The immune response in autism: a new frontier for autism research

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Abstract: Autism spectrum disorders (ASD) are part of a broad spectrum of neurodevelopmental disorders known as pervasive developmental disorders, which occur in childhood. They are characterized by impairments in social interaction, verbal and nonverbal communication and the presence of restricted and repetitive stereotyped behaviors. At the present time, the etiology of ASD is largely unknown, but genetic, environmental, immunological, and neurological factors are thought to play a role in the development of ASD. Recently, increasing research has focused on the connections between the immune system and the nervous system, including its possible role in the development of ASD. These neuroimmune interactions begin early during embryogenesis and persist throughout an individual's lifetime, with successful neurodevelopment contingent upon a normal balanced immune response. Immune aberrations consistent with a dysregulated immune response, which so far, have been reported in autistic children, include abnormal or skewed T helper cell type 1 (T_H1)/T_H2 cytokine profiles, decreased lymphocyte numbers, decreased T cell mitogen response, and the imbalance of serum immunoglobulin levels. In addition, autism has been linked with autoimmunity and an association with immune-based genes including human leukocyte antigen (HLA)-DRB1 and complement C4 alleles described. There is potential that such aberrant immune activity during vulnerable and critical periods of neurodevelopment could participate in the generation of neurological dysfunction characteristic of ASD. This review will examine the status of the research linking the immune response with ASD. *J. Leukoc. Biol.* 80: 1–15; 2006.

Key Words: *autism spectrum disorder (ASD) · neurodevelopment · neurokine · immunity · inflammation · cytokines*

INTRODUCTION

Autism spectrum disorders (ASD) are part of a broad spectrum of heterogeneous, neurodevelopmental disorders known as pervasive developmental disorders (PDD), which include autism, Asperger's syndrome, Rett's disorder, and childhood disintegrative disorder. By definition, ASD are characterized by disturbances and impairments in social interaction, verbal and nonverbal communication [1], with onset usually occuring in the first 36 months of childhood. Repetitive and stereotyped behaviors as well as attention and sensory abnormalities are common findings in patients with ASD. Recently, the prevalence of ASD has increased dramatically, which many agree, cannot be attributed completely to improved diagnostic techniques and increased awareness [2]. Reports estimate that ASD affects approximately nine per thousand persons, with a biased male-to-female ratio of three or four to one (3–4:1) [2]. The exact etiology of autism and ASD remains largely unknown, although it is likely to result from a complex combination of environmental, neurological, immunological, and genetic factors. Strong genetic links have been shown for cases with Tuberous sclerosis, Fragile X, neurofibromatosis, and chromosomal abnormalities [3–5]. In addition, environmental factors have been implicated in ASD, such as prenatal rubella infection, anticonvulsants, and antiemetics taken during pregnancy, perinatal hypoxia, postnatal infections such as encephalitis, and in metabolic disorders such as phenylketonuria [6]. Population-based twin studies have demonstrated a higher concordance rate among monozygotic twins compared with dizygotic twins [7]. The concordance rate in monozygotic twins is estimated to be approximately 90% when considering a broader phenotype of ASD, whereas in dizygotic twins, this rate is between 0% and 24% [8, 9]. Furthermore, the familial risk is five to 10 times higher than the general population, such that the ASD rate in siblings of children with ASD has been estimated between 2% and 6% [8]. One of the most confounding aspects of ASD is the phenotypic heterogeneity that encompasses this disease, suggesting that ASD may actually be comprised of several disorders with separate and specific etiologies that all share a common behavioral diagnosis. Due to the heterogeneity inherent in ASD, as many as 15 weak gene interactions are thought to play a role in its etiology [10, 11]. Moreover, as a consequence of the great heterogeneity in ASD, broad ranges of genes have been studied and are thought to have an impact on the development of ASD. These include genes involved in the patterning of the central nervous system (CNS) (including reelin, bcl-2, engrailed-2, Wnt), those that

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govern biochemical pathways (such as serotonin transporter gene variants), those responsible for the development of dendrites and synapses (brain-derived neurotrophic factor (BDNF), MeCP2, neuroligin), and genes associated with the immune system and autoimmune disorders (chromosome 6, human leukocyte antigen (HLA)-DRB1*04, complement component C4B [12, 13]).

There is emerging evidence and growing concern that a dysregulated or abnormal immune response may be involved in some forms of ASD. In general, the links between the immune and neurological systems are becoming increasingly well known. Cytokines and other products of immune activation have widespread effects on neuronal pathways and can alter behaviors such as mood and sleep. Aberrant immune activity during critical periods of brain and neuronal development could potentially play a role in neural dysfunction, typical of autism. Various hypotheses have attempted to link dysfunctional immune activity and autism, such as maternal immune abnormalities during early pregnancy, increased incidence of familial autoimmunity, and childhood vaccinations. Several lines of research have shown abnormalities in the nature, extent, and regulation of the immune response in autism, including a skewed generation of antibodies, cytokines, and immune cells. This is a review of current research linking immune dysfunction to autism.

NEUROLOGICAL ABNORMALITIES IN AUTISM

During neural development, billions of neurons differentiate, migrate, extend axons, and form synapses with their targets in a precisely choreographed sequence of events. In ASD, many neurological abnormalities have been found, which suggest that normal neurodevelopment was disturbed during a critical window of development. There are multiple, critical timepoints in neurodevelopment, including proliferation, migration, differentiation, synaptogenesis, gliogenesis, myelination, and apoptosis of neurons [14]. These periods have considerable overlap which extend from the embryonic stage up until adolescence. It is noteworthy that between 20% and 30% of autism patients undergo a period of autistic regression, in which they experience loss of previously acquired language and behavioral skills [2], a phenomenon that typically occurs after 18–24 months of age. Neurological aberrations found in the brains of patients with autism have been observed through postmortem and neuroimaging magnetic resonance imaging (MRI) studies and suggest many major brain structures may be affected in autism, including cerebellum, cerebral cortex, amygdala, hippocampus, corpus collosum, basal ganglia, and brain stem [15–17]. These aberrations point toward multiple periods of prenatal onset, and in particular, the areas found to be abnormal in ASD are regions of the brain that develop later during neurogenesis. Moreover, brain regions implicated in ASD tend to develop more slowly and are more vulnerable to disturbances. The limbic system, whose components include the amygdala, hippocampus, cingulate gyrus, and septal nuclei, consists of a group of nuclei unified by a common function. The limbic system controls emotional behavior and any changes in body state that accompany this behavior, such as heart rate, blood pressure, and respiration rate. Due to its role in emotion, the limbic system is of major interest in ASD patients; so far, findings include increased cell packing and small neuronal size, indicative of cellular, maturational arrest [15, 18]. Another region of interest, the cerebellum, mainly modulates sensory input and integrates sensory and motor information but can also influence emotional behavior and some cognitive behaviors. Cerebellar abnormalities are also among the most consistent finding in ASD, typified by a paucity of Purkinje and granular cells [17]. Other neurological abnormalities have been described in ASD; for example, ~30% of children with ASD develop epilepsy by adolescence [19], and an additional, significant minority has subclinical epilepsy, as measured by epileptiform encephalogram, especially during sleep [20, 21]. These findings clearly indicate that there are neurological involvements in ASD that affect the development and differentiation of neurons in the brain. Immune dysregulation could result in the generation of localized or systemic inflammation and/or the release of immunomodulatory molecules that could influence, alter, or modify neurodevelopment and/or neuronal function, especially at critical times of development.

IMMUNE SYSTEM ABNORMALITIES IN AUTISM

The interface between the cellular immune system and the nervous system is exceedingly complex with extensive communication occurring between them in health and disease. Immune cells and immune molecules, such as cytokines and chemokines, can modulate brain function, affecting cognitive and emotional processing, and have assorted effects on neuronal tissue, such as the modulation of systemic and CNS responses to infection, injury, and inflammation. The cytokine milieu has been shown to directly affect neural tissue function and development, especially the proinflammatory cytokines such as interleukin (IL)-1, IL-6, IL-12, interferon-γ (IFN-γ), and tumor necrosis factor α (TNF-α), which have pleiotropic effects in the CNS, including an emerging role in neurodevelopment [22]. For example, the inflammatory cytokine IL-6 can induce sleep, and TNF-α can induce anorexia [23, 24]. Indeed, products of immune activation including cytokines may be responsible for many common features of autism, such as mood and sleep disturbances. In turn, neuropeptides, derived from the central and peripheral nervous system, have profound effects on the immune system, including the chemotaxis and recruitment of innate immune cells [25]. A number of findings in the immune system of patients with ASD point toward immune system dysregulation/dysfunction (**Table 1**). Systemic, immunologic aberrations in autism have been linked with autoimmunity, leading to the generation of antibodies that are reactive to CNS proteins and have the potential for neuronal tissue destruction, and second, with dysfunctional immunity, such as abnormalities or deficits of function in immune cell subsets, leading to an inappropriate or ineffective immune response to pathogen challenge [56].

Immune aberrations consistent with a dysregulated immune response reported in autistic children include decreased peripheral lymphocyte numbers [30], decreased response to T

TABLE 1. Immune Findings in ASD

Immune system component	Findings	References
T cells	Decreased response to T cell mitogens	[26–29]
	Reduced frequency of naïve $CD4^+$ T cells	[30–33]
	Partially activated T cells—a finding that is correlated inversely with decreased C4B complement component	[28, 34]
Monocytes/macrophages	Elevated number of circulating monocytes. Increased monocyte number correlates with plasma IFN-γ and neopterin levels	[35]
	Decreased neopterin, quinolinic acid, increased biopterin in the cerebrospinal fluid (CSF) of ASD patients. Potential link with IFN-γ and nitric oxide (NO)	[35, 36]
	Increased neopterin and biopterin in urine analysis	[37]
Natural killer (NK) cells	Altered NK cell frequency. Reduced NK cell lytic activity compared with controls.	[38, 39]
Cytokine profiles	T helper cell type 1 (T_H1)-to-T_H2 ratio imbalanced. Conflicting reports of increased plasma IL-12 and IFN-γ but increased frequency of lymphocyte positive for IL-4 and decreased for IFN-γ and IL-2 in patients with autism compared with controls.	[40, 41]
	Increased monocyte chemoattractant protein 1 (MCP-1) and transforming growth factor-β1 (TGF-β1) in CSF and anterior cingulate gyrus and cerebellum. Increased eotaxin, IL-6, IL-10, and MCP-3 in the anterior cingulate gyrus in ASD brain specimens.	[42]
	Increased TNF-α and IL-12 with decreased IL-10 in ASD patients with gastrointestinal symptoms	[43–46]
Immunoglobulin (Ig)	Skewed serum Ig imbalance; increased IgG, IgG4	[30, 47, 48]
	Autoantibodies to brain and CNS "self" proteins	[49–53]
Autoimmune-based genes	HLA-DRB1*04, complement C4B	[54, 55]

cell mitogens [26, 27], incomplete or partial T cell activation evinced by increased numbers of DR+ T cells without the expression of the IL-2 receptor (IL-2R) [27, 28, 34], dysregulated apoptosis mechanisms [29], and the imbalance of serum Ig levels [30, 57]. In addition, several publications have associated autism with immune-based genes including class II HLA-DRB1 alleles, class III complement C4 alleles, and HLA-extended haplotypes [54, 55]. Further studies support the notion of a skewed T_H1 versus T_H2 cytokine response in individuals with autism [56]. Moreover, evidence for an immune role in autism comes from recent animal models, which indicate that the maternal immune response to infection can influence fetal brain development via increased levels of circulating cytokines [58, 59]. For example, infection of neonatal rats with Borna disease virus (BDV) leads to neuronal death in the hippocampus, cerebellum, and neocortex and a behavioral syndrome that has similarities to autism [60]. These abnormalities are correlated with major alterations of cytokine expression in various brain regions, indicating a likely role of cytokines as mediators of CNS injury in this model [61, 62]. Mouse models of maternal influenza virus infection at mid-gestation have similar neuropathological and behavioral abnormalities in the offspring, which are consistent with those seen in autism and were again suggestive of a strong immune component [59, 63].

