

Autism  
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## ABSTRACTS

Autism: A Unique Type of Mercury Poisoning.

Bernard S.

2000;

Written Supplement to Oral Testimony at the Hearing of the Government Reform Committee, Congress of the United States, United States House of Representatives.

Bradstreet JJ.

2002;2002 Jun 19;

Application of genomeceuticals to the molecular and immunological aspects of autism.

Brudnak MA.

*Med Hypotheses*. 2001 Aug; 57(2):186-91.

Autism is a developmental disease affecting as many as 1 in 300 children and is often characterized as a mental disorder originating in infancy that is associated with self-absorption, inability to interact socially, behavior, and language dysfunction (e.g. echolalia). Current theories indicate an important role of diet in the development of disease. It is thought that, as a result of maldigestion of casein and gluten, opioid-type peptides, or exorphins, are produced. Additionally, because of the time-frame of development of the disease, there has been an association with childhood vaccination. Consequently, prevailing therapies attempt to address these causes in one, or a combination, of three ways: diet restriction (removing casein and gluten); supplementation with exogenous enzymes; and probiotic bacteria. Until recently, none of the therapies addressed the molecular mechanisms that may be at work in the development and progression of autism. This paper presents potential molecular and cellular mechanism related to autism as well as discusses their application to the treatment of the disease through the application of genomeceuticals. Additionally, a link between developmentally associated aberrant immune and inflammatory responses, and autism is suggested and explored

Severe non-obstructive sleep disturbance as an initial presentation of gastroesophageal reflux disease.

Carr MM, Brodsky L.

*Int J Pediatr Otorhinolaryngol*. 1999 Dec 5; 51(2):115-20.

A 2.5-year-old child presented with a sleep disturbance initially diagnosed as a behavioral problem. The child had several atypical symptoms of gastroesophageal reflux disease (GERD). The sleep disturbance resolved quickly after treatment of GERD. GERD is a disease with protean manifestations which is becoming of greater interest to the pediatric otolaryngologist. We discuss diagnosis of this entity

Secretin and autism: a two-part clinical investigation.

Chez MG, Buchanan CP, Bagan BT, et al.

*J Autism Dev Disord*. 2000 Apr; 30(2):87-94.

Recent anecdotal reports have touted the gastrointestinal (GI) hormone secretin as a treatment modality for autism, though there is little clinical evidence or literature to support its viability. We undertook a two-part clinical trial to investigate these claims.

Fifty-six patients (49 boys, 7 girls, mean age = 6.4 years, SD = 2.7) enrolled in an open-label trial of secretin, during which they received one injection of the hormone (2 IU/kg). All subjects were evaluated by their parents at baseline and follow-up visits (3-6 weeks later, M = 3.7, SD = 1.4 weeks) with Childhood Autism Rating Scales (CARS). Thirty-four patients were labeled with Pervasive Developmental Disorder Not Otherwise Specified, and 22 met diagnostic criteria for Autistic Disorder. Forty-five patients were concurrently on other drug treatments. At follow-up, some reported minimal but potentially significant improvements including changes in GI symptoms, expressive and/or receptive language function, and improved awareness and social interactions. No adverse effects were reported or observed. Subsequently, 17 of the most responsive patients from Study 1 began a double-blind trial that also included 8 newly enrolled patients. Patients in this second study were alternatively entered into one of two groups and received injections of secretin or placebo with crossover at 4 weeks. Patients from Study 1 entered into Study 2 at an average of 6.5 (SD = 0.8) weeks after beginning Study 1. Results of both inquiries indicate that although treatment with secretin was reported to cause transient changes in speech and behavior in some children, overall it produced few clinically meaningful changes when compared to children given placebo injections

Double-blind, placebo-controlled study of L-carnosine supplementation in children with autistic spectrum disorders.

Chez MG, Buchanan CP, Aimonovitch MC, et al.

*J Child Neurol.* 2002 Nov; 17(11):833-7.

