Which 65 important and relevant references appear not to have been considered in the FSANZ review 2012?

Australia's food regulator FSANZ commissioned a "Review of Intolerance Reactions to Food and Food Additives" by Hayder H, Mueller U and Bartholomaeus A (Int. food risk anal. j., 2011, Vol. 1, No. 2, 23-32. http://www.intechopen.com/source/pdfs/26271/InTech-Review_of_intolerance_reactions_to_food_and_food_additives.pdf)

Unfortunately the review was been written from an allergist's point of view and appears uncomfortable with considering behavioural and learning dimensions to reactions. Many of the conclusions drawn are not drawn from quoted evidence but from personal views. Of the authors and those acknowledged, only Dr Loblay has written sparingly in this area. It is a pity that the Food Intolerance Network was not consulted in the process of this review so that other references could have been considered.

Allen, D. H., J. Delohery, et al. (1987)."Monosodium L-glutamate-induced asthma." J Allergy Clin Immunol **80**(4): 530-7.

> Ingested chemicals, including aspirin and sulfites, are becoming increasingly recognized as provokers of acute severe asthma. In order to investigate the asthma-provoking potential of the widely used flavor enhancer, monosodium L-glutamate (MSG), we challenged 32 subjects with asthma, a number of whom gave histories of severe asthma after Chinese restaurant meals or similarly spiced meals. The subjects received an additive-free diet for 5 days before challenge and were challenged in hospital, after an overnight fast, with 500 mg capsules of MSG. They were challenged in a single-blind, placebo-controlled fashion with increasing doses of MSG from 0.5 gm to 5.0 gm. Thirteen subjects reacted. Seven subjects (group 1) developed asthma and symptoms of the Chinese restaurant syndrome 1 to 2 hours after ingestion of MSG. Six subjects (group 2) did not develop symptoms of Chinese restaurant syndrome, and their asthma developed 6 to 12 hours after ingestion of MSG. These challenge studies confirm that MSG can provoke asthma. The reaction to MSG is dose dependent and may be delayed up to 12 hours, making recognition difficult for both patient and physician.

Arnold, L. E. (1999). "Treatment alternatives for Attention-deficit/hyperactivity disorder." Journal of Attention Disorders 3(1):30-48.

Baker, G. J., P. Collett, et al. (1981). "Bronchospasm induced by metabisulphite-containing foods and drugs." Med J Aust **2**(11): 614-7.

Bateman, B., J. O. Warner, et al. (2004). "The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children." Arch Dis Child **89**(6): 506-11.

> AIMS: To determine whether artificial food colourings and a preservative in the diet of 3 year old children in the general population influence hyperactive behaviour. METHODS: A sample of 1873 children were screened in their fourth year for the presence of hyperactivity at baseline (HA), of whom 1246 had skin prick tests to identify atopy (AT). Children were selected to form the following groups: HA/AT, not-HA/AT, HA/not-AT, and not-HA/not-AT (n = 277). After baseline assessment, children were subjected to a diet eliminating artificial colourings and benzoate preservatives for one week; in the subsequent three week within subject double blind crossover study they received, in random order, periods of dietary challenge with a drink containing artificial colourings (20 mg daily) and sodium benzoate (45 mg daily) (active period), or a placebo mixture, supplementary to their diet. Behaviour was

assessed by a tester blind to dietary status and by parents' ratings. RESULTS: There were significant reductions in hyperactive behaviour during the withdrawal phase. Furthermore, there were significantly greater increases in hyperactive behaviour during the active than the placebo period based on parental reports. These effects were not influenced by the presence or absence of hyperactivity, nor by the presence or absence of atopy. There were no significant differences detected based on objective testing in the clinic. CONCLUSIONS: There is a general adverse effect of artificial food colouring and benzoate preservatives on the behaviour of 3 year old children which is detectable by parents but not by a simple clinic assessment. Subgroups are not made more vulnerable to this effect by their prior levels of hyperactivity or by atopy.

Baud, O., V. Laudenbach, et al. (2001). "Neurotoxic effects of fluorinated glucocorticoid preparations on the developing mouse brain: role of preservatives." Pediatr Res **50**(6): 706-11.

Prenatal betamethasone (Celestene) therapy reduces the incidence of brain damage, whereas prenatal or neonatal dexamethasone (Soludecadron) increases the risk of brain lesions or neuromotor deficits. To determine whether this increase is ascribable to the sulfites used as preservatives in Soludecadron, we investigated the effects of 12 h of exposure to pure dexamethasone, Soludecadron, pure betamethasone, Celestene, and sulfites on in vitro and in vivo death of neurons cultured under basal conditions or with excitotoxic agents (N-methyl-D-aspartate or (S)-5-bromowillardiine) or hypoxia. Apoptotic features were quantitated using a fluorescent chromatin stain (Hoechst 33258). Neuronal viability was unaffected by pure dexamethasone, pure betamethasone, or Celestene. Soludecadron or sulfites significantly increased neuronal loss. Pure dexamethasone or pure betamethasone produced a 40-50% decrease in neuronal death induced by N-methyl-D-aspartate, (S)-5-bromowillardiine, or hypoxia, whereas Soludecadron had no effect and sulfites significantly increased the neurotoxicity of excitotoxic agents. In in vivo experiments involving terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling after several i.p. injections of fluorinated glucocorticoids, Soludecadron, but not pure dexamethasone, significantly increased the number of terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling-stained cells in neocortical layers and thalamus. These experimental findings suggest that injectable dexamethasone should be used with caution during the perinatal period.

Bennett CPW, McEwen LM, et al. (1998). "The Shipley Project: treating food allergy to prevent criminal behaviour in community settings." J Nutr Envir Med **8**: 77-83.

Boris, M. and F. S. Mandel (1994). "Foods and additives are common causes of the attention deficit hyperactive disorder in children." Ann Allergy **72**(5): 462-8.

The attention deficit hyperactive disorder (ADHD) is a neurophysiologic problem that is detrimental to children and their parents. Despite previous studies on the role of foods, preservatives and artificial colorings in ADHD this issue remains controversial. This investigation evaluated 26 children who meet the criteria for ADHD. Treatment with a multiple item elimination diet showed 19 children (73%) responded favorably, $P < .001$. On open challenge, all 19 children reacted to many foods, dyes, and/or preservatives. A double-blind placebo controlled food challenge (DBPCFC) was completed in 16 children. There was a significant improvement on placebo days compared with challenge days ($P = .003$). Atopic children with ADHD had a significantly higher response rate than the nonatopic group. This study demonstrates a beneficial effect of eliminating reactive foods and artificial colors in children with ADHD. Dietary factors may play a significant role in the etiology of the majority of children with ADHD.

Breakey, J., M. Hill, et al. (1991). "A report on a trial of the low additive, low salicylate diet in the treatment of behaviour and learning problems in children." Aust J Nutr Diet **48**(3): 89-94.

Brusque, A. M., C. F. Mello, et al. (1999). "Effect of chemically induced propionic acidemia on neurobehavioral development of rats." Pharmacol Biochem Behav **64**(3): 529-34.

