

## **Autism and the Immune Connection**

Infantile autism begins early in life, usually before the child is 30 months of age. While "in the past" a rare condition with a "disputed" incidence of just 2-5 in 10,000 live births, it is seen as a devastating handicap on psychologic and neurologic development, with potentially long-term serious consequences. As described in the past, Autistic infants did not demand attention, they did not enjoy being picked up, nor did they cuddle or cling when someone held them. They rarely smile at other people or look directly at them. In fact they often appear to be the happiest when they are left alone. Mothers of autistic children have noted an understandable lessened pleasure in their maternal efforts. They complain that they feel they are caring for an "object" rather than a person. Sometimes this condition is not noticed at first, because physical development generally appears normal in the autistic infant. These infants are often viewed as "placid" babies. These children begin to display various abnormal behaviors in the preschool years often including:

1. A need to preserve sameness
2. Marked language abnormalities
3. Indexes of developmental disorder - strange body movements, posturing and "soft" signs of neurological impairment

### **Etiology**

While the cause of autism is speculative different theories have surfaced in the past including:

- a) Brain injury
- b) Constitutional vulnerability
- c) Developmental aphasia
- d) Deficits in the reticular activating system
- e) An unfortunate interplay between psychogenic and neurodevelopmental factors
- f) Structural cerebellar changes

With several different etiologies or biological cause's, autism is considered a syndrome rather than a disease. Some researchers have proposed genetic causes, viral causes,, and immunological ties,,to be the cause. An increased incidence of two or more miscarriages and infertility, as well as preeclampsia and bleeding during pregnancy, have been shown to occur in mothers of autistic children. Perhaps the disorders occurring in pregnancy are affecting the fetus and showing up as autism in the children. Studies have also been done comparing the maternal antibodies of mothers with their autistic children. These findings suggest that abnormal maternal immunity may be associated with autism because plasma reactivity against lymphocytes was found in several of the mothers. Antibodies reactive with lymphocytes of the father were also found, suggesting the target antigen of the reactivity was a parental antigen inherited from the father. Assuming maternal antibodies may be associated with the development of autism, McConnachie and McIntyre suggested maternal antibodies of mothers with repeated pregnancy losses caused fetal demise, causing immunopathy by reacting with antigens expressed on the trophoblasor extraembryonic tissues of the developing

embryo. It has been shown by some researchers that antigens on the trophoblast cross-react with antigens found on lymphocytes.

Conceivably, maternal antibodies could react with trophoblastic tissue, causing a transitory obstruction of blood flow to the fetus resulting in nonlethal brain damage.

Equally, the abnormal behavior seen in autism might be caused by the immunopathological damage done to the developing neural tissue of the fetus by the maternal antibodies. While the literature has speculated regarding the above hypothesis and many others, at this time there appears to be an enlarging group of children, whose origin seems linked to the concept of an Immune-Dysregulatory phenomenon. Whether due to an underlying viral, retro-viral, other related entity, a likely underlying genetic disposition, and/or other "environmental" changes, the number of children affected seems to be rapidly increasing. Many of these children do not fit classic autistic profiles, but are frequently labeled high functioning autistic, atypical autistic, PDD, etc.

#### **PATHOPHYSIOLOGY:**

Similarities between behavioral deficits reported in animals with hippocampal lesions and autistic behavior have been noted by Boucher and Warrington. They found memory deficits in infantile autism similar to the memory deficits found in the amnesic syndrome. Medial temporal lobe damage on pneumoencephalograms has previously been reported in a subset of autistic children. These findings were particularly evident on the left side. Damasio and Mauer have also proposed that "the syndrome results from dysfunction in a system of bilateral neural structures that includes the ring of mesolimbic cortex located in the mesial frontal and temporal lobes, the neostriatum, and the anterior and medial nuclear groups of the thalamus." (Noteworthy is that much emphasis is put on the medial temporal lobe).

By definition, autism has an early onset before 30 months of age, while disorders appearing later in life have been thought to be symptomatically different from autistic handicap conditions. Publications over the last 13 years have cast some doubt on these relationships. While the rationale for an age limit for the onset of autism has been discussed, it has been pointed out that there is no firm evidence that similar or identical syndromes might not develop in older children.

Autism can be associated with a variety of disorders affecting the central nervous system including encephalitis. In 1981, DeLong, Bean, and Brown described three children between 5 and 11 years of age who developed autistic features while having an encephalitic illness. While these autistic features resolved after clinical recovery, one patient had high serum herpes simplex titers, and a CT scan revealing a lesion of the temporal lobes, mainly on the left side. The other two patients had normal CT scans. Gillberg in 1986 described the case of a 14-year old girl who developed a "typical" autistic syndrome after an attack of herpes simplex encephalitis. Widespread bilateral destruction of the brain parenchyma and the temporal lobes was found on CT; there was also some involvement of the lower parts of the parietal lobes. The autistic symptoms persisted long after the acute phase of the encephalitic illness. This case contributes circumstantial evidence that a full blown autistic syndrome may be produced by temