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Hyperbaric oxygen therapy might improve certain pathophysiological findings in autism

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Summary Autism is a neurodevelopmental disorder currently affecting as many as 1 out of 166 children in the United States. Numerous studies of autistic individuals have revealed evidence of cerebral hypoperfusion, neuroinflammation and gastrointestinal inflammation, immune dysregulation, oxidative stress, relative mitochondrial dysfunction, neurotransmitter abnormalities, impaired detoxification of toxins, dysbiosis, and impaired production of porphyrins. Many of these findings have been correlated with core autistic symptoms. For example, cerebral hypoperfusion in autistic children has been correlated with repetitive, self-stimulatory and stereotypical behaviors, and impairments in communication, sensory perception, and social interaction. Hyperbaric oxygen therapy (HBOT) might be able to improve each of these problems in autistic individuals. Specifically, HBOT has been used with clinical success in several cerebral hypoperfusion conditions and can compensate for decreased blood flow by increasing the oxygen content of plasma and body tissues. HBOT has been reported to possess strong anti-inflammatory properties and has been shown to improve immune function. There is evidence that oxidative stress can be reduced with HBOT through the upregulation of antioxidant enzymes. HBOT can also increase the function and production of mitochondria and improve neurotransmitter abnormalities. In addition, HBOT upregulates enzymes that can help with detoxification problems specifically found in autistic children. Dysbiosis is common in autistic children and HBOT can improve this. Impaired production of porphyrins in autistic children might affect the production of heme, and HBOT might help overcome the effects of this problem. Finally, HBOT has been shown to mobilize stem cells from the bone marrow to the systemic circulation. Recent studies in humans have shown that stem cells can enter the brain and form new neurons, astrocytes, and microglia. It is expected that amelioration of these underlying pathophysiological problems through the use of HBOT will lead to improvements in autistic symptoms. Several studies on the use of HBOT in autistic children are currently underway and early results are promising.

Abbreviations: HBOT, hyperbaric oxygen therapy; PDD, pervasive developmental disorder; SPECT, single photon emission computed tomography; PET, positron emission tomography; fMRI, functional magnetic resonance imaging; HIF-1α, hypoxia-inducible factor-1α; VEGF, vascular endothelial growth factor; IL, interleukin; PMN, polymorphonuclear neutrophil; MCP-1, macrophage chemoattractant protein-1; CSF, cerebral spinal fluid; GFAP, glial fibrillary acidic protein; BDNF, brain derived neurotrophic factor; LNH, lymphoid nodular hyperplasia; TNF-α, tumor necrosis factor-α; IFN, interferon; atm, atmosphere; COX-2, cyclooxygenase-2; SOD, superoxide dismutase; HSP, heat shock protein; SSRI, selective serotonin reuptake inhibitors; CP, cerebral palsy.

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Background

Autism is a neurodevelopmental disorder currently affecting as many as 1 out of 166 children in the United States [1] and as many as 1 in 86 in certain areas of England [2]. Over 1.5 million children and adults in the United States alone are affected with some form of autism [3]. Autism is characterized by impairments in social interaction, difficulty with communication, and restrictive and repetitive behaviors [4]. Traditionally, autism has been considered a highly genetic disorder, yet the identification of a specific genetic cause has been elusive despite numerous studies [5—7]. One recent study has demonstrated that many children with autism typically have worsening of core autistic clinical features with increasing age [8]. Moreover, young children diagnosed with Pervasive Developmental Disorder (PDD) tend to get worse clinically over time, and almost all are diagnosed with autism at a later age [9]. According to these two studies, improvements in core autistic features are uncommon. Therefore, any treatment that can improve autistic symptoms demands additional study and implementation.

Hypothesis

Recent analysis has furthered our understanding of the underlying pathophysiology of autism that was not apparent even several years ago. Novel clinical findings in autism have lately been described, including cerebral hypoperfusion, neuroinflammation and gastrointestinal inflammation, immune dysregulation, oxidative stress, relative mitochondrial dysfunction, neurotransmitter abnormalities, impaired detoxification enzymes, dysbiosis, and impaired production of porphyrins. Many of these findings have been correlated with core autistic symptoms. Hyperbaric oxygen therapy (HBOT) might be able to improve each of these problems and has been shown to mobilize stem cells from the bone marrow to the systemic circulation. Recent human studies have demonstrated that stem cells can enter the brain and form new neurons, astrocytes, and microglia. It is expected that amelioration of these underlying pathophysiological problems through the use of HBOT will lead to improvements in autistic symptoms.

Review of the pathophysiology of autism and possible benefits of HBOT

Cerebral hypoperfusion in autism

Numerous independent single photon emission computed tomography (SPECT) and positron emission tomography (PET) research studies have demonstrated hypoperfusion to several areas of the autistic brain, most notably the temporal lobes [10—23]. In one study, this hypoperfusion typically worsened as the age of the autistic child increased, and become ''quite profound'' in older children compared to younger [11]. The maximal decrease in blood flow in autistic children compared to control children was approximately 8% in another study [18]. This cerebral hypoperfusion has been correlated with many of the core clinical features associated with autism (see Table 1). Repetitive, self-stimulatory, and unusual behaviors including resistance to changes in routine and environment have been correlated with decreased blood flow to the thalamus [13]. ''Obsessive desire for sameness'' and ''impairments in communication and social interaction'' have been correlated with decreased blood flow to the temporal lobes [15]. Impairments in processing facial expressions and emotions have been correlated with decreased blood flow to the temporal lobes and amygdala [24]. Diminished blood flow to the fusiform gyrus has been correlated with difficulty in recognizing familiar faces [25]. Decreased language development [11] and auditory processing [17] have been correlated with decreased blood flow to Wernicke's and Brodmann's area. Finally, hypoperfusion of the temporal and frontal lobes has been correlated with decreased IQ in autistic individuals [20].

In addition, not only do autistic individuals have decreased blood flow at baseline, but when autistic children attend to a task, they often do not have a compensatory increase in blood flow like typical

Table 1 Selected areas of cerebral hypoperfusion in autism and clinical correlations

Area of cerebral hypoperfusion	Clinical correlation
Thalamus	Repetitive, self-stimulatory, and unusual behaviors [13]
Temporal lobes	Desire for sameness and social/communication impairments [15]
Temporal lobes and amygdala	Impairments in processing facial expressions/emotions [24]
Fusiform gyrus	Difficulty recognizing familiar faces [25]
Wernicke's and Brodmann's areas	Decreased language development and auditory processing problems [11,17]
Temporal and frontal lobes	Decreased IQ [20]

children, and instead sometimes demonstrate decreased blood flow. Neurotypical children have an increase in cerebral blood flow as measured by functional magnetic resonance imaging (fMRI) when performing a task that requires attention or sensory input; autistic children typically lack this increase in blood flow [26]. Control children also have an increase in cerebral blood flow when listening to tones and generating sentences; whereas autistic children typically have a decrease in cerebral blood flow [27]. Upon an auditory stimulation, ''normal'' children have a drop in the left middle cerebral artery resistance index as measured by transcranial doppler ultrasound (which means blood flow increases); while autistic children have an increase in resistance index, which causes blood flow to decrease [28]. These findings might indicate that the brain metabolic rate and function are diminished in autistic children because blood flow is tightly coupled with these two parameters [29,30].

The cause of this cerebral hypoperfusion in autistic individuals is unknown but might be due to inflammation. One recent study on autopsy brain samples from autistic individuals described accumulation of perivascular macrophages and microglia [31], which could be consistent with vasculitis. This accumulation could cause stiffening of the vessel wall and decrease the size of the lumen, leading to decreased cerebral blood flow. Furthermore, elevated urinary levels of 8-isoprostane-F2α have recently been described in some autistic individuals [32]. In some studies, this isoprostane elevation has been shown to cause *in vivo* vasoconstriction and increase the aggregation of platelets [33]. A more recent study on autistic individuals also demonstrated increased urinary levels of isoprostane $F_{2\alpha}$-VI (a marker of lipid peroxidation), 2,3-dinor-thromboxane B_2 (which reflects platelet activation), and 6-keto-prostaglandin $F_{1\alpha}$ (a marker of endothelium activation) [34]. These elevated markers indicate that some autistic children have increased platelet aggregation, endothelium activation, and vasoconstriction. This is important because vasoconstriction can cause decreased blood flow to the brain, which could result in relative hypoxia. Hypoxia has been shown to activate brain microglia which in turn produce inflammatory mediators, such as Tumor Necrosis Factor-α (TNF-α) and Interleukin-1 (IL-1) [35]. Treatment of this inflammation might help restore normal blood flow. In fact, many inflammatory conditions such as lupus, Kawasaki disease, Behçet's disease, encephalitis, and Sjögren's syndrome are characterized by cerebral hypoperfusion [36—42], and treatment with anti-inflammatory medication can restore normal cerebral blood flow in some of these conditions [43,44].

Unfortunately, a viscous cycle could ensue as increased inflammation could lead to increased cerebral hypoperfusion (see Fig. 1). This, in turn, can lead to hypoxia. Hypoxia causes an increase in hypoxia-inducible factor-1α (HIF-1α), which in turn causes an increase in inflammation, including redness and swelling of tissues, and the attraction of lymphocytes [45]. HIF-1α is essential for inflammation mediated by myeloid cells [46]. In fact, in one study, rats that were null for HIF-1α demonstrated almost complete inhibition of the inflammatory response [47]. HIF-1α is also responsible for angiogenesis that is secondary to hypoxia [47,48]. In addition, HIF-1α induces Vascular Endothelial Growth Factor (VEGF), which increases the permeability of blood vessels [45] and causes tissue edema. This edema can lead to increased interstitial space between cells [49] and cause an increase in the distance that oxygen must diffuse from the blood vessel to the cells and can thus lead to cellular hypoxia [50]. Chronic inflammation is commonly associated with the infiltration of polymorphonuclear neutrophils (PMN's) and other immune cells, along with the cytokines that are released by these cells. This causes an increase in local oxygen usage due to the resultant oxygen requirements of these new cells. Yet, at the same time, inflammation causes reduced oxygen extraction by normal cells [51]. For instance, in one study, elevated markers of inflammation (including IL-6, TNF receptors 1 and 2, and high-sensitivity C-reactive protein) were correlated with decreased maximum oxygen uptake at peak exercise (VO_2max) in patients with known or suspected coronary artery disease [52]. Therefore, inflammation prevents maximal uptake of oxygen by cells. Inflammation also increases oxidative stress and can cause neutrophils to become more adherent and attach to vessel walls [53]. This infiltration and increased adherence of inflammatory cells can contribute to brain injury by decreasing microvascular blood flow, causing thrombosis, and increasing the production of free radicals [54].

HBOT and cerebral hypoperfusion

HBOT can overcome the effects of cerebral hypoperfusion (see Table 2) by providing more oxygen to the brain [55,56], and by causing angiogenesis of new blood vessels over time by increasing VEGF levels [57]. Furthermore, if cerebral hypoperfusion is causing hypoxia that is also driving inflammation through the induction of HIF-1α, the oxygen

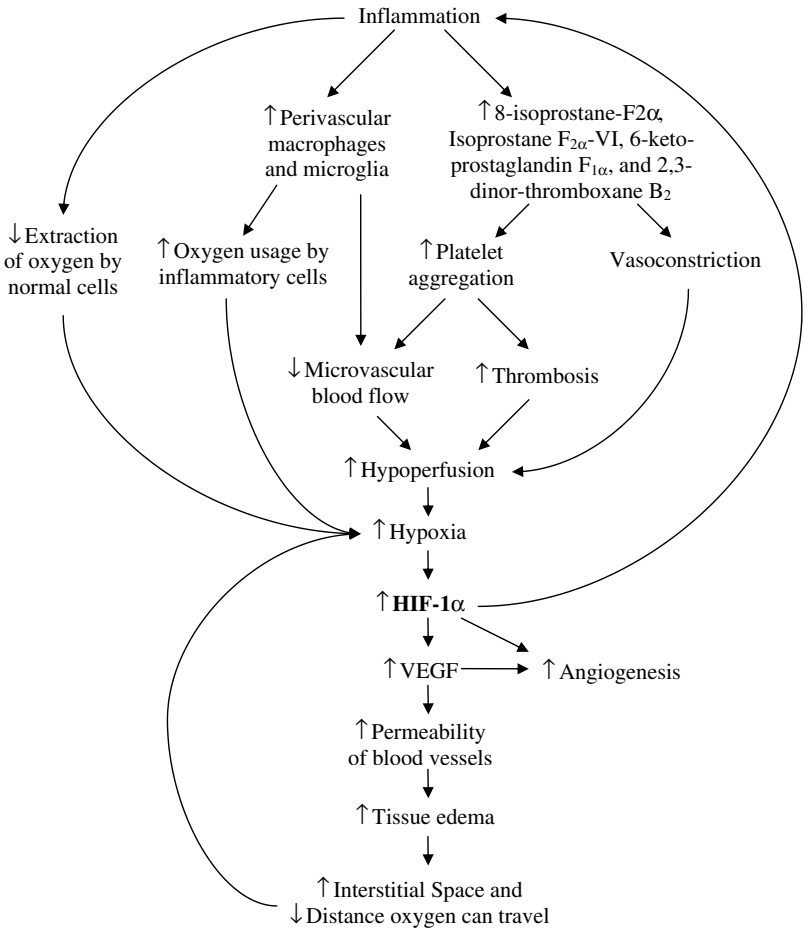

Figure 1 Proposed cycle of inflammation and resultant cerebral hypoperfusion in autism.

delivered by HBOT can improve hypoxia, and thus downregulate HIF-1α. Hypoxia can lead to apoptosis [58] regulated by HIF-1α [59]. HBOT has been shown to inhibit the expression of HIF-1α and its target genes [60], and prevent apoptosis [61] by inhibiting proapototic BNIP-1 [60] and by increasing

Table 2 Proposed mechanisms of inflammatory-induced cerebral hypoperfusion found in autism and HBOT effects

Autism inflammatory finding	Mechanism of hypoperfusion	HBOT effect
↑ 8-isoprostane-F2α [32] and isoprostane $F_{2\alpha}$-VI [34]	Vasoconstriction causes decreased blood flow which leads to decreased delivery of oxygen [33]	Increases the amount of oxygen in plasma and thus increases delivery of oxygen to cells [55,56]
↑ 2,3-dinor-thromboxane B_2 [34]	Increased aggregation of platelets	No effect on platelet aggregation [77][a]
↑ 6-keto-prostaglandin $F_{1\alpha}$ [34]	Endothelial activation	Decreases aggregation of PMN's to endothelium [66]
Cerebral infiltration of perivascular macrophages and microglia [31]	Vasculitis-like condition	Decreases PMN infiltration in injured areas [54]
Cerebral infiltration of perivascular macrophages and microglia [31]	Increased oxygen usage by inflammatory cells and reduced oxygen extraction by normal cells [51]	Increases oxygen in plasma and thus increases delivery of oxygen to cells [55,56]

[a] In this study, platelet aggregation decreased slightly after one hyperbaric treatment, but returned to normal with repeated HBOT.

the expression of Bcl-2, an inhibitor of apoptosis [62]. Interestingly, Bcl-2 levels in the brains of some autistic people are diminished [63].

Since the cerebral hypoperfusion in autism is likely secondary to inflammation, HBOT might be especially helpful because it possesses strong anti-inflammatory properties as will be discussed in detail shortly. Inflammation is often accompanied by PMN infiltration which can decrease microvascular blood flow; however, HBOT has been shown to decrease the infiltration of PMN's after an ischemic injury to the brain [54,64,65]. In addition, HBOT inhibits neutrophil attachment to blood vessel walls [66], reduces leukocyte adherence [67], and increases the distance that oxygen can travel in the interstitial space [68]. HBOT has also been used in cases of vasculitis with good results [69], and with success in disorders characterized by cerebral hypoperfusion including fetal alcohol syndrome [70], cerebral palsy [71,72], autism [73], chronic brain injury [74], closed head injury [75], and stroke [76].

Table 3 Evidence of neuroinflammation in autism

A. Elevated markers of neuroinflammation
Activation of microglia and astroglia [31]
Brain IL-6 [31]
Brain MCP-1 [31]
Brian GFAP [79]
CSF GFAP [81]
B. Elevated serum antibodies to brain proteins
Neuron-axon filament protein [82]
GFAP [82]
Brain epithelial cells and nuclei [84,83]
Myelin basic protein [85,87]
Myelin associated glycoprotein [85]
Ganglioside [85]
Sulfatide [85]
Chondroitin sulfate [85]
Myelin oligodendrocyte glycoprotein [85]
a,h-crystallin [85]
Neurofilament proteins [85]
Tubulin [85]
Cerebellar Purkinje cells [86]
Caudate nucleus [89]
Cerebral cortex [89]
BDNF [90]

Neuroinflammation in autism

Several recent studies have revealed that children with autism have evidence of neuroinflammation [31,78,79]. Marked activation of microglia and astroglia with elevations in IL-6 and macrophage chemoattractant protein-1 (MCP-1) were found in autistic brain samples upon autopsy, along with increased proinflammatory cytokines in the cerebral spinal fluid (CSF) of living autistic children [31]. Activated microglia have been shown to release inflammatory mediators such as IL-1 and TNF-α, and have been implicated as the primary cell type that controls inflammation-mediated neuronal injury [35]. A cell-mediated immune response to brain tissue in autistic individuals has also been described [80]. In addition, some autistic children have increased glial fibrillary acidic protein (GFAP) in brain samples [79] and the CSF [81], which is also indicative of inflammation and reactive injury. Autoantibodies to neuron-axon filament protein and GFAP were also increased in the plasma of autistic individuals compared to control individuals [82]. Autistic children make more serum autoantibodies to the brain [83], including IgG and IgM autoantibodies to brain epithelial cells and nuclei when compared to typical children [84]. Elevated serum autoantibodies to many neuron-specific antigens and cross-reactive peptides have been found in autistic children [85], including antibodies directed against cerebellar Purkinje cells [86], and other neural proteins (see Table 3) such as myelin basic protein [85,87,88]. Furthermore, 49% of autistic children in one study created serum antibodies against the caudate nucleus, and 18% produced serum antibodies to the cerebral cortex [89]. Another recent study demonstrated that autistic children, when compared to control children, developed serum autoantibodies to brain derived neurotrophic factor (BDNF) and had higher levels of serum BDNF. This is important because an elevation of BDNF predicts abnormalities in intellect and social development [90]. Finally, maternal neuronal antibodies might play a role in the development of autism in some children [91].

Gastrointestinal inflammation in autism

In addition, some patients with autism have chronic ileocolonic lymphoid nodular hyperplasia (LNH) and enterocolitis characterized by mucosal inflammation of the colon, stomach, and small intestine [92–94]. These findings might represent a ''new variant inflammatory bowel disease'' [93], and have been described as a ''panenteric IBD-like disease'' [95]. As many as 90% of autistic children with gastrointestinal symptoms have evidence of ileal LNH, with 68% having moderate to severe ileal LNH [92]. In one study, the gastrointestinal mucosa was shown to have increased lymphocytic infiltration and density, crypt cell

proliferation, and epithelial IgG deposits mimicking an autoimmune lesion [96]. Another study demonstrated that the gastrointestinal mucosa in autistic individuals had evidence of increased lymphocytes and proinflammatory cytokines including TNF-α and Interferon-γ (IFN-γ), and less of the anti-inflammatory cytokine IL-10, which is counter-regulatory [97]. Some autistic children also had evidence of an eosinophilic infiltrate of the gastrointestinal mucosa [98]. Autistic children typically make significantly more serum antibodies against gliadin and casein peptides resulting in autoimmune reactions [99]. More than 25% of autistic individuals make serum IgG, IgM, and IgA antibodies against gliadin, which can cross-react with cerebellar peptides [86]. Furthermore, when compared to typical children, autistic children produce more proinflammatory cytokines, including TNF-α, IL-1β, and IL-6 [100]. One study has shown that the genetic loci for autism have a propensity to cluster with recognized loci for inflammatory diseases [101].

Interestingly, children on a gluten and/or casein free diet produced less TNF-α in the colonic mucosa [97], and had less evidence of eosinophilic infiltration of the mucosa [98]. In addition, the use of anti-inflammatory treatments might improve autistic symptomology [102]. In fact, treatment with corticosteroids of one child who developed an autoimmune lymphoproliferative syndrome and subsequent autism led to objective improvements in speech and developmental milestones [103]. In another child with PDD, whose behavior and language regressed at 22 months of age, treatment with corticosteroids ameliorated abnormal behaviors such as hyperactivity, tantrums, impaired social interaction, echolalia, and stereotypies [104].

HBOT and inflammation

HBOT has potent anti-inflammatory tissue effects [57] as revealed by several recent animal studies [105,106], with equivalence to diclofenac 20 mg/kg noted in one study [107]. HBOT has been shown to attenuate the production of proinflammatory cytokines including TNF-α [108—111], IL-1 [108,112], IL-1β [110,111], and IL-6 [108], and increase the production of anti-inflammatory IL-10 [113]. HBOT has also been shown to reduce neuroinflammation in a rat model after traumatic brain injury [65]. HBOT also reduced both inflammation and pain in an animal model of inflammatory pain [114], decreased the symptoms of advanced arthritis in rats [115], and attenuated the inflammatory response in the peritoneal cavity caused by injected meconium [116]. HBOT has been used in animal studies to improve colitis [105,117—119], and has been used in humans to achieve remission of Crohn's disease [120—124] and ulcerative colitis [125,126] not responding to conventional medications, including corticosteroids. Interestingly, in some studies, the decrease in inflammation with HBOT appeared to be caused by the increased pressure, not necessarily by the increased oxygen tension. In one animal study, hyperbaric pressure without additional oxygen was shown to decrease TNF-α levels [127]. In another human study, HBOT at 2 atmosphere (atm) and 100% oxygen, and hyperbaric pressure at 2 atm and 10.5% oxygen (thus supplying 21% oxygen, equal to room air oxygen) both showed anti-inflammatory activity by inhibiting IFN-γ release, whereas 100% oxygen at room air pressure (1 atm) actually increased IFN-γ release [128].

The anti-inflammatory effect of HBOT might occur through the relief of hypoxia and the down-regulation of HIF-1α [47,60]. HBOT also decreases Prostaglandin E_2 production [112] which decreases inflammation because prostglandins increase inflammation, pain, and edema [57]. In one study, HBOT decreased cyclooxygenase-2 (COX-2) enzyme expression after transient cerebral ischemia [129]. The COX-2 enzyme is responsible for increased prostaglandin production, leading to increased inflammation. Blockade of the COX-2 enzyme has been shown to decrease inflammation and cytokine levels including IL-6 [130]. For these reasons, HBOT might help ameliorate the inflammation found in autism (see Table 4).

Immune function in autism

There is mounting evidence of immune dysregulation in autistic individuals (see Table 5), and new research is revealing the link between the immune system and the nervous system [131]. An increased number of autoimmune diseases exist in autistic families compared to control families [132,133] with as much as a 6—8 fold increased incidence [134]. Some researchers believe that autistic children might have ''an underlying autoimmune disorder'' [135] and that a ''genetic relationship'' exists between autism and immune dysregulation [101]. Two early studies revealed that 38% of autistic children had no detectible Rubella titers despite vaccination [136], and 60% produced abnormal serum antibodies to measles hemagglutinin protein when compared to control children [87]. Autistic individuals also make more serum antibodies to Heat

Table 4 Effects of HBOT on inflammatory markers and inflammation in autism

Marker	Classification	Autism finding	HBOT effect
TNF-α	Inflammatory	↑ [100,97]	↓ [111,108,110,109], [127][a]
IL-1β	Inflammatory	↑ [100]	↓ [111,110]
IL-6	Inflammatory	↑ [100,31]	↓ [108]
IL-10	Anti-inflammatory	↓ [97]	↑ [113]
IFN-γ	Inflammatory	↑ [97]	↓ [128][b]
Neuroinflammation		↑ [31,78,79]	↓ [65]
Gastrointestinal inflammation		↑ [92–94]	↓ [120,125]

[a] Hyperbaric pressure without additional oxygen decreased TNF-α.
[b] Hyperbaric pressure without additional oxygen also decreased IFN-γ.

Shock Protein-90 (HSP-90) [137], which could cause HSP-90 levels to be lower. HSP-90 is a signal transducer which regulates development and cell differentiation. In one study, decreased levels of HSP-90 allowed natural genetic abnormalities hidden in fruit fly populations to suddenly appear [138]. Attempts to improve the underlying immune deficiency in autistic individuals with intravenous immune globulin have shown promising results [139–141].