High levels of propionic acid (PPA) comparable to those of human propionic acidemia were achieved in blood (1-5 mmol/l) and brain (1 micromol/g) of rats by administering saline-buffered propionate (pH 7.4) subcutaneously twice a day from the 6th to the 28th day of life. PPA doses ranged from 1.44 to 1.92 micromol/g body weight as a function of animal age. Control rats were treated with saline in the same volumes. Growth and development of physical landmarks were assessed by monitoring the following parameters daily: body weight, upper incisor eruption, eye opening, and hair coat. Development of some reflexes was also monitored, and a specific subset of motor skills was evaluated at days 14 and 21 of life by the free-fall righting test and the spontaneous alternation test. Chronic PPA administration had no effect on body weight, cerebral cortex weight, or cerebellum weight, but caused slight but significant delays in the day of appearance of hair coat and eye opening, indicating an effect of PPA on the development of physical parameters. Free-fall righting was impaired in PPA-treated animals. On the other hand, PPA administration had no effect on the performance of the animals in the spontaneous alternation tests. Long-term effects of early PPA administration were investigated by assessing animal performance in an aversive task (two-way shuttle avoidance task) and in a nonaversive (open-field task) behavioral task at 60 days of age. PPA-treated rats did not habituate to the open field, and presented a lack of retention of the shuttle-avoidance task. Our results suggest that early postnatal PPA administration to rats alters normal development and induces long-term behavioral deficits in aversive and nonaversive tasks.

Brusque, A. M., S. T. Terracciano, et al. (1998). "Chronic administration of propionic acid reduces ganglioside N-acetylneuraminic acid concentration in cerebellum of young rats." J Neurol Sci **158**(2): 121-4.

Elevated levels of propionate comparable to those of human propionic acidaemia were achieved in the blood of young rats by injecting subcutaneously buffered propionic acid (PPA) twice a day at 8-h intervals from the 6th to the 28th day of life. A matched group of animals (controls) was treated with the same volumes of saline. The animals were weighed and sacrificed by decapitation at 28, 35 or 60 days of age. Cerebellum and cerebrum were weighed and their protein and ganglioside N-acetylneuraminic acid (G-NeuAc) contents determined. Body, cerebral and cerebellar weights were similar in both groups, suggesting that PPA per se neither alters the appetite of the rats nor causes malnutrition. Brain protein concentration was also not affected by chronic administration of PPA, in contrast to G-NeuAc concentration which was significantly reduced in the cerebellum. Since ganglioside concentration is closely related to the dendritic surface and indirectly reflects synaptogenesis, our results of an important ganglioside deficit in the brain of PPA-treated animals may be related to the neurologic dysfunction characteristic of propionic acidaemic patients.

Carter, C. M., J. Egger, et al. (1985). "A dietary management of severe childhood migraine." Hum Nutr Appl Nutr **39**(4): 294-303.

We describe in detail a dietary treatment which has been shown to be effective in most children with severe migraine. Potential adverse nutritional and allergic effects are outlined; because of the diet should be undertaken only in those ill enough to justify it. In the first stage very few foods are given, and if the child responds to this oligoantigenic diet, foods are reintroduced one by one at weekly intervals. In this way foods causing symptoms are identified and eliminated. Research is urgently needed to establish simpler empirical diets and diagnostic tests.

Carter, C. M., M. Urbanowicz, et al. (1993). "Effects of a few food diet in attention deficit disorder." Arch Dis Child **69**(5): 564-8.

Seventy-eight children, referred to a diet clinic because of hyperactive behaviour, were placed on a 'few foods' elimination diet. Fifty nine improved in behaviour during this open trial. For 19 of these children it was possible to disguise foods or additives, or both, that reliably provoked behavioural problems by mixing them with other tolerated foods and to test their effect in a

placebo controlled double blind challenge protocol. The results of a crossover trial on these 19 children showed a significant effect for the provoking foods to worsen ratings of behaviour and to impair psychological test performance. This study shows that observations of change in behaviour associated with diet made by parents and other people with a role in the child's care can be reproduced using double blind methodology and objective assessments. Clinicians should give weight to the accounts of parents and consider this treatment in selected children with a suggestive medical history.

Chafee, F. H. and G. A. Settipane (1967). "Asthma caused by FD&C approved dyes." J Allergy **40**(2): 65-72.

Cho JH, Kwun YS, Jang HS, Kang JM, Won YS, Yoon HR.(2000) Long-term use of preservatives on rat nasal respiratory mucosa: effects of benzalkonium chloride and potassium sorbate. Laryngoscope. 2000 Feb;110(2 Pt 1):312-7.

OBJECTIVES: The preservatives benzalkonium chloride (BZC) and potassium sorbate (PS) are widely used, not only for nasal drops, but also for eyedrops and cosmetics. However, there have been many case reports that consider lesions such as dermatitis or conjunctivitis to be the results of irritation induced by BZC or PS. METHODS: We evaluated the histological changes after the long-term administration of BZC or PS on rat nasal respiratory mucosa. Forty rats were used for the BZC group and 40 rats for PS group. Animals in each group were divided into four subgroups The first subgroup received a low-concentration preservative solution that was commonly used for nasal sprays. The second subgroup received a high-concentration preservative solution that was reported to induce dermatitis in humans. The third and fourth subgroups received a steroid mixed preservative solution of low and high concentrations, respectively. The control group was administrated normal saline. After each group received 1, 2, and 4 weeks of topical administration, the symptomatic and histological changes on H&E stain were observed. RESULTS: Sneezing and nasal rubbing with forelegs were observed in almost all subgroups by the seventh day of treatment. The preservatives induced nasal lesions, including intraepithelial glandular formation, inflammatory cell infiltration, vascular hyperplasia, and edematous change. The symptomatic and histological changes were pronounced with the prolonged duration of administration. Similar results were observed in the steroid mixed-solution groups. In the PS steroid mixed-solution group, however, symptoms and nasal lesions were reduced with the prolonged duration of administration. CONCLUSION: It is our finding that even a low-concentration solution of preservative can lead to nasal lesion. Hence there is a strong need to develop both a preservative that can be safely and widely used and a nasal spray without preservatives.

Clemmensen O, Hjorth N. (1982) Perioral contact urticaria from sorbic acid and benzoic acid in a salad dressing. Contact Dermatitis. 1982 Jan;8(1):1-6.

Contact urticaria was observed in a kindergarten in 18 of 20 children following the intake and accidental perioral application of a mayonnaise salad cream. In healthy adult controls, stinging tests and closed 20 minute patch test with the salad dressing were positive in 9 out of 12 and 4 out of 10 cases respectively. Twenty minute patch tests with the different components of the salad dressing were positive only so sorbic acid (SA) and benzoic acid (BA). Urticaria was provoked by inunction of the salad dressing periorally in two healthy boys. Serial 20 minute closed patch testing with varying concentrations of SA in 91 patients and BA in 41 patients gave almost identical results: positive reactions in two thirds of the patients with the highest concentrations.

