**

One ubiquitous factor in animal models of colitis and in the human disease is the relationship with bacteria. In experimental models of IBD, colitis does not develop in animals that are raised in germ-free environments. Commensal bacteria, not pathogens, are sufficient to induce colitis, but this is determined by both host and bacterial specificities. In addition, different phenotypic patterns of colitis are seen in specific animal models and with specific bacterial species. Commensal bacteria can also induce a protective effect that can be transmitted by bacteria-responsive regulatory CD4+ T cells.
IMMUNOLOGIC FACTORS

From an immunologic perspective, ulcerative colitis has less of a Th1 response pattern than Crohn's disease. Recent evidence indicates that, in contrast to the Th1 cytokines that are associated with the pathogenesis of Crohn's disease (interferon-\(\gamma\), tumor necrosis factor-\(\alpha\) and interleukin-12), animal models of ulcerative colitis may be associated with increased natural-killer-cell activity and interleukin-13. In addition, attention is being directed at the downregulatory role of transforming growth factor-\(\beta\) in colitis and the possibility that defective signaling of transforming growth factor-\(\beta\) may account for inadequate tissue repair.

Microscopically, UC involves only the mucosa, with the formation of crypt abscesses and a coexisting depletion of goblet cell mucin. In severe cases, the submucosa can be involved, and in some cases, the deeper muscular layers of the colonic wall can also be affected. Further microscopic changes include inflammation of the crypts of Lieberkuhn and abscesses. Ulcerated areas are soon covered by granulation tissue. The underlining of mucosa and the excesses of granulation tissue form polypoidal mucosal excrescences, known as inflammatory polyps or pseudopolyps.

Endoscopic

- Biopsy sample (H&E stain) that demonstrates marked lymphocytic infiltration (blue/purple) of the intestinal mucosa and architectural distortion of the crypts.
- The best test for diagnosis of ulcerative colitis remains endoscopy. Full colonoscopy to the cecum and entry into the terminal ileum is attempted only if diagnosis of UC is unclear. Otherwise, a flexible sigmoidoscopy is sufficient to support the diagnosis. The physician may elect to limit the extent of the exam if severe colitis is encountered to minimize the risk of perforation of the colon. Endoscopic findings in ulcerative colitis include the following:
  - Loss of the vascular appearance of the colon
  - Erythema (or redness of the mucosa) and friability of the mucosa
Superficial ulceration, which may be confluent, and
Pseudopolyps.

Ulcerative colitis is usually continuous from the rectum, with the rectum almost universally being involved. There is rarely peri-anal disease, but cases have been reported. The degree of involvement endoscopically ranges from proctitis or inflammation of the rectum, to left sided colitis, to pancolitis, which is inflammation involving the ascending colon.

**Histopathology**
Biopsies of the mucosa are taken to definitively diagnose UC and differentiate it from Crohn's disease, which is managed differently clinically. Microbiological samples are typically taken at the time of endoscopy. The pathology in ulcerative colitis typically involves distortion of crypt architecture, inflammation of crypts (cryptitis), frank crypt abscesses, and hemorrhage or inflammatory cells in the lamina propria. In cases where the clinical picture is unclear, the histomorphologic analysis often plays a pivotal role in determining the diagnosis and thus the management. By contrast, a biopsy analysis may be indeterminate, and thus the clinical progression of the disease must inform its treatment.

*Comparison of normal colon & ulcerative colitis.*
Alternative medicine

- About 21% of inflammatory bowel disease patients use alternative treatments. A variety of dietary treatments show promise, but they require further research before they can be recommended.

- In vitro research, animal evidence, and limited human study suggest that melatonin may be beneficial.

- Dietary fiber, meaning indigestible plant matter, has been recommended for decades in the maintenance of bowel function. Of peculiar note is fiber from brassica, which seems to contain soluble constituents capable of reversing ulcers along the entire human digestive tract before it is cooked. Oatmeal is also commonly prescribed.

- Fish oil. Eicosapentaenoic acid (EPA), derived from fish oil. This is an Eicosanoid that inhibits leukotriene activity, the latter which may be a key factor of inflammation. As an IBD therapy, there are no conclusive studies in support and no recommended dosage. But dosages of EPA between 180 to 1500 mg/day are recommended for other conditions, most commonly cardiac.