L-Carnosine, a dipeptide, can enhance frontal lobe function or be neuroprotective. It can also correlate with gamma-aminobutyric acid (GABA)-homocarnosine interaction, with possible anticonvulsive effects. We investigated 31 children with autistic spectrum disorders in an 8-week, double-blinded study to determine if 800 mg L-carnosine daily would result in observable changes versus placebo. Outcome measures were the Childhood Autism Rating Scale, the Gilliam Autism Rating Scale, the Expressive and Receptive One-Word Picture Vocabulary tests, and Clinical Global Impressions of Change. Children on placebo did not show statistically significant changes. After 8 weeks on L-carnosine, children showed statistically significant improvements on the Gilliam Autism Rating Scale (total score and the Behavior, Socialization, and Communication subscales) and the Receptive One-Word Picture Vocabulary test (all  $P < .05$ ). Improved trends were noted on other outcome measures. Although the mechanism of action of L-carnosine is not well understood, it may enhance neurologic function, perhaps in the enterorhinal or temporal cortex

Abnormal intestinal permeability in children with autism.

D'Eufemia P, Celli M, Finocchiaro R, et al.

*Acta Paediatr.* 1996 Sep; 85(9):1076-9.

We determined the occurrence of gut mucosal damage using the intestinal permeability test in 21 autistic children who had no clinical and laboratory findings consistent with known intestinal disorders. An altered intestinal permeability was found in 9 of the 21 (43%) autistic patients, but in none of the 40 controls. Compared to the controls, these nine patients showed a similar mean mannitol recovery, but a significantly higher mean lactulose recovery (1.64% +/- 1.43 vs 0.38% +/- 0.14;  $P < 0.001$ ). We speculate that an altered intestinal permeability could represent a possible mechanism for the increased passage through the gut mucosa of peptides derived from foods with subsequent behavioural abnormalities

The sleep patterns of infants and young children with gastro-oesophageal reflux.

Ghaem M, Armstrong KL, Trocki O, et al.

*J Paediatr Child Health.* 1998 Apr; 34(2):160-3.

**OBJECTIVE:** Sleep disturbance in gastro-oesophageal reflux disease (GORD) in infants and young children has not been systematically studied nor has this manifestation been compared with population norms. **METHODS:** Sleep patterns of 102 infants and children aged 1 to 36 months with and without GORD, defined by pH monitoring, were analysed using the same questionnaire as in recent studies of normal sleep behaviour in this age range. Main outcome measures included time taken to settle at night, the number of night time awakenings requiring parental intervention, day time sleep patterns and parents problems with their child's sleep behaviour. **RESULTS:** Compared with the population norms (n=3102), those with GORD (n=76) had greater prevalence of night time waking >3/night (50% vs 13% aged 3-12 months; 60% vs 10% aged 12-24 months,  $P < 0.001$ ), requirement of parental intervention (82% vs 55% aged 3-12 months,  $P < 0.05$ ; 92% vs 55% aged 12-24 months,  $P < 0.001$ ), significantly delayed onset of sleeping through the night, and greater prevalence of daytime sleep beyond 24 months. Similar but less striking differences were seen comparing those with (n="76") and without GORD (n="26"). **CONCLUSIONS:** Sleep interruption occurs more frequently in infants and children with GORD than population norms. Objective evaluation of infants and children with sleep disturbance after the age of 3 months may avoid unnecessary over or under diagnosis of GORD. Systematic investigation of the contribution of GORD to sleep disturbance in infants and young children is warranted

Intestinal microflora and bacterial overgrowth in early life.

Gracey M.

*J Pediatr Gastroenterol Nutr.* 1982; 1(1):13-22.

At birth the gut is sterile but later is continually exposed to potentially harmful agents: infective, toxic, and antigenic. The development of a strictly contained intestinal microflora reflects an important aspect of control over potentially noxious, environmental influences. Control of the intestinal microecology is dependent on many factors including intestinal peristalsis, the intraluminal environment, and microbial interactions. When these regulating mechanisms are lost, microbial contamination of the gut occurs and leads to the so-called "contaminated small-bowel syndrome." This has serious clinical consequences, including diarrhoea and malabsorption, and can occur in a wide range of clinical situations in infants and young children

Improved social and language skills after secretin administration in patients with autistic spectrum disorders.