Dengate, S. (1997). "Dietary management of Attention Deficit Hyperactivity Disorder". Aust J Early Childhood 22(4): 29-33. Download this paper (0.7Mb pdf)

Dengate, S. and A. Ruben (2002). "Controlled trial of cumulative behavioural effects of a common bread preservative." J Paediatr Child Health **38**(4): 373-6.

OBJECTIVE: Many anecdotes and one scientific report describe cumulative behavioural effects of bread preservative on children. METHODOLOGY: Twenty-seven children, whose behaviour improved significantly on the Royal Prince Alfred Hospital diet, which excludes food additives, natural salicylates, amines and glutamates, were challenged with calcium propionate (preservative code 282) or placebo through daily bread in a double-blind placebo-controlled crossover trial. RESULTS: Due to four placebo responders, there was no significant difference by ANOVA of weighted placebo and challenge Rowe Behaviour Rating Inventory means, but a statistically significant difference existed in the proportion of children whose behaviours 'worsened' with challenge (52%), compared to the proportion whose behaviour 'improved' with challenge (19%), relative to placebo (95% confidence intervals 14-60%). CONCLUSIONS: Irritability, restlessness, inattention and sleep disturbance in some children may be caused by a preservative in healthy foods consumed daily. Minimizing the concentrations added to processed foods would reduce adverse reactions. Testing for behavioural toxicity should be included in food additive safety evaluation. Download this paper (6Mb pdf)

Egger, J., C. H. Carter, et al. (1992). "Effect of diet treatment on enuresis in children with migraine or hyperkinetic behavior." Clin Pediatr (Phila) **31**(5): 302-7.

Twenty-one children with migraine and/or hyperkinetic behavior disorder which was successfully treated with an oligoantigenic (few-foods) diet also suffered from nocturnal and/or diurnal enuresis. On diet, the enuresis stopped in 12 of these children and improved in an additional four. Identification of provoking foods was by sequential reintroduction of the foods that were avoided on the oligoantigenic diet. In eight of the 12 children who recovered on the oligoantigenic diet and in the four who improved, reintroduction of one or more foods provoked a reproducible relapse of the enuresis. Nine children were subjected to a placebo-controlled, double-blind reintroduction of provoking foods. Six children relapsed during testing with incriminated foods; none reacted to placebo. Enuresis in food-induced migraine and/or behavior disorder seems to respond, in some patients, to avoidance of provoking foods.

Egger, J., C. M. Carter, et al. (1985). "Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome." Lancet **1**(8428): 540-5.

76 selected overactive children were treated with an oligoantigenic diet, 62 improved, and a normal range of behaviour was achieved in 21 of these. Other symptoms, such as headaches, abdominal pain, and fits, also often improved. 28 of the children who improved completed a double-blind, crossover, placebo-controlled trial in which foods thought to provoke symptoms were reintroduced. Symptoms returned or were exacerbated much more often when patients were on active material than on placebo. 48 foods were incriminated. Artificial colorants and preservatives were the commonest provoking substances, but no child was sensitive to these alone.

Egger, J., C. M. Carter, et al. (1989). "Oligoantigenic diet treatment of children with epilepsy and migraine." J Pediatr **114**(1): 51-8.

We studied the role of oligoantigenic diets in 63 children with epilepsy; 45 children had epilepsy with migraine, hyperkinetic behavior, or both, and 18 had epilepsy alone. Of the 45 children who had epilepsy with recurrent headaches, abdominal symptoms, or hyperkinetic behavior, 25 ceased to have seizures and 11 had fewer seizures during diet therapy. Headaches, abdominal pains, and hyperkinetic behavior ceased in all those whose seizures ceased, and in some of those whose seizures did not cease. Foods provoking symptoms were identified by systematic reintroduction of foods, one by one; symptoms recurred with 42 foods, and seizures recurred with 31; most children reacted to several foods. Of 24 children with generalized epilepsy, 18 recovered or improved (including 4 of 7 with myoclonic seizures and all with petit mal), as did 18 of 21 children with partial epilepsy. In double-blind, placebo-controlled provocation studies, symptoms recurred in 15 of 16 children, including seizures in

eight; none recurred when placebo was given. Eighteen other children, who had epilepsy alone, were similarly treated with an oligoantigenic diet; none improved.

Egger, J., C. M. Carter, et al. (1983). "Is migraine food allergy? A double-blind controlled trial of oligoantigenic diet treatment." Lancet **2**(8355): 865-9.

93% of 88 children with severe frequent migraine recovered on oligoantigenic diets; the causative foods were identified by sequential reintroduction, and the role of the foods provoking migraine was established by a double-blind controlled trial in 40 of the children. Most patients responded to several foods. Many foods were involved, suggesting an allergic rather than an idiosyncratic (metabolic) pathogenesis. Associated symptoms which improved in addition to headache included abdominal pain, behaviour disorder, fits, asthma, and eczema. In most of the patients in whom migraine was provoked by non-specific factors, such as blows to the head, exercise, and flashing lights, this provocation no longer occurred while they were on the diet.

Evangeliou, A., I. Vlachonikolis, et al. (2003). "Application of a ketogenic diet in children with autistic behavior: pilot study." J Child Neurol **18**(2): 113-8.

A pilot prospective follow-up study of the role of the ketogenic diet was carried out on 30 children, aged between 4 and 10 years, with autistic behavior. The diet was applied for 6 months, with continuous administration for 4 weeks, interrupted by 2-week diet-free intervals. Seven patients could not tolerate the diet, whereas five other patients adhered to the diet for 1 to 2 months and then discontinued it. Of the remaining group who adhered to the diet, 18 of 30 children (60%), improvement was recorded in several parameters and in accordance with the Childhood Autism Rating Scale. Significant improvement (> 12 units of the Childhood Autism Rating Scale) was recorded in two patients (pre-Scale: 35.00 +/- 1.41[mean +/- SD]), average improvement (> 8-12 units) in eight patients (pre-Scale: 41.88 +/- 3.14[mean +/- SD]), and minor improvement (2-8 units) in eight patients (pre-Scale: 45.25 +/- 2.76 [mean +/- SD]). Although these data are very preliminary, there is some evidence that the ketogenic diet may be used in autistic behavior as an additional or alternative therapy.

Feingold, B. F. (1968). "Recognition of food additives as a cause of symptoms of allergy." Ann Allerg **26**(309-13).

Feingold, B. F. (1977). "Behavioral disturbances linked to the ingestion of food additives." Del Med J **49**(2): 89-94.

Feingold, B. F. (1979). "Dietary management of nystagmus." J Neural Transm **45**: 107-115.

Fisherman EW and Cohen G (1973). "Chemical intolerance to butylated-hydroxyanisole (BHA) and butylated-hydroxytoluene (BHT) and vascular response as an indicator and monitor of drug intolerance." Ann Allerg **31**: 126-33.

Fontella, F. U., V. Pulrolnik, et al. (2000). "Propionic and L-methylmalonic acids induce oxidative stress in brain of young rats." Neuroreport **11**(3): 541-4.