CYTOKINES IN AUTISM

In plasma cytokine analysis studies, levels of IL-12 and IFN-γ were increased in autistic children compared with controls, but no changes were seen for IL-6, TNF-α, and IFN-α [40], suggesting a potential T_H1 shift. However, in a previous study, plasma IFN-α was elevated in 10 autistic children when compared with four adult, control subjects [64]. In another study, increased plasma IFN-γ levels were observed in 29 autistic children; it is interesting that these findings correlated positively with the generation of the intercellular CNS messenger and marker of oxidative stress, nitric oxide (NO) [35]. In a separate study, the same authors observed that the macrophage product neopterin was present at high levels in serum samples from individuals with ASD compared with controls, which may reflect increased cell-mediated immune activation and IFN-γ production [36]. These higher IFN-γ and neopterin levels correlated significantly with elevated, circulating numbers of monocytes observed in autistic children [36]. In addition, neopterin and biopterin were shown to be increased in urine samples of ASD children [37]. Recently, Zimmerman et al. [42] found decreased levels of neopterin and quinolinic acid but increased levels of biopterin in the CSF from ASD patients compared with a control group of other neurological diseases. Increased soluble TNF receptor 1 was also observed in ASD serum samples, but cytokine levels were similar in ASD compared with neurological disease controls [42]. Conversely, in cell culture experiments in which intracellular cytokine production was examined in 20 autistic patients compared with 20 aged-matched controls, intracellular production of IL-4 was increased, but IFN-γ and IL-2 were decreased in $CD4^+$ and $CD8^+$ lymphocytes following stimulation [41], suggesting a T_H2 bias. Further in vitro studies of peripheral blood mononuclear cells stimulated with lipopolysaccharide (LPS) have shown an inappropriate innate immune response evinced by amplified production of proinflammatory cytokines TNF-α and IL-1β in ASD patients compared with controls [43]. It is interesting that similar immune dysregulation of increased TNF-α was also found in primary sibling family members of patients with ASD, indicating a possible similar genetic susceptibility in the patients studied. Taken together, these papers, while revealing differences in cytokine levels between ASD and typically developing or neurological disease controls,

highlight the importance of carefully controlled, age-matched studies in the field. Many of these papers compare young ASD patients with adult controls or have a wide range of ages in both controls and case groups. Furthermore, drug treatments prescribed for the symptoms of ASD, including naltrexone, clozapine, risperidone, and tricyclic antidepressants, are all capable of affecting the immune response and cytokine production. Therefore, it cannot be discounted that medication status is a confounding factor in a number of these studies. Moreover, there is an increasing realization that ASD may be comprised of many different phenotypes, which share the same behavioral commonalities. The wide variety of disorders encompassed on the autism spectrum, the degree of severity, and variety of symptoms and co-morbidities often make it difficult to interpret the results of individual studies; however, it would appear that cytokine immune abnormalities are consistently observed in ASD subjects. Overall, these cytokine studies indicate first that a more complex pattern of cytokine production occurs in autism, which is not defined easily by the traditional T_H1/T_H2 paradigm, and second, that the differences between studies may be indicative of a possible patient selection bias and that particular cytokine profiles may potentially reflect different autism behavioral phenotypes.

Cytokines can activate and exert trophic effects on glial cells, which can in turn produce cytokines and chemokines upon such activation. Cell culture studies have shown that neuropoietic cytokines such as IL-6 can have direct effects on neurons and glia, including changes in proliferation, survival, death, neurite outgrowth, and gene expression [65, 66]. As the CNS is populated largely by astroglia and microglial cells, these cytokine-cell interactions are important for neuronal cell functioning and development. Recently, Vargas et al. [67] investigated the presence of immune activation in postmortem brain specimens and CSF from subjects with autism. The authors found active neuroinflammation in the cerebral cortex and cerebellum of brain tissue in autism. This inflammatory process was characterized by a marked cellular activation of microglial and astroglial cells and the presence of an altered cytokine pattern. In addition to activated microglia and astroglia, there was an accumulation of perivascular macrophages and monocytes but an absence of lymphocytes and antibody from the brain specimens, thus pointing toward an innate immune activation. In addition, an enhanced proinflammatory cytokine profile was observed in their CSF. These results suggest that abnormal immune responses in the neuroglia of autistic patients may influence neural function and neural development and that an aberrant immune response may contribute to the development of autism.

In general, the brain and CNS are considered to be protected and isolated from potentially harmful pathogens or agents within the blood, including inflammatory immune cells and proteins, by the blood brain barrier (BBB). Cytokines however, can gain entry into the brain through active transport mechanisms or at circumventricular regions, where the barrier is less controlling [68]. Cytokines and inflammatory mediators may impair BBB function by binding to receptors on the endothelial cells directly. In addition, lymphocytes capable of mediating immune responses and production of cytokines can migrate into the brain from the blood via the CSF to the choroid plexus or from the blood to either the subarachnoid space or parenchymal perivascular space [69]. It is important to note that peripheral cytokines could also directly affect afferent neurons and their functions [70]. Autonomic innervation of immune organs such as the bone marrow, thymus, spleen, and lymph nodes plays a major role in immune system development; equally, the immune response is capable of changing expression and distribution of neural receptors in these organs [71]. Cytokines can affect many behaviors including mood, sleep, appetite and nutritional uptake, exploratory behavior, and social interactions. For example, systemic cytokine administration at therapeutic doses of IFN-α, IL-2, and TNF-α has effects, including mood depression, sleep disorder, impaired cognitive function, decreased exploratory behavior, and changes in motivation [72, 73]. Systemic administration of cytokines can induce increased noradrenergic, dopaminergic, and serotonergic metabolism in the hypothalamus, hippocampus, and nucleus accumbens and modulate synaptic plasticity and thereby alter memory and learning [74].

Together with aberrant cytokine profiles, several studies have shown abnormal levels of blood lymphocytes in autism. Significantly decreased CD4+ T cells have been observed in ASD [30–33]. It is interesting that in mouse models, systemic T cell deficiency leads to learning and memory impairment, which can be ameliorated by T cell replacement [75]. In early studies, decreased responsiveness to T cell mitogens such as phytohemagglutinin has been shown in ASD [26, 27]. Furthermore, an incomplete or partial activation of T cells following stimulation, with an increased expression of HLA-DR+ but not the IL-2Rα chain (CD25), was observed in ASD [28, 29]. NK cells are an important cytotoxic cell subset of the innate immune system and an important cytokine contributor, in particular, IFN-γ. In children with autism and in children with the related disorder Rett syndrome, lower levels of circulating numbers of NK cells are noted compared with controls [38, 39]. Furthermore, decreased NK cell activity demonstrated by target cell lysis has been shown in ASD children [39]. Reduced numbers and activity of NK cells could impair the ability to eradicate or prevent viral infections in these children, which could potentially be damaging to neural tissues during critical windows of CNS development.

Abnormal concentrations of plasma Ig classes have been observed in some ASD children [30, 47, 48]. Moreover, a skewing or imbalance in Ig isotype has been observed, with increased IgG2 and IgG4 present in ASD [47]. Trajkovski et al. [48] showed a similar skewing with skewed IgG1 and IgG4 as well as IgM and IgG levels. These imbalances in Ig levels may be indicative of an underlying autoimmune disorder and/or an aberrant susceptibility to infections.

"NEUROKINES" IN AUTISM

The immune and nervous systems are complex, highly evolved networks, which convey signals through the release of chemical mediators such as neuropeptides and cytokines. In addition, the neuronal synapse and the contact interface between T cells and antigen-presenting cells share a structurally similar architecture. There is continual communication between the im-

mune and nervous systems with many peptides playing a role in both. It has been proposed frequently that abnormalities in the levels and actions of neurotransmitters or neuroactive compounds during early critical windows of neurodevelopment may lead to the onset of autism. Neurotransmitters and neuropeptides not only have important key roles in the development and organization of neural tissue but also influence almost all body functions including the immune system. Numerous transmitter systems, including acetylcholine, serotonin (5-HT), dopamine, epinephrine, norepinephrine, oxytocin, vasopressin, glutamate, and γ-aminobutryic acid (GABA), have been studied in ASD [76]. For example, in postmortem brain specimens obtained from patients with ASD, there was a 48–61% decrease in glutamic acid decarboxylase, an enzyme that converts glutamate into GABA, in the parietal and cerebellar regions of the brain compared with controls [77]. In ASD, this may cause suppression of the GABA-ergic system, resulting in heightened stimulation of the glutamate system, which has been associated with seizures. Second, excitotoxic damage of neurons, possibly resulting from glutamate hyperactivity, may result in abnormal, structural development of the brain [78].

The neurotransmitter serotonin has a wide range of affects on normal physiological functions including circadian rhythyms, appetite, mood, sleep, anxiety, motor activity, and cognition. Serotonin is detected, not only in neurons of the nervous system but also in platelets and lymphocytes of the immune system, where it can exert dose-dependent, suppressive, or proliferative effects. In normal development, serotonin levels are high in the brain up until the age of five and then decrease dramatically [79]. Serotonin levels increase in the hypothalamus, hippocampus, and cortex in response to various cytokines, such as IL-1β, IFN-γ, and TNF-α [74, 80]. Moreover, enzymes that control the conversion of tryptophan into serotonin are under the influence of IFN-γ and IL-1 [81]. Increased serotonin levels in peripheral blood platelets have been described in approximately one-third of patients with autism [82]. It is interesting that selective serotonin (5-HT) reuptake inhibitors have been shown to be beneficial in treating obsessional and repetitive behaviors in some ASD patients [83]. The reason for the difference in serotonin levels is unknown; potentially, it may be a result of the presence of inflammatory cytokines or more likely, to alterations in the platelets themselves, which could modify serotonin uptake [84]. In addition, proinflammatory cytokines IL-1β, IFN-γ, and TNF-α are capable of affecting the activity of the serotonin transporter gene, a potential susceptibility gene in ASD [85, 86].

Cytokines and chemokines play a major role in many stages of development of the CNS and are known to induce the secretion of many neurotransmitters and neuropeptides [22, 87]. In turn, neuropeptides play an important role in all phases of immune system development, often acting as trophic factors, which has led to the hypothesis that neurotrophins (NTs) should be considered as neurokines, as they act in a cytokine-like manner, influencing the development and function of the immune system [88]. Several NTs with potent immunomodulatory actions, including neuropeptide Y, substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), BDNF, and NT-4/5, which have multiple affects on neurodevelopment and neuron maintenance, have been implicated in ASD. Analysis of neonatal blood spots by recycling immunoaffinity chromatography found that BDNF, VIP, CGRP, and NT-4/5 were elevated in ASD compared with typically developing control children but could not be distinguished from those with mental retardation [89]. Brain-derived neurotrophic factor is a major player in neurodevelopment known to regulate neuronal cell survival, growth, plasticity and differentiation, and is now considered to be a growth factor with a wide spectrum of functions outside the nervous system, including modulation and regulation of immune function [90, 91].

Based on animal studies, two structurally related neuropeptides, oxytocin and vasopressin, are believed to play a critical role in the formation of social bonding and recognition and in the processing of social cues [92]. Prairie voles are highly social animals, which form long-lasting pair bonds; in contrast, montane voles are asocial or solitary and do not form pair bonds [93]. Central infusion of oxytocin in female or vasopressin in male prairie voles helps establish partner-bonding; this phenomenon can be blocked using specific antagonists [94, 95]. Furthermore, oxytocin knockout mice have normal, cognitive abilities but diminished social recognition, suggesting a key role of oxytocin in social interactions [96]. In ASD patients, Modahl et al. [97] found significantly lower levels of plasma oxytocin when compared with age-matched, normal subjects. Moreover, this decrease in oxytocin levels may be a result of a reduction in the processing of oxytocin, as increased levels of the pro-hormone form of oxytocin were found in autism patients [98]. In prairie voles, oxytocin and vasopressin receptors are located in the ventral forebrain, whereas the pattern of expression of oxytocin receptors differs in montane voles [92]. It would seem that not only the concentration of neuropeptides but also the pattern of receptor distribution may be important in the establishment of socially rewarding interactions. So far, signature patterns of neuropeptides and neurotransmitters and their respective receptors have yet to be established in ASD. Further studies that address this issue in ASD may provide clues into the development of impaired social interactions that are present in ASD.

It is interesting that Dunzendorfer et al. [25] have suggested a novel role for neuropeptides in the regulation of dendritic cell (DC) migration. They investigated locomotion of mononuclear cell-derived DCs at different maturation stages toward gradients of sensory neuropeptides in vitro. Calcitonin gene-related peptide, VIP, secretin, and secretoneurin induced immature DC chemotaxis comparable with the potency of the chemokine regulated on activation, normal T expressed and secreted (RANTES), whereas substance P and macrophage-inflammatory protein-3β (MIP-3β) stimulated immature cell migration only slightly [25]. Moreover, the neuropeptide VIP synergized with cytokines such as TNF-α in the induction of DC maturation [99]. In the CNS, DCs have been found in normal meninges, the choroid plexus, and CSF and are actively recruited during inflammation, where they may play equal roles in the defense against infections and contribute to the break-down of tolerance to CNS autoantigens [100]. These findings suggest a central role for DC- and neuropeptide-mediated chemotaxis in the control of CNS inflammation and the generation of T cell reactivity against CNS antigens, and present an intriguing concept in the context of autism.

AUTOIMMUNITY AND AUTISM

Autoimmune diseases arise when the immune system is inappropriately directed to recognize and exert an exaggerated response to self components. These include, but are not restricted to, diseases such as myasthenia gravis, multiple sclerosis, systemic lupus erythematosus (SLE), primary biliary cirrhosis, and Graves' thyrotoxicosis. The exact mechanism of autoimmunity in these diseases is not identical, but they all possess autoreactive antibodies and T cells. The presence of antibodies directed against components of the CNS in the sera of autistic children is indicative of an autoimmune process that may be involved in the pathology of some cases of ASD. Autoimmunity was first linked to autism in a study of a child with autism, who had an expansive family history of autoimmune diseases [101]. This study proposed that an inherited risk of autoimmunity could increase the risk of developing autism. A more recent study of family autoimmunity and autism, which investigated the frequency of autoimmune disorders in family members of 61 ASD children and 46 typically developing normal controls, showed the mean number of autoimmune disorders was greater in families with autism children [102]. In most of these cases, the individual with the autoimmune disorder was a first-degree relative (i.e., a sibling or a parent) of the autism child [102]. In a study by Sweeten et al. [103], these findings were replicated in families of PDD probands. However, these studies were based on self-reporting rather than medical records and thus may have a significant margin of reporting error. In a 2005 study by Croen et al. [104], maternal immune abnormalities such as autoimmune diseases, asthma, and allergies during pregnancy were investigated for a link to autism. In contrast to the previous studies, with the exception of Type 1 diabetes and psoriasis, they found no strong evidence linking maternal autoimmune diseases and autism. However, it was found that mothers diagnosed with asthma or allergies during their second trimester were more than twice as likely to have a child with autism [104]. So far, no studies have addressed whether ASD children have an increased frequency of other autoimmune disease, the exception being whether ASD itself could be considered an autoimmune disease. Furthermore, as the majority of autoimmune disorders are manifest between 30 years of age upwards, and on the whole, the ASD cases studied are pediatric cases, it is difficult to determine whether more autoimmune diseases will be observed as the ASD cases mature. In a recent paper, serum from a mother with an autistic child was found to bind to Purkinje cells and other neurons. When injected into gestating mice, these autoantibodies induced behavioral changes including altered exploration, motor coordination, and changes in cerebrallar magnetic resonance spectroscopy in the offspring. In contrast, mice injected with sera from mothers with typically developing children showed no behavioral changes [105]. This study supports the notion that maternal antibodies may influence neurodevelopmental processes in a subset of autism cases.

Various anti-brain antibodies have been found in autistic patients, including autoantibodies to serotonin receptor [20], myelin basic protein (MBP), neuron axon filament protein, cerebellar neurofilaments, nerve growth factor, α-2-adrenergic-binding sites, anti-brain endothelial cell proteins, and antibodies directed against an as-yet unknown brain protein [49–53, 106]. The pathophysiological significance of these antibodies reported in children with autism is uncertain. For example, increased autoantibodies would suggest that there is increased neuronal damage, as is the case in multiple sclerosis, where following demyelination, MBP is unmasked, and there is a subsequent generation of antibodies. However, evidence of demyelination in autism has remained elusive [107]. Glial fibrillary acidic protein (GFAP), measured in the CSF of 47 autistic childen, was elevated significantly compared with 10 age-matched control children, suggesting that gliosis and unspecific brain damage may occur in autism [108]. However, as GFAP correlates strongly with age, most likely as a result of age-dependent expansion of fibrillary astrocytes, caution must be shown in interpreting these data [99]. Needless to say, in the absence of neuronal damage, the presence of serum antibodies to brain tissues may be abnormal and may be detrimental to appropriate development and function of the CNS. In a study by Singh and Rivas [109], antibodies directed to the rat caudate nucleus (the portion of the brain responsible for assembly of peripheral information) were found in 49% of the autism patients evaluated and in none of the control cases.

It is also important to note that for each antibody tested, the number of autistic children showing positivity is far from 100%. The observations of elevated anti-CNS antibodies in autism are at best unconfirmed and in some cases, such as serotonin receptors and MBP, markedly conflicting. Furthermore, it is difficult to determine whether the autoantibodies present in the plasma of patients with autism contribute to the development of the disorder or if they are a consequence of the disease. However, the collective findings of autoimmunity in families and the plethora of anti-brain antibodies suggest that in some patients, autoantibodies that target the CNS may be a pathological or an exacerbating factor in neuronal development in children with ASD. It can be inferred that increased autoimmunity may be confined to a subset of autistic patients. Indeed, large cohort studies with thoroughly defined and specifically phenotyped autistic patient groups and well-matched age and sex controls need to be performed to confirm the potential role of autoantibodies in the pathology of all or subsets of autistic patients. Moreover, the development of an animal model will be crucial to determine the role of autoantibodies in the pathology of autism.

MUCOSAL IMMUNE RESPONSE AND AUSTISM

Gastrointestinal (GI) symptoms have been described in a number of ASD patients, in whom symptoms include abdominal pain, bloating, diarrhea, and constipation [110, 111]. The exact prevelance of GI symptoms in ASD is unknown. Two retrospective studies, which analyzed representative populations of children with autism, reported GI symptoms in ~20% of young children previously diagnosed with autism [112]. In contrast, prospective reports from pediatric gastroenterology and general autism clinics have described GI symptoms in 46–84% of patients with ASD [110]. However, prevalence estimates from

population-based epidemiologic studies are largely lacking. Reported GI abnormalities include low activities of disaccharidase enzymes, defective sulfation of ingested phenolic amines (tylenol), bacterial overgrowth with greater diversity and number of clostridial species, more numerous Paneth cells, increased intestinal permeability, and positive effects on behavioral cognition following dietary intervention [110, 113–116]. Clinical and pathological studies have described an apparently characteristic GI immunopathology in this subset of children with ASD [117, 118], in which chronic, ileo-colonic lymphoid nodular hyperplasia (LNH) and entero-colitis are key features [118]. The mucosal lesion consists of a pan-enteric lymphocytic infiltrate with a variable degree of acute inflammation and eosinophil infiltration [118–120]. Flow cytometric and immunohistochemical analyses of mucosal lymphocyte populations in this ASD subgroup have demonstrated qualitatively consistent abnormalities at different anatomical sites including stomach, duodenum, ileum, and colon [120–122], which indicate a relatively homogenous, mucosal lymphocyte infiltrate. Although LNH is not an uncommon finding in children with allergies or immunodeficiency, there is increased frequency and severity in patients with autism [123]. Indeed, these findings, in particular, LNH and associated colitis, have been described by others as "not normal" [124, 125]. In addition, other findings included a focal deposition of serum IgG from ASD children with GI symptoms, which colocalize with complement C1q on the basolateral enterocyte membrane; these changes were not seen in histologically normal and inflamed mucosa of developmentally normal children or children with cerebral palsy [121]. This focused immune response direct to the epithelia may firstly be indicative of an autoimmune process directed against self-antigen contained within epithelial cells and secondly, is suggestive of an inflammatory process that may perturb the intestinal barrier function in this ASD subgroup. Increased basement membrane thickness and abnormal patterns of epithelial glycosaminoglycans in this ASD subgroup are a further indication of inflammatory degradation, which could contribute to disruption of the intestinal barrier function [120].

Although there is a great deal of speculation, the exact mechanism of how mucosal changes may influence autistic development or behavior is still not clear. It is plausible that these data reflect a primary intestinal immune activation and immunopathology, which leads to heightened, systemic immune activation and results in neuroinflammation. Indeed, in a recent study, the generation of chronic colitis in an animal model through the rectal administration of trinitrobenzene sulfonic acid not only caused GI inflammation but also led to the activation of brain areas that are abnormal in autism, as measured by c-*Fos* expression [126]. In celiac disease, it is recognized that primary mucosal immunopathology, as a result of gliadin intolerance, can produce secondary neurological disease including cerebral inflammation, dementia, cerebellar ataxia, epilepsy, and heterotopic cerebral calcification [127]. Further investigation of gut-brain interactions in this cohort of children with ASD and GI symptoms is necessary to clarify the potential links with the intestinal pathology and the effect on behaviors.

It is interesting that mucosal lymphocytes isolated from the duodenum, ileum, and colon as well as peripheral lymphocytes of ASD patients with GI symptoms showed increased, spontaneous production of proinflammatory, intracellular cytokines, most notably TNF-α, when compared with aged-matched controls, including those with similar symptoms of constipation [44, 45]. These data support the hypothesis that there is mucosal immune dysregulation with a proinflammatory lymphocyte cytokine profile in ASD children. These findings have since been confirmed in peripheral blood, where proinflammatory cytokines were increased upon stimulation with dietary proteins in similarly affected autistic children compared with controls [46]. In some studies, circulating antibodies to food substances, namely the casein and gliadin, have been found [128, 129]. However, these antibodies are also found with similar frequency to that in the general population. Furthermore, antibodies to neuronal-specific antigens in the sera of children with autism could cross-react with dietary peptides, including milk butyrophilin, *Streptococcus* M protein, and *Chlamydia pneumoniae* [129], suggesting that bacterial infections and milk antigens may modulate an autoimmune process in autism.

It may be that antigens in the diet can cross into the mucosa more easily via a disrupted intestinal barrier, where they cause local, inflammatory reactions generating proinflammatory cytokine signals, which interact with afferent neurons. Another possibility is that the failure to detoxify neuroactive antigens from the gut may lead to cognitive impairments. In an open-label trial administration of vancomycin, an antibiotic, which is poorly absorbed, resulted in objective, cognitive improvements in autistic children [130], presumably as a result of treatment of intestinal dysbiosis. However, once administration of vancomycin was ceased, the patients' cognitive functions regressed, suggesting that the initial improvement was a result of beneficial effects on the intestinal pathology [130]. The exacerbation of GI and behavioral symptoms in autism induced by certain foods, particularly those containing gluten and casein, has been shown through dietary intervention and their removal from the diet [131]. Autistic children on gluten and casein-free diets also showed significantly lower eosinophil infiltrate in intestinal biopsies compared with those on a conventional diet [30]. The significance of this finding is still unclear. However, it has been proposed recently that immune responses associated with allergy may contribute to the pathogenesis of autoimmune diseases of the CNS in humans and in animal models [132].

The increased passage of exorphins and/or opioids from the diet such as gliadomorphin and casomorphin into the body, where they may interact with the CNS, could play a role in inducing the behavioral features of autism. Opioid peptides and opioid receptors are important modulators of neural development, influencing migration, proliferation, and differentiation within the CNS [133]. Peripherally, opioid peptides are contained and/or produced by the gut, lung, placenta, testis, lymphoid tissue, and immune cells, but also another important source of opioids is from the diet. The endogenous opiates β, α, and γ endorphins can directly influence the immune response, enhancing generation of cytotoxic T cells and NK cells, and antibody synthesis and act as chemoattractants for monocytes

and neutrophils [134]. The precise mechanisms that underlie the immunosuppressive effects of opioids remain unknown; however, they may operate as cytokines, acting through receptors on peripheral blood and/or glial cells [135]. It has been hypothesized that an excess of opioid peptides will have detrimental effects on brain development and behavior, and that autism may result from abnormal levels or activity of opioid peptides. β-Casemorphine-7, an opioid exclusively of dietary origin, has been shown to be present in patients with psychoses including autism [136]. Indeed, the beneficial effects on autistic behavior following dietary exclusion therapy are thought, in part, to be a result of reduced opioid intake [136, 137]. Furthermore, therapeutic trials using the oral opioid antagonist naltrexone in some patients with ASD have shown improvements in behavioral characteristics such as repetitive stereotypes, hyperactivity, social contact, and self-injurious behavior [138].