Horvath K, Stefanatos G, Sokolski KN, et al.

*J Assoc Acad Minor Phys.* 1998; 9(1):9-15.

We report three children with autistic spectrum disorders who underwent upper gastrointestinal endoscopy and intravenous administration of secretin to stimulate pancreaticobiliary secretion. All three had an increased pancreaticobiliary secretory response when compared with nonautistic patients (7.5 to 10 mL/min versus 1 to 2 mL/min). Within 5 weeks of the secretin infusion, a significant amelioration of the children's gastrointestinal symptoms was observed, as was a dramatic improvement in their behavior, manifested by improved eye contact, alertness, and expansion of expressive language. These clinical observations suggest an association between gastrointestinal and brain function in patients with autistic behavior

Gastrointestinal abnormalities in children with autistic disorder.

Horvath K, Papadimitriou JC, Rabsztyrn A, et al.

*J Pediatr.* 1999 Nov; 135(5):559-63.

**OBJECTIVES:** Our aim was to evaluate the structure and function of the upper gastrointestinal tract in a group of patients with autism who had gastrointestinal symptoms. **STUDY DESIGN:** Thirty-six children (age: 5.7 +/- 2 years, mean +/- SD) with autistic disorder underwent upper gastrointestinal endoscopy with biopsies, intestinal and pancreatic enzyme analyses, and bacterial and fungal cultures. The most frequent gastrointestinal complaints were chronic diarrhea, gaseousness, and abdominal discomfort and distension. **RESULTS:** Histologic examination in these 36 children revealed grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15, and chronic duodenitis in 24. The number of Paneth's cells in the duodenal crypts was significantly elevated in autistic children compared with non-autistic control subjects. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children (58.3%), although there was no abnormality found in pancreatic function. Seventy-five percent of the autistic children (27/36) had an increased pancreatico-biliary fluid output after intravenous secretin administration. Nineteen of the 21 patients with diarrhea had significantly higher fluid output than those without diarrhea. **CONCLUSIONS:** Unrecognized gastrointestinal disorders, especially reflux esophagitis and disaccharide malabsorption, may contribute to the behavioral problems of the non-verbal autistic patients. The observed increase in pancreatico-biliary secretion after secretin infusion suggests an upregulation of secretin receptors in the pancreas and liver. Further studies are required to determine the possible association between the brain and gastrointestinal dysfunctions in children with autistic disorder

Secretin treatment for autism.

Horvath K.

*N Engl J Med.* 2000 Apr 20; 342(16):1216.

Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism.

Kawashima H, Mori T, Kashiwagi Y, et al.

*Dig Dis Sci.* 2000 Apr; 45(4):723-9.

It has been reported that measles virus may be present in the intestine of patients with Crohn's disease. Additionally, a new syndrome has been reported in children with autism who exhibited developmental regression and gastrointestinal symptoms (autistic enterocolitis), in some cases soon after MMR vaccine. It is not known whether the virus, if confirmed to be present in these patients, derives from either wild strains or vaccine strains. In order to characterize the strains that may be present, we have carried out the detection of measles genomic RNA in peripheral mononuclear cells (PBMC) in eight patients with Crohn's disease, three patients with ulcerative colitis, and nine children with autistic enterocolitis. As controls, we examined healthy children and patients with SSPE, SLE, HIV-1 (a total of eight cases). RNA was purified from PBMC by Ficoll-paque, followed by reverse transcription using AMV; cDNAs were subjected to nested PCR for detection of specific regions of the hemagglutinin (H) and fusion (F) gene regions. Positive samples were sequenced directly, in nucleotides 8393-8676 (H region) or 5325-5465 (from noncoding F to coding F region). One of eight patients with Crohn disease, one of three patients with ulcerative colitis, and three of nine children with autism, were positive. Controls were all negative. The sequences obtained from the patients with Crohn's disease shared the characteristics with wild-strain virus. The sequences obtained from the patients with ulcerative colitis and children with autism were consistent with being vaccine strains. The results were concordant with the exposure history of the patients. Persistence of measles virus was confirmed in PBMC in some patients with chronic intestinal inflammation

Reports on dietary intervention in autistic disorders.