The in vitro effects of propionic and L-methylmalonic acids on some parameters of oxidative stress were investigated in the cerebral cortex of 21-day-old rats. Chemiluminescence, thiobarbituric acid-reactive substances (TBA-RS) and total radical-trapping antioxidant capacity (TRAP) were measured in brain tissue homogenates in the presence of propionic or L-methylmalonic acids at concentrations ranging from 1 to 10mM. Both acids significantly increased chemiluminescence and TBA-RS and decreased TRAP, indicating a simulation of lipid peroxidation and a reduction of tissue antioxidant potential. Other organic acids tested which accumulate in some organic acidemias (suberic, sebacic, adipic, 3-methylglutaric and 4-hydroxybutyric acids) did not affect these parameters. This study provides evidence that

free radical generation may participate in the neurological dysfunction of propionic and methylmalonic acidemias.

Freedman, B. J. (1977). "Asthma induced by sulphur dioxide, benzoate and tartrazine contained in orange drinks." Clin Allergy **7**(5): 407-15.

Of 272 patients with asthma, thirty (11%) gave a history of exacerbations occurring after ingestion, solutions of orange orange drinks. Fourteen of these were given provocation tests by drinking, on separate occasions of sulphur dioxide, sodium benzoate and tartrazine, which are present in all orange drinks. Eight reacted to sulphur dioxide with a fall in FEV1, four to sodium benzoate and one to tartrazine, and four did not react to any of these agents. Three of the benzoate patients were also sensitive to sulphur dioxide. The sulphur dioxide sensitive patients were predominantly young, with extrinsic asthma. The benzoate sensitive patients were predominantly middle-aged and the proportion with intrinsic asthma was higher. Prior inhalation of sodium cromoglycate by four patients inhibited the reaction to these substances. Sulphur dioxide has not previously been reported to cause exacerbations of asthma when ingested as a food preservative. It is used as a preservative in a wide range of acidic beverages and foods, and should be considered as possibly causal in patients suffering from apparently cryptogenic asthma, and asthma seemingly due to food allergy.

Friedman ME and Easton JG (1987). "Prevalence of positive metabisulfite challenges in children with asthma." Pediatr Asthma Allerg Immunol **1**: 53-59.

Gastaminza, G., S. Quirce, et al. (1995). "Pickled onion-induced asthma: a model of sulfite-sensitive asthma?" Clin Exp Allergy **25**(8): 698-703.

BACKGROUND: Asthma elicited by sulfite ingestion has been mainly described in steroid-dependent and in non-atopic asthmatics. We have studied a group of 18 young extrinsic asthmatics who presented with asthma attacks immediately after eating pickled onions. OBJECTIVE: The aim of this study is to ascertain if these asthma attacks are elicited by sulfites contained in pickled onions and the influence of the dose and pH of onions. METHODS: The bronchial hyperreactivity of the patients was assessed by a methacholine challenge test. Oral challenge tests were performed with sodium metabisulfite (MSB) diluted in lemon juice at pH 4.2 and at pH 3.3 (only in patients who did not react with pH 4.2). Two types of pickled onions, Spanish and Dutch pickled onions, were used for oral challenge in seven of the patients. The Monier-Williams method was used to measure the SO2 concentration in pickled onions. RESULTS: The oral provocation test with MBS, pH 4.2, elicited a positive response in six patients (33.3%) and the test at pH 3.3 was positive in three out of 12. No significant difference in PD20 values was found between these groups. Three of the seven patients challenged with Spanish pickled onions had a positive reaction but had no reaction with Dutch pickled onions. The SO2 concentration in Spanish pickled onions varied between 765 and 1182 ppm while in Dutch pickled onions were 200 ppm; this exceeded the permitted level (100 ppm). SO2 release in Spanish pickled onion samples was nearly 2.5 times higher when the pH of the sample decreased from 4.2 to 3.3. CONCLUSION: High levels of SO2 in Spanish pickled onions, and their low pH (3.3) would be the responsible factors of the asthmatic outbreaks after ingestion of Spanish pickled onions by these patients.

Hodge, L., K. Y. Yan, et al. (1996). "Assessment of food chemical intolerance in adult asthmatic subjects." Thorax **51**(8): 805-9.

BACKGROUND: Identification of food chemical intolerance in asthmatic subjects can be reliably assessed by changes in the forced expiratory volume in one second (FEV1) in response to double blind, placebo controlled challenges on a strict elimination diet. However, this method is cumbersome and time consuming. A study was undertaken to determine whether changes in bronchial responsiveness to histamine following food chemical challenge without an elimination diet might be a faster, more convenient method. METHODS: Eleven adult asthmatic subjects were challenged twice with metabisulphite, aspirin, monosodium

glutamate, artificial food colours, sodium nitrite/ nitrate, 0.5% citric acid solution (placebo), and sucrose (placebo) on separate days. During the first set of challenges subjects consumed a normal diet. Bronchial responsiveness to histamine was assessed 90 minutes after each challenge. A greater than twofold increase in bronchial responsiveness was considered positive. For one month prior to and during the second set of challenges subjects followed a strict elimination diet and FEV1 was monitored during and for two hours after each challenge. A fall in FEV1 of 20% or more was considered positive. RESULTS: Of the 77 food chemical challenges performed on an unmodified diet, 20 were positive (six placebo responses). In two subjects it was not possible to perform a histamine test after one of the chemical challenges because of poor spirometric function. Of the 77 food chemical challenges performed on an elimination diet, 11 were positive (no placebo responses). Excluding the two challenges in which there were no corresponding histamine tests, only on two occasions did the positive responses in both methods coincide, giving the unmodified diet method a sensitivity of 22%. CONCLUSIONS: Strict dietary elimination and measurement of FEV1 after double blind food chemical challenge remains the most reliable method for the detection of food chemical intolerance in asthmatic subjects.

Jacobson MF and Schardt MS (1999). Diet, ADHD and behaviour: a quarter-century review. Washington DC, Centre for Science in the Public Interest. http://fedup.com.au/images/stories/CSPIReview1999.pdf

Kochen J (1973). "Sulfur dioxide, a respiratory tract irritant, even if ingested." Pediatrics **52**(1): 145-6.

Lockey, S. D. (1959). "Allergic reactions due to F D and C Yellow No. 5, tartrazine, an aniline dye used as a coloring and identifying agent in various steroids." Ann Allergy **17**: 719-21.

Mikkelsen, H., J. Larsen, et al. (1978). "Hypersensitivity reactions to food colours with special reference to the natural colour annatto extract (butter colour)." Arch Toxicol Suppl(1): 141-3.

It is well known that synthetic food colours especially some azo dyes can provoke hypersensitivity reactions such as urticaria, angioneurotic oedema, and astma (Michaelsson and Juhlin, 1973, Granholt and Thune, 1975). Natural food colours are scarcely investigated with respect to potential allergic properties. Annatto extract, a commonly used food colour in edible fats e.g. butter, has been tested in patients. Among 61 consecutive patients suffereing from chornic urticaria and/or angioneurotic oedema 56 patients were orally provoked by annatto extract during elimination diet. Challenge was performed with a dose equivalent to the amount used in 25 grammes of butter. Twentysix per cent of the patients reacted to this colour 4 hours (SD: 2,6) after intake. Similar challenges with synthetic dyes showed the following results: Tartrazine 11%, Sunset Yellow FCF 17%, Food Red 17 16%, Amaranth 9%, Ponceau 4 R 15%, Erythrosine 12% and Brillant Blue FCF 14%. The present study indicates that natural food colours may induce hypersensitivity reactions as frequent as synthetic dyes.