ANIMAL MODELS OF AUTISM/AUTISTIC BEHAVIOR

There are an increasing number of hypotheses that try to explain the immune abnormalities discussed in the preceding sections. Some of these include maternal immune defects or infections during pregnancy, congenital viral infections, or xenobiotic-induced abnormalities. The high incidence of autoimmune disorders in first-degree relatives of autistic children suggests the possibility that maternal factors may play a role in the development of autism. Furthermore, as autism is a neurodevelopmental disorder that manifests early in childhood, it is important to investigate prenatal exposures and other health factors present early during CNS development. Maternal viral infections during pregnancy have been implicated in the manifestation of neurological diseases in children, including autism and schizophrenia [59]. Shi et al. [63] found that infection of pregnant mice with the human influenza virus led to offspring with highly abnormal behavioral responses. At midgestation, pregnant mice were infected with a mouse-adapted human influenza virus. The offspring demonstrated defects in prepulse inhibition, an acoustic startle response, also seen in schizophrenia and ASD, when compared with offspring from noninfected, control animals. The offspring of infected mice also exhibited irregularities in exploratory behavior and social interaction [63]. Anatomical findings included thinning of the neocortex and hippocampus, pyramidal cell atrophy, decreased reelin immunoreactivity, and macrocephaly. In addition, prenatal exposure of pregnant mice to influenza led to deleterious effects on the development of brain structure in the progeny [139]. In further experiments, it was seen that administration of polyinosinic:polycytidylic acid (pdy I:C), a synthetic double-stranded RNA able to induce an immune response without viral infection, was sufficient to cause behavioral changes in the offspring in this model [59]. In humans, pregnancy is an overall immunosuppressive state, involving cytokines such as TGF-β [140], which may produce a state in which the pregnant mother is potentially more vulnerable to a number of infections, which could result in an ensuing immune response during a critical window of neurodevelopment and function. Indeed, tentatively, these studies indicate that maternal exposure to viral infection may lead to ASD-like symptoms in animal models.

Several lines of research have suggested that direct viral infection of the fetal CNS during a critical time in development could lead to autism (reviewed in ref. [141]). Congenital cytomegalovirus (CMV), BDV, and congenital rubella and measles virus are examples of such infections that have been linked to autism. A recent retrospective case study of a child with autism found evidence of a congenital CMV infection through dried blood spots taken at birth [142]. In animal models, several studies have shown that neonatal infection with BDV, a persistent, neurotropic RNA virus, leads to ASD-like symptoms, including neuroanatomical, neurochemical, neuroimmune, and behavioral changes [143]. A 2004 study demonstrated that BDV infection could interfere directly with proper neuronal connectivity and function in vitro using a rat model [144]. It is interesting that genetic background effects were seen in the BDV rat model of Pletnikov et al. [145]. Inbred Lewis and Fisher rats, and outbred Sprague-Daley rats were shown to exhibit differential patterns of irregularity dependent on their genetic background, which highlights the importance of the complex interaction of genes on the development of ASD. Congenital rubella has also been related to ASD in a similar manner to CMV and BDV. Fetal infection with rubella has been known to cause miscarriage, stillbirths, and severe birth defects. In the 1970s, several studies demonstrated a correlation between congenital rubella and the development of autism-like behavioral symptoms [146, 147].

Extreme controversy has erupted recently over the possible role of mercury-containing vaccines in the development of ASD. Two different mechanisms have been proposed for the potential role of vaccines in autism. The first suggests that antibodies stimulated by the viral components within the vaccines could potentially cross-react with host tissues and induce autoimmunity. Alternatively, the mercury-containing preservative thimerosal (ethylmercurithiosalicylate), previously found in several vaccines, has been proposed to induce a host response that leads to autism. Organic mercury, such as methyl mercury and ethyl mercury, are potent immunosuppressors, more so than inorganic mercury. Thimerosal is metabolized rapidily to ethyl mercury, and many of its potential effects on the immune system and general health and its toxicology in general are largely unknown and in many quarters, hotly debated. Information about thimerosal has generally been derived as a comparison with methyl mercury, which has been more widely examined as a result of its presence as a common environmental contaminant, primarily through fish consumption. Many hypothesis are based on the assumption that the effects of ethyl mercury and ergo thimerosal on the immune system are similar to those of methyl mercury. One study demonstrated that injection of thimerosal into young SJL mice, a strain that is highly susceptible to the development of autoimmune disorders, caused ASD-like behavioral symptoms, whereas injection into mice, that are less susceptible to autoimmunity (C57BL/6J and BALB/cJ strains) did not cause symptoms [148]. The thimerosal dosing and timing regime were designed to mimic the potential exposure present in the pediatric immunization schedule. These findings suggest that ge-

netic factors, such as a predisposition to autoimmune diseases, may play a role in thimerosal-related neurotoxicity. A population study by Geier and Geier [149] demonstrated evidence for an association between increasing concentrations of thimerosal in vaccines and the occurrence of neurodevelopmental disorders. However, the overwhelming majority of epidemiological population studies indicates there is no established correlation between vaccinations and autism.

Other potential animal models of ASD have been developed that utilize biochemical anomalies, transgenic models, and neural structural defects. For example, the administration of valproic acid to rats prior to the closure of the neural tube results in behavioral abnormalities similar to those seen in autism [150]. In humans, such exposure could arise as a result of the administration of antiseizure medication to pregnant mothers. Experiments where lesions are generated in specific regions of the brain have been performed in order to study the behavioral abnormalities that result from their injury at different time-points during neurodevelopment. Amygdala lesions in primates resulted in social and emotional deficits that were similar to those found in ASD [151]. Similar behavioral abnormalities were observed in rats that had undergone the same procedure [152]. Other examples of ASD models include the Brattleboro rats, which are unable to secrete vasopressin; the disheveled 1 null mouse, which is homozygous for a targeted deletion of the disheveled 1 gene; and oxytocin knockout mice [153–155], which show deficits in social memory and social interaction (i.e., pup separation-distress calling, huddling behaviors, and nest-building). The guinea pigs of Caston and colleagues [156] were thought to be one of the closest animal models to ASD. Naturally occurring cerebellar defects were seen 3 weeks postnatally, including neuronal dropout and decreases in dendritic arborization and slight cell body shrinkage. The neuroanatomical changes were similar to those found in some patients with ASD. In addition, social interaction and performance of motor learning tasks were deficient compared with controls. However, as a result of "reproduction difficulties", this model is no longer available. The complexity of ASD increases the difficulty of obtaining a multilateral animal model that is complete for all the neuroanatomical, genetic, neurochemical, immunological, and behavioral irregularities, which are present in ASD. However, the development of such a model would greatly enhance research into various aspects of the ASD phenotype and may highlight possible clues to the etiology and pathogenesis of ASD.

Nonhuman primates may represent the best animal model of autism in which several complex and sensitive social behaviors can be assessed in particular animals or in mother-infant pairings. However, these experiments require a high level of expertise and are highly expensive and time-consuming, especially when considering the study of neurodevelopment, which may be protracted to last several years. Murine models hold several advantages in the study of neurodevelopment as a result of their significantly increased rate of development and that in general, neurodevelopmental timelines for specific brain regions are comparable with those in humans. However, in murine models, most neurodevelopment is postnatal compared with humans and can make the interpretation of data regarding exposures difficult. The differences in mass/volume of relative structures may also complicate findings (for example, the olfactory system). Moreover, the greatest problem for any animal model is the identification and consistent measurement of measures of key autistic-like phenomena, such as social behavior, repetitive behavior, and restricted interests. At present, the test of a good animal model strongly depends on the further development of standard behavioral measures of social interaction along with measures of repetitive and stereotyped patterns of behavior, which are essential in a valid animal model.

POTENTIAL IMMUNE COMMONALITIES WITH OTHER NEURODEVELOPMENTAL DISORDERS

Numerous recent publications have focused on immune dysfunction and autoimmunity in various neuropsychiatric disorders such as schizophrenia, Gilles de la Tourette's syndrome (TS), pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), obsessive compulsive disorder (OCD), Alzheimer's disease (AD), and Sydenham's Chorea (**Table 2**) [157]. For example, immune dysregulations in schizophrenia have been widely reported and include morphological changes and altered frequency of blood lymphocytes, imbalanced serum Ig, dysregulated or abnormal cytokine levels, and the presence of autoantibodies [158, 159]. In postmortem studies, activated microglia, a sign of immune system

TABLE 2. Potential Shared Immune Commonalities among Different Psychiatric Disorders

	Detection of autoantibodies	Altered levels of antibodies to microbial antigens	Altered cytokine levels	Lymphocyte abnormalities	Innate immune cell dysfunction	Abnormal serum Ig levels
Schizophrenia	Present	Conflicting	Present	Present	Present	Conflicting
Tourette's syndrome	Present	Present	Present	Present	ND	ND
Obsessive-compulsive disorder	Present	Present	Present	ND	ND	ND
PANDAS	Present	ND	ND	ND	ND	ND
Alzheimer's disease	Present	ND	Present	ND	Present	ND
Sydenham's chorea	Present	ND	ND	ND	ND	ND
Autism spectrum disorder (ASD)	Present	Conflicting	Present	Present	Present	Present

Immune findings in schizophrenia, TS, OCD, PANDAS, AD, Sydenham's chorea, and ASD. Published findings related to the category are denoted as "Present," if there is some evidence to show the specific presence or absence of a particular finding. Opposing profiles or observations noted in separate investigations are denoted "Conflicting." ND, Not done. Please note: many of these findings remain controversial and need independent and thorough replication.

activation, in brain specimens has been found in a subset of schizophrenic patients [160, 161]. Approximately 48% of schizophrenia patients are reported to have elevated heat shock protein antibody levels and anti-brain antibodies present in the CSF and serum [162, 163]. In a Korean population study, cytotoxic T lymphocyte antigen-4 (CTLA-4) polymorphisms, a finding associated with autoimmune diseases such as SLE, multiple scleorosis, and type I diabetes mellitus, were reported in patients with schizophrenia [164]. Similar to ASD, cytokine, Ig, and lymphocyte studies have often been inconsistent, in part, as a result of a failure to control for factors such as medication, current clinical status of schizophrenia, substance abuse, or concurrent illness. Most recently, increased IL-6 and IL-8 and abnormal IL-2 levels have been reported in schizophrenia [165, 166]. Between 18% and 29% of patients with schizophrenia have an abnormal BBB [167]. Pre- and postnatal viral infections have been implicated in the etiology of schizophrenia and include infections such as herpes simplex virus, CMV, Epstein-Barr virus, and BDV [168–170]. It is interesting that many of the antipsychotic drugs prescribed to patients with schizophrenia, such as clozapine and haloperidol, although not their primary action, are known to have potent, immunosuppressant effects [171]. The scope and patterns of immune dysfunction in schizophrenia patients strike a familiar note to those seen in ASD. Further studies in both disorders are needed before common immunological phenomena, which may have an impact on the respective disease behaviors, are known. It is contentious but of interest that in recent history, many children were diagnosed with childhood schizophrenia, which if diagnosed today, using modern criteria, would more likely be described as ASD.

Gilles de la Tourette's syndrome is a heterogeneous, neurodevelopmental disorder characterized by motor and vocal tics, which begin in childhood [172]. It is associated with many behavioral and psychiatric disorders, as well as social dysfunction. Obsessive-compulsive symptoms are often a common comorbid disorder in TS, whereas attention deficit/hyperactivity disorder has been reported in an estimated 50% of TS patients [173, 174]. Like ASD, there are a number of suggested genetic causes, and there is also a male-to-female bias [172]. D8/17-specific antibody is a monoclonal antibody made by repeated immunization of mice with isolated B cells isolated from patients with rheumatic fever or rheumatic heart disease, which cross-reacts with myosin and troponin as well as streptococcal M proteins. Elevated D8/17 expression was found on B cells of a subset of patients with tic disorders, although a significant number (39.4%) of subjects had levels comparable with controls [175]. In ASD patients with repetitive behaviors, increased D8/17 expression has also been observed [176]. Elevated levels of markers of cellular immune activation, such as kynurenine and neopterin, have also been observed in TS patients [177]. Recently, increased serum levels of IL-12 and TNF-α were found in patients with TS [178]. In addition, an increased frequency of specific antibodies for neural proteins have recently been observed in a few patients with TS and in their first-degree family members compared with control groups, pointing toward a potential genetic susceptibility [179]. In one proposed model of pathogenesis, molecular mimicry may play a role in TS, exhibiting similarities with Sydenham's chorea [180]. Sydenham's chorea is characterized by involuntary movements, obsessive-compulsive and neuropsychiatric symptoms [181]. Group A streptococcal infection is thought to be responsible for the development of Sydenham's chorea and rheumatic fever, although the pathogenesis is unknown. In genetically susceptible individuals who have group A β-hemolytic streptococci infection, antibodies directed against the streptococci are thought to cross-react with CNS structures, particularly gangliosides, that induce abnormal signal transduction leading to CaM kinase II activation, which could result in neurotransmitter imbalance [182].