Knivsber AM, Reichelt KL, Nodland M.

*Nutr Neurosci.* 2001; 4(1):25-37.

Autism is a developmental disorder for which no cure currently exists. Gluten and/or casein free diet has been implemented to reduce autistic behaviour, in addition to special education, since early in the eighties. Over the last twelve years various studies on this dietary intervention have been published in addition to anecdotal, parental reports. The scientific studies include both groups of participants as well as single cases, and beneficial results are reported in all, but one study. While some studies are based on urinary peptide abnormalities, others are not. The reported results are, however, more or less identical; reduction of autistic behaviour, increased social and communicative skills, and reappearance of autistic traits after the diet has been broken

Partial amplification of the measles virus nucleocapsid gene from stored sera and cerebrospinal fluids for molecular epidemiological studies.

Kreis S, Schoub BD.

*J Med Virol.* 1998 Oct; 56(2):174-7.

The analysis of stored sera for retrospective molecular epidemiological studies provides a powerful tool to investigate strain variation in measles viruses that had circulated up to 20 years ago. For this purpose, a rapid and simple method for extraction of RNA from stored sera and cerebrospinal fluids (CSF) was developed. When used on sera and CSFs that have been frozen for as long as 20 years, this method proved to be more efficient than established techniques. The extracted RNA was reverse transcribed into cDNA by using random hexamer primers. The PCR amplification of the 3' terminus of the nucleocapsid gene (N) was divided into two overlapping fragments of 375 and 384 bp length, covering the entire region of interest. This region is thought to have the highest variability within the MV genome and has previously been shown to be suitable for strain characterization. The resulting PCR fragments were sequenced manually by using standard methods without the need of further clean-up steps

Transdermal secretin for autism - a case report.

Lamson DW, Plaza SM.

*Altern Med Rev.* 2001 Jun; 6(3):311-3.

Secretin hormone given daily in transdermal cream was associated with marked and sustained developmental progress in an aphasic two-and-a-half year old child diagnosed with autism

Special Diets for Special Kids.

Lewis L.

1998;

Early measles virus infection is associated with the development of inflammatory bowel disease.

*Am J Gastroenterol.* 2000 Jun; 95(6):1480-5.

**OBJECTIVE:** The measles virus has been implicated as a possible etiological agent in the development of inflammatory bowel disease (IBD). Measles infection at an early age is associated with subacute sclerosing panencephalitis, a degenerative neurological condition caused by persistent measles infection of the central nervous system. We sought to determine whether infection with measles virus at an early age was also associated with an increased risk of developing IBD. **METHODS:** Patients with measles infection diagnosed before the age of 5 yr were identified through the diagnostic indices of the Mayo Clinic and the Rochester Epidemiology Project. A questionnaire was used to ascertain a subsequent history of IBD, which was confirmed by records from the subjects' physicians. The risks of developing Crohn's disease and ulcerative colitis were calculated relative to expected rates for these conditions in the Olmsted County, Minnesota population. **RESULTS:** Of 1164 eligible cases, 662 (57%) completed the questionnaire. There were six confirmed cases of Crohn's disease and six of ulcerative colitis. The expected number of cases was 1.9 for Crohn's disease (standardized incidence ratio [SIR] 3.1, 95% confidence interval [CI] 1.1-6.8) and 2.0 for ulcerative colitis (SIR 3.0, CI 1.1-6.5). There was a trend towards a higher risk of developing IBD with an earlier age of infection. **CONCLUSIONS:** Early measles infection is associated with an increased risk of developing Crohn's disease and ulcerative colitis. The risk may be higher with earlier infection

Invited review: the scientific basis of *Lactobacillus acidophilus* NCFM functionality as a probiotic.