Moneret-Vautrin, D. A. (1987). "Monosodium glutamate-induced asthma: study of the potential risk of 30 asthmatics and review of the literature." Allerg Immunol (Paris) **19**(1): 29-35.

Monosodium glutamate is a physiological nutrient, and food additive used as a taste enhancer. Several cases of intolerance to MSG in patients with asthma and with a Chinese Restaurant Syndrome have been published. A high dose of 2.5 g was tested in 6 healthy controls and 30 asthmatics (7: allergic asthma; 15: intrinsic asthma with intolerance to aspirin; 8: intrinsic asthma with aspirin intolerance, intolerance to alcohol or to food additives). Two patients presented with a mild bronchospasm, occurring 6 to 10 hours after the ingestion. Different mechanisms are discussed. A cholinergic mechanism might be incriminated, either due to stimulation of the synthesis of acetylcholine, or due to a vagal reflex elicited by a reflux esophagitis. However, a high vagal hyperreactivity seems to be needed for the occurrence of asthma. It is concluded that a very small subset of patients with intrinsic asthma might present with an intolerance to MSG if high doses are consumed.

Murphy, P., S. Likhodii, et al. (2004). "The antidepressant properties of the ketogenic diet." Biol Psychiatry **56**(12): 981-3.

BACKGROUND: The ketogenic diet is used to treat epilepsy refractory to anticonvulsant medication. Individuals with epilepsy often have behavioral problems and deficits in attention and cognitive functioning. The ketogenic diet has been found to effect improvements in these domains. It has also been suggested that the ketogenic diet may act as a mood stabilizer. METHODS: The present research used the Porsolt test, an animal model of depression, to determine whether the ketogenic diet has antidepressant properties. Porsolt test scores of rats on the ketogenic diet were compared with those of rats on a control diet. RESULTS: The rats on the ketogenic diet spent less time immobile, suggesting that rats on the ketogenic diet, like rats treated with antidepressants, are less likely to exhibit "behavioral despair." CONCLUSIONS: It is concluded that the ketogenic diet may have antidepressant properties.

Murphy, P., S. S. Likhodii, et al. (2005). "Effect of the ketogenic diet on the activity level of Wistar rats." Pediatr Res **57**(3): 353-7.

Children, adolescents, and adults with epilepsy often also show symptoms associated with attention-deficit/hyperactivity disorder (ADHD). The ketogenic diet, which is administered to children with epilepsy refractory to drug therapy, seems to improve behavior in individuals with symptoms of ADHD. The basis for this improvement is unknown, although it seems to be unrelated to seizure control. The present research was designed to investigate the effect of two ketogenic diets on the behavior of normal adult male rats. Two experiments were conducted. In experiment 1, 36 subjects were placed on one of three diets: a control diet, a 6.3:1 ketogenic diet, and a 4:1 ketogenic diet. In experiment 2, 20 subjects were placed either on a control diet or on a 4:1 ketogenic diet. The activity level of each subject was measured using an open field test. Time spent immobile, grooming, and in exploratory behavior was measured for 600 s. Subjects were tested once before initiation of the diets and once while on the diets. No significant group differences were found in activity level before initiation of the diets. After initiation of the diets, subjects in both ketogenic groups showed a significantly lower activity level than the rats on the control diet. The ketogenic diet decreases activity level in an animal model. This behavioral change may relate to the improved behavior seen when children with symptoms of ADHD are placed on the diet.

Nyhan, W. L., C. Bay, et al. (1999). "Neurologic nonmetabolic presentation of propionic acidemia." Arch Neurol **56**(9): 1143-7.

BACKGROUND: Patients with propionic acidemia usually present in the neonatal period with life-threatening ketoacidosis, often complicated by hyperammonemia. It was thought that the neurologic abnormalities seen in this disease were exclusively the consequences of these acute crises. Experience with 2 patients with propionic acidemia indicates that this disease may present first with prominent neurologic disease without the life-threatening episodes of ketoacidosis that usually serve as the alerting signals for a diagnosis of an organic acidemia. OBJECTIVE: To examine the clinical and metabolic aspects of 2 patients with a phenotype that suggested disease of the basal ganglia. DESIGN: Examination of patterns of organic acids of the urine and enzyme assay for propionyl-CoA carboxylase in fibroblasts and lymphocytes. SETTING: Referral population to a biochemical genetics laboratory. PATIENTS: Two patients whose prominent features were hypotonia followed by spastic quadriparesis and choreoathetosis. Both had seizures. One patient was mildly mentally retarded but grew normally physically. The other had profound mental retardation and failure to thrive; he also self-mutilated his lower lip. Self-injurious behavior has not been reported in this disease. MAIN OUTCOME MEASURES: Clinical description, blood ammonia levels, organic acid levels in the urine, and enzyme activity. RESULTS: Excretion of metabolites, including methylcitrate, was typical. Residual activity of propionyl-CoA carboxylase approximated 5% of the control in each patient. CONCLUSIONS: Propionic acidemia can present as a pure neurologic disease without acute episodes of massive ketoacidosis. Hyperammonemia may occur after infancy in some patients, presenting as Reye syndrome.

Parker, G. and T. Watkins (2002). "Treatment-resistant depression: when antidepressant drug intolerance may indicate food intolerance." Aust N Z J Psychiatry **36**(2): 263-5.

Pelsser LM and others Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet. 2011;377(9764):494-503.

This repeat of the 2002 study involved 100 children aged four to eight. Fifty of them followed an elimination diet – removing all known problem foods until some of them consumed only rice, turkey, pear, vegetables and water. After five weeks, two-thirds of the children on the special diet no longer had any behavioural problems. There was no difference in the behaviour of the control group on a 'healthy' diet. The children were followed for a year, with foodstuffs being added back into their diet to determine what caused the hyperactive reaction. Researchers concluded that 'dietary intervention should be considered in all children with ADHD, provided parents are willing to follow a diagnostic restricted elimination diet for a five-week period, and provided expert supervision is available.' they wrote. This diet is not new, but it is the first time it has been trialled on so many children for such a long time. Full study at http://www.adhdenvoeding.nl/cms/wp-content/uploads/2011/02/Pelsser-The-Lancet-2011-Publication-INCA-study.pdf

Pelsser, L. M. and J. K. Buitelaar (2002). "[Favourable effect of a standard elimination diet on the behavior of young children with attention deficit hyperactivity disorder (ADHD): a pilot study]." Ned Tijdschr Geneeskd **146**(52): 2543-7.