Table 5 Evidence of immunological abnormalities in autism

A. Non-neuronal serum antibodies produced in autistic individuals
HSP-90 [137]
Gliadin [99]
Casein [99]
Milk butyrophilin [85]
Chlamydia pneumoniae [85]
Streptococcal M protein [85]
Measles hemagglutinin protein [87]

B. Cellular, immunoglobulin, and cytokine abnormalities
↑ Serum IgG2 and IgG4 [135]
↓ Responsiveness of lymphocytes [155]
↓ Natural killer cells [156]
↓ Number of total CD4+ cells [143,142]
↓ Number of T-helper cells ($CD4^+CD8^-$) [143]
↑ Number of suppressor T-cells ($CD4^-CD8^+$) [143]
Imbalance of $CD4^+$and $CD8^+$ cells [153]
↑ IFN-γ [149]
↑ Markers of cell-mediated immunity (urinary neopterin and biopterin) [152]
↑ IL-4 [154]
↑ IL-5 [154]
↑ IL-12 [149]
↑ IL-13 [154]
↓ IL-10 [97]
↑ Serum IgE [139,148]
↓ Serum IgA [139]

In addition, several studies have reported abnormalities in T-lymphocytes, including a decreased number of $CD4^+$ cells [142] in approximately 35% of autistic individuals [139]. This has led to an altered ratio of CD4/CD8 cells with a reduced number of T-helper cells ($CD4^+CD8^-$) and an increased number of suppressor T-cells ($CD4^-CD8^+$) in some autistic individuals [143]. One study demonstrated that treatment with naltrexone increased the number of T-helper inducers and reduced the number of T-cytotoxic suppressors, resulting in a normalization of the CD4/CD8 ratio and improvement of symptoms in over half of the autistic children studied [144]. $CD4^+$ cells are divided into Th1 and Th2 subsets. Th1 cells produce IL-2 and IFN-γ and are involved in T-cell proliferation, activation of macrophages, and cell-mediated immunity including phagocytosis of intracellular pathogens like viruses. Th2 cells are part of the adaptive immune system and produce IL-4, IL-5, IL-6, IL-10, and IL-13. IL-4 is involved in the B-cell production of IgE. IL-5 stimulates the production of eosinophils, and IL-6 is involved in the production of immunoglobulins. IL-1 and IL-6 are proinflammatory cytokines, and IL-10 inhibits Th1 cytokine production and thus down-regulates the inflammatory response [145]. Skewing toward Th2 is often seen in allergic responses [146]. Interestingly, a history of allergies in the mother during pregnancy led to a greater than 2-fold elevated risk of autism [147], and children with autism tend to have more food allergies than control children [148].

Some earlier studies demonstrated activation of the Th1 system in autistic children with increased production of IL-12 and interferon when compared to control children [149,150]. Autistic individuals make more IFN-γ and IL-1 receptor antagonist, which can cause a Th1 skewing [151]. Autistic children also have increased markers of cell-mediated

immunity, a Th-1 function, including elevated urinary neopterin and biopterin [152]. Finally, a cell-mediated immune response to brain tissues in autistic individuals has also been described [80].

More recent studies indicate that autistic children exhibit a shift from Th1 to Th2 T-cell type [135,140], as evidenced by an increased production of IgE [139,148] and IL-4 producing $CD4^+$ T-cells, and lower levels of IL-2 producing $CD4^+$ T-cells compared to control children [153]. Furthermore, about one-third of autistic children in one study demonstrated IgG subclass deficiency not confined to the 4 subclasses of IgG [139]. Approximately 5% of autistic individuals have IgA deficiency, which is normally present in 1 in 700—1000 people, and about 30-40% have low serum IgA levels [139]. In spite of these deficiencies, a new study suggests that autism is characterized by a heightened immune system. This is evidenced by an increased activation of both the Th1 and Th2 arms with Th2 predominance as indicated by increased IL-4, IL-5 and IL-13 when compared to control individuals, without a compensatory increase in IL-10 [154].

Shifting from a Th1 to a Th2 T-cell type might enhance susceptibility to chronic viral infections in some autistic individuals [135]. In fact, depressed responsiveness of lymphocytes was found in one study on autistic children [155], and another study demonstrated a 40% decrease in the number of natural killer cells when compared to control children [156]. Therefore, autistic individuals might have ''enhanced susceptibility to infections resulting in chronic viral infections'' [135].

HBOT and immune function

HBOT might be useful in some autoimmune diseases [157], and has shown promise in rheumatic diseases, including lupus and scleroderma [158], and rheumatoid arthritis [159]. HBOT has been used in animal models to completely suppress autoimmune encephalomyelitis by blocking mononuclear infiltration and demyelination of the CNS [160], and acted as an immunosuppressive agent to delay skin allograft rejection [161]. HBOT has been shown to suppress immune responses such as proteinuria, facial erythema, and lymphadenopathy in an autoimmune mouse model [162]. In addition, one animal study showed increased survival and decreased proteinuria, anti-dsDNA antibody titers, and immune-complex deposition in lupus-prone autoimmune mice treated with HBOT [163]. HBOT improved symptoms in patients with atopic dermatitis and also decreased IgE immunoglobulin and complement levels [164]. In patients with multiple sclerosis, HBOT produced a significant increase in total and helper T-lymphocyte numbers and serum IgA levels [165]. Two other studies demonstrated an increase in lymphocyte count, with variable subset population increases depending on which organ (spleen, thymus, or blood) was examined and how much oxygen was given with HBOT [166,167]. HBOT has also been shown to increase IL-10, the anti-inflammatory interleukin [113], and induce the production of HSP-90 [168]. Interestingly, some of the immunomodulatory effects of HBOT might be due to the increased pressure, not necessarily the increased oxygen tension [169]. Even low hyperbaric pressures, without additional oxygen, can affect the immune system. One study demonstrated that hyperbaric pressure at just 20 mmHg (approximately 1.03 atm) can have an effect on the immune system [127]. Based upon these reasons, HBOT might help improve the immune dysregulation found in autistic individuals (see Table 6).

Oxidative stress in autism

Autistic children have evidence of increased oxidative stress including lower serum glutathione levels [170,171]. Some autistic children have increased red blood cell nitric oxide, which is a known free radical and toxic to the brain [172]. Of note, HIF-1α increases the production of nitric oxide [45]. Lower serum antioxidant enzyme, antioxidant nutrient, and glutathione levels, as well as higher pro-oxidants have been found in multiple studies of autistic children [173]. Autistic children have evidence of increased lipid peroxidation [34,174], including increased malondialdehyde which is a marker of oxidative stress and lipid peroxidation [175]. Decreased activities of certain antioxidant enzymes have also been described in autistic individuals including superoxide dismutase (SOD)

Table 6 Effects of HBOT on immune dysregulation in autism

Marker	Autism finding	HBOT effect
HSP-90	↓? (due to increased antibodies to HSP-90) [137]	↑ [168]
Serum IgA	↓ [139]	↑ [165]
Serum IgE	↑ [148,139]	↓ [164]
Lymphocytic activity	↓ [155]	↑ [166]
T-helper cells	↓ [143]	↑ [165]

[176], glutathione peroxidase [176], and catalase [174]. Some autistic children also have decreased activity of paraoxonase, an antioxidant enzyme that prevents lipid oxidation and also detoxifies organophosphates in humans [177]. The gene for Heat Shock Protein 70 (HSP-70), which protects against oxidative stress, was downregulated in multiple cases of autism [178]. Antioxidants such as ceruloplasmin [175] and zinc [179] tend to be lower in autistic patients, and the ratio of copper to zinc is abnormal in many autistic children [180]. Furthermore, in one study, treatment with antioxidants was shown to raise the levels of reduced glutathione in the serum of autistic children and appeared to improve symptoms [170]. In another study, the use of antioxidants improved behavior in some autistic children [181].

HBOT and oxidative stress

Concerns have been previously raised that HBOT might increase oxidative stress through the production of reactive oxygen species [182]. This is a relevant concern because of the increased oxidative stress just described in autistic children. However, oxidative stress from HBOT appears to be less of a concern at pressures under 2.0 atm [183] which are often used clinically. Oxidative stress is caused by an imbalance of oxidants and antioxidants. With long-term and repeated administration, HBOT below 2.0 atm can actually decrease oxidative stress [184–186] by reducing lipid peroxidation [187], and increasing the activity of antioxidant enzymes including SOD [185,188], glutathione peroxidase [118], catalase [189], paraoxonase [190], and heme-oxygenase-1 [191–193]. HBOT has also been shown to increase HSP-70, which protects against oxidative stress [194,195]. One recent animal study has demonstrated that HBOT can suppress oxidative stress in brain tissues after a stroke [196]. HBOT also increases zinc, decreases copper [185], and increases ceruloplasmin levels [197]. Thus, HBOT might help improve the oxidative stress found in some autistic individuals (see Table 7).

Mitochondrial dysfunction in autism

Lombard hypothesized that autism might be caused by mitochondrial dysfunction [199]. Several recent case reports supporting this concept have been published including two autistic children with hypotonia, lactic acidosis and abnormal mitochondrial enzyme assays on muscle biopsy [200], an autistic child with developmental regression and mitochondrial dysfunction [201], and an autistic child with mitochondrial dysfunction [202]. A larger case series of 12 children with hypotonia, epilepsy, and autism also found mitochondrial dysfunction [203]. Another study on 100 children with autism suggested mild mitochondrial dysfunction as evidenced by reduced carnitine and pyruvate levels and increased ammonia and alanine levels [204]. Further research reveals that mitochondrial point mutations might be the cause of autism in some people [205]. An association between autism and the mitochondrial aspartate/glutamate carrier SLC25A12 gene polymorphism was recently described [206] and confirmed [207]. A mitochondrial A3243G mutation has also been associated with autism [208], and both autosomal recessive and maternally inherited mitochondrial defects can cause autism [209]. Some of the more common blood abnormalities associated with mitochondrial dysfunction include elevated aspartate aminotransferase, creatine kinase, and fasting lactic acid. In one study of 120 autistic children, 7.2%

Table 7 Effects of HBOT on measures of oxidative stress in autism

Measure	Classification	Autism finding	HBOT effect
Glutathione peroxidase	Antioxidant enzyme	↓ [176]	↑ [118]
Superoxide dismutase	Antioxidant enzyme	↓ [176]	↑ [118,188,185]
Heme-oxygenase 1	Antioxidant enzyme	?	↑ [191–193]
Catalase	Antioxidant enzyme	↓ [174]	↑ [189]
Paraoxonase	Antioxidant enzyme; organophosphate detoxification	↓ [177,198]	↑ [190]
HSP-70	Cellular protection against oxidative stress	↓ [178]	↑ [194,195]
Malondialdehyde	Marker of oxidative stress and lipid peroxidation	↑ [175]	↓ [118,185]
Ceruloplasmin	Antioxidant	↓ [175]	↑ [197]
Glutathione	Antioxidant	↓ [170]	↑ [185]
Zinc	Antioxidant	↓ [179]	↑ [185]
Copper	Metal	↑ [180]	↓ [185]

had a ''definite mitochondrial respiratory chain disorder'', and plasma lactate levels were elevated in 20% of the children [210]. In another study of 159 autistic children, compared to 94 control children, autistic children had higher aspartate aminotransferase levels ($p = 0.00005$), and 47% had elevated creatine kinase levels, which might be consistent with relative mitochondrial dysfunction [201]. Recently, mitochondrial abnormalities were discovered in a mouse model of Rett Syndrome [211], a disorder classified as a PDD.

HBOT and mitochondrial dysfunction

Hypoxia can impair mitochondrial function [212]. Since only approximately 0.3% of inhaled oxygen is ultimately delivered to the mitochondria [213], increasing the oxygen delivery to dysfunctional mitochondria by HBOT might aid in improving function [214,215]. In a mouse model with an intrinsic impairment of mitochondrial complex IV, HBOT at 2 atm ''significantly ameliorate[d] mitochondrial dysfunction'' and delayed the onset of motor neuron disease when compared to control mice [215]. In animals studies, HBOT increased the amount of work done by mitochondria [216], improved mitochondrial function after brain injury [214], and was shown to ''protect mitochondria from deterioration'' when compared to normal oxygen and pressure [217]. HBOT also has been shown to increase sperm motility by augmenting mitochondrial oxidative phosphorylation in fructolysis-inhibited sperm cells [218]. HBOT also prevented apoptosis and improved neurological recovery after cerebral ischemia by opening mitochondrial ATP-sensitive potassium channels [61]. Finally, HBOT has recently been shown to activate mitochondrial DNA transcription and replication, and increase the biogenesis of mitochondria in the brains of animals [219]. For these reasons, HBOT might improve the relative mitochondrial dysfunction found in some autistic individuals.

Neurotransmitter abnormalities in autism

Early childhood is typified by an increased production of serotonin when compared to adulthood; however, one study showed that autistic children synthesized less serotonin during childhood when compared to control children [220]. Another study demonstrated lower levels of serotonin in both autistic children and their mothers [221]. Plasma levels of tryptophan, which is the precursor to serotonin, are lower in autistic children compared to control children, and are suggestive of a serotonergic abnormality [222]. In addition, tryptophan uptake by brain cells as seen on PET scan was less in autistic children compared to control children [220], and tryptophan depletion can cause a significant increase in autistic behaviors such as ''whirling, flapping, pacing, banging and hitting self, rocking, and toe walking'' [223]. Antibodies against cerebral serotonin receptors, which preclude the binding of serotonin, are more common in autistic individuals when compared to control individuals [224,225]. Selective serotonin reuptake inhibitors (SSRI's) have been shown to be beneficial for obsessive and repetitive behaviors [226]. In some studies, SSRI's including fluoxetine [227], fluvoxamine [226], and escitalopram [228] have shown benefit for autism.

In addition, some autistic children have evidence of dopamine overactivity, including higher CSF levels of homovanillic acid, the main metabolite of dopamine [229]. Treatment of autistic children with dopamine agonists has led to worsening of aggression, hyperactivity, and stereotypies [230]. Dopamine antagonists such as pimozide [231] and bromocriptine [232] have shown improvements in some autistic children.

HBOT and neurotransmitter abnormalities

HBOT has also been shown to reduce the uptake of serotonin by pulmonary endothelial cells [233,234], and thus might function like an SSRI. In one study, HBOT demonstrated ''antidepressant-like activity'' similar to that seen with some SSRI antidepressants like fluoxetine [235]. In another study on patients with cluster headaches, HBOT improved pain and was shown to act through serotonergic pathways [236]. Furthermore, in an animal model, HBOT was shown to decrease the release of dopamine after cerebral injury [237]. In another animal study, 90% oxygen at room air pressure (1 atm) decreased extracellular dopamine levels in the brain [238]. Therefore, HBOT might improve the neurotransmitter imbalances found in some autistic individuals.

Toxin exposure in autism and HBOT

Recent data has shown that organophosphate poisoning can cause atypical autism [239]. Paraoxonase

is the enzyme responsible for organophosphate detoxification in humans. In North America, autism has been associated with variants in the paraoxonase gene which can decrease the activity of this enzyme by 50 percent [177]. This was recently confirmed in another study that demonstrated reduced activity of paraoxonase in some autistic children [198].

HBOT has been shown to increase the activity of paraoxonase [190], and to prevent a decrease in paraoxonase activity normally seen with a high cholesterol diet [187]. Thus, HBOT might lead to an improved ability to excrete organophosphates in some autistic children by upregulating paraoxonase activity.

Dysbiosis in autism

Significant alterations in intestinal flora, with increased amounts of *Clostridia* bacteria [240–242], and overgrowth of other abnormal bacteria [241], exist in some autistic children when compared to control children. In fact, one author has hypothesized that *Clostridia* infection in the gut might cause autistic-like symptoms [243]. Furthermore, treatment of these abnormal gut bacteria with antibiotics has led to improvements of autistic symptoms as measured by a clinical psychologist blinded to the treatment status [244]. Some autistic children also have overgrowth of yeast, viruses, and parasites in the gut [245].

HBOT and dysbiosis

HBOT has been shown to decrease the amount of abnormal bacteria in the gut and therefore can function as an antibiotic [246]. In animal studies, HBOT decreased intestinal bacterial colony counts after bacteria overgrowth in the distal ileum associated with bile duct ligation [247]. HBOT is also bactericidal against many bacteria [248], including *Pseudomonas* [249,250], *Salmonella* and *Proteus* [249], *Staphylococcus* [251], *Mycobacterium tuberculosis* [248], and anaerobic bacteria such as *Clostridia* [252]. In addition, the killing of bacteria by phagocytic leukocytes is dependent upon oxygen [253], and HBOT has been shown to improve leukocyte phagocytic killing of *Staphyloccus aureus* in animals [254]. HBOT has also been shown to inhibit the growth of some yeast [255] and to possess virucidal activity against some enveloped viruses [256]. HBOT also appears to have an antiviral effect against HIV [257]. In an animal model, HBOT improved symptoms in a virus-induced leukemia compared to a control group [258]. HBOT can also kill parasites, including *Leishmania amazonensis* [259]. Thus HBOT might lead to an improvement in the dysbiosis found in some autistic children by reducing counts of abnormal pathogens.

Porphyrin production in autism and HBOT

Children with autism might have impaired production of some porphyrins [260] which are involved in the synthesis of heme, which carries oxygen in the body. Therefore, the ability to deliver oxygen on hemoglobin could be compromised in some autistic children [261], and HBOT might help overcome this by increasing the amount of oxygen dissolved in plasma.

Stem cells and HBOT

Recently, HBOT at 2.0 atm was shown to mobilize stem/progenitor cells from the bone marrow of humans into the systemic circulation. Elevations were found in the number of colony-forming cells as demonstrated by an increase in the number of $CD34^+$ cells by 8-fold after 20 HBOT sessions [262]. Since stem cells are also produced in the brain, this gives rise to the possibility of neuropoiesis [263], which might aid in reversing chronic neurodegenerative disorders. Furthermore, in two human case reports, female bone-marrow-transplant patients received cells from male donors. On autopsy of these females, staining for the male Y-chromosome in their brains demonstrated that male donor stem cells from the bone marrow had crossed into the brain and formed new neurons, astrocytes, and microglia [264,265].

Additional HBOT and future study considerations

HBOT pressure considerations

Previous studies have shown improvements of symptoms in children with autism and cerebral palsy (CP) at hyperbaric pressures of 1.3 atm with or without additional oxygen [72,73,266]. The use of HBOT in children appears generally safe, even at pressures up to 2.0 atm for 2 h per day for 40 sessions [267]. Many of the potential benefits of HBOT as described above were found in studies at higher hyperbaric pressures. Further study is neces-

sary to determine if these benefits also hold true at the lower hyperbaric pressures (1.3—1.5 atm) commonly being utilized for autistic individuals and to establish the optimal hyperbaric pressure for autism and related disorders.

HBOT oxygen concentration considerations

As described above, in one study, the decrease in inflammation with HBOT appeared to be caused by the increased pressure, not necessarily by the increased oxygen tension. In this human study, both HBOT and hyperbaric pressure demonstrated anti-inflammatory activity by inhibiting IFN-γ release, whereas 100% oxygen at room air pressure (1 atm) actually increased IFN-γ release [128]. Further study is needed to verify this finding, to determine if this phenomenon equally applies to the other noted benefits of HBOT, to better understand the mechanisms of action of HBOT, and to determine the optimal oxygen concentration for use in autistic individuals.

HBOT session count considerations

The number of HBOT sessions needed to produce full clinical improvements is unclear. In one study combining the use of SPECT and HBOT, an average of 70 treatments was needed to show a significant increase in cerebral blood oxygenation and metabolism in patients with chronic neurological disorders including CP, stroke, and traumatic brain injury. Of note, the rate of improvement in cerebral blood oxygenation and metabolism was more profound during the last 35 HBOT sessions when compared to the first 35 [74]. In another study of children with CP using HBOT at 1.7 atm, serial functional measurements after 40 and 80 HBOT sessions showed continuing objective improvements including a decrease in the total time of custodial care and improved gross motor function. At the end of 80 treatments, children in the study were continuing to improve, and the authors noted that the optimal number of treatments could not be determined as it appeared that further HBOT sessions would yield additional improvements [268]. Further study is needed to clarify the optimal number of HBOT sessions for autistic individuals.

Pathophysiology as a primary acceptance criterion for HBOT

HBOT has been used by the Navy since 1943 for air embolism and decompression sickness, two indications that are widely accepted. However, no prospective, double-blind, placebo-controlled trials have been performed on these 2 indications; rather, the use of HBOT is justified based upon the underlying pathophysiology of these 2 conditions and the mechanism of action of HBOT [68]. The use of HBOT for autism is considered ''off-label'' [269]. However, examining the pathophysiology of autism continues to indicate that HBOT might be effective for treating autism [270]. Several studies on the use of HBOT in autism are currently underway and early results are promising. It is hoped that a clearer understanding of the potential benefits of HBOT in treating the common symptoms of autism will spur other researchers to investigate the use of HBOT in autistic individuals.

Conclusions

Numerous studies of autistic individuals have revealed evidence of cerebral hypoperfusion, neuroinflammation and gastrointestinal inflammation, immune dysregulation, oxidative stress, relative mitochondrial dysfunction, neurotransmitter abnormalities, impaired detoxification of toxins, dysbiosis, and impaired production of porphyrins. HBOT has been shown to increase oxygen delivery to hypoperfused or hypoxic tissues, decrease inflammation and oxidative stress, and increase the production of mitochondria and the number of circulating stem cells. HBOT might also improve the immune dysfunction, neurotransmitter abnormalities, and dysbiosis specifically found in autistic individuals. Further studies are necessary to test this hypothesis and are currently underway. The possible effects of HBOT on autism are summarized in Table 8.

Table 8 Summary of the proposed HBOT effects on the pathophysiology found in autism

Problem	Autism finding	HBOT effect
Cerebral perfusion	↓	↑
Neuroinflammation inflammation	↑	↓
Gastrointestinal inflammation	↑	↓
Immune dysregulation	↑	↓
Oxidative stress	↑	↓
Mitochondrial function	↓	↑
Neurotransmitter abnormalities	↑	↓
Detoxification enzyme function	↓	↑
Dysbiosis	↑	↓
Porphyrin production	↓	↑
Circulating stem cells		↑

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References

[1] Singh N. (contact). Press release: CDC launches ''Learn the signs. Act early.'' Campaign. http://www.cdc.gov/od/oc/media/pressrel/r050222.htm. February 22, 2005 [accessed 9.5.06].
[2] Baird G, Simonoff E, Pickles A, et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the special needs and autism project (SNAP). Lancet 2006;368(9531):210—5.
[3] Shaul M. (contact). GAO-05-220. United States Government Accountability Office. Report to the chairman and ranking minority member, subcommittee on human rights and wellness, committee on government reform, house of representatives. Special education: children with autism. http://www.gao.gov/new.items/d05220.pdf. January 2005 [accessed 9.5.06].
[4] Kanner L. Autistic disturbances of affective contact. Nervous Child 1943;2:217—50.
[5] London EA. The environment as an etiologic factor in autism: a new direction for research. Environ Health Perspect 2000;108(S3):401—4.
[6] Baird G, Cass H, Slonims V. Diagnosis of autism. BMJ 2003;327(7413):488—93.
[7] Klauck SM. Genetics of autism spectrum disorder. Eur J Hum Genet 2006;14(6):714—20.
[8] Charman T, Taylor E, Drew A, Cockerill H, Brown JA, Baird G. Outcome at 7 years of children diagnosed with autism at age 2: predictive validity of assessments conducted at 2 and 3 years of age and pattern of symptom change over time. J Child Psychol Psychiatry 2005;46(5):500—13.
[9] Lord C, Risi S, DiLavore PS, Shulman C, Thurm A, Pickles A. Autism for 2 to 9 years of age. Arch Gen Psychiatry 2006;63(6):694—701.
[10] Ryu YH, Lee JD, Yoon PH, Kim DI, Lee HB, Shin YJ. Perfusion impairments in infantile autism on technetium-99m ethyl cysteinate dimer brain single-photon emission tomography: comparison with findings on magnetic resonance imaging. Eur J Nucl Med 1999;26(3):253—9.
[11] Wilcox J, Tsuang MT, Ledger E, Algeo J, Schnurr T. Brain perfusion in autism varies with age. Neuropsychobiology 2002;46(1):13—6.
[12] Chiron C, Leboyer M, Leon F, Jambaque I, Nuttin C, Syrota A. SPECT of the brain in childhood autism: evidence for a lack of normal hemispheric asymmetry. Dev Med Child Neurol 1995;37(10):849—60.
[13] Starkstein SE, Vazquez S, Vrancic D, et al. SPECT findings in mentally retarded autistic individuals. J Neuropsychiatry Clin Neurosci 2000;12(3):370—5.
[14] Mountz JM, Tolbert LC, Lill DW, Katholi CR, Liu HG. Functional deficits in autistic disorder: characterization by technetium-99m-HMPAO and SPECT. J Nucl Med 1995;36(7):1156—62.
[15] Ohnishi T, Matsuda H, Hashimoto T, et al. Abnormal regional cerebral blood flow in childhood autism. Brain 2000;123(Pt9):1838—44.
[16] George MS, Costa DC, Kouris K, Ring HA, Ell PJ. Cerebral blood flow abnormalities in adults with infantile autism. J Nerv Ment Dis 1992;180(7):413—7.
[17] Boddaert N, Zilbovicius M. Functional neuroimaging and childhood autism. Pediatr Radiol 2002;32(1):1—7.
[18] Zilbovicius M, Boddaert N, Belin P, et al. Temporal lobe dysfunction in childhood autism: a PET study. Am J Psychiatry 2000;157(12):1988—93.
[19] Kaya M, Karasalihoglu S, Ustun F, et al. The relationship between 99mTc-HMPAO brain SPECT and the scores of real life rating scale in autistic children. Brain Dev 2002;24(2):77—81.
[20] Hashimoto T, Sasaki M, Fukumizu M, Hanaoka S, Sugai K, Matsuda H. Single-photon emission computed tomography of the brain in autism: effect of the developmental level. Pediatr Neurol 2000;23(5):416—20.
[21] Gillberg IC, Bjure J, Uvebrant P, Vestergren E, Gillberg C. SPECT (single photon emission computed tomography) in 31 children and adolescents with autism and autism-like conditions. Eur Child Adolesc Psychiatry 1993;2(1):50—9.
[22] Boddaert N, Chabane N, Belin P, et al. Perception of complex sounds in autism: abnormal auditory cortical processing in children. Am J Psychiatry 2004;161(11):2117—20.
[23] Ito H, Mori K, Hashimoto T, et al. Findings of brain ^{99m}Tc-ECD SPECT in high-functioning autism-3-dimensional stereotactic ROI template analysis of brain SPECT. J Med Invest 2005;52(1—2):49—56.
[24] Critchley HD, Daly EM, Bullmore ET, et al. The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions. Brain 2000;123(Pt11):2203—12.
[25] Pierce K, Haist F, Sedaghat F, Courchesne E. The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. Brain 2004;127(Pt12):2703—16.
[26] Allen G, Courchesne E. Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: an fMRI study of autism. Am J Psychiatry 2003;160(2):262—73.
[27] Muller RA, Behen ME, Rothermel RD, et al. Brain mapping of language and auditory perception in high-functioning autistic adults: a PET study. J Autism Dev Disord 1999;29(1):19—31.
[28] Bruneau N, Dourneau MC, Garreau B, Pourcelot L, Lelord G. Blood flow response to auditory stimulations in normal, mentally retarded, and autistic children: a preliminary transcranial Doppler ultrasonographic study of the middle cerebral arteries. Biol Psychiatry 1992;32(8):691—9.
[29] Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. Proc Natl Acad Sci USA 1986;83(4):1140—4.
[30] Parri R, Crunelli V. An astrocyte bridge from synapse to blood flow. Nat Neurosci 2003;6(1):5—6.
[31] Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol 2005;57(1):67—81.
[32] Ming X, Stein TP, Brimacombe M, Johnson WG, Lambert GH, Wagner GC. Increased excretion of a lipid peroxidation biomarker in autism. Prostaglandins Leukot Essent Fatty Acids 2005;73(5):379—84.
[33] Pratico D, Lawson JA, Rokach J, FitzGerald GA. The isoprostanes in biology and medicine. Trends Endocrinol Metab 2001;12(6):243—7.
[34] Yao Y, Walsh WJ, McGinnis WR, Pratico D. Altered vascular phenotype in autism: correlation with oxidative stress. Arch Neurol 2006;63(8):1161—4.

[35] Lu DY, Liou HC, Tang CH, Fu WM. Hypoxia-induced iNOS expression in microglia is regulated by the PI3-kinase/Akt/mTOR signaling pathway and activation of hypoxia inducible factor-1α. Biochem Pharmacol 2006. doi:10.1016/j.bcp.2006.06.038, in press.
[36] Ichiyama T, Nishikawa M, Hayashi T, Koga M, Tashiro N, Furukawa S. Cerebral hypoperfusion during acute Kawasaki Disease. Stroke 1998;29(7):1320—1.
[37] Huang WS, Chiu PY, Tsai CH, Kao A, Lee CC. Objective evidence of abnormal regional cerebral blood flow in patients with systemic lupus erythematosus on Tc-99m ECD brain SPECT. Rheumatol Int 2002;22(5):178—81.
[38] Postiglione A, De Chiara S, Soricelli A, et al. Alterations of cerebral blood flow and antiphospholipid antibodies in patients with systemic lupus erythematosus. Int J Clin Lab Res 1998;28(1):34—8.
[39] Lass P, Krajka-Lauer J, Homziuk M, et al. Cerebral blood flow in Sjögren's syndrome using 99Tcm-HMPAO brain SPET. Nucl Med Commun 2000;21(1):31—5.
[40] Caca I, Nazaroglu H, Unlu K, Cakmak SS, Ari S, Sakalar YB. Color Doppler imaging of ocular hemodynamic changes in Behçet's disease. Jpn J Ophthalmol 2004;48(2):101—5.
[41] Wakamoto H, Ohta M, Nakano N, Kunisue K. SPECT in focal enterovirus encephalitis: evidence for local cerebral vasculitis. Pediatr Neurol 2000;23(5):429—31.
[42] Nishikawa M, Matsubara T, Yoshitomi T, Ichiyama T, Hayashi T, Furukawa S. Abnormalities of brain perfusion in echovirus type 30 meningitis. J Neurol Sci 2000;179(S1—2):122—6.
[43] Mathieu A, Sanna G, Mameli A, et al. Sustained normalization of cerebral blood-flow after iloprost therapy in a patient with neuropsychiatric systemic lupus erythematosus. Lupus 2002;11(1):52—6.
[44] Liu FY, Huang WS, Kao CH, Yen RF, Wang JJ, Ho ST. Usefulness of Tc-99m ECD brain SPECT to evaluate the effects of methylprednisolone pulse therapy in lupus erythematosus with brain involvement: a preliminary report. Rheumatol Int 2003;23(4):182—5.
[45] Nathan C. Immunology: oxygen and the inflammatory cell. Nature 2003;422(6933):675—6.
[46] Cramer T, Yamanishi Y, Clausen BE, et al. HIF-1α Is Essential for Myeloid Cell-Mediated Inflammation. Cell 2003;112(5):645—57.
[47] Cramer T, Johnson RS. A novel role for the hypoxia inducible transcription factor HIF-1α: critical regulation of inflammatory cell function. Cell Cycle 2003;2(3):192—3.
[48] Ryan HE, Lo J, Johnson RS. HIF-1α is required for solid tumor formation and embryonic vascularization. EMBO J 1998;17(11):3005—15.
[49] Lu G, Qian X, Berezin I, Telford GL, Huizinga JD, Sarna SK. Inflammation modulates in vitro colonic myoelectric and contractile activity and interstitial cells of Cajal. Am J Physiol 1997;273(6 Pt 1):G1233—45.
[50] Ishii Y, Ushida T, Tateishi T, Shimojo H, Miyanaga Y. Effects of different exposures of hyperbaric oxygen on ligament healing in rats. J Orthop Res 2002;20(2):353—6.
[51] Harrison DK, Abbot NC, Carnochan FM, Beck JS, James PB, McCollum PT. Protective regulation of oxygen uptake as a result of reduced oxygen extraction during chronic inflammation. Adv Exp Med Biol 1994;345:789—96.
[52] Van de Veire NR, De Winter O, Philippe J, et al. Maximum oxygen uptake at peak exercise in elderly patients with coronary artery disease and preserved left ventricular function: the role of inflammation on top of tissue Doppler-derived systolic and diastolic function. Am Heart J 2006;152(2):297e.1—7.
[53] Suematsu M, Schmid-Schonbein GW, Chavez-Chavez RH, et al. In vivo visualization of oxidative changes in microvessels during neutrophil activation. Am J Physiol 1993;264(3Pt2):H881—91.
[54] Miljkovic-Lolic M, Silbergleit R, Fiskum G, Rosenthal RE. Neuroprotective effects of hyperbaric oxygen treatment in experimental focal cerebral ischemia are associated with reduced brain leukocyte myeloperoxidase activity. Brain Res 2003;971(1):90—4.
[55] Sheffield PJ, Davis JC. Application of hyperbaric oxygen therapy in a case of prolonged cerebral hypoxia following rapid decompression. Aviat Space Environ Med 1976;47(7):759—62.
[56] Neubauer RA, James P. Cerebral oxygenation and the recoverable brain. Neurol Res 1998;20(Suppl. 1):S33—6.
[57] Al-Waili NS, Butler GJ. Effects of hyperbaric oxygen on inflammatory response to wound and trauma: possible mechanism of action. Scientific World J 2006;6:425—41.
[58] Banasiak KJ, Xia Y, Haddad GG. Mechanisms underlying hypoxia-induced neuronal apoptosis. Prog Neurobiol 2000;62(3):215—49.
[59] Carmeliet P, Dor Y, Herbert JM, et al. Role of HIF-1alpha in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. Nature 1998;394(6692):485—90.
[60] Ostrowski RP, Colohan AR, Zhang JH. Mechanisms of hyperbaric oxygen-induced neuroprotection in a rat model of subarachnoid hemorrhage. J Cereb Blood Flow Metab 2005;25(5):554—71.
[61] Lou M, Chen Y, Ding M, Eschenfelder CC, Deuschl G. Involvement of the mitochondrial ATP-sensitive potassium channel in the neuroprotective effect of hyperbaric oxygenation after cerebral ischemia. Brain Res Bull 2006;69(2):109—16.
[62] Wada K, Miyazawa T, Nomura N, et al. Mn-SOD and Bcl-2 expression after repeated hyperbaric oxygenation. Acta Neurochir Suppl 2000;76:285—90.
[63] Fatemi SH, Stary JM, Halt AR, Realmuto GR. Dysregulation of reelin and Bcl-2 proteins in autistic cerebellum. J Autism Dev Disord 2001;31(6):529—35.
[64] Atochin DN, Fisher D, Demchenko IT, Thom SR. Neutrophil sequestration and the effect of hyperbaric oxygen in a rat model of temporary middle cerebral artery occlusion. Undersea Hyperb Med 2000;27(4):185—90.
[65] Vlodavsky E, Palzur E, Soustiel JF. Hyperbaric oxygen therapy reduces neuroinflammation and expression of matrix meralloproteinase-9 in the rat model of traumatic brain injury. Neuropathol Appl Neurobiol 2006;32(1):40—50.
[66] Thom SR. Effects of hyperoxia on neutrophil adhesion. Undersea Hyperb Med 2004;31(1):123—31.
[67] Zamboni WA, Roth AC, Russell RC, Graham B, Suchy H, Kucan JO. Morphologic analysis of the microcirculation during reperfusion of ischemic skeletal muscle and the effect of hyperbaric oxygen. Plast Reconstr Surg 1993;91(6):1110—23.
[68] Williams RL. Hyperbaric oxygen therapy and the diabetic foot. J Am Podiatr Med Assoc 1997;87(6):279—92.
[69] Efrati S, Bergan J, Fishlev G, Tishler M, Golik A, Gall N. Hyperbaric oxygen therapy for nonhealing vasculitic ulcers. Clin Dermatol, in press. doi:10.1111/j.1365-2230.2006.02240.x.
[70] Stoller KP. Quantification of neurocognitive changes before, during, and after hyperbaric oxygen therapy in a case of fetal alcohol syndrome. Pediatrics 2005;116(4):e586—91.
[71] Montgomery D, Goldberg J, Amar M, et al. Effects of hyperbaric oxygen therapy on children with spastic diplegic