- Short chain fatty acid (butyrate) enema. The colon utilizes butyrate from the contents of the intestine as an energy source. The amount of butyrate available decreases toward the rectum. Inadequate butyrate levels in the lower intestine have been suggested as a contributing factor for the disease. This might be addressed through butyrate enemas. The results however are not conclusive.

- Herbal medications are used by patients with ulcerative colitis. Compounds that contain sulphhydryl may have an effect in ulcerative colitis (under a similar hypothesis that the sulpha moiety of sulfasalazine may have activity in addition to the active 5-ASA component). One randomized control trial evaluated the over-the-counter medication methionine-methyl sulphonium chloride (abbreviated MMSC, but more commonly referred to as Vitamin U) and found a significant decreased rate of relapse when the medication was used in conjunction with oral sulfasalazine.

- Boswellia is an Ayurvedic (Indian traditional medicine) herb, used as a natural alternative to drugs. One study has found its effectiveness similar to sulfasalazine.
Progression or remission
Patients with ulcerative colitis usually have an intermittent course, with periods of disease inactivity alternating with "flares" of disease. Patients with proctitis or left-sided colitis usually have a more benign course: only 15% progress proximally with their disease, and up to 20% can have sustained remission in the absence of any therapy. Patients with more extensive disease are less likely to sustain remission, but the rate of remission is independent of the severity of disease.

Ulcerative colitis and colorectal cancer
There is a significantly increased risk of colorectal cancer in patients with ulcerative colitis after ten years if involvement is beyond the splenic flexure. Those with only proctitis or rectosigmoiditis usually have no increased risk. It is recommended that patients have screening colonoscopies with random biopsies to look for dysplasia after eight years of disease activity.

Primary sclerosing cholangitis
Ulcerative colitis has a significant association with primary sclerosing cholangitis (PSC), a progressive inflammatory disorder of small and large bile ducts. As many as 5% of patients with ulcerative colitis may progress to develop primary sclerosing cholangitis.

Mortality
The effect of ulcerative colitis on mortality is unclear, but it is thought that the disease primarily effects quality of life, and not lifespan.

Other long-term features
Changes that can be seen in chronic ulcerative colitis include granularity, loss of the vascular pattern of the mucosa, loss of haustra, effacement of the ileocecal valve, mucosal bridging, strictures and pseudopolyps.

Epidemiology
Ulcerative colitis is global in distribution and varies in incidence relative to Crohn disease, supporting the concept that they are separate disease. In the United States, incidence is about 4 to 12 per 100,000 populations slightly greater than Crohn disease. As with Crohn disease, the incidence of this condition has risen in recent decades. In the United States, it is more common among whites than among blacks and women are affected more often than men.
onset of disease peaks between the ages of 20 and 25 years but the condition may arise in both younger and considerably older individuals.

**Signs and symptoms**

Diarrhea with blood and mucus, abdominal cramps, and tenesmus are the most important symptoms for many years. Six to fifteen years ago, 50 per cent of the patients died, 115 and collected series of over 1200 more recent cases; 9 of 11, have an average mortality of 7.3 per cent. A few patients are cured, and the remainder affected intermittently for life. Clinically, Ulcerative colitis tends to be a chronic irreversible disease, varying in extent, activity, and severity. Among our 60 fatal cases, a definite statement of the duration of Ulcerative colitis was made in 54. Seven patients lived 2 months or less thus 22 patients (37 per cent) had histories of 1 year or less. The disease lasted from 1 to 5 years in 9 cases (32 per cent). There were 7 cases of 5 to 10 years’ duration, 5 cases with 10 to 20 years of colitis, and 1 patient succumbed after 27 years. Symptoms of more than 5 years’ duration are often prominent. Ulcerative colitis may have either a sudden or insidious onset, 15 to 16 and may pursue a fulminating, 17 slowly progressive, or irregular course present in 13 (22 per cent).