OBJECTIVE: To determine whether a standard elimination diet can decrease the ADHD-symptoms in a heterogeneous group of young children with ADHD. DESIGN: Open, descriptive. METHOD: 40 children, 36 boys and 4 girls, aged 3-7 (average 4.8 years), who met the DSM-IV-criteria for ADHD, followed their usual diet for two weeks and thereafter for two weeks an elimination diet, based on the few foods diet (rice, turkey, pear and lettuce). The behaviour of the child was evaluated at study entry, after the baseline period and at the end of the diet. Parents completed the 10-item Conners list, the ADHD Rating Scale and a physical complaints list. The teachers completed the 10-item Conners list and the ADHD Rating Scale twice, at the beginning and at the end of the diet. RESULTS: According to the parent-ratings, 25 children (62%) showed an improvement in behaviour of at least 50% on both the Conners list and the ADHD Rating Scale at the end of the elimination diet. Nine children (23%) withdrew from the study because the parents were unable to stick to the diet or because the child fell ill. Among the 15 children with both parent and teacher ratings, 10 responded both at home and in school. CONCLUSION: In young children with ADHD an elimination diet can lead to a statistically significant decrease in symptoms.

Petrus, M., S. Bonaz, et al. (1996). "Asthmé et intolérance aux benzoates." Arch Pédiatr **3**(10): 984-7.

BACKGROUND: Some foods and drug additives may induce allergic reactions. CASE REPORT: A girl with a family history of asthma in both parents developed asthma in her early life. She was successfully given continuous bronchodilator therapy until the age of 7 years. At that time, she had more frequent and severe exacerbations (8 within 10 months) despite reinforced continuous treatment. Oral challenges with bisulfite and sodium benzoate, both additives abundantly ingested by the patient, revealed heightened sensitivity to administration of sodium benzoate. Avoidance of this additive was followed by complete and prolonged disappearance of episodes of coughing and wheezing. CONCLUSION: Adverse reactions to benzoate in this patient required avoidance of some drugs, some of those classically prescribed under the form of syrups in asthma.

Pulsifer, M. B., J. M. Gordon, et al. (2001). "Effects of ketogenic diet on development and behavior: preliminary report of a prospective study." Dev Med Child Neurol **43**(5): 301-6.

The ketogenic diet is increasingly used for the management of difficult-to-control seizures in children. Here, we describe the first prospective study of the effects of the diet on development, behavior, and parenting stress. Participants were 65 children (36 males, 29 females) with intractable seizures, ages 18 months to 14 years 6 months, enrolled in a prospective study at the Johns Hopkins Hospital, Baltimore, MD, USA, to study the diet's efficacy. Children were assessed before diet initiation and at 1-year follow-up. At follow-up, 52% (34 of 65) children remained on the diet. Mean seizure frequency decreased from 25 per day before diet initiation to less than two per day 1 year later. At follow-up, mean developmental quotient showed statistically significant improvement ($p<0.05$), with significant behavioral improvements in attention and social functioning. Parental stress was essentially unchanged. No baseline factor examined predicted diet adherence, and the primary reason for diet discontinuation was insufficient seizure control. These preliminary results support prior anecdotal reports of the beneficial effects of the diet on cognition and behavior.

Quattrucci, E. and V. Masci (1992). "Nutritional aspects of food preservatives." Food Addit Contam **9**(5): 515-25.

Despite the benefits attributed to food preservatives, some concern still remains regarding their safety and possible influence on nutrients. Surprisingly, there is quite a lack of scientific knowledge in this field. In order to describe a few examples, the effects of the extensively used sulphite on thiamine, folates, pyridoxal and other nutrients have been reported. Among its antibrowning effects, inhibition of ascorbic acid browning is also considered. As far as sorbic acid is concerned, notwithstanding its easy reaction with protein, probably the acid environment of the stomach determines the breakdown of the sorbic-protein adducts. Detoxication of nitrite by tocopherol and ascorbic acid leads, in the last case, to dehydroascorbic acid and its oxidative products with loss of vitamin activity. Any oxidizing substance destroys ascorbic acid, vitamin E and free vitamin A. Phosphates are largely used with different aims, including preservation, in food processing. Their antimicrobial activity is due to both a direct effect and an interaction with other antimicrobials. Sequestering capacity of phosphates and its nutritional implications are discussed. Also mechanisms of action of organic acids are reported, focusing on sorbic acid effects on single amino acids and proteins. Finally, the little information available about the potential impact of food preservatives on nutritional functions is presented.

Rietschel, R. L. (1978). "Contact urticaria from synthetic cassia oil and sorbic acid limited to the face." Contact Dermatitis **4**(6): 347-9.

A patient with contact urticaria with skin and respiratory symptoms was found to be sensitive to both sorbic acid and synthetic oil of cassia. The contact urticaria was only elicitable on intact skin of the face by open testing. The source of the patient's contactants was her shampoo and toothpaste.

Rowe, K. S. (1988). "Synthetic food colourings and 'hyperactivity': a double-blind crossover study." Aust Paediatr J **24**(2): 143-7.

Of 220 children referred for suspected 'hyperactivity', 55 were subjected to a 6 week trial of the Feingold diet. Forty (72.7%) demonstrated improved behaviour and 26 (47.3%) remained improved following liberalization of the diet over a period of 3-6 months. The parents of 14 children claimed that a particular cluster of behaviours was associated with the ingestion of foods containing synthetic colourings. A double-blind crossover study, employing a single-subject repeated measures design was conducted, using eight of these children. Subjects were maintained on a diet free from synthetic additives and were challenged daily for 18 weeks with either placebo (during lead-in and washout periods) or 50 mg of either tartrazine or carmoisine, each for 2 separate weeks. Two significant reactors were identified whose behavioural pattern featured extreme irritability, restlessness and sleep disturbance. One of the reactors did not have inattention as a feature. The findings raise the issue of whether the strict criteria for inclusion in studies concerned with 'hyperactivity' based on 'attention deficit

disorder' may miss children who indicate behavioural changes associated with the ingestion of food colourings. Moreover, for further studies, the need to construct a behavioural rating instrument specifically validated for dye challenge is suggested.

Rowe, K. S. and K. J. Rowe (1994). "Synthetic food coloring and behavior: a dose response effect in a double-blind, placebo-controlled, repeated-measures study." J Pediatr **125**(5 Pt 1): 691-8.

OBJECTIVE: To establish whether there is an association between the ingestion of synthetic food colorings and behavioral change in children referred for assessment of "hyperactivity." PARTICIPANTS: From approximately 800 children referred to the Royal Children's Hospital (Melbourne) for assessment of suspected hyperactivity, 200 were included in a 6-week open trial of a diet free of synthetic food coloring. The parents of 150 children reported behavioral improvement with the diet, and deterioration on the introduction of foods noted to contain synthetic coloring. A 30-item behavioral rating inventory was devised from an examination of the clinical histories of 50 suspected reactors. Thirty-four other children (23 suspected reactors, 11 uncertain reactors) and 20 control subjects, aged 2 to 14 years, were studied. DESIGN: A 21-day, double-blind, placebo-controlled, repeated-measures study used each child as his or her own control. Placebo, or one of six dose levels of tartrazine (1, 2, 5, 10, 20, 50 mg), was administered randomly each morning, and behavioral ratings were recorded by parents at the end of each 24 hours. RESULTS: The study identified 24 children as clear reactors (19 of 23 "suspected reactors," 3 of 11 "uncertain reactors," and 2 of 20 "control subjects"). They were irritable and restless and had sleep disturbance. Significant reactions were observed at all six dose levels. A dose response effect was obtained. With a dose increase greater than 10 mg, the duration of effect was prolonged. CONCLUSION: Behavioral changes in irritability, restlessness, and sleep disturbance are associated with the ingestion of tartrazine in some children. A dose response effect was observed.