cerebral palsy: a pilot project. Undersea Hyperb Med 1999;26(4):235–42.
[72] Collet JP, Vanasse M, Marois P, et al. Hyperbaric oxygen for children with cerebral palsy: a randomised multicentre trial. Lancet 2001;357(9256):582–6.
[73] Heuser G, Heuser SA, Rodelander D, Aguilera O, Uszler M. Treatment of neurologically impaired adults and children with ''mild'' hyperbaric oxygenation (1.3 ATM and 24% oxygen). In: Joiner JT, editor. Hyperbaric oxygenation for cerebral palsy and the brain-injured child. Flagstaff Arizona: Best Publications; 2002. p. 109–15.
[74] Golden ZL, Neubauer R, Golden CJ, Greene L, Marsh J, Mleko A. Improvement in cerebral metabolism in chronic brain injury after hyperbaric oxygen therapy. Int J Neurosci 2002;112(2):119–31.
[75] Rockswold GL, Ford SE, Anderson DC, Bergman TA, Sherman RE. Results of a prospective randomized trial for the treatment of severely brain-injured patients with hyperbaric oxygen. J Neurosurg 1992;76(6):929–34.
[76] Nighoghossian N, Trouillas P, Adeleine P, Salord F. Hyperbaric oxygen in the treatment of acute ischemic stroke. Stroke 1995;26:1369–72.
[77] Ersoz G, Ocakcioglu B, Bastug M, Ficicilar H, Yavuzer S. Platelet aggregation and release function in hyperbaric oxygenation. Undersea Hyperb Med 1998;25(4): 229–32.
[78] Pardo CA, Vargas DL, Zimmerman AW. Immunity, neuroglia and neuroinflammation in autism. Int Rev Psychiatry 2005;17(6):485–95.
[79] Laurence JA, Fatemi SH. Glial fibrillary acidic protein is elevated in superior frontal, parietal and cerebellar cortices of autistic subjects. Cerebellum 2005;4(3): 206–10.
[80] Weizman A, Wiezman R, Szekely GA, Wijsenbeek H, Livni E. Abnormal immune response to brain tissue antigen in the syndrome of autism. Am J Psychiatry 1982;139(11): 1462–5.
[81] Ahlsen G, Rosengren L, Belfrage M, et al. Glial fibrillary acidic protein in the cerebrospinal fluid of children with autism and other neuropsychiatric disorders. Biol Psychiatry 1993;33(10):734–43.
[82] Singh VK, Warren R, Averett R, Ghaziuddin M. Circulating autoantibodies to neuronal and glial filament proteins in autism. Pediatr Neurol 1997;17(1):88–90.
[83] Singer HS, Morris CM, Williams PN, Yoon DY, Hong JJ, Zimmerman AW. Antibrain antibodies in children with autism and their unaffected siblings. J Neuroimmunol 2006;178(1–2):149–55.
[84] Connolly AM, Chez MG, Pestronk A, Arnold ST, Mehta S, Deuel RK. Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders. J Pediatr 1999;134(5):607–13.
[85] Vojdani A, Campbell AW, Anyanwu E, Kashanian A, Bock K, Vojdani E. Antibodies to neuron-specific antigens in children with autism: possible cross-reaction with encephalitogenic proteins from milk, Chlamydia pneumoniae and Streptococcus group A. J Neuroimmunol 2002;129(1–2): 168–77.
[86] Vojdani A, O'Bryan T, Green JA, et al. Immune response to dietary proteins, gliadin and cerebellar peptides in children with autism. Nutr Neurosci 2004;7(3):151–61.
[87] Singh VK, Lin SX, Newell E, Nelson C. Abnormal measles-mump-rubella antibodies and CNS autoimmunity in children with autism. J Biomed Sci 2002;9(4):359–64.
[88] Singh VK, Warren RP, Odell JD, Warren WL, Cole P. Antibodies to myelin basic protein in children with autistic behavior. Brain Behav Immun 1993;7(1):97–103.
[89] Singh VK, Rivas WH. Prevalence of serum antibodies to caudate nucleus in autistic children. Neurosci Lett 2004;355(1–2):53–6.
[90] Connolly AM, Chez M, Streif EM, et al. Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic disorders, Landau-Kleffner syndrome, and epilepsy. Biol Psychiatry 2006;59(4): 354–63.
[91] Dalton P, Deacon R, Blamire A, et al. Maternal neuronal antibodies associated with autism and a language disorder. Ann Neurol 2003;53(4):533–7.
[92] Wakefield AJ, Ashwood P, Limb K, Anthony A. The significance of ileo-colonic lymphoid nodular hyperplasia in children with autistic spectrum disorder. Eur J Gastroenterol Hepatol 2005;17(8):827–36.
[93] Uhlmann V, Martin CM, Sheils O, et al. Potential viral pathogenic mechanism for new variant inflammatory bowel disease. J Clin Pathol: Mol Pathol 2002;55(2): 84–90.
[94] Furlano RI, Anthony A, Day R, et al. Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. J Pediatr 2001;138(3):366–72.
[95] Balzola F, Barbon V, Repici A, et al. Panenteric IBD-like disease in a patient with regressive autism shown for the first time by the wireless capsule enteroscopy: another piece in the jigsaw of this gut-brain syndrome? Am J Gastroenterol 2005;100(4):979–81.
[96] Torrente F, Ashwood P, Day R, et al. Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism. Mol Psychiatry 2002;7(4):375–82.
[97] Ashwood P, Anthony A, Torrente F, Wakefield AJ. Spontaneous mucosal lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms: mucosal immune activation and reduced counter regulatory interleukin-10. J Clin Immunol 2004;24(6):664–73.
[98] Ashwood P, Anthony A, Pellicer AA, Torrente F, Walker-Smith JA, Wakefield AJ. Intestinal lymphocyte populations in children with regressive autism: evidence for extensive mucosal immunopathology. J Clin Immunol 2003;23(6): 504–17.
[99] Vojdani A, Pangborn JB, Vojdani E, Cooper EL. Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism. Int J Immunopathol Pharmacol 2003;16(3):189–99.
[100] Jyonouchi H, Sun S, Le H. Proinflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression. J Neuroimmunol 2001;120(1–2):170–9.
[101] Becker KG, Freidlin B, Simon RM. Comparative genomics of autism, Tourette syndrome and autoimmune/inflammatory disorders. http://www.grc.nia.nih.gov/branches/rrb/dna/pubs/cgoatad.pdf. April 23, 2003 [accessed 9.26.06].
[102] Wakefield AJ, Puleston JM, Montgomery SM, Anthony A, O'Leary JJ, Murch SH. Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. Aliment Pharmacol Ther 2002;16(4):663–74.
[103] Shenoy S, Arnold S, Chatila T. Response to steroid therapy in autism secondary to autoimmune lymphoproliferative syndrome. J Pediatr 2000;136(5):682–7.
[104] Stefanatos GA, Grover W, Geller E. Case study: corticosteroid treatment of language regression in pervasive developmental disorder. J Am Acad Child Adolesc Psychiatry 1995;34(8):1107–11.

[105] Akin ML, Gulluoglu BM, Uluutku H, et al. Hyperbaric oxygen improves healing in experimental rat colitis. Undersea Hyperb Med 2002;29(4):279–85.
[106] Luongo C, Imperatore F, Cuzzocrea S, et al. Effects of hyperbaric oxygen exposure on a zymosan-induced shock model. Crit Care Med 1998;26(12):1972–6.
[107] Sumen G, Cimsit M, Eroglu L. Hyperbaric oxygen treatment reduces carrageenan-induced acute inflammation in rats. Eur J Pharmacol 2001;431(2):265–8.
[108] Weisz G, Lavy A, Adir Y, et al. Modification of in vivo and in vitro TNF-alpha, IL-1, and IL-6 secretion by circulating monocytes during hyperbaric oxygen treatment in patients with perianal Crohn's disease. J Clin Immunol 1997;17(2): 154–9.
[109] Yang ZJ, Bosco G, Montante A, Ou XI, Camporesi EM. Hyperbaric oxygen reduces intestinal ischemia-reperfusion-induced TNF-alpha production and lung neutrophil sequestration. Eur J Appl Physiol 2001;85(1–2):96–103.
[110] Benson RM, Minter LM, Osborne BA, Granowitz EV. Hyperbaric oxygen inhibits stimulus-induced proinflammatory cytokine synthesis by human blood-derived monocyte-macrophages. Clin Exp Immunol 2003;134(1): 57–62.
[111] Yang Z, Nandi J, Wang J, et al. Hyperbaric oxygenation ameliorates indomethacin-induced enteropathy in rats by Modulating TNF-alpha and IL-1beta production. Dig Dis Sci 2006;51(8):1426–33.
[112] Inamoto Y, Okuno F, Saito K, et al. Effect of hyperbaric oxygenation on macrophage function in mice. Biochem Biophys Res Commun 1991;179(2):886–91.
[113] Buras JA, Holt D, Orlow D, Belikoff B, Pavlides S, Reenstra WR. Hyperbaric oxygen protects from sepsis mortality via an interleukin-10-dependent mechanism. Crit Care Med 2006;34(10):2624–9.
[114] Wilson HD, Wilson JR, Fuchs PN. Hyperbaric oxygen treatment decreases inflammation and mechanical hypersensitivity in an animal model of inflammatory pain. Brain Res 2006;1098(1):126–8.
[115] Warren J, Sacksteder MR, Thuning CA. Therapeutic effect of prolonged hyperbaric oxygen in adjuvant arthritis of the rat. Arthritis Rheum 1979;22(4):334–9.
[116] Tokar B, Gundogan AH, Ilhan H, Bildirici K, Gultepe M, Elbuken E. The effects of hyperbaric oxygen treatment on the inflammatory changes caused by intraperitoneal meconium. Pediatr Surg Int 2003;19(9–10):673–6.
[117] Rachmilewitz D, Karmeli F, Okon E, Rubenstein I, Better OS. Hyperbaric oxygen: a novel modality to ameliorate experimental colitis. Gut 1998;43(4):512–8.
[118] Gulec B, Yasar M, Yildiz S, et al. Effect of hyperbaric oxygen on experimental acute distal colitis. Physiol Res 2004;53(5):493–9.
[119] Gorgulu S, Yagci G, Kaymakcioglu N, et al. Hyperbaric oxygen enhances the efficiency of 5-aminosalicylic acid in acetic acid-induced colitis in rats. Dig Dis Sci 2006;51(3): 480–7.
[120] Takeshima F, Makiyama K, Doi T. Hyperbaric oxygen as adjunct therapy for Crohn's intractable enteric ulcer. Am J Gastroenterol 1999;94(11):3374–5.
[121] Colombel JF, Mathieu D, Bouault JM, et al. Hyperbaric oxygenation in severe perineal Crohn's disease. Dis Colon Rectum 1995;38(6):609–14.
[122] Nelson Jr EW, Bright DE, Villar LF. Closure of refractory perineal Crohn's lesion: integration of hyperbaric oxygen into case management. Dig Dis Sci 1990;35(12):1561–5.
[123] Lavy A, Weisz G, Adir Y, Ramon Y, Melamed Y, Eidelman S. Hyperbaric oxygen for perianal Crohn's disease. J Clin Gastroenterol 1994;19(3):202–5.
[124] Brady 3rd CE, Cooley BJ, Davis JC. Healing of severe perineal and cutaneous Crohn's disease with hyperbaric oxygen. Gastroenterology 1989;97(3):756–60.
[125] Buchman AL, Fife C, Torres C, Smith L, Aristizibal J. Hyperbaric oxygen therapy for severe ulcerative colitis. J Clin Gastroenterol 2001;33(4):337–9.
[126] Gurbuz AK, Elbuken E, Yazgan Y, Yildiz S. A different therapeutic approach in patients with severe ulcerative colitis: hyperbaric oxygen treatment. South Med J 2003;96(6):632–3.
[127] Shiratsuch H, Basson MD. Differential regulation of monocyte/macrophage cytokine production by pressure. Am J Surg 2005;190(5):757–62.
[128] Granowitz EV, Skulsky EJ, Benson RM, et al. Exposure to increased pressure or hyperbaric oxygen suppresses interferon-γ secretion in whole blood cultures of healthy humans. Undersea Hyperb Med 2002;29(3):216–25.
[129] Yin W, Badr AE, Mychaskiw G, Zhang JH. Down regulation of COX-2 is involved in hyperbaric oxygen treatment in a rat transient focal ischemia model. Brain Res 2002;926 (1–2):165–71.
[130] Anderson GD, Hauser SD, McGarity KL, Bremer ME, Isakson PC, Gregory SA. Selective inhibition of cyclooxygenase (COX)-2 reverses inflammation and expression of COX-2 and interleukin 6 in rat adjuvant arthritis. J Clin Invest 1996;97(11):2672–9.
[131] Ashwood P, Van de Water J. A review of autism and the immune response. Clin Dev Immunol 2004;11(2):165–74.
[132] Sweeten TL, Bowyer SL, Posey DJ, Halberstadt GM, McDougle CJ. Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. Pediatrics 2003;112(5):e420.
[133] Valicenti-McDermott M, McVicar K, Rapin I, Wershil BK, Cohen H, Shinnar S. Frequency of gastrointestinal symptoms in children with autistic spectrum disorders and association with family history of autoimmune disease. J Dev Behav Pediatr 2006;27(Suppl. 2):S128–36.
[134] Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. J Child Neurol 1999;14(6):388–94.
[135] Croonenberghs J, Wauters A, Devreese K, et al. Increased serum albumin, gamma globulin, immunoglobulin IgG, and IgG2 and IgG4 in autism. Psychol Med 2002;32(8):1457–63.
[136] Stubbs EG. Autistic children exhibit undetectable hemagglutination-inhibition antibody titers despite previous rubella vaccination. J Autism Child Schizophr 1976;6(3): 269–74.
[137] Evers M, Cunningham-Rundles C, Hollander E. Heat shock protein 90 antibodies in autism. Mol Psychiatry 2002;7(Suppl. 2):S26–8.
[138] Queitsch C, Sangster TA, Lindquist S. Hsp90 as a capacitor of phenotypic variation. Nature 2002;417(6889):618–24.
[139] Gupta S, Aggarwal S, Heads C. Dysregulated immune system in children with autism: beneficial effects of intravenous immune globulin on autistic characteristics. J Autism Dev Disord 1996;26(4):439–52.
[140] Gupta S. Immunological treatments for autism. J Autism Dev Disorder 2000;30(5):475–9.
[141] Plioplys AV. Intravenous immunoglobulin treatment of children with autism. J Child Neurol 1998;13(2):79–82.
[142] Denney DR, Frei BW, Gaffney GR. Lymphocyte subsets and interleukin-2 receptors in autistic children. J Autism Dev Disord 1996;26(1):87–97.
[143] Warren RP, Margaretten NC, Pace NC, Foster A. Immune abnormalities in patients with autism. J Autism Dev Disord 1986;16(2):189–97.