Sanders ME, Klaenhammer TR.

*J Dairy Sci.* 2001 Feb; 84(2):319-31.

*Lactobacillus acidophilus* NCFM is a probiotic strain available in conventional foods (milk, yogurt, and toddler formula) and dietary supplements. Its commercial availability in the United States since the mid-1970s is predicated on its safety, its amenability to commercial manipulation, and its biochemical and physiological attributes presumed to be important to human probiotic functionality. The strain has been characterized in vitro, in animal studies, and in humans. NCFM is the progenitor of the strain being used for complete chromosome sequencing and therefore will be a cornerstone strain for understanding the relationship between genetics and probiotic functionality. Both phenotypic and genotypic techniques have verified its taxonomic status as a type A1 *L. acidophilus* strain. It adheres to Caco-2 and mucus-secreting HT-29 cell culture systems, produces antimicrobial compounds, and is amenable to genetic manipulation and directed DNA introduction. NCFM survives gastrointestinal tract transit in both healthy and diseased populations. NCFM inhibits aberrant crypt formation in mutagenized rats, indicative of activity that could decrease the risk of colon cancer. A blend of probiotic strains containing NCFM decreased the incidence of pediatric diarrhea. NCFM led to a significant decrease in levels of toxic amines in the blood of dialysis patients with small bowel bacterial overgrowth. At adequate daily feeding levels, NCFM may facilitate lactose digestion in lactose-intolerant subjects. Further validation of the probiotic properties of NCFM in humans and clarification of its mechanisms of probiotic action are needed to better understand the role this strain might play in promoting human health

Lack of benefit of a single dose of synthetic human secretin in the treatment of autism and pervasive developmental disorder.

Sandler AD, Sutton KA, DeWeese J, et al.

*N Engl J Med.* 1999 Dec 9; 341(24):1801-6.

**BACKGROUND:** Secretin is a peptide hormone that stimulates pancreatic secretion. After recent publicity about a child with autism whose condition markedly improved after a single dose of secretin, thousands of children with autistic disorders may have received secretin injections. **METHODS:** We conducted a double-blind, placebo-controlled trial of a single intravenous dose of synthetic human secretin in 60 children (age, 3 to 14 years) with autism or pervasive developmental disorder. The children were randomly assigned to treatment with an intravenous infusion of synthetic human secretin (0.4 microg per kilogram of body weight) or saline placebo. We used standardized behavioral measures of the primary and secondary features of autism, including the Autism Behavior Checklist, to assess the degree of impairment at base line and over the course of a four-week period after treatment. **RESULTS:** Of the 60 children, 4 could not be evaluated - 2 received secretin outside the study, and 2 did not return for follow-up. Thus, 56 children (28 in each group) completed the study. As compared with placebo, secretin treatment was not associated with significant improvements in any of the outcome measures. Among the children in the secretin group, the mean total score on the Autism Behavior Checklist at base line was 59.0 (range of possible values, 0 to 158, with a larger value corresponding to greater impairment), and among those in the placebo group it was 63.2. The mean decreases in scores over the four-week period were 8.9 in the secretin group and 17.8 in the placebo group (mean difference, -8.9; 95 percent confidence interval, -19.4 to 1.6; P=0.11). None of the children had treatment-limiting adverse effects. After they were told the results, 69 percent of the parents of the children in this study said they remained interested in secretin as a treatment for their children. **CONCLUSIONS:** A single dose of synthetic human secretin is not an effective treatment for autism or pervasive

developmental disorder

Unraveling the Mystery of Autism and Pervasive Developmental Disorder: A Mother's Story of Research and Recovery.

Seroussi K.

2000;

Biomodulation of the toxic and nutritional effects of small bowel bacterial overgrowth in end-stage kidney disease using freeze-dried *Lactobacillus acidophilus*.

Simenhoff ML, Dunn SR, Zollner GP, et al.

*Miner Electrolyte Metab.* 1996; 22(1-3):92-6.

Small bowel bacterial overgrowth (SBBO), well known to occur in end-stage kidney failure, is responsible for producing uremic toxins and contributing to the patient's decreased nutritional well-being. In this study, 8 hemodialysis patients were treated with a course of oral *Lactobacillus acidophilus* (LBA) in an attempt to alter this SBBO. LBA treatment was effective in lowering 2 compounds generated in vivo. Serum dimethylamine (DMA) levels dropped from 224 +/- 47 to 154 +/- 47 micrograms/dl at the end of LBA treatment ( $p < 0.001$ ). Nitrosodimethylamine, a carcinogen, levels also decreased significantly from 178 +/- 67 (untreated) to 83 +/- 49 ng/kg (after LBA treatment). Patients nutritional status, assessed as serum albumin, body weight, caloric intake, midarm muscle area (MAMA) and appetite improved modestly, but not significantly. LBA changed small bowel pathobiology by modifying metabolic actions of SBBO, reducing in vivo generation of toxins and carcinogens and promoting nutrition with no adverse side effects

Abnormal measles-mumps-rubella antibodies and CNS autoimmunity in children with autism.

Singh VK, Lin SX, Newell E, et al.

*J Biomed Sci.* 2002 Jul; 9(4):359-64.

Autoimmunity to the central nervous system (CNS), especially to myelin basic protein (MBP), may play a causal role in autism, a neurodevelopmental disorder. Because many autistic children harbor elevated levels of measles antibodies, we conducted a serological study of measles-mumps-rubella (MMR) and MBP autoantibodies. Using serum samples of 125 autistic children and 92 control children, antibodies were assayed by ELISA or immunoblotting methods. ELISA analysis showed a significant increase in the level of MMR antibodies in autistic children. Immunoblotting analysis revealed the presence of an unusual MMR antibody in 75 of 125 (60%) autistic sera but not in control sera. This antibody specifically detected a protein of 73-75 kD of MMR. This protein band, as analyzed with monoclonal antibodies, was immunopositive for measles hemagglutinin (HA) protein but not for measles nucleoprotein and rubella or mumps viral proteins. Thus the MMR antibody in autistic sera detected measles HA protein, which is unique to the measles subunit of the vaccine. Furthermore, over 90% of MMR antibody-positive autistic sera were also positive for MBP autoantibodies, suggesting a strong association between MMR and CNS autoimmunity in autism. Stemming from this evidence, we suggest that an inappropriate antibody response to MMR, specifically the measles component thereof, might be related to pathogenesis of autism

Is measles vaccination a risk factor for inflammatory bowel disease?

Thompson NP, Montgomery SM, Pounder RE, et al.

*Lancet.* 1995 Apr 29; 345(8957):1071-4.

Measles virus may persist in intestinal tissue, particularly that affected by Crohn's disease, and early exposure to measles may be a risk factor for the development of Crohn's disease. Crohn's disease and ulcerative colitis occur in the same families and may share a common aetiology. In view of the rising incidence of inflammatory bowel disease (Crohn's disease and ulcerative colitis), we examined the impact of measles vaccination upon these conditions. Prevalences of Crohn's disease, ulcerative colitis, coeliac disease, and peptic ulceration were determined in 3545 people who had received live measles vaccine in 1964 as part of a measles vaccine trial. A longitudinal birth cohort of 11,407 subjects was one unvaccinated comparison cohort, and 2541 partners of those vaccinated was another. Compared with the birth cohort, the relative risk of developing Crohn's disease in the vaccinated group was 3.01 (95% CI 1.45-6.23) and of developing ulcerative colitis was 2.53 (1.15-5.58). There was no significant difference between these two groups in coeliac disease prevalence. Increased prevalence of inflammatory bowel disease, but not coeliac disease or peptic ulceration, was found in the vaccinated cohort compared with their partners. These findings suggest that measles virus may play a part in the development not only of Crohn's disease but also of ulcerative colitis

Potential viral pathogenic mechanism for new variant inflammatory bowel disease.