Pediatric autoimmune neuropsychiatric disorders associated with striptoeoccal infections (PANDAS) is the term given to the subgroup of patients on the TS and OCD spectrum, who acquire OCD and/or tic disorders following streptococcal infection but do not meet the criteria for Sydenham's chorea [183]. Unlike OCD alone, PANDAS has a relapsing-remitting disease course [184]. Rates of tic disorders and OCD in first degree relatives of patients with PANDAS are increased compared with individuals in the general population [185]. Effectiveness of immunotherapy, such as plasmapheresis, has been shown to alleviate symptom severity in some patients [186]. Enlargement of the basal ganglia, caudate, putamen, and globus pallidus has been reported in functional MRI study of PANDAS patients, as have serum autoantibodies that react with the basal ganglia [187], and may pertain to the presence of inflammation in these regions. The effect of antibiotic prophylaxis as a means of preventing the exacerbations of obsessive-compulsive traits and tic disorders in PANDAS patients was found to be effective in preventing post-streptococcal neuropsychiatric episodes [188]. PANDAS is still a controversial concept, in part, as a result of the lack of strictly defined classification criteria of symptoms and in part, as a result of the temporal connection between streptococcal infection and neuropsychiatric symptoms, which can be as long as six months [189].

It is estimated that as many as 75% of SLE patients have neurological complications [190]. A study by Kowal and colleagues [191] showed that neuropsychiatric symptoms of lupus are caused by anti-DNA antibodies, which are able to cross-react with N-methyl-D-aspartate (glutamate) receptors, resulting in excitotoxic death of neurons. These autoantibodies have recently been shown to cause neuronal death and affect cognitive processes in an animal model [191]. This study showed that systemic immune dysregulation can lead to brain effects in the presence of a BBB made permeable with LPS, which suggests that BBB abrogation by infection, stress, or disease-related factors may also be pivotal in SLE. It is notable that an increase in circulating immune complexes, capable of abrogating the BBB, has also been demonstrated in SLE [192].

In Alzheimer's disease, β-amyloid is believed to inflict vascular damage to the BBB, facilitating the entry of autoantibodies, which cause antibody-mediated neuronal death and memory impairment [193]. In normal controls, the entry into the CNS of these naturally occurring antibodies is prevented by presence of an intact BBB. Vascular changes related with aging (artherosclerosis, hypertension) are risk factors for AD [194, 195]. In addition to amyloid plaques that can be detected in the cerebral cortex, deposits are found in capillaries, meninges, and choroid plexus and are often associated with

endothelial damage and basement membrane defects, all of which may affect BBB permeability [196, 197]. Reactive microglia associated with plaques are found in AD brains [198]. The dysfunction of the BBB does not always lead to AD; the avidity and affinity of the antibody must be taken into account, as should the cytokine environment, which can affect the permeability and adhesion molecule properties of the BBB [199].

CONCLUSION

The ASD are an extremely heterogenous group of disorders with multiple phenotypes and subgroups that share behavioral commanalities. This inherent complexity has made deciphering the etiology of the broad spectrum of ASD extremely difficult. Within the literature describing immune-based studies in ASD, there are a number of discrepancies and unreplicated reports. Numerous studies report apparently conflicting results, and thus far, no consensus about the described immune findings has been reached. However, with increasing reports of immune dysfunction in autism, there is a growing awareness and concern that immune dysfunction may play a role in, if not all, at least a subgroup(s) of patients with autism. Moreover, various hypotheses have attempted to link dysfunctional immune activity and autism, such as maternal immune abnormalities during early pregnancy, increased incidence of familial autoimmunity, childhood vaccinations, and the generation of autism animal models based on immune parameters. A clear-cut definition of the groups or subgroups of ASD patients using modern diagnostic tools may help to better define these study results. The neurological and immune systems are inextricably intertwined beginning in the embryonic stage of life. Pre- or perinatal immune dysregularities are capable of altering levels of cytokines, chemokines, neurotransmitters, neuropeptides, as well as hormones. Each of these substances may influence the course of development in the nervous and/or immune systems primarily or through secondary action. A development perturbation may be the beginning of a continual cycle of damage or disruption to both systems. There are numerous pathways that may lead to the diagnosis of ASD. In some, it may begin with genetic susceptibility, and in others, infection or immune abnormalities may play a key role. Further study of the reciprocal actions of the nervous, immune, and endocrine systems may help to unravel the mystery of ASD. Moreover, while the extent to which many of the observations discussed herein are involved in the pathogenesis of autism is unknown, it cannot be discounted that immune dysfunction is an epiphenomenon or a consequence of the disease. Comprehensive studies of autism and age-matched control individuals and their families are necessary for more conclusive results.

REFERENCES

1. Association, A. P. (1994) *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, Washington, DC, American Psychiatric Association.
2. Fombonne, E. (2003) The prevalence of autism. *JAMA* **289,** 87–89.
3. Wiznitzer, M. (2004) Autism and tuberous sclerosis. *J. Child Neurol.* **19,** 675–679.
4. Rutter, M. (2000) Genetic studies of autism: from the 1970s into the millennium. *J. Abnorm. Child Psychol.* **28,** 3–14.
5. Cohen, D., Pichard, N., Tordjman, S., Baumann, C., Burglen, L., Excoffier, E., Lazar, G., Mazet, P., Pinquier, C., Verloes, A., Heron, D. (2005) Specific genetic disorders and autism: clinical contribution towards their identification. *J. Autism Dev. Disord.* **35,** 103–116.
6. Baird, G., Cass, H., Slonims, V. (2003) Diagnosis of autism. *BMJ* **327,** 488–493.
7. Cook, E. (1998) Genetics of autism. *Ment. Retard. Dev. Disabil. Res. Rev.* **4,** 113–120.
8. Bailey, A., Le Couteur, A., Gottesman, I., Bolton, P., Simonoff, E., Yuzda, E., Rutter, M. (1995) Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol. Med.* **25,** 63–77.
9. Hallmayer, J., Glasson, E. J., Bower, C., Petterson, B., Croen, L., Grether, J., Risch, N. (2002) On the twin risk in autism. *Am. J. Hum. Genet.* **71,** 941–946.
10. Cook Jr., E. H. (2001) Genetics of autism. *Child Adolesc. Psychiatr. Clin. N. Am.* **10,** 333–350.
11. Risch, N., Spiker, D., Lotspeich, L., Nouri, N., Hinds, D., Hallmayer, J., Kalaydjieva, L., McCague, P., Dimiceli, S., Pitts, T., et al. (1999) A genomic screen of autism: evidence for a multilocus etiology. *Am. J. Hum. Genet.* **65,** 493–507.
12. Polleux, F., Lauder, J. M. (2004) Toward a developmental neurobiology of autism. *Ment. Retard. Dev. Disabil. Res. Rev.* **10,** 303–317.
13. Burger, R. A., Warren, R. P. (1998) Possible immunogenetic basis for autism. *Ment. Retard. Dev. Disabil. Res. Rev.* **4,** 137–141.
14. Rice, D., Barone Jr., S. (2000) Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ. Health Perspect.* **108** (Suppl. 3), 511–533.
15. Akshoomoff, N., Pierce, K., Courchesne, E. (2002) The neurobiological basis of autism from a developmental perspective. *Dev. Psychopathol.* **14,** 613–634.
16. Acosta, M. T., Pearl, P. L. (2004) Imaging data in autism: from structure to malfunction. *Semin. Pediatr. Neurol.* **11,** 205–213.
17. Courchesne, E., Karns, C. M., Davis, H. R., Ziccardi, R., Carper, R. A., Tigue, Z. D., Chisum, H. J., Moses, P., Pierce, K., Lord, C., et al. (2001) Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology* **57,** 245–254.
18. Palmen, S. J., van Engeland, H., Hof, P. R., Schmitz, C. (2004) Neuropathological findings in autism. *Brain* **127,** 2572–2583.
19. Volkmar, F., Cook Jr., E. H., Pomeroy, J., Realmuto, G., Tanguay, P. (1999) Practice parameters for the assessment and treatment of children, adolescents, and adults with autism and other pervasive developmental disorders. American Academy of Child and Adolescent Psychiatry Working Group on Quality Issues. *J. Am. Acad. Child Adolesc. Psychiatry* **38,** 32S–54S.
20. Tuchman, R. F., Rapin, I., Shinnar, S. (1991) Autistic and dysphasic children. I: clinical characteristics. *Pediatrics* **88,** 1211–1218.
21. Villalobos, R., T. R., Jayakar, P., Yaylali, I. (1996) Prolonged EEG monitoring findings in children with pervasive developmental disorder and regression. *Ann. Neurol.* **40,** 300.
22. Jarskog, L. F., Xiao, H., Wilkie, M. B., Lauder, J. M., Gilmore, J. H. (1997) Cytokine regulation of embryonic rat dopamine and serotonin neuronal survival in vitro. *Int. J. Dev. Neurosci.* **15,** 711–716.
23. Steinman, L., Conlon, P., Maki, R., Foster, A. (2003) The intricate interplay among body weight, stress, and the immune response to friend or foe. *J. Clin. Invest.* **111,** 183–185.
24. Tracey, K. J., Wei, H., Manogue, K. R., Fong, Y., Hesse, D. G., Nguyen, H. T., Kuo, G. C., Beutler, B., Cotran, R. S., Cerami, A., et al. (1988) Cachectin/tumor necrosis factor induces cachexia, anemia, and inflammation. *J. Exp. Med.* **167,** 1211–1227.
25. Dunzendorfer, S., Kaser, A., Meierhofer, C., Tilg, H., Wiedermann, C. J. (2001) Cutting edge: peripheral neuropeptides attract immature and arrest mature blood-derived dendritic cells. *J. Immunol.* **166,** 2167–2172.
26. Stubbs, E. G., Crawford, M. L. (1977) Depressed lymphocyte responsiveness in autistic children. *J. Autism Child. Schizophr.* **7,** 49–55.
27. Warren, R. P., Margaretten, N. C., Pace, N. C., Foster, A. (1986) Immune abnormalities in patients with autism. *J. Autism Dev. Disord.* **16,** 189–197.
28. Plioplys, A. V., Greaves, A., Kazemi, K., Silverman, E. (1994) Lymphocyte function in autism and Rett syndrome. *Neuropsychobiology* **29,** 12–16.
29. Engstrom, A. H., Ohlson, S., Stubbs, E. G., Maciulus, A., Caldwell, V., Odell, J. D., Torres, A. R. (2003) Decreased expression of CD95 (FAS/