[144] Scifo R, Cioni M, Nicolosi A. Opioid-immune interactions in autism: behavioural and immunological assessment during a double-blind treatment with naltrexone. Ann Ist Super Sanita 1996;32(3):351–9.
[145] Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 2001;19:683–765.
[146] Ngoc PL, Gold DR, Tzianabos AO, Weiss ST, Celedon JC. Cytokines, allergy, and asthma. Curr Opin Allergy Clin Immunol 2005;5(2):161–6.
[147] Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case–control study. Arch Pediatr Adolesc Med 2005;159(2):151–7.
[148] Lucarelli S, Frediani T, Zingoni AM, et al. Food allergy and infantile autism. Panminerva Med 1995;37(3):137–41.
[149] Singh VK. Plasma increase of interleukin-12 and interferon-gamma: Pathological significance in autism. J Neuroimmunol 1996;66(1–2):143–5.
[150] Stubbs G. Interferonemia and autism. J Autism Dev Disord 1995;25(1):71–3.
[151] Croonenberghs J, Bosmans E, Deboutte D, Kenis G, Maes M. Activation of the inflammatory response system in autism. Neuropsychobiology 2002;45(1):1–6.
[152] Messahel S, Pheasant AE, Pall H, Ahmed-Choudhury J, Sungum-Paliwal RS, Vostanis P. Urinary levels of neopterin and biopterin in autism. Neurosci Lett 1998;241(1):17–20.
[153] Gupta S, Aggarwal S, Rashanravan B, Lee T. Th1- and Th2-like cytokines in CD4+ and CD8+ T cells in autism. J Neuroimmunol 1998;85(1):106–9.
[154] Molloy CA, Morrow AL, Meinzen-Derr J, et al. Elevated cytokine levels in children with autism spectrum disorder. J Neuroimmunol 2006;172(1–2):198–205.
[155] Stubbs EG, Crawford ML. Depressed lymphocytes responsiveness in autistic children. J Autism Child Schizophr 1977;7(1):49–55.
[156] Warren RP, Foster A, Margaretten NC. Reduced natural killer cell activity in autism. J Am Acad Child Adolesc Psych 1987;26(3):333–5.
[157] Xu X, Yi H, Kato M, et al. Differential sensitivities to hyperbaric oxygen of lymphocyte subpopulations of normal and autoimmune mice. Immunol Lett 1997;59(2):79–84.
[158] Wallace DJ, Silverman S, Goldstein J, Hughes D. Use of hyperbaric oxygen in rheumatic diseases: case report and critical analysis. Lupus 1995;4(3):172–5.
[159] Lukich VL, Poliakova LV, Sotnikova TI, Belokrinitskii DV. Hyperbaric oxygenation in the comprehensive therapy of patients with rheumatoid arthritis. FIZIOL ZH 1991;37(5):55–60.
[160] Warren J, Sacksteder MR, Thuning CA. Oxygen immunosuppression: modification of experimental allergic encephalomyelitis in rodents. J Immunol 1978;121(1):315–20.
[161] Erdmann D, Roth AC, Hussmann J, et al. Skin allograft rejection and hyperbaric oxygen treatment in immune-histoincompatible mice. Undersea Hyperb Med 1995;22(4):395–9.
[162] Saito K, Tanaka Y, Ota T, Eto S, Yamashita U. Suppressive effect of hyperbaric oxygenation on immune responses of normal and autoimmune mice. Clin Exp Immunol 1991;86(2):322–7.
[163] Chen SY, Chen YC, Wang JK, et al. Early hyperbaric oxygen therapy attenuates disease severity in lupus-prone autoimmune (NZB X NZW) F1 mice. Clin Immunol 2003;108(2):103–10.
[164] Olszanski R, Pachut M, Sicko Z, Sztaba-Kania M, Wilkowska A. Efficacy of hyperbaric oxygenation in atopic dermatitis. Bull Inst Marit Trop Med Gdynia 1992;43(1–4):79–82.
[165] Nyland H, Naess A, Eidsvik S, Glette J, Matre R, Hordnes C. Effect of hyperbaric oxygen treatment on immunological parameters in multiple sclerosis. Acta Neurol Scand 1989;79(4):306–10.
[166] Lee AK, Hester RB, Coggin JH, Gottlieb SF. Increased oxygen tensions modulate the cellular composition of the adaptive immune system in BALB/c mice. Cancer Biother 1993;8(3):241–52.
[167] Lee AK, Hester RB, Coggin JH, Gottlieb SF. Increased oxygen tensions influence subset composition of the cellular immune system in aged mice. Cancer Biother 1994;9(1):39–54.
[168] Thom SR, Bhopale V, Fisher D, Manevich Y, Huang PL, Buerk DG. Stimulation of nitric oxide synthase in cerebral cortex due to elevated partial pressures of oxygen: an oxidative stress response. J Neurobiol 2002;51(2):85–100.
[169] van den Blink B, van der Kleij AJ, Versteeg HH, Peppelenbosch MP. Immunomodulatory effect of oxygen and pressure. Comp Biochem Physiol A Mol Integr Physiol 2002;132(1):193–7.
[170] James SJ, Cutler P, Melnyk S, et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr 2004;80(6):1611–7.
[171] James SJ, Melnyk S, Jernigan S, et al. Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism. Am J Med Genet Part B, in press. doi:10.1002/ajmg.b.30366.
[172] Sogut S, Zoroglu SS, Ozyurt H, et al. Changes in nitric oxide levels and antioxidant enzyme activities may have a role in the pathophysiological mechanisms involved in autism. Clin Chim Acta 2003;331(1–2):111–7.
[173] McGinnis WR. Oxidative stress in autism. Altern Ther Health Med 2004;10(6):22–36.
[174] Zoroglu SS, Armutcu F, Ozen S, et al. Increased oxidative stress and altered activities of erythrocyte free radical scavenging enzymes in autism. Eur Arch Psychiatry Clin Neurosci 2004;254(3):143–7.
[175] Chauhan A, Chauhan V, Brown WT, Cohen I. Oxidative stress in autism: increased lipid peroxidation and reduced serum levels of ceruloplasmin and transferrin – the antioxidant proteins. Life Sci 2004;75(21):2539–49.
[176] Yorbik O, Sayal A, Akay C, Akbiyik DI, Sohmen T. Investigation of antioxidant enzymes in children with autistic disorder. Prostaglandins Leukot Essent Fatty Acids 2002;67(5):341–3.
[177] D'Amelio M, Ricci I, Sacco R, et al. Paraoxonase gene variants are associated with autism in North America, but not in Italy: possible regional specificity in gene-environment interactions. Mol Psychiatry 2005;10(11):1006–16.
[178] Purcell AE, Jeon OH, Zimmerman AW, Blue ME, Pevsner J. Postmortem brain abnormalities of the glutamate neurotransmitter system in autism. Neurology 2001;57(9):1618–28.
[179] Yorbik O, Akay C, Sayal A, Cansever A, Sohmen T, Cavdar AO. Zinc status in autistic children. J Trace Elem Exp Med 2004;17(2):101–7.
[180] Adams JB, Holloway C. Pilot study of a moderate dose multivitamin/mineral supplement for children with autistic spectrum disorder. J Altern Complement Med 2004;10(6):1033–9.
[181] Dolske MC, Spollen J, McKay S, Lancashire E, Tolbert L. A preliminary trial of ascorbic acid as supplemental therapy

for autism. Prog Neuropsychopharmacol Biol Psychiatry 1993;17(5):765—74.
[182] Alleva R, Nasole E, Di Donato F, Borghi B, Neuzil J, Tomasetti M. alpha-Lipoic acid supplementation inhibits oxidative damage, accelerating chronic wound healing in patients undergoing hyperbaric oxygen therapy. Biochem Biophys Res Commun 2005;333(2):404—10.
[183] Wada K, Miyazawa T, Nomura N, Tsuzuki N, Nawashiro H, Shima K. Preferential conditions for and possible mechanisms of induction of ischemic tolerance by repeated hyperbaric oxygenation in gerbil hippocampus. Neurosurgery 2001;49(1):160—7.
[184] Yatsuzuka H. Effects of hyperbaric oxygen therapy on ischemic brain injury in dogs. Masui 1991;40(2):208—23.
[185] Ozden TA, Uzun H, Bohloli M, et al. The effects of hyperbaric oxygen treatment on oxidative and antioxidants levels during liver regeneration in rats. Tohoku J Exp Med 2004;203(4):253—65.
[186] Yasar M, Yildiz S, Mas R, et al. The effect of hyperbaric oxygen treatment on oxidative stress in experimental acute necrotizing pancreatitis. Physiol Res 2003;52(1): 111—6.
[187] Kudchodkar BJ, Wilson J, Lacko A, Dory L. Hyperbaric oxygen reduces the progression and accelerates the regression of atherosclerosis in rabbits. Arterioscler Thromb Vasc Biol 2000;20(6):1637—43.
[188] Gregorevic P, Lynch GS, Williams DA. Hyperbaric oxygen modulates antioxidant enzyme activity in rat skeletal muscles. Eur J Appl Physiol 2001;86(1):24—7.
[189] Nie H, Xiong L, Lao N, Chen S, Xu N, Zhu Z. Hyperbaric oxygen preconditioning induces tolerance against spinal cord ischemia by upregulation of antioxidant enzymes in rabbits. J Cereb Blood Flow Metab 2006;26(5):666—74.
[190] Sharifi M, Fares W, Abdel-Karim I, et al. Usefulness of hyperbaric oxygen therapy to inhibit restenosis after percutaneous coronary intervention for acute myocardial infarction or unstable angina pectoris. Am J Cardiol 2004;93(12):1533—5.
[191] Speit G, Dennog C, Eichhorn U, Rothfuss A, Kaina B. Induction of heme oxygenase-1 and adaptive protection against the induction of DNA damage after hyperbaric oxygen treatment. Carcinogenesis 2000;21(10):1795—9.
[192] Rothfuss A, Radermacher P, Speit G. Involvement of heme-oxygenase-1 (HO-1) in the adaptive protection of human lymphocytes after hyperbaric oxygen (HBO) treatment. Carcinogenesis 2001;22(12):1979—85.
[193] Rothfuss A, Speit G. Investigations on the mechanism of hyperbaric oxygen (HBO)-induced adaptive protection against oxidative stress. Mutat Res 2002;508(1—2): 157—65.
[194] Dennog C, Radermacher P, Barnett YA, Speit G. Antioxidant status in humans after exposure to hyperbaric oxygen. Mutat Res 1999;428(1—2):83—9.
[195] Shyu WC, Lin SZ, Saeki K, et al. Hyperbaric oxygen enhances the expression of prion protein and heat shock protein 70 in a mouse neuroblastoma cell line. Cell Mol Neurobiol 2004;24(2):257—68.
[196] Ostrowski RP, Tang J, Zhang JH. Hyperbaric oxygen suppresses NADPH oxidase in a rat subarachnoid hemorrhage model. Stroke 2006;37(5):1314—8.
[197] Moak SA, Greenwald RA. Enhancement of rat serum ceruloplasmin levels by exposure to hyperoxia. Proc Soc Exp Biol Med 1984;177(1):97—103.
[198] Pasca SP, Nemes B, Vlase L, et al. High levels of homocysteine and low serum paraoxonase 1 arylesterase activity in children with autism. Life Sci 2006;78(19): 2244—8.
[199] Lombard J. Autism: a mitochondrial disorder? Med Hypotheses 1998;50(6):497—500.
[200] Filipek PA, Juranek J, Smith M, et al. Mitochondrial dysfunction in autistic patients with 15q inverted duplication. Ann Neurol 2003;53(6):801—4.
[201] Poling JS, Frye RE, Shoffner J, Zimmerman AW. Developmental regression and mitochondrial dysfunction in a child with autism. J Child Neurol 2006;21(2):170—2.
[202] Clark-Taylor T, Clark-Taylor BE. Is autism a disorder of fatty acid metabolism? Possible dysfunction of mitochondrial β-oxidation by long chain acyl-CoA dehydrogenase. Med Hypotheses 2004;62(6):970—5.
[203] Fillano JJ, Goldenthal MJ, Rhodes CH, Marin-Garcia J. Mitochondrial dysfunction in patients with hypotonia, epilepsy, autism, and developmental delay: HEADD syndrome. J Child Neurol 2002;17(6):435—9.
[204] Filipek PA, Juranek J, Nguyen MT, Cummings C, Gargus JJ. Relative carnitine deficiency in autism. J Autism Dev Disord 2004;34(6):615—23.
[205] Graf WD, Marin-Garcia J, Gao HG, et al. Autism associated with the mitochondrial DNA G8363A transfer RNA(Lys) mutation. J Child Neurol 2000;15(6):357—61.
[206] Ramoz N, Reichert JG, Smith CJ, et al. Linkage and association of the mitochondrial aspartate/glutamate carrier SLC25A12 gene with autism. Am J Psychiatry 2004;161(4):662—9.
[207] Segurado R, Conroy J, Meally E, Fitzgerald M, Gill M, Gallagher L. Confirmation of association between autism and the mitochondrial aspartate/glutamate carrier SLC25A12 gene on chromosome 2q31. Am J Psychiatry 2005;162(11):2182—4.
[208] Pons R, Andreu AL, Checcarelli N, et al. Mitochondrial DNA abnormalities and autistic spectrum disorders. J Pediatr 2004;144(1):81—5.
[209] Lerman-Sagie T, Leshinsky-Silver E, Watemberg N, Lev D. Should autistic children be evaluated for mitochondrial disorders? J Child Neurol 2004;19(5):379—81.
[210] Oliveira G, Diogo L, Grazina M, et al. Mitochondrial dysfunction in autism spectrum disorders: a population-based study. Dev Med Child Neurol 2005;47(3): 185—99.
[211] Kriaucionis S, Paterson A, Curtis J, Guy J, MacLeod N, Bird A. Gene expression analysis exposes mitochondrial abnormalities in a mouse model of Rett Syndrome. Mol Cell Biol 2006;26(13):5033—42.
[212] Magalhães J, Ascensão A, Soares JMC, et al. Acute and severe hypobaric hypoxia increases oxidative stress and impairs mitochondrial function in mouse skeletal muscle. J Appl Physiol 2005;99:1247—53.
[213] Lane N. Oxygen: the molecule that made the world. Oxford University Press; 2002. p. 166—7.
[214] Daugherty WP, Levasseur JE, Sun D, Rockswold GL, Bullock MR. Effects of hyperbaric oxygen therapy on cerebral oxygenation and mitochondrial function following moderate lateral fluid-percussion injury in rats. J Neurosurg 2004;101(3):499—504.
[215] Dave KR, Prado R, Busto R, et al. Hyperbaric oxygen therapy protects against mitochondrial dysfunction and delays onset of motor neuron disease in Wobbler mice. Neuroscience 2003;120(1):113—20.
[216] Boveris A, Chance B. The mitochondrial generation of hydrogen peroxide: general properties and effect of hyperbaric oxygen. Biochem J 1973;134(3):707—16.
[217] Gosalvez M, Castillo Olivares J, De Miguel E, Blanco M, Figuera D. Mitochondrial respiration and oxidative phosphorylation during hypothermic hyperbaric hepatic preservation. J Surg Res 1973;15(5):313—8.