Uhlmann V, Martin CM, Sheils O, et al.

*Mol Pathol.* 2002 Apr; 55(2):84-90.

**AIMS:** A new form of inflammatory bowel disease (ileocolonic lymphonodular hyperplasia) has been described in a cohort of children with developmental disorder. This study investigates the presence of persistent measles virus in the intestinal tissue of these patients (new variant inflammatory bowel disease) and a series of controls by molecular analysis. **METHODS:** Formalin fixed, paraffin wax embedded and fresh frozen biopsies from the terminal ileum were examined from affected children and histological normal controls. The measles virus Fusion (F) and Haemagglutinin (H) genes were detected by TaqMan reverse transcription polymerase chain reaction (RT-PCR) and the Nucleocapsid (N) gene by RT in situ PCR. Localisation of the mRNA signal was performed using a specific follicular dendritic cell antibody. **RESULTS:** Seventy five of 91 patients with a histologically confirmed diagnosis of ileal lymphonodular hyperplasia and enterocolitis were positive for measles virus in their intestinal tissue compared with five of 70 control patients. Measles virus was identified within the follicular dendritic cells and some lymphocytes in foci of reactive follicular hyperplasia. The copy number of measles virus ranged from one to 300,00 copies/ng total RNA. **CONCLUSIONS:** The data confirm an association between the presence of measles virus and gut pathology in children with developmental disorder

Crohn's disease: pathogenesis and persistent measles virus infection.

Wakefield AJ, Ekbohm A, Dhillon AP, et al.

*Gastroenterology.* 1995 Mar; 108(3):911-6.

The Inflammatory Bowel Disease Study Group at the Royal Free Hospital School of Medicine has tested the hypothesis that the primary pathological abnormality in Crohn's disease is in the mesenteric blood supply. Early morphological studies involved arterial perfusion-fixation and either resin casting and scanning electron microscopy or vascular immunostaining of resected intestine affected by Crohn's disease. Granulomatous and lymphocytic damage to intramural blood vessels, even in macroscopically normal areas, was observed. We put forward possible mechanisms by which a chronic ischemic process might account for many of the idiosyncracies of Crohn's disease. It was proposed that persistent viral infection of the mesenteric microvascular endothelium might underly this vasculitic process; based on certain behavioral characteristics of measles virus, including its tropism for the submucosal endothelium of the intestine, this agent was investigated further. This report reviews the preliminary evidence from both epidemiological and basic scientific data for persistent measles virus in the intestine of patients with Crohn's disease. Possible mechanisms for virus persistence and subsequent reactivation are discussed. In conclusion, we believe that Crohn's disease may be a chronic granulomatous vasculitis in reaction to a persistent infection with measles virus within the vascular endothelium. This granulomatous inflammation, perhaps aggravated by either a hypercoagulable state or mechanical stress, results in the clinical features of Crohn's disease

Crohn's disease: the case for measles virus.

Wakefield AJ, Montgomery SM, Pounder RE.

*Ital J Gastroenterol Hepatol.* 1999 Apr; 31(3):247-54.

Crohn's disease has the epidemiological and pathological hallmarks of an infection with a long natural history. Its emergence in developed countries in the middle of the 20th Century represents an instant in the continuum of human evolution, indicating either a new infection or, as with poliomyelitis, a changing pattern of exposure to a common childhood pathogen. Both short- and long-term outcomes from viral infection are largely dependent upon age and dose of exposure. We and others have suggested that measles virus may be causally related to Crohn's disease, and that the associated risk is an atypical pattern of exposure. Early, intensive, and concurrent infections have been identified as risks for subacute sclerosing panencephalitis, a delayed sequelae to measles virus infection, possibly through a process of high zone immunological tolerance and persistent infection. The data for Crohn's disease suggest that persistent infection may follow early low dose exposure and low zone immunological tolerance. The changing pattern of measles virus exposure this century would be consistent with a shift towards lower dose of infection. Such an exposure would also be consistent with persistence of the virus at very low copy number within discrete foci of granulomatous inflammation. The ability of measles virus to profoundly disrupt mucosal immune responses may provide the human counterpart of the cytokine-gene knockout

Measles virus as a risk for inflammatory bowel disease: an unusually tolerant approach.