Samuels, A. (1999). "The toxicity/safety of processed free glutamic acid (MSG): a study in suppression of information." Account Res **6**(4): 259-310.

Schmidt, M. H., P. Mocks, et al. (1997). "Does oligoantigenic diet influence hyperactive/conduct-disordered children--a controlled trial." Eur Child Adolesc Psychiatry **6**(2): 88-95.

A crossover 'placebo'-controlled, double-blind design was used to examine the effectiveness of an oligoantigenic diet in 49 children with hyperactive/disruptive behavior disorder. Effects of diet were compared with those yielded by stimulant medication (methylphenidate). The study was conducted in an inpatient unit at the Department of Child and Adolescent Psychiatry, Central Institute of Mental Health, Mannheim. Change in behavior was measured in standardized situations by trained raters, including behavior assessment when testing with CPT and PAT, during a free play situation, and at school. Twelve children (24%) showed significant behavioral improvement in two behavior ratings during diet relative to control diet conditions. Methylphenidate used in 36 children yielded more responders (44%) than diet. The amount of positive changes in behavior in those who received both treatments was about the same. Although only effective in a minority of children, dietary treatment cannot be neglected as a possible access to treating hyperactive/disruptive children and merits further investigation.

Schoenthaler, S., W. Doraz, et al. (1986). "The impact of a low food additive and sucrose diet on academic performance in 803 New York City public schools." International Journal of Biosocial Research **8**(2): 185-195.

Schulte-Korne, G., W. Deimel, et al. (1996). "[Effect of an oligo-antigen diet on the behavior of hyperkinetic children]." Z Kinder Jugendpsychiatr Psychother **24**(3): 176-83.

The influence of an oligoantigenic diet on different dimensions of the behavior of 21 children diagnosed as having attention-deficit hyperactivity disorder (ADHD) was examined. Treatment effects were assessed with three subjective measures (two questionnaires and an interview)

and three objective measures (two attention tests and actometer). The study was divided into three phases: baseline, diet and provocation, each lasting three weeks. A crossover design was used. A significant effect was found for the subjective measures, but not for the objective measures. The results are discussed in terms of possible types of effects, e. g. rater effects and environmental effects. It may be that the oligoantigenic diet influences only certain dimensions of hyperactivity.

Settipane, G. A., F. H. Chafee, et al. (1976). "Significance of tartrazine sensitivity in chronic urticaria of unknown etiology." J Allergy Clin Immunol **57**(6): 541-6.

Of 38 patients with chronic urticaria of unknown etiology who were evaluated for food and drug additive sensitivity, 53% (20/38) had urticaria for 1 yr or more. Total eosinophil counts were not elevated in most patients, and the frequency of atopy was found to be similar to that in a general population. Of these 38 patients, 10 (26%) had a personal history of aspirin intolerance, but elimination of aspirin did not relieve the urticaria. In a double-blind crossover challenge with 0.22 mg of tartrazine and a control, tartrazine sensitivity was found in 8% (3/38) of patients with chronic urticaria and 20% (2/10) of patients with aspirin intolerance.

Steel, R. J. (1997). "Thiamine deficiency in a cat associated with the preservation of 'pet meat' with sulphur dioxide." Aust Vet J **75**(10): 719-21.

A cat with allergic dermatitis was fed a diet of fresh meat and a multi-vitamin supplement for 38 days to exclude food allergy as a cause of its dermatopathy. The cat died as a result of acute thiamine deficiency, which was caused by inactivation of thiamine by the preservative, sulphur dioxide. The continuing undeclared usage of sulphites in the Australian pet food industry is discussed.

Steinman, H. A., M. Le Roux, et al. (1993). "Sulphur dioxide sensitivity in South African asthmatic children." S Afr Med J **83**(6): 387-90.

Sulphur dioxide (SO2) is a well-known precipitant of asthmatic attacks. Many foodstuffs are preserved with SO2 and other sulphites. In this study 37 asthmatic children attending the Allergy Clinic at the Red Cross Children's Hospital were challenged with SO2 in apple juice in a dose similar to that commonly ingested in soft-drinks containing this preservative. The responses of these children were compared with the responses of 22 asthmatics challenged with apple juice alone. Sixteen out of 37 children (43.2%) challenged with SO2 reacted with a fall in forced expiratory volume in 1 second (FEV1) of more than 10% compared with none of the 22 control asthmatic children challenged with apple juice alone (P = 0.0016). Girls were found to be more sensitive than boys. A 20% or more fall in FEV1 occurred in 8 (21.6%) of the children challenged with SO2 compared with none in the control group (P = 0.039). There was an individual variability in the responses of sensitive individuals to the SO2 challenge. Reactions occurred in spite of maintenance medication and occurred within 5-30 minutes of challenge. Since sulphite sensitivity is common in asthmatic children, ingestion of sulphites should be avoided.

Steinman, H. A. and E. G. Weinberg (1986). "The effects of soft-drink preservatives on asthmatic children." S Afr Med J **70**(7): 404-6.

Sulphites, used extensively as preservatives in foods and soft drinks, are known to precipitate asthma attacks in 5-10% of susceptible children. Among children attending the Allergy Clinic at the Red Cross War Memorial Children's Hospital, Cape Town, many were found to be sensitive to sulphites. The basis of asthma therapy is modification of the environment and avoidance of precipitating factors. Medical personnel counselling parents of asthmatic children should be aware of this factor. A list of soft drinks containing sulphites and other preservatives is included.

Studdert, V. P. and R. H. Labuc (1991). "Thiamin deficiency in cats and dogs associated with feeding meat preserved with sulphur dioxide." Aust Vet J **68**(2): 54-7.

Thiamin deficiency was diagnosed in cats and dogs being fed fresh minced meat, which contained sulphur dioxide as a preservative and less than 0.5 mg/kg thiamin. Thiamin in the meat and in added dietary ingredients, including a supplementary vitamin mixture, was destroyed by the sulphur dioxide.

Swain, A., V. Soutter, et al. (1985). "Salicylates, oligoantigenic diets, and behaviour." Lancet **2**(8445): 41-2.

Swanson, J. M. and M. Kinsbourne (1980). "Food dyes impair performance of hyperactive children on a laboratory learning test." Science **207**(4438): 1485-7.