[218] Bar-Sagie D, Mayevsky A, Bartoov B. Effects of hyperbaric oxygenation on spermatozoan motility driven by mitochondrial respiration. J Appl Physiol 1981;50(3):531–7.
[219] Gutsaeva DR, Suliman HB, Carraway MS, Demchenko IT, Piantadosi CA. Oxygen-induced mitochondrial biogenesis in the rat hippocampus. Neuroscience 2006;137(2): 493–504.
[220] Chugani DC, Muzik O, Behen M, et al. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. Ann Neurol 1999;45(3):287–95.
[221] Connors SL, Matteson KJ, Sega GA, Lozzio CB, Carroll RC, Zimmerman AW. Plasma serotonin in autism. Pediatr Neurol 2006;35:182–6.
[222] Croonenberghs J, Delmeire L, Verkerk R, et al. Peripheral markers of serotonergic and noradrenergic function in post-pubertal, caucasian males with autistic disorder. Neuropsychopharmacology 2000;22(3):275–83.
[223] McDougle CJ, Naylor ST, Cohen DJ, Aghajanian GK, Heninger GR, Price LH. Effects of tryptophan depletion in drug-free adults with autistic disorder. Arch Gen Psychiatry 1996;53(11):993–1000.
[224] Todd RD, Ciaranello RD. Demonstration of inter- and intraspecies differences in serotonin binding sites by antibodies from an autistic child. Proc Natl Acad Sci, USA 1985;82(2):612–6.
[225] Singh VK, Singh EA, Warren RP. Hyperserotoninemia and serotonin receptor antibodies in children with autism but not mental retardation. Biol Psychiatry 1997;41(6):753–5.
[226] McDougle CJ, Naylor ST, Cohen DJ, Volkmar FR, Heninger GR, Price LH. A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. Arch Gen Psychiatry 1996;53(11):1001–8.
[227] Hollander E, Phillips A, Chaplin W, et al. A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism. Neuropsychopharmacology 2005;30(3):582–9.
[228] Owley T, Walton L, Salt J, et al. An open-label trial of escitalopram in pervasive developmental disorders. J Am Acad Child Adolesc Psychiatry 2005;44(4):343–8.
[229] Gillberg C, Svennerholm L. CSF monoamines in autistic syndromes and other pervasive developmental disorders of early childhood. Br J Psychiatry 1987;151:89–94.
[230] Young JG, Kavanagh ME, Anderson GM, Shaywitz BA, Cohen DJ. Clinical neurochemistry of autism and associated disorders. J Autism Dev Disord 1982;12(2):147–65.
[231] Ernst M, Magee HJ, Gonzalez NM, Locascio JJ, Rosenberg CR, Campbell M. Pimozide in autistic children. Psychopharmacol Bull 1992;28(2):187–91.
[232] Simon-Soret C, Borenstein P. A trial of bromocriptine in the treatment of infantile autism. Presse Med 1987;16(26):1286 [in French].
[233] Fisher AB, Block ER, Pietra G. Environmental influences on uptake of serotonin and other amines. Environ Health Perspect 1980;35:191–8.
[234] Block ER, Stalcup SA. Depression of serotonin uptake by cultured endothelial cells exposed to high O2 tension. J Appl Physiol 1981;50(6):1212–9.
[235] Sumen-Secgin G, Cimsit M, Ozek M, Eroglu L. Antidepressant-like effect of hyperbaric oxygen treatment in forced-swimming test in rats. Methods Find Exp Clin Pharmacol 2005;27(7):471–4.
[236] Di Sabato F, Rocco M, Martelletti M, Giacovazzo M. Hyperbaric oxygen in chronic cluster headaches: influence on serotonergic pathways. Undersea Hyperb Med 1997;24(2):117–22.
[237] Yang Z, Camporesi C, Yang X, et al. Hyperbaric oxygenation mitigates focal cerebral injury and reduces striatal dopamine release in a rat model of transient middle cerebral artery occlusion. Eur J Appl Physiol 2002;87(2): 101–7.
[238] Adachi YU, Watanabe K, Higuchi H, Satoh T, Vizi ES. Oxygen inhalation enhances striatal dopamine metabolism and monoamineoxidase enzyme inhibition prevents it: a microdialysis study. Eur J Pharmacol 2001;422(1-3):61–8.
[239] Worth J. Paraoxonase polymorphisms and organophosphates. Lancet 2002;360(9335):802–3.
[240] Finegold SM, Molitoris D, Song Y, et al. Gastrointestinal microflora studies in late-onset autism. Clin Infect Dis 2002;35(Suppl. 1):S6–S16.
[241] Song Y, Liu C, Finegold SM. Real-time PCR quantitation of Clostridia in feces of autistic children. Appl Environ Microbiol 2004;70(11):6459–65.
[242] Parracho HM, Bingham MO, Gibson GR, McCartney AL. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. J Med Microbiol 2005;54(Pt 10):987–91.
[243] Bolte ER. Autism and Clostridium tetani. Med Hypotheses 1998;51(2):133–44.
[244] Sandler RH, Finegold SM, Bolte ER, et al. Short-term benefit from oral vancomycin treatment of regressive-onset autism. J Child Neurol 2000;15(7):429–35.
[245] Cave S. Autism in children. Int J Pharmaceut Compd 2001;5(1):18–9.
[246] Knighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic. The effect of inspired oxygen on infection. Arch Surg 1984;119(2):199–204.
[247] Akin ML, Erenoglu C, Dal A, Erdemoglu A, Elbuken E, Batkin A. Hyperbaric oxygen prevents bacterial translocation in rats with obstructive jaundice. Dig Dis Sci 2001;46(8):1657–62.
[248] Gottlieb SF. Effect of hyperbaric oxygen on microorganisms. Annu Rev Microbiol 1971;25:111–52.
[249] Bornside GH, Pakman LM, Ordonez Jr AA. Inhibition of pathogenic enteric bacteria by hyperbaric oxygen: enhanced antibacterial activity in the absence of carbon dioxide. Antimicrob Agents Chemother 1975;7(5):682–7.
[250] Clark JM, Pakman LM. Inhibition of pseudomonas aeruginosa by hyperbaric oxygen: II. Ultrastructural changes. Infect Immun 1971;4(4):488–91.
[251] Bornside GH. Enhancement of antibiotic activity against staphylococcus aureus by exposure to hyperbaric oxygen. Appl Microbiol 1967;15(5):1020–4.
[252] Unsworth IP, Sharp PA. Gas Gangrene. An 11-year review of 73 cases managed with hyperbaric oxygen. Med J Aust 1984;140(5):256–60.
[253] Babior BM. Oxygen-dependent microbial killing by phagocytes: Part I. N Engl J Med 1978;298(12):659–68.
[254] Mader JT, Brown GL, Guckian JC, Wells CH, Reinarz JA. A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis 1980;142(6):915–22.
[255] Arao T, Hara Y, Suzuki Y, Tamura K. Effects of high-pressure gas on yeast growth. Biosci Biotechnol Biochem 2005;69(7):1365–71.
[256] Baugh MA. HIV: reactive oxygen species, enveloped viruses and hyperbaric oxygen. Med Hypotheses 2000;55(3): 232–8.
[257] Reillo MR, Altieri RJ. HIV antiviral effects of hyperbaric oxygen therapy. J Assoc Nurses AIDS Care 1996;7(1):43–5.
[258] Libet B, Siegel BV. Response of a virus-induced leukemia in mice to high oxygen tension. Cancer Res 1962;22(6): 737–42.
[259] Arrais-Silva WW, Collhone MC, Ayres DC, de Souza Souto PC, Giorgio S. Effects of hyperbaric oxygen on Leishmania

amazonensis promastigotes and amastigotes. Parasitol Int 2005;54(1):1—7.
[260] Nataf R, Skorupka C, Amet L, Lam A, Springbett A, Lathe R. Porphyrinuria in childhood autistic disorder: implications for environmental toxicity. Toxicol Appl Pharmacol 2006;214(2):99—108.
[261] Haley BE, Small T. Interview with Dr. Boyd E. Haley: biomarkers supporting mercury toxicity as the major exacerbator of neurological illness, recent evidence via the urinary porphyrin tests. Medical Veritas 2006;3: 921—34.
[262] Thom SR, Bhopale VM, Velazquez OC, Goldstein LJ, Thom LH, Buerk DG. Stem cell mobilization by hyperbaric oxygen. Am J Physiol Heart Circ Physiol 2006;290(4): H1378—86.
[263] Steindler DA, Pincus DW. Stem cells and neuropoiesis in the adult human brain. Lancet 2002;359(9311):1047—54.
[264] Mezey E, Key S, Vogelsang G, Szalayova I, Lange GD, Crain B. Transplanted bone marrow generates new neurons in human brains. Proc Natl Acad Sci USA 2003;100(3): 1364—69.
[265] Cogle CR, Yachnis AT, Laywell ED, et al. Bone marrow transdifferentiation in brain after transplantation: a retrospective study. Lancet 2004;363(9419): 1432—7.
[266] Marois P, Vanasse M. Hyperbaric oxygen therapy and cerebral palsy. Dev Med Child Neurol 2003;45(9): 646—8.
[267] Ashamalla HL, Thom SR, Goldwein JW. Hyperbaric oxygen therapy for the treatment of radiation-induced sequelae in children: the University of Pennsylvania experience. Cancer 1996;77(11):2407—12.
[268] Waalkes P, Fitzpatrick DT, Stankus S, Topolski R. Adjunctive HBO treatment of children with cerebral anoxic injury. Army Med Dept J 2002(April—June):13—21.
[269] Feldmeier JJ, editor. Hyperbaric oxygen 2003: indications and results: the hyperbaric oxygen therapy committee report. Kensington, MD: Undersea and Hyperbaric Medical Society; 2003.
[270] Rossignol DA, Rossignol LW. Hyperbaric oxygen therapy may improve symptoms in autistic children. Med Hypotheses 2006;67(2):216—28.