Wakefield AJ, Montgomery SM.

*Am J Gastroenterol.* 2000 Jun; 95(6):1389-92.

Enterocolitis in children with developmental disorders.

Wakefield AJ, Anthony A, Murch SH, et al.

*Am J Gastroenterol.* 2000 Sep; 95(9):2285-95.

**OBJECTIVE:** Intestinal pathology, i.e., ileocolonic lymphoid nodular hyperplasia (LNH) and mucosal inflammation, has been described in children with developmental disorders. This study describes some of the endoscopic and pathological characteristics in a group of children with developmental disorders (affected children) that are associated with behavioral regression and bowel symptoms, and compares them with pediatric controls. **METHODS:** Ileocolonoscopy and biopsy were performed on 60 affected children (median age 6 yr, range 3-16; 53 male). Developmental diagnoses were autism (50 patients), Asperger's syndrome (five), disintegrative disorder (two), attention deficit hyperactivity disorder (ADHD) (one), schizophrenia (one), and dyslexia (one). Severity of ileal LNH was graded (0-3) in both affected children and 37 developmentally normal controls (median age 11 yr, range 2-13 yr) who were investigated for possible inflammatory bowel disease (IBD). Tissue sections were reviewed by three pathologists and scored on a standard proforma. Data were compared with ileocolonic biopsies from 22 histologically normal children (controls) and 20 children with ulcerative colitis (UC), scored in an identical manner. Gut pathogens were sought routinely. **RESULTS:** Ileal LNH was present in 54 of 58 (93%) affected children and in five of 35 (14.3%) controls ( $p < 0.001$ ). Colonic LNH was present in 18 of 60 (30%) affected children and in two of 37 (5.4%) controls ( $p < 0.01$ ). Histologically, reactive follicular hyperplasia was present in 46 of 52 (88.5%) ileal biopsies from affected children and in four of 14 (29%) with UC, but not in non-IBD controls ( $p < 0.01$ ). Active ileitis was present in four of 51 (8%) affected children but not in controls. Chronic colitis was identified in 53 of 60 (88%) affected children compared with one of 22 (4.5%) controls and in 20 of 20 (100%) with UC. Scores of frequency and severity of inflammation were significantly greater in both affected children and those with UC, compared with controls ( $p < 0.001$ ). **CONCLUSIONS:** A new variant of inflammatory bowel disease is present in this group of children with developmental disorders

Measles, mumps, rubella vaccine: through a glass, darkly.

Wakefield AJ, Montgomery SM.

*Adverse Drug React Toxicol Rev.* 2000 Dec; 19(4):265-83.

Detection of maternal antibodies in infantile autism.

Warren RP, Cole P, Odell JD, et al.

*J Am Acad Child Adolesc Psychiatry.* 1990 Nov; 29(6):873-7.

Maternal antibodies reactive with antigenic proteins expressed on the cell surface of paternal lymphocytes can be detected in couples with histories of more than one miscarriage or stillbirth. It is possible, but not proven, that these antibodies also react with tissues of the fetus and result in fetal death. Since many mothers of autistic children have a history of pregnancy disorder, antibodies were studied in 11 mothers of autistic children who were 6 years of age or younger. Six of the mothers had antibodies that reacted with lymphocytes of the autistic child. Five of these six mothers had a history of pregnancy disorder. Since antigens expressed on lymphocytes are found on cells of the central nervous system and, perhaps, other tissues of the developing embryo, it is suggested that aberrant maternal immunity may be associated with the development of some cases of infantile autism

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