APO-1) on CD4+ T-lymphocytes from participants with autism. *J. Dev. Phys. Disabil.* **15,** 155–163.
30. Ashwood, P., Anthony, A., Pellicer, A. A., Torrente, F., Walker-Smith, J. A., Wakefield, A. J. (2003) Intestinal lymphocyte populations in children with regressive autism: evidence for extensive mucosal immunopathology. *J. Clin. Immunol.* **23,** 504–517.
31. Ferrante, P., Saresella, M., Guerini, F. R., Marzorati, M., Musetti, M. C., Cazzullo, A. G. (2003) Significant association of HLA A2-DR11 with CD4 naive decrease in autistic children. *Biomed. Pharmacother.* **57,** 372–374.
32. Yonk, L. J., Warren, R. P., Burger, R. A., Cole, P., Odell, J. D., Warren, W. L., White, E., Singh, V. K. (1990) CD4+ helper T cell depression in autism. *Immunol. Lett.* **25,** 341–345.
33. Warren, R. P., Yonk, L. J., Burger, R. A., Cole, P., Odell, J. D., Warren, W. L., White, E., Singh, V. K. (1990) Deficiency of suppressor-inducer (CD4+CD45RA+) T cells in autism. *Immunol. Invest.* **19,** 245–251.
34. Denney, D. R., Frei, B. W., Gaffney, G. R. (1996) Lymphocyte subsets and interleukin-2 receptors in autistic children. *J. Autism Dev. Disord.* **26,** 87–97.
35. Sweeten, T. L., Posey, D. J., Shanker, S., McDougle, C. J. (2004) High nitric oxide production in autistic disorder: possible role for interferon-γ. *Biol. Psychiatry* **55,** 434–437.
36. Sweeten, T. L., Posey, D. J., McDougle, C. J. (2003) High blood monocyte counts and neopterin levels in children with autistic disorder. *Am. J. Psychiatry* **160,** 1691–1693.
37. Messahel, S., Pheasant, A. E., Pall, H., Ahmed-Choudhury, J., Sungum-Paliwal, R. S., Vostanis, P. (1998) Urinary levels of neopterin and biopterin in autism. *Neurosci. Lett.* **241,** 17–20.
38. Fiumara, A., Sciotto, A., Barone, R., D'Asero, G., Munda, S., Parano, E., Pavone, L. (1999) Peripheral lymphocyte subsets and other immune aspects in Rett syndrome. *Pediatr. Neurol.* **21,** 619–621.
39. Warren, R. P., Foster, A., Margaretten, N. C. (1987) Reduced natural killer cell activity in autism. *J. Am. Acad. Child Adolesc. Psychiatry* **26,** 333–335.
40. Singh, V. K. (1996) Plasma increase of interleukin-12 and interferon-γ. Pathological significance in autism. *J. Neuroimmunol.* **66,** 143–145.
41. Gupta, S., Aggarwal, S., Rashanravan, B., Lee, T. (1998) Th1- and Th2-like cytokines in CD4+ and CD8+ T cells in autism. *J. Neuroimmunol.* **85,** 106–109.
42. Zimmerman, A. W., Jyonouchi, H., Comi, A. M., Connors, S. L., Milstien, S., Varsou, A., Heyes, M. P. (2005) Cerebrospinal fluid and serum markers of inflammation in autism. *Pediatr. Neurol.* **33,** 195–201.
43. Jyonouchi, H., Sun, S., Le, H. (2001) Proinflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression. *J. Neuroimmunol.* **120,** 170–179.
44. Ashwood, P., Wakefield, A. J. (2006) Immune activation of peripheral blood and mucosal $CD3^+$ lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms. *J. Neuroimmunol.* **173,** 126–134.
45. Ashwood, P., Anthony, A., Torrente, F., Wakefield, A. J. (2004) Spontaneous mucosal lymphocyte cytokine profiles in children with autism and gastrointestinal symptoms: mucosal immune activation and reduced counter regulatory interleukin-10. *J. Clin. Immunol.* **24,** 664–673.
46. Jyonouchi, H., Geng, L., Ruby, A., Reddy, C., Zimmerman-Bier, B. (2005) Evaluation of an association between gastrointestinal symptoms and cytokine production against common dietary proteins in children with autism spectrum disorders. *J. Pediatr.* **146,** 605–610.
47. Croonenberghs, J., Wauters, A., Devreese, K., Verkerk, R., Scharpe, S., Bosmans, E., Egyed, B., Deboutte, D., Maes, M. (2002) Increased serum albumin, γ globulin, immunoglobulin IgG, and IgG2 and IgG4 in autism. *Psychol. Med.* **32,** 1457–1463.
48. Trajkovski, V., Ajdinski, L., Spiroski, M. (2004) Plasma concentration of immunoglobulin classes and subclasses in children with autism in the Republic of Macedonia: retrospective study. *Croat. Med. J.* **45,** 746–749.
49. Singh, V. K., Warren, R. P., Odell, J. D., Warren, W. L., Cole, P. (1993) Antibodies to myelin basic protein in children with autistic behavior. *Brain Behav. Immun.* **7,** 97–103.
50. Singh, V. K., Warren, R., Averett, R., Ghaziuddin, M. (1997) Circulating autoantibodies to neuronal and glial filament proteins in autism. *Pediatr. Neurol.* **17,** 88–90.
51. Todd, R. D., Hickok, J. M., Anderson, G. M., Cohen, D. J. (1988) Antibrain antibodies in infantile autism. *Biol. Psychiatry* **23,** 644–647.
52. Connolly, A. M., Chez, M. G., Pestronk, A., Arnold, S. T., Mehta, S., Deuel, R. K. (1999) Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders. *J. Pediatr.* **134,** 607–613.
53. Silva, S. C., Correia, C., Fesel, C., Barreto, M., Coutinho, A. M., Marques, C., Miguel, T. S., Ataide, A., Bento, C., Borges, L., Oliveira, G., Vicente, A. M. (2004) Autoantibody repertoires to brain tissue in autism nuclear families. *J. Neuroimmunol.* **152,** 176–182.
54. Odell, D., Maciulis, A., Cutler, A., Warren, L., McMahon, W. M., Coon, H., Stubbs, G., Henley, K., Torres, A. (2005) Confirmation of the association of the C4B null allelle in autism. *Hum. Immunol.* **66,** 140–145.
55. Torres, A. R., Maciulis, A., Odell, D. (2001) The association of MHC genes with autism. *Front. Biosci.* **6,** D936–D943.
56. Korvatska, E., Van de Water, J., Anders, T. F., Gershwin, M. E. (2002) Genetic and immunologic considerations in autism. *Neurobiol. Dis.* **9,** 107–125.
57. Krause, I., He, X. S., Gershwin, M. E., Shoenfeld, Y. (2002) Brief report: immune factors in autism: a critical review. *J. Autism Dev. Disord.* **32,** 337–345.
58. Yamashita, Y., Fujimoto, C., Nakajima, E., Isagai, T., Matsuishi, T. (2003) Possible association between congenital cytomegalovirus infection and autistic disorder. *J. Autism Dev. Disord.* **33,** 455–459.
59. Patterson, P. H. (2002) Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. *Curr. Opin. Neurobiol.* **12,** 115–118.
60. Hornig, M., Solbrig, M., Horscroft, N., Weissenbock, H., Lipkin, W. I. (2001) Borna disease virus infection of adult and neonatal rats: models for neuropsychiatric disease. *Curr. Top. Microbiol. Immunol.* **253,** 157–177.
61. Plata-Salaman, C. R., Ilyin, S. E., Gayle, D., Romanovitch, A., Carbone, K. M. (1999) Persistent Borna disease virus infection of neonatal rats causes brain regional changes of mRNAs for cytokines, cytokine receptor components and neuropeptides. *Brain Res. Bull.* **49,** 441–451.
62. Sauder, C., de la Torre, J. C. (1999) Cytokine expression in the rat central nervous system following perinatal Borna disease virus infection. *J. Neuroimmunol.* **96,** 29–45.
63. Shi, L., Fatemi, S. H., Sidwell, R. W., Patterson, P. H. (2003) Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J. Neurosci.* **23,** 297–302.
64. Stubbs, G. (1995) Interferonemia and autism. *J. Autism Dev. Disord.* **25,** 71–73.
65. Gadient, R. A., Patterson, P. H. (1999) Leukemia inhibitory factor, interleukin 6, and other cytokines using the GP130 transducing receptor: roles in inflammation and injury. *Stem Cells* **17,** 127–137.
66. Mehler, M. F., Kessler, J. A. (1998) Cytokines in brain development and function. *Adv. Protein Chem.* **52,** 223–251.
67. Vargas, D. L., Nascimbene, C., Krishnan, C., Zimmerman, A. W., Pardo, C. A. (2005) Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann. Neurol.* **57,** 67–81.
68. Wilson, C. J., Finch, C. E., Cohen, H. J. (2002) Cytokines and cognition—the case for a head-to-toe inflammatory paradigm. *J. Am. Geriatr. Soc.* **50,** 2041–2056.
69. Ransohoff, R. M., Kivisakk, P., Kidd, G. (2003) Three or more routes for leukocyte migration into the central nervous system. *Nat. Rev. Immunol.* **3,** 569–581.
70. Dantzer, R., Bluthe, R. M., Laye, S., Bret-Dibat, J. L., Parnet, P., Kelley, K. W. (1998) Cytokines and sickness behavior. *Ann. N. Y. Acad. Sci.* **840,** 586–590.
71. Mignini, F., Streccioni, V., Amenta, F. (2003) Autonomic innervation of immune organs and neuroimmune modulation. *Auton. Autacoid Pharmacol.* **23,** 1–25.
72. Larson, S. J. (2002) Behavioral and motivational effects of immune-system activation. *J. Gen. Psychol.* **129,** 401–414.
73. Licinio, J., Kling, M. A., Hauser, P. (1998) Cytokines and brain function: relevance to interferon-α-induced mood and cognitive changes. *Semin. Oncol.* **25,** 30–38.
74. Zhao, B., Schwartz, J. P. (1998) Involvement of cytokines in normal CNS development and neurological diseases: recent progress and perspectives. *J. Neurosci. Res.* **52,** 7–16.
75. Kipnis, J., Cohen, H., Cardon, M., Ziv, Y., Schwartz, M. (2004) T cell deficiency leads to cognitive dysfunction: implications for therapeutic vaccination for schizophrenia and other psychiatric conditions. *Proc. Natl. Acad. Sci. USA* **101,** 8180–8185.
76. Lam, K. S., Aman, M. G., Arnold, L. E. (2006) Neurochemical correlates of autistic disorder: a review of the literature. *Res. Dev. Disabil.* **27,** 254–289.
77. Fatemi, S. H., Halt, A. R., Stary, J. M., Kanodia, R., Schulz, S. C., Realmuto, G. R. (2002) Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. *Biol. Psychiatry* **52,** 805–810.
78. Bittigau, P., Ikonomidou, C. (1997) Glutamate in neurologic diseases. *J. Child Neurol.* **12,** 471–485.