**Different animal models of ulcerative colitis**

Animal models are useful for studying disease, but there is a shortage of suitable models of ulcerative colitis. The aim of the present study was to set up an oxazolone-induced murine colitis model and use it to research the pathogenesis of inflammatory bowel disease.

**METHODS:** BALB/c mice were presensitized by painting the skin with 0.2 mL 3% oxazolone in 100% ethanol on days 0 and 1 followed by intrarectal administration of 0.15 mL 1% oxazolone in 50% ethanol on day 7. The disease activity index (DAI), histological changes of the colon, myeloperoxidase (MPO) activity and production of cytokines (TNF-alpha, IL-4, IFN-gamma) by the mucosa were evaluated. **RESULTS:** There were obvious changes in the DAI, histology and MPO activity, and the production of interleukin-4 was markedly increased compared with the concentrations of TNF-alpha and IFN-gamma, which remained normal, in the lesions. **CONCLUSION:** Oxazolone colitis is Th2-mediated and has similar histologic features and distribution of inflammation to ulcerative colitis (UC), which has important implications for the use of this model in the study of the pathogenesis and treatment of UC.
Dss induced colitis in mice model
Inflammatory bowel diseases (IBDs), primarily ulcerative colitis and Crohn's disease, are inflammatory disorders caused by multiple factors. Research on IBD has often used the dextran sodium sulfate (DSS)-induced colitis mouse model. DSS induces *in vivo* but not *in vitro* intestinal inflammation. In addition, no DSS-associated molecule (free glucose, sodium sulfate solution, free dextran) induces *in vitro* or *in vivo* intestinal inflammation. We find that DSS but not dextran associated molecules established linkages with medium-chain-length fatty acids (MCFAs), such as dodecanoate, that are present in the colonic lumen. DSS complexed to MCFAs forms nanometer-sized vesicles ~200 nm in diameter that can fuse with colonicocyte membranes. The arrival of nanometer-sized DSS/MCFA vesicles in the cytoplasm may activate intestinal inflammatory signaling pathways. We also show that the inflammatory activity of DSS is mediated by the dextran moieties. The deleterious effect of DSS is localized principally in the distal colon; therefore it will be important to chemically modify DSS to develop materials beneficial to the colon without affecting colon-targeting specificity.

Oxozolone induced colitis
Animal models of intestinal inflammation are indispensable for our understanding of the pathogenesis of Crohn disease and ulcerative colitis, the two major forms of inflammatory bowel disease in humans. Here, we provide protocols for establishing murine 2, 4, 6-trinitro benzene sulfonic acid (TNBS)-, oxazolone- and both acute and chronic dextran sodium sulfate (DSS) colitis, the most widely used chemically induced models of intestinal inflammation. In the former two models, colitis is induced by intrarectal administration of the covalently reactive reagents TNBS/oxazolone, which are believed to induce a T-cell-mediated response against hapten-modified autologous proteins/luminal antigens. In the DSS model, mice are subjected several days to drinking water supplemented with DSS, which seems to be directly toxic to colonic epithelial cells of the basal crypts. The procedures for the hapten models of colitis and acute DSS colitis can be accomplished in about 2 weeks but the protocol for chronic DSS colitis takes about 2 months.

Murine tnbs induced colitis model
Probiotic bacteria have been shown to exert promising beneficial effects in different types of intestinal disorders, including chronic inflammation. In this context, animal models of inflammatory bowel disease are useful in studying the possible prophylactic role of candidate
probiotic strains. This study aimed at evaluating the critical technological and microbiological parameters as well as the robustness of the murine trinitrobenzene sulfonic acid (TNBS)–induced model of colitis, after intragastric administration of lactic acid bacteria (LAB) preparations. A standardized methodology was applied to assess the protective effect achieved by various bacterial concentrations and culture conditions of the reference strain *Lactobacillus plantarum* NCIMB 8826. Not only was protection found to vary in function in different levels of colitis, but also repeated experiments showed a clear bacterial dose-dependent attenuation of colitis. The physiological stage of bacteria was shown to impact as well, with substantial, mild, or reduced improvement of inflammatory scores for exponentially growing, stationary-phase, or killed bacteria, respectively. A recombinant strain, secreting murine interleukin-10 (IL-10) and previously reported to successfully treat colitis in two different models of murine colitis (dextran sulfate sodium DSS and IL-10-deficient mice), was used to validate the final experimental conditions. In conclusion, we identified and optimized some of the key parameters that need to be controlled in order to ensure reliable comparison of results generated over a long period of time or independent experiments. The recommendations for an improved model presented here will prove to be helpful for reproducible, independent comparison of the anti-inflammatory potential of wild-type or recombinant candidate probiotic strains, whether administered as pure cultures or as blends.

**A murine model of ulcerative colitis induced with sinusitis - derived super antigen and food allergen**

The etiology of ulcerative colitis (UC) is to be understood. The basic pathological feature of UC is intestinal chronic inflammation. Superantigen, such as Staphylococcus enterotoxin B (SEB), is reported to compromise intestinal barrier function by increasing epithelial permeability and initiate inflammation in the intestinal mucosa. Inasmuch as anatomic position of the sinus, chronic sinusitis-derived SEB may follow the secretion and to be swallowed down to the gastrointestinal tract and induce lesions to the intestinal mucosa. Introducing Sinusitis-derived SEB-containing SWF to the gastrointestinal tract compromised colonic mucosal barrier function increasing epithelial permeability to luminal macromolecular protein in mice. The SWF facilitated colonic mucosal sensitization to luminal antigen. Multiple challenging the sensitized colonic mucosa with specific antigen OVA induced inflammation, induced a condition similar to human ulcerative colitis.
**Dinitro benzene induced murine colitis**

Numerous therapies used for inflammatory bowel disease (IBD) target the transcription factor NF-κB, which is involved in the production of cytokines and chemokines integral for inflammation. Here we show that curcumin, a component of the spice turmeric, is able to attenuate colitis in the dinitrobenzene sulfonic acid (DNB)-induced murine model of colitis. When given before the induction of colitis it reduced macroscopic damage scores and NF-κB activation. This was accompanied by a reduction in myeloperoxidase activity, and using semiquantitative RT-PCR, an attenuation of the DNB-induced message for IL-1β was detected. Western blotting analysis revealed that there was a reproducible DNB-induced activation of p38 MAPK detected in intestinal lysates by using a phosphospecific antibody. This signal was significantly attenuated by curcumin. Furthermore, we show that the immunohistochemical signal is dramatically attenuated at the level of the mucosa by curcumin. We conclude that the widely used food additive curcumin is able to attenuate experimental colitis through a mechanism correlated with the inhibition of the activation of NF-κB and effects a reduction in the activity of p38 MAPK. We propose that this agent may have therapeutic implications for human IBD.

**Dinitrochlorobenzene induced colitis in guinea pig**

Dinitrochlorobenzene-induced colitis in guinea-pigs may be immunologically mediated: animals must be presensitised to dinitrochlorobenzene to develop colitis, sensitivity can be passively transferred by lymphocytes and the injury can be mitigated by immunosuppression. In this study, we examined lamina propria lymphocytes isolated from colons of animals with dinitrochlorobenzene-induced colitis, and appropriate controls. Lamina propria lymphocytes from colitis animals have a greater percentage of rabbit erythrocyte-rosetting cells (T cells) (20.1 +/- 3.0 vs 2.3 +/- 0.8, p<01) and a greater capacity to mediate mitogen-induced cellular cytotoxicity with phytohaemagglutinin than lamina propria lymphocytes from normal colon (% specific cytotoxicity = 29.4 +/- 8.7 vs 5.0 +/- 4.5, P less than .005). There was no difference in the percentage of rosetting cells or cytotoxicity index of spleen or mesenteric lymph node lymphocytes between the colitis animals and controls. These data suggest that there are changes in the distribution and functional characteristics of lamina propria lymphocytes which correlate with mucosal cell injury in the dinitrochlorobenzene-colitis model.
Effect of chondroitin sulfate on colitis induced Dss in rats
Chondroitin sulfate (CS) is currently marketed as a therapeutic drug for neuropathy, lumbago and arthrodynia. Recently, many clinical studies have demonstrated the therapeutic effects of orally administered CS against diseases with inflammation. Furthermore, these reports suggest CS plays an important role in the protection of the base of ulcers and has anti-inflammatory activity. We investigated the effects of CS against dextran sulfate sodium (DSS)-induced rat colitis. Rats were given 3% DSS solution for 10 days ad libitum. CS and 5-aminosalicylic acid (5-ASA) were orally administered daily. The doses of the CS groups were 20 or 100 mg/kg and that for the 5-ASA group was 100 mg/kg. Evaluations were made of bloody stools, areas of erosion and hematological data. CS improved the symptoms of bloody stools, areas of erosion and hematological data. CS improved the symptoms of bloody stools, erosion and increase of white blood cells. Especially, CS (100 mg/kg) group showed markedly more improvement than the 5-ASA group. We think that the major mechanism of the therapeutic effects of CS is the prevention of tissue damage by the protection of digestive mucosa and anti-inflammatory effects. Therefore, CS may have therapeutic value for alimentary tract diseases such as inflammatory bowel disease or ulcer.