Forty children were given a diet free of artificial food dyes and other additives for 5 days. Twenty of the children had been classified as hyperactive by scores on the Conners Rating Scale and were reported to have favorable responses to stimulant medication. A diagnosis of hyperactivity had been rejected in the other 20 children. Oral challenges with large doses (100 or 150 milligrams) of a blend of FD & C approved food dyes or placebo were administered on days 4 and 5 of the experiment. The performance of the hyperactive children on paired-associate learning tests on the day they received the dye blend was impaired relative to their performance after they received the placebo, but the performance of the nonhyperactive group was not affected by the challenge with the food dye blend.

Timberlake, C. M., A. K. Toun, et al. (1992). "Precipitation of asthma attacks in Melanesian adults by sodium metabisulphite." P N G Med J **35**(3): 186-90.

Seven Melanesian asthmatic patients were challenged with substances that have been shown to precipitate asthma attacks in asthma patients in developed countries. Patients were challenged in a double-blind fashion using placebo and active substances. The active substances were tartrazine, sodium metabisulphite, aspirin and betel nut. All 7 patients were challenged with tartrazine and sodium metabisulphite; 5 were challenged with aspirin also, but only 2 were challenged with betel nut. Asthma attacks were precipitated by sodium metabisulphite in 3 patients. No other substances precipitated asthma. As sodium metabisulphite is a common food additive, these results suggest that processed foods introduced into developing countries may have an important role in precipitating asthma attacks in susceptible persons.

Towns, S. J. and C. M. Mellis (1984). "Role of acetyl salicylic acid and sodium metabisulfite in chronic childhood asthma." Pediatrics **73**(5): 631-7.

The role of a commonly ingested food additive, the preservative sodium metabisulfite (MBS), and aspirin (ASA), in chronic asthma has been studied in 29 children. After 1 week on a strict elimination diet, all 29 children were challenged, in a single-blind fashion, in the pulmonary function laboratory on three consecutive days with placebo, MBS (capsule form and solution), and ASA. Children with a positive response to MBS were prescribed a diet that excluded foods containing MBS. Patients with a positive response to ASA were prescribed a diet excluding medications containing aspirin and natural salicylates. After 3 months on these restricted diets, the children were reassessed to determine whether there had been any therapeutic response. There was a 66% (19/29) incidence of positive challenge (greater than 20% decrease in forced expiratory volume in one second) with MBS and a 21% (6/29) incidence of positive challenge with ASA. None of the children reacted to MBS in capsule form (maximum dose = 100 mg), but 19/29 reacted to MBS in solution with 30 mL of 0.5% citric acid. After 3 months on the restricted diet, four of 19 children on the MBS-free diet and one of six on the salicylate-free diet had objective signs of improvement, namely, reduction in asthma medications and/or improvement in lung function. Unfortunately, compliance with the

restrictive diet during this 3-month period was poor, particularly with the ASA-sensitive children.(ABSTRACT TRUNCATED AT 250 WORDS)

Trindade, V. M., A. M. Brusque, et al. (2002). "Ganglioside alterations in the central nervous system of rats chronically injected with methylmalonic and propionic acids." Metab Brain Dis **17**(2): 93-102.

Neurological dysfunction and structural cerebral abnormalities are commonly found in patients with methylmalonic and propionic acidemia. However, the mechanisms underlying the neuropathology of these disorders are poorly understood. We have previously demonstrated that methylmalonic and propionic acids induce a significant reduction of ganglioside N-acetylneuraminic acid in the brain of rats subjected to chronic administration of these metabolites. In the present study, we investigated the in vivo effects of chronic administration of methylmalonic (MMA) and propionic (PA) acids (from the 6th to the 28th day of life) on the distribution and composition of gangliosides in the cerebellum and cerebral cortex of rats. Control rats were treated with the same volumes of saline. It was first verified that MMA and PA treatment did not modify body, cerebellum, or cortical weight, nor the ganglioside concentration in the cerebral cortex of the animals. In contrast, a significant reduction in total ganglioside content in the cerebellum of approximately 20-30% and 50% of control levels occurred in rats injected with MMA and PA, respectively. Moreover, chronic MMA and PA administration did not interfere with the ganglioside pattern in the cerebral cortex, whereas the distribution of individual gangliosides was altered in the cerebellum of MMA- and PA-treated animals. Rats injected with MMA demonstrated a marked decrease in GM1 and GD3, whereas chronic PA treatment provoked a significant reduction of all ganglioside species, with the exception of an increase in GM2. Since gangliosides are closely related to the dendritic surface and other neural membranes, indirectly reflecting synaptogenesis, these ganglioside abnormalities may be associated with the brain damage found in methylmalonic and propionic acidemias.

Uhlig, T., A. Merkenschlager, et al. (1997). "Topographic mapping of brain electrical activity in children with food-induced attention deficit hyperkinetic disorder." Eur J Pediatr **156**(7): 557-61.

In 15 children suffering from food induced attention deficit hyperkinetic syndrome, topographic EEG mapping of brain electrical activity was carried out following avoidance and ingestion of previously identified provoking foods. A crossover design was used and recordings were interpreted independently by two investigators, one of whom was blind to the order of testing. During consumption of provoking foods there was a significant increase in betal activity in the frontotemporal areas of the brain. This investigation is the first one to show an association between brain electrical activity and intake of provoking foods in children with food-induced attention deficit hyperactivity disorder. CONCLUSIONS: These data support the hypothesis that in a subgroup of children with attention deficit hyperactivity disorder certain foods may not only influence clinical symptoms but may also alter brain electrical activity.

Weiss, B., J. H. Williams, et al. (1980). "Behavioral responses to artificial food colors." Science **207**(4438): 1487-9.

Twenty-two young children, maintained on a diet that excluded certain foods, were challenged intermittently with a blend of seven artificial colors in a double-blind trial. Parents' observations provided the criteria of response. One child that responded mildly to the challenge and one that responded dramatically were detected. The latter, a 34-month-old female, showed a significant increase in aversive behaviors. These results further confirm previous controlled studies.

Wyse, A. T., A. M. Brusque, et al. (1998). "Inhibition of Na+,K+-ATPase from rat brain cortex by propionic acid." Neuroreport **9**(8): 1719-21.

Buffered propionic acid was injected s.c. into rats twice a day at 8 h intervals from the 6 to 21 days of age. Control rats received saline in the same volumes. The animals were weighed

and killed by decapitation at 23 days. Whole brain and cerebral cortex were weighed and synaptic plasma membranes were prepared from cortex for the determination of Na+,K+-ATPase and Mg2+-ATPase activities. Body, whole brain and cortical weights were similar in the two groups, suggesting that propionic acid does not cause malnutrition in rats. Na+,K+-ATPase activity was significantly reduced by 30% in membranes from the propionate-treated group, whereas Mg2+-ATPase activity was not. In another set of experiments, synaptic plasma membranes were prepared from cerebral cortex of 23-day-old rats and incubated with propionic acid at final concentrations ranging from 0.1 to 2.0 mM. Na+,K+-ATPase activity, but not Mg2+-ATPase activity, was inhibited by 22-32%. Since propionic acid concentrations in plasma of chronically treated rats and of propionic acidemic children are of the same order of magnitude as those tested in vitro, the results suggest that the inhibition of Na+,K+-ATPase activity may be related to the neurological dysfunction of patients affected by propionic acidaemia.