79. Chugani, D. C., Muzik, O., Behen, M., Rothermel, R., Janisse, J. J., Lee, J., Chugani, H. T. (1999) Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. *Ann. Neurol.* **45,** 287–295.
80. Simmons, D. A., Broderick, P. A. (2005) Cytokines, stressors, and clinical depression: augmented adaptation responses underlie depression pathogenesis. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **29,** 793–807.
81. Wirleitner, B., Neurauter, G., Schrocksnadel, K., Frick, B., Fuchs, D. (2003) Interferon-γ-induced conversion of tryptophan: immunologic and neuropsychiatric aspects. *Curr. Med. Chem.* **10,** 1581–1591.
82. Anderson, G. M., Horne, W. C., Chatterjee, D., Cohen, D. J. (1990) The hyperserotonemia of autism. *Ann. N. Y. Acad. Sci.* **600,** 331–340.
83. McDougle, C. J., Naylor, S. T., Cohen, D. J., Volkmar, F. R., Heninger, G. R., Price, L. H. (1996) A double-blind, placebo-controlled study of fluvoxamine in adults with autistic disorder. *Arch. Gen. Psychiatry* **53,** 1001–1008.
84. Cook, E. H., Leventhal, B. L. (1996) The serotonin system in autism. *Curr. Opin. Pediatr.* **8,** 348–354.
85. Coutinho, A. M., Oliveira, G., Morgadinho, T., Fesel, C., Macedo, T. R., Bento, C., Marques, C., Ataide, A., Miguel, T., Borges, L., Vicente, A. M. (2004) Variants of the serotonin transporter gene (SLC6A4) significantly contribute to hyperserotonemia in autism. *Mol. Psychiatry* **9,** 264–271.
86. Conroy, J., Meally, E., Kearney, G., Fitzgerald, M., Gill, M., Gallagher, L. (2004) Serotonin transporter gene and autism: a haplotype analysis in an Irish autistic population. *Mol. Psychiatry* **9,** 587–593.
87. Biber, K., Zuurman, M. W., Dijkstra, I. M., Boddeke, H. W. G. M. (2002) Chemokines in the brain: neuroimmunology and beyond. *Curr. Opin. Pharmacol.* **2,** 63–68.
88. Levi-Montalcini, R., Skaper, S. D., Dal Toso, R., Petrelli, L., Leon, A. (1996) Nerve growth factor: from neurotrophin to neurokine. *Trends Neurosci.* **19,** 514–520.
89. Nelson, K. B., Grether, J. K., Croen, L. A., Dambrosia, J. M., Dickens, B. F., Jelliffe, L. L., Hansen, R. L., Phillips, T. M. (2001) Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation. *Ann. Neurol.* **49,** 597–606.
90. Vega, J. A., Garcia-Suarez, O., Hannestad, J., Perez-Perez, M., Gennana, A. (2003) Neurotrophins and the immune system. *J. Anat.* **203,** 1–19.
91. Nockher, W. A., Renz, H. (2003) Neurotrophins in inflammatory lung disease; modulators of cell differentiation and neuroimmune interactions. *Cytokine Growth Factor Rev.* **14,** 559–578.
92. Young, L. J., Pitkow, L. J., Ferguson, J. N. (2002) Neuropeptides and social behavior: animal models relevant to autism. *Mol. Psychiatry* **7** (Suppl. 2), S38–S39.
93. Young, L. J., Wang, Z., Insel, T. R. (1998) Neuroendocrine bases of monogamy. *Trends Neurosci.* **21,** 71–75.
94. Williams, J. R., Insel, T. R., Harbaugh, C. R., Carter, C. S. (1994) Oxytocin administered centrally facilitates formation of a partner preference in female prairie voles (*Microtus ochrogaster*). *J. Neuroendocrinol.* **6,** 247–250.
95. Young, L. J., Lim, M. M., Gingrich, B., Insel, T. R. (2001) Cellular mechanisms of social attachment. *Horm. Behav.* **40,** 133–138.
96. Ferguson, J. N., Young, L. J., Hearn, E. F., Matzuk, M. M., Insel, T. R., Winslow, J. T. (2000) Social amnesia in mice lacking the oxytocin gene. *Nat. Genet.* **25,** 284–288.
97. Modahl, C., Green, L., Fein, D., Morris, M., Waterhouse, L., Feinstein, C., Levin, H. (1998) Plasma oxytocin levels in autistic children. *Biol. Psychiatry* **43,** 270–277.
98. Green, L., Fein, D., Modahl, C., Feinstein, C., Waterhouse, L., Morris, M. (2001) Oxytocin and autistic disorder: alterations in peptide forms. *Biol. Psychiatry* **50,** 609–613.
99. Delneste, Y., Herbault, N., Galea, B., Magistrelli, G., Bazin, I., Bonnefoy, J. Y., Jeannin, P. (1999) Vasoactive intestinal peptide synergizes with TNF-α in inducing human dendritic cell maturation. *J. Immunol.* **163,** 3071–3075.
100. Pashenkov, M., Teleshova, N., Link, H. (2003) Inflammation in the central nervous system: the role for dendritic cells. *Brain Pathol.* **13,** 23–33.
101. Money, J., Bobrow, N. A., Clarke, F. C. (1971) Autism and autoimmune disease: a family study. *J. Autism Child. Schizophr.* **1,** 146–160.
102. Comi, A. M., Zimmerman, A. W., Frye, V. H., Law, P. A., Peeden, J. N. (1999) Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *J. Child Neurol.* **14,** 388–394.
103. Sweeten, T. L., Bowyer, S. L., Posey, D. J., Halberstadt, G. M., McDougle, C. J. (2003) Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. *Pediatrics* **112,** e420.
104. Croen, L. A., Grether, J. K., Yoshida, C. K., Odouli, R., Van de Water, J. (2005) Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. *Arch. Pediatr. Adolesc. Med.* **159,** 151–157.
105. Dalton, P., Deacon, R., Blamire, A., Pike, M., McKinlay, I., Stein, J., Styles, P., Vincent, A. (2003) Maternal antibodies associated with autism and language disorder. *Ann. Neurol.* **53,** 533–537.
106. Todd, R. D., Ciaranello, R. D. (1985) Demonstration of inter- and intraspecies differences in serotonin binding sites by antibodies from an autistic child. *Proc. Natl. Acad. Sci. USA* **82,** 612–616.
107. Rumsey, J. M., Ernst, M. (2000) Functional neuroimaging of autistic disorders. *Ment. Retard. Dev. Disabil. Res. Rev.* **6,** 171–179.
108. Ahlsen, G., Rosengren, L., Belfrage, M., Palm, A., Haglid, K., Hamberger, A., Gillberg, C. (1993) Glial fibrillary acidic protein in the cerebrospinal fluid of children with autism and other neuropsychiatric disorders. *Biol. Psychiatry* **33,** 734–743.
109. Singh, V. K., Rivas, W. H. (2004) Prevalence of serum antibodies to caudate nucleus in autistic children. *Neurosci. Lett.* **355,** 53–56.
110. Horvath, K., Papadimitriou, J. C., Rabsztyn, A., Drachenberg, C., Tildon, J. T. (1999) Gastrointestinal abnormalities in children with autistic disorder. *J. Pediatr.* **135,** 559–563.
111. Afzal, N., Murch, S., Thirrupathy, K., Berger, L., Fagbemi, A., Heuschkel, R. (2003) Constipation with acquired megarectum in children with autism. *Pediatrics* **112,** 939–942.
112. Fombonne, E., Simmons, H., Ford, T., Meltzer, H., Goodman, R. (2001) Prevalence of pervasive developmental disorders in the British nationwide survey of child mental health. *J. Am. Acad. Child Adolesc. Psychiatry* **40,** 820–827.
113. Finegold, S. M., Molitoris, D., Song, Y., Liu, C., Vaisanen, M. L., Bolte, E., McTeague, M., Sandler, R., Wexler, H., Marlowe, E. M., et al. (2002) Gastrointestinal microflora studies in late-onset autism. *Clin. Infect. Dis.* **35,** S6–S16.
114. Knivsberg, A. M., Reichelt, K. L., Hoien, T., Nodland, M. (2002) A randomised, controlled study of dietary intervention in autistic syndromes. *Nutr. Neurosci.* **5,** 251–261.
115. D'Eufemia, P., Celli, M., Finocchiaro, R., Pacifico, L., Viozzi, L., Zaccagnini, M., Cardi, E., Giardini, O. (1996) Abnormal intestinal permeability in children with autism. *Acta Paediatr.* **85,** 1076–1079.
116. Alberti, A., Pirrone, P., Elia, M., Waring, R. H., Romano, C. (1999) Sulphation deficit in "low-functioning" autistic children: a pilot study. *Biol. Psychiatry* **46,** 420–424.
117. Wakefield, A. J., Murch, S. H., Anthony, A., Linnell, J., Casson, D. M., Malik, M., Berelowitz, M., Dhillon, A. P., Thomson, M. A., Harvey, P., Valentine, A., Davies, S. E., Walker-Smith, J. A. (1998) Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* **351,** 637–641.
118. Wakefield, A. J., Ashwood, P., Limb, K., Anthony, A. (2005) The significance of ileo-colonic lymphoid nodular hyperplasia in children with autistic spectrum disorder. *Eur. J. Gastroenterol. Hepatol.* **17,** 827–836.
119. Wakefield, A. J., Anthony, A., Murch, S. H., Thomson, M., Montgomery, S. M., Davies, S., O'Leary, J. J., Berelowitz, M., Walker-Smith, J. A. (2000) Enterocolitis in children with developmental disorders. *Am. J. Gastroenterol.* **95,** 2285–2295.
120. Furlano, R. I., Anthony, A., Day, R., Brown, A., McGarvey, L., Thomson, M. A., Davies, S. E., Berelowitz, M., Forbes, A., Wakefield, A. J., Walker-Smith, J. A., Murch, S. H. (2001) Colonic CD8 and γ δ T-cell infiltration with epithelial damage in children with autism. *J. Pediatr.* **138,** 366–372.
121. Torrente, F., Ashwood, P., Day, R., Machado, N., Furlano, R. I., Anthony, A., Davies, S. E., Wakefield, A. J., Thomson, M. A., Walker-Smith, J. A., Murch, S. H. (2002) Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism. *Mol. Psychiatry* **7,** 375–382.
122. Ashwood, P., Anthony, A., Pellicier, A. A., Torrente, F., Walker-Smith, J. A., Wakefield, A. (2003) Intestinal lymphoctye populations in children with regressive autism: evidence for extensive mucosal immunopathology. *J. Clin. Immunol.* **23,** 504–517.
123. Wakefield, A. J. (2002) Enterocolitis, autism and measles virus. *Mol. Psychiatry* **7** (Suppl. 2), S44–S46.
124. Jass, J. R. (2005) The intestinal lesion of autistic spectrum disorder. *Eur. J. Gastroenterol. Hepatol.* **17,** 821–822.
125. Kokkonen, J., Ruuska, T., Karttunen, T. J., Maki, M. (2002) Lymphonodular hyperplasia of the terminal ileum associated with colitis shows an increase γδ+ T-cell density in children. *Am. J. Gastroenterol.* **97,** 667–672.
126. Welch, M. G., Welch-Horan, T. B., Anwar, M., Anwar, N., Ludwig, R. J., Ruggiero, D. A. (2005) Brain effects of chronic IBD in areas abnormal in autism and treatment by single neuropeptides secretin and oxytocin. *J. Mol. Neurosci.* **25,** 259–274.