TNBS INDUCED COLITIS IN RATS
Effect of various TNBS doses on myeloperoxidase (MPO) activity, colon damage and weight. A total of 30 rats were randomized into five groups, 6 rats each group (in a cage), consisting of a 30% ethanol control group as well as four dose TNBS groups. The animals were anesthetized with 20% ethyl carbarnate (ip, 6mL/kg) and 0.5mL of either 30% ethanol (controls) or various concentrations of TNBS was slowly administered into the lumen of the colon via the anus using a rubber catheter (12cm long, external diameter 2mm). The rats were killed after 3 wk and the distal colon (8cm) was removed, opened longitudinally and washed to remove lumina contents, colon wet weight was weighed and colonic injuries were evaluated. The excised colon was pinned out on a wax block washed with 0.9% saline and assigned a code number. The colon was immediately examined under a stereomicroscope and any visible damage was scored on a 0-5 scale. Small sections of colon were taken from two distinct areas from each colon and placed in 10% formalin for histological examination. The colon was fixed, cut longitudinally into 5mm sections, stained with hematoxylin and eosin. The second segment (200mg-400mg) was immediately frozen for subsequent estimation of MPO activity. TNBS used in subsequent experiments was 100 mg/kg per rat. A total of 40 rats (5 rats per cage) administered a single intracolonic dose of TNBS ethanol solution (0.5 mL/rat). In control experiments, 5 rats received 0.5 mL 30% ethanol. At various times (24 h
and 1 wk-8 wk) after intracolonic administration of TNBS or one of the control solutions, 5 rats from each treatment group were randomly selected and killed, the colon tissue MPO activity was determined as the indices of inflammation.

**Mitomycin-c induced colitis in rats**

The mechanism of the tissue damage induced by colonic inflammation in ulcerative colitis is not established. We therefore developed and characterized a simple new rat model of acute colonic inflammation induced by a single systemic injection of mitomycin C. After an intraperitoneal injection of mitomycin-C, colon histologic examination revealed transient (3 to 14 days) diffuse, colonic inflammation and injury that, like human ulcerative colitis, was limited to the mucosal layer. The rest of the gastrointestinal tract was spared. Gut permeability, as measured by urinary excretion of orally administered lactulose and mannitol, was unchanged 3 days after injection, when inflammation was already present; permeability was increased at 7 days, when inflammation was maximal. Mitomycin C did not produce inflammation in experimentally bypassed segments of small bowel despite the presence of colonic-type bacteria, suggesting that lack of intraluminal bacteria was not responsible for the absence of inflammation in the small intestine. Chemiluminescence, a means of estimating levels of reactive oxygen species, was greater in the intact, inflamed colon of mitomycin C-treated rats than in bypassed segments. Moreover, inflamed mucosal scrapings produced more in vitro luminol-enhanced chemiluminescence. Furthermore, the reactive oxygen species scavengers allopurinol, catalase, and WR-2721 decreased inflammation severity. We therefore conclude: (1) the mitomycin C-treated rat is a novel, easy to prepare animal model of acute inflammation of colonic mucosa, with morphologic similarities to the acute phase of ulcerative colitis in human beings; (2) increased gut permeability in mitomycin C-treated rats is the result, not the cause, of the inflammation; and (3) reactive oxygen species play an important role in colonic inflammation and tissue injury in this model, and possibly in human ulcerative colitis colitis and runs for 7 days. In contrast to TNBS-induced colitis, the pathology is not dependant on T cells and is therefore a more useful model to study the role of non lymphoid cells such as macrophages in induction of disease and is similar to ulcerative colitis.

**Chemically induced inflammation**

Animal models of intestinal inflammation are indispensable for our understanding of the pathogenesis of Crohn disease and ulcerative colitis, the two major forms of inflammatory
bowel disease in humans. Here, we provide protocols for establishing murine 2, 4, 6-trinitrobenzene sulfonic acid (TNBS), oxazolone- and both acute and chronic dextran sodium sulfate (DSS) colitis, the most widely used chemically induced models of intestinal inflammation. In the former two models, colitis is induced by intrarectal administration of the covalently reactive reagents TNBS/oxazolone, which are believed to induce a T-cell-mediated response against hapten-modified autologous proteins/luminal antigens. In the DSS model, mice are subjected several days to drinking water supplemented with DSS, which seems to be directly toxic to colonic epithelial cells of the basal crypts. The procedures for the hapten models of colitis and acute DSS colitis can be accomplished in about 2 weeks but the protocol for chronic DSS colitis takes about 2 months.

2. Induction of DSS colitis
First report on the use of DSS dates back in the year 1985, when Ohkusa with co-workers published their investigation on DSS-induced colitis in hamsters 12. Thereafter DSS colitis was induced also in mice 13. Today there are numerous studies using DSS-induced colitis model to investigate pathogenesis of colitis and different factors affecting colitis. Colitis is induced by addition of DSS to drinking water. Depending on the concentration, the duration and frequency of DSS administration, the animals may develop acute or chronic colitis or even colitis induced dysplastic lesions. Mice show differential susceptibilities and responsiveness to DSS-induced colitis. The varying responses to DSS appear to be dependent on not only DSS (concentration, molecular weight, duration of DSS exposure, manufacturer, batch) but also genetic (strain and substrain, gender) and microbiological (microbiological state and intestinal flora) factors of animal, which are discussed in the present paper. Colitis
onset and severity may vary with many of these factors. Stress can be one of them 14. Differences in the DSS susceptibility do not correlate with differences in the consumption of DSS-supplemented water 15. However there is a need to monitor DSS consumption, especially when animals are exposed to different therapeutic strategies that may lower the consumption of DSS.

3. The molecular weight of DSS

DSS is sulfated polysaccharide with a highly variable molecular weight, ranging from 5 kDa to up to 1400 kDa. It was found that the molecular weight of DSS is very important factor in the induction of colitis 17 or colitis induced dysplastic lesions (carcinogenicity) 18. The severity of colitis 17 and carcinogenic activity 18 differ with the administration of DSS at different molecular weights (i.e. 5 kDa, 40 kDa and 500 kDa). The most severe colitis in BALB/c mice was observed when mice were treated with DSS of 40 kDa molecular weight, while mice treated with DSS of 5 kDa developed milder form of colitis. Mice treated with DSS of 500 kDa had no lesions in the large bowel 17. Similarly, carcinogenic activity in colon was induced by DSS of 54 kDa, while DSS of larger (520 kDa) or smaller (9.5 kDa) molecular weights induced no carcinogenic activity 18. Examination of uptake and tissue distribution of DSS by histochemical techniques showed that failure in the induction of colitis with 500 kDa DSS is due to its high molecular weight that prevents passage of the molecule through the mucosal membrane 17. Molecular weight of DSS can affect location of colitis as well. Mice treated with 40 kDa DSS developed most severe diffuse colitis in the middle and distal third of the large bowel, while mice treated with 5 kDa DSS developed relatively patchy lesions mainly in the cecum and upper colon.

3. EXPERIMENTAL WORK

1). Animals used: BALB/C mice.
2). **Weight**: 23gm - 30gm
3). **Sex**: FEMALE
4). **Age of animal**: 8-9 week old.

Eight-weeks-old Balb/c mice (weighing 24.0 ± 2.0 g) were randomly divided into 3 groups, housed in clean filter-top cages under Standard conditions (50% ± 10% humidity) in a 12-h Dark/12-h light cycle, and fed with standard chow diet.

All mice were acclimatised under standard conditions for 5 days. Mice’s are divided into 3 groups.

1). Normal group.
2). 4% DSS group.
3). 5% DSS group.

5). **Induced agent**
DEXTRAN SODIUM SULPHATE.

6). **Solubility**
STERILE WATER.

7). **Preparation of various DSS concentrations**
4% **DSS**: 4gm of DSS was dissolved in 100ml of sterile water.
5% **DSS**: 5gm of DSS was dissolved in 100ml of sterile water.

8). **Route of administration**
oral administration drinking water.
10). Number of mice in each group

Five.

11). Parameters

1. BODY WEIGHT
2. COLON LENGTH
3. COLON WEIGHT
4. VOLUME CONSUMED

PROCEDURE

- Animals were acclimatized for 4 to 5 days prior to the start of the experiment.
- Animals were randomly distributed to various groups based on their body weight.
- They are divided into three experimental groups with five animals in each group, housed in clean filter top cages under standard conditions in a 12 hr dark/12 hr light cycle and fed with standard mouse chow.

- **GROUP-1**: Normal drinking water
- **GROUP-2**: DSS-4% drinking water + DSS
- **GROUP-3**: DSS-5% drinking water + DSS

**Induction of colitis**

*DSS* was added into drinking water at a concentration of 4% and 5% to BALB/c mice.

- Balb/c mice were received to DSS for 7 days, and then studied for recovery; the symptoms and histopathological changes were aggravated, leading to high mortality.

Therefore, we chose to study the 6-day exposure. Briefly, mice receiving DSS for 7 days were used to analyze the response during the acute phase. Mice were weighed daily up to the ending of experiment.

- Mice were received to DSS for 7 days in different concentrations 4%, 5%. Study the progression from the acute phase to chronic inflammation or recovery.
- Healthy control animals received normal drinking water only.
The clinical symptoms recorded in DSS-treated and control mice were body weight, stool consistency, fecal bleeding, and diarrhea.

On day 7, animals were euthanized and the colon was removed, for the measurement of the colon weight, colon length.

Observe the change in the body weight, colon length, and colon weight.

Calculate the percentage induction of ulcerative colitis of different groups.

Model Development of colitis

All mice were treated with 4%, 5% DSS developed signs of ulcerative colitis: hunched posture; ruffled fur; wet, bloody or faecal stained perianal area; hyperemic colon. At the end of the experimental period, DSS treated mice showed significant wasting and shortening of the colon compared to the normal.

RESULTS:
Parameters measured are:
1) Body weight
2) Colon length
3) Colon weight

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Graph 1: changes in body weight of different groups of dextran sulfate sodium induced colitis in mice model. Results were expressed as mean±mean.

Graph 2: Changes In Colon Weight Of Different Groups Of Dextran Sulphate Sodium Induced In Mice Model. Results were expressed as mean±-mean.
Graph 3: Changes in colon length of different groups of dextran sulphate sodium induced colitis in mice model. Results were expressed as mean.

CONCLUSION

Dextran sulphate induced colitis in Balb/c mice is a good animal model to study drug action on experimental ulcerative colitis. Since impaired colonic regeneration can lead to chronic intestinal inflammation, the DSS model in Balb/c mice can be useful to study colonic regeneration and thus contribute to unravelling the pathogenesis of human IBD. Our present study involves Dextran sodium sulphate of 4%, 5% induced colitis in balb/c mice provides that at 5% dextran sodium sulphate induces severe colitis compared to 4%. At 5% DSS administration affects notonly distal, but also proximal colon.

We compared the change in body weight, colon length, colon weight to normal animals. Therefore our model is validated to do screening of ulcerative colitis compounds.

REFERENCES


40. Beatty PL, Narayanan S, Gariepy J, Ranganathan S and Finn OJ Vaccine against MUC1 antigen expressed in inflammatory bowel disease and cancer lessens colonic