127. Bushara, K. O. (2005) Neurologic presentation of celiac disease. *Gastroenterology* **128,** S92–S97.
128. Lucarelli, S., Frediani, T., Zingoni, A. M., Ferruzzi, F., Giardini, O., Quintieri, F., Barbato, M., D'Eufemia, P., Cardi, E. (1995) Food allergy and infantile autism. *Panminerva Med.* **37,** 137–141.
129. Vojdani, A., Campbell, A. W., Anyanwu, E., Kashanian, A., Bock, K., Vojdani, E. (2002) 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.* **129,** 168–177.
130. Sandler, R. H., Finegold, S. M., Bolte, E. R., Buchanan, C. P., Maxwell, A. P., Vaisanen, M. L., Nelson, M. N., Wexler, H. M. (2000) Short-term benefit from oral vancomycin treatment of regressive-onset autism. *J. Child Neurol.* **15,** 429–435.
131. Knivsberg, A. M., Reichelt, K. L., Hoien, T., Nodland, M. (2002) A randomized, controlled study of dietary intervention in autistic syndromes. *Nutr. Neurosci.* **5,** 251–261.
132. Pedotti, R., De Voss, J. J., Steinman, L., Galli, S. J. (2003) Involvement of both "allergic" and "autoimmune" mechanisms in EAE, MS and other autoimmune diseases. *Trends Immunol.* **24,** 479–484.
133. Zagon, I. S., McLaughlin, P. J. (1991) Identification of opioid peptides regulating proliferation of neurons and glia in the developing nervous system. *Brain Res.* **542,** 318–323.
134. Weigent, D. A., Blalock, J. E. (1997) Neuroendocrine-immune interactions. In *Immunology of the Nervous System* (Keane, R. W., Hickey, W. F., eds.) pp. 548–575, Oxford University Press, New York.
135. Peterson, P. K., Molitor, T. W., Chao, C. C. (1998) The opioid-cytokine connection. *J. Neuroimmunol.* **83,** 63–69.
136. Wakefield, A. J., Puleston, J. M., Montgomery, S. M., Anthony, A., O'Leary, J. J., Murch, S. H. (2002) Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. *Aliment. Pharmacol. Ther.* **16,** 663–674.
137. Whitely, P., Rogers, J., Savery, D., Shattock, P. (1999) A gluten-free diet as an intervention for autism and associated spectrum disorders: preliminary findings. *Autism* **3,** 45–65.
138. Symons, F. J., Thompson, A., Rodriguez, M. C. (2004) Self-injurious behavior and the efficacy of naltrexone treatment: a quantitative synthesis. *Ment. Retard. Dev. Disabil. Res. Rev.* **10,** 193–200.
139. Fatemi, S. H., Earle, J., Kanodia, R., Kist, D., Emamian, E. S., Patterson, P. H., Shi, L., Sidwell, R. (2002) Prenatal viral infection leads to pyramidal cell atrophy and macrocephaly in adulthood: implications for genesis of autism and schizophrenia. *Cell. Mol. Neurobiol.* **22,** 25–33.
140. Luppi, P. (2003) How immune mechanisms are affected by pregnancy. *Vaccine* **21,** 3352–3357.
141. Libbey, J. E., Sweeten, T. L., McMahon, W. M., Fujinami, R. S. (2005) Autistic disorder and viral infections. *J. Neurovirol.* **11,** 1–10.
142. Lopez-Pison, J., Rubio-Rubio, R., Urena-Hornos, T., Omenaca-Teres, M., Sans, A., Cabrerizo de Diago, R., Pena-Segura, J. L. (2005) Retrospective diagnosis of congenital infection by cytomegalovirus in the case of one infant. *Rev. Neurol.* **40,** 733–736.
143. Pletnikov, M. V., Moran, T. H., Carbone, K. M. (2002) Borna disease virus infection of the neonatal rat: developmental brain injury model of autism spectrum disorders. *Front. Biosci.* **7,** d593–d607.
144. Hans, A., Bajramovic, J. J., Syan, S., Perret, E., Dunia, I., Brahic, M., Gonzalez-Dunia, D. (2004) Persistent, noncytolytic infection of neurons by Borna disease virus interferes with ERK 1/2 signaling and abrogates BDNF-induced synaptogenesis. *FASEB J.* **18,** 863–865.
145. Pletnikov, M. V., Jones, M. L., Rubin, S. A., Moran, T. H., Carbone, K. M. (2001) Rat model of autism spectrum disorders. Genetic background effects on Borna disease virus-induced developmental brain damage. *Ann. N. Y. Acad. Sci.* **939,** 318–319.
146. Chess, S., Fernandez, P., Korn, S. (1978) Behavioral consequences of congenital rubella. *J. Pediatr.* **93,** 699–703.
147. Swisher, C. N., Swisher, L. (1975) Letter: congenital rubella and autistic behavior. *N. Engl. J. Med.* **293,** 198.
148. Hornig, M., Chian, D., Lipkin, W. I. (2004) Neurotoxic effects of postnatal thimerosal are mouse strain dependent. *Mol. Psychiatry* **9,** 833–845.
149. Geier, D. A., Geier, M. R. (2004) A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism. *Med. Sci. Monit.* **10,** PI33–PI39.
150. Ingram, J. L., Peckham, S. M., Tisdale, B., Rodier, P. M. (2000) Prenatal exposure of rats to valproic acid reproduces the cerebellar anomalies associated with autism. *Neurotoxicol. Teratol.* **22,** 319–324.
151. Bachevalier, J. (1996) Brief report: medial temporal lobe and autism: a putative animal model in primates. *J. Autism Dev. Disord.* **26,** 217–220.
152. Wolterink, G., Daenen, L. E., Dubbeldam, S., Gerrits, M. A., van Rijn, R., Kruse, C. G., Van Der Heijden, J. A., Van Ree, J. M. (2001) Early amygdala damage in the rat as a model for neurodevelopmental psychopathological disorders. *Eur. Neuropsychopharmacol.* **11,** 51–59.
153. Birkett, S. D., Pickering, B. T. (1988) The vasopressin precursor in the Brattleboro (di/di) rat. *Int. J. Pept. Protein Res.* **32,** 565–572.
154. Long, J. M., LaPorte, P., Paylor, R., Wynshaw-Boris, A. (2004) Expanded characterization of the social interaction abnormalities in mice lacking Dvl1. *Genes Brain Behav.* **3,** 51–62.
155. Winslow, J. T., Insel, T. R. (2002) The social deficits of the oxytocin knockout mouse. *Neuropeptides* **36,** 221–229.
156. Caston, J., Yon, E., Mellier, D., Godfrey, H. P., Delhaye-bouchaud, N., Mariani, J. (1998) An animal model of autism: behavioural studies in the GS guinea-pig. *Eur. J. Neurosci.* **10,** 2677–2684.
157. Lang, B., Dale, R. C., Vincent, A. (2003) New autoantibody mediated disorders of the central nervous system. *Curr. Opin. Neurol.* **16,** 351–357.
158. Gaughran, F. (2002) Immunity and schizophrenia: autoimmunity, cytokines, and immune responses. *Int. Rev. Neurobiol.* **52,** 275–302.
159. Jones, A. L., Mowry, B. J., Pender, M. P., Greer, J. M. (2005) Immune dysregulation and self-reactivity in schizophrenia: do some cases of schizophrenia have an autoimmune basis? *Immunol. Cell Biol.* **83,** 9–17.
160. Radewicz, K., Garey, L. J., Gentleman, S. M., Reynolds, R. (2000) Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. *J. Neuropathol. Exp. Neurol.* **59,** 137–150.
161. Bayer, T. A., Buslei, R., Havas, L., Falkai, P. (1999) Evidence for activation of microglia in patients with psychiatric illnesses. *Neurosci. Lett.* **271,** 126–128.
162. Pandey, R. S., Gupta, A. K., Chaturvedi, U. C. (1981) Autoimmune model of schizophrenia with special reference to antibrain antibodies. *Biol. Psychiatry* **16,** 1123–1136.
163. Kim, J. J., Lee, S. J., Toh, K. Y., Lee, C. U., Lee, C., Paik, I. H. (2001) Identification of antibodies to heat shock proteins 90 kDa and 70 kDa in patients with schizophrenia. *Schizophr. Res.* **52,** 127–135.
164. Jun, T. Y., Pae, C. U., Chae, J. H., Bahk, W. M., Kim, K. S., Han, H. (2002) Polymorphism of CTLA-4 gene at position 49 of exon 1 may be associated with schizophrenia in the Korean population. *Psychiatry Res.* **110,** 19–25.
165. Zhang, X. Y., Zhou, D. F., Zhang, P. Y., Wu, G. Y., Cao, L. Y., Shen, Y. C. (2002) Elevated interleukin-2, interleukin-6 and interleukin-8 serum levels in neuroleptic-free schizophrenia: association with psychopathology. *Schizophr. Res.* **57,** 247–258.
166. Zhang, X. Y., Zhou, D. F., Cao, L. Y., Zhang, P. Y., Wu, G. Y. (2002) Decreased production of interleukin-2 (IL-2), IL-2 secreting cells and CD4+ cells in medication-free patients with schizophrenia. *J. Psychiatr. Res.* **36,** 331–336.
167. Muller, N., Ackenheil, M. (1995) Immunoglobulin and albumin content of cerebrospinal fluid in schizophrenic patients: relationship to negative symptomatology. *Schizophr. Res.* **14,** 223–228.
168. Albrecht, P., Torrey, E. F., Boone, E., Hicks, J. T., Daniel, N. (1980) Raised cytomegalovirus-antibody level in cerebrospinal fluid of schizophrenic patients. *Lancet* **2,** 769–772.
169. Delisi, L. E., Smith, S. B., Hamovit, J. R., Maxwell, M. E., Goldin, L. R., Dingman, C. W., Gershon, E. S. (1986) Herpes simplex virus, cytomegalovirus and Epstein-Barr virus antibody titres in sera from schizophrenic patients. *Psychol. Med.* **16,** 757–763.
170. Yamaguchi, K., Sawada, T., Naraki, T., Igata-Yi, R., Shiraki, H., Horii, Y., Ishii, T., Ikeda, K., Asou, N., Okabe, H., et al. (1999) Detection of Borna disease virus-reactive antibodies from patients with psychiatric disorders and from horses by electrochemiluminescence immunoassay. *Clin. Diagn. Lab. Immunol.* **6,** 696–700.
171. Leykin, I., Mayer, R., Shinitzky, M. (1997) Short and long-term immunosuppressive effects of clozapine and haloperidol. *Immunopharmacology* **37,** 75–86.
172. Jankovic, J. (2001) Tourette's syndrome. *N. Engl. J. Med.* **345,** 1184–1192.
173. Coffey, B. J., Park, K. S. (1997) Behavioral and emotional aspects of Tourette syndrome. *Neurol. Clin.* **15,** 277–289.
174. Muller, N., Putz, A., Kathmann, N., Lehle, R., Gunther, W., Straube, A. (1997) Characteristics of obsessive-compulsive symptoms in Tourette's syndrome, obsessive-compulsive disorder, and Parkinson's disease. *Psychiatry Res.* **70,** 105–114.
175. Hoekstra, P. J., Bijzet, J., Limburg, P. C., Steenhuis, M. P., Troost, P. W., Oosterhoff, M. D., Korf, J., Kallenberg, C. G., Minderaa, R. B. (2001) Elevated D8/17 expression on B lymphocytes, a marker of rheumatic

fever, measured with flow cytometry in tic disorder patients. *Am. J. Psychiatry* **158,** 605–610.
176. Hollander, E., DelGiudice-Asch, G., Simon, L., Schmeidler, J., Cartwright, C., DeCaria, C. M., Kwon, J., Cunningham-Rundles, C., Chapman, F., Zabriskie, J. B. (1999) B lymphocyte antigen D8/17 and repetitive behaviors in autism. *Am. J. Psychiatry* **156,** 317–320.
177. Rickards, H., Dursun, S. M., Farrar, G., Betts, T., Corbett, J. A., Handley, S. L. (1996) Increased plasma kynurenine and its relationship to neopterin and tryptophan in Tourette's syndrome. *Psychol. Med.* **26,** 857–862.
178. Leckman, J. F., Katsovich, L., Kawikova, I., Lin, H., Zhang, H., Kronig, H., Morshed, S., Parveen, S., Grantz, H., Lombroso, P. J., King, R. A. (2005) Increased serum levels of interleukin-12 and tumor necrosis factor-α in Tourette's syndrome. *Biol. Psychiatry* **57,** 667–673.
179. Yeh, C. B., Wu, C. H., Tsung, H. C., Chen, C. W., Shyu, J. F., Leckman, J. F. (2006) Antineural antibody in patients with Tourette's syndrome and their family members. *J. Biomed. Sci.* **13,** 101–112.
180. Hoekstra, P. J., Kallenberg, C. G., Korf, J., Minderaa, R. B. (2002) Is Tourette's syndrome an autoimmune disease? *Mol. Psychiatry* **7,** 437–445.
181. Marques-Dias, M. J., Mercadante, M. T., Tucker, D., Lombroso, P. (1997) Sydenham's chorea. *Psychiatr. Clin. North Am.* **20,** 809–820.
182. Kirvan, C. A., Swedo, S. E., Heuser, J. S., Cunningham, M. W. (2003) Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. *Nat. Med.* **9,** 914–920.
183. Snider, L. A., Swedo, S. E. (2004) PANDAS: current status and directions for research. *Mol. Psychiatry* **9,** 900–907.
184. Asbahr, F. R., Negrao, A. B., Gentil, V., Zanetta, D. M., da Paz, J. A., Marques-Dias, M. J., Kiss, M. H. (1998) Obsessive-compulsive and related symptoms in children and adolescents with rheumatic fever with and without chorea: a prospective 6-month study. *Am. J. Psychiatry* **155,** 1122–1124.
185. Lougee, L., Perlmutter, S. J., Nicolson, R., Garvey, M. A., Swedo, S. E. (2000) Psychiatric disorders in first-degree relatives of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). *J. Am. Acad. Child Adolesc. Psychiatry* **39,** 1120–1126.
186. Perlmutter, S. J., Leitman, S. F., Garvey, M. A., Hamburger, S., Feldman, E., Leonard, H. L., Swedo, S. E. (1999) Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* **354,** 1153–1158.
187. Singer, H. S., Loiselle, C. R., Lee, O., Minzer, K., Swedo, S., Grus, F. H. (2004) Anti-basal ganglia antibodies in PANDAS. *Mov. Disord.* **19,** 406–415.
188. Garvey, M. A., Perlmutter, S. J., Allen, A. J., Hamburger, S., Lougee, L., Leonard, H. L., Witowski, M. E., Dubbert, B., Swedo, S. E. (1999) A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biol. Psychiatry* **45,** 1564–1571.
189. Kurlan, R. (2004) The PANDAS hypothesis: losing its bite? *Mov. Disord.* **19,** 371–374.
190. McLean, B. N. (1998) Neurological involvement in systemic lupus erythematosus. *Curr. Opin. Neurol.* **11,** 247–251.
191. Kowal, C., DeGiorgio, L. A., Nakaoka, T., Hetherington, H., Huerta, P. T., Diamond, B., Volpe, B. T. (2004) Cognition and immunity; antibody impairs memory. *Immunity* **21,** 179–188.
192. Hoffman, S. A., Narendran, A., Shucard, D. W., Harbeck, R. J. (1988) Autoantibodies, immune complexes and behavioral disorders: neuropsychiatric involvement in systemic lupus erythematosus. *Drug Dev. Res.* **15,** 237–251.
193. D'Andrea, M. (2004) Add Alzheimer's disease to the list of autoimmune diseases. *Med. Hypotheses* **64,** 458–463.
194. Hofman, A., Ott, A., Breteler, M. M., Bots, M. L., Slooter, A. J., van Harskamp, F., van Duijn, C. N., Van Broeckhoven, C., Grobbee, D. E. (1997) Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam study. *Lancet* **349,** 151–154.
195. Mecocci, P., Parnetti, L., Reboldi, G. P., Santucci, C., Gaiti, A., Ferri, C., Gernini, I., Romagnoli, M., Cadini, D., Senin, U. (1991) Blood-brain-barrier in a geriatric population: barrier function in degenerative and vascular dementias. *Acta Neurol. Scand.* **84,** 210–213.
196. Kalaria, R. N. (1996) Cerebral vessels in ageing and Alzheimer's disease. *Pharmacol. Ther.* **72,** 193–214.
197. Premkumar, D. R., Kalaria, R. N. (1996) Altered expression of amyloid β precursor mRNAs in cerebral vessels, meninges, and choroid plexus in Alzheimer's disease. *Ann. N. Y. Acad. Sci.* **777,** 288–292.
198. Giulian, D. (1999) Microglia and the immune pathology of Alzheimer disease. *Am. J. Hum. Genet.* **65,** 13–18.
199. Mark, K. S., Miller, D. W. (1999) Increased permeability of primary cultured brain microvessel endothelial cell monolayers following TNF-α exposure. *Life Sci.* **64,** 1941–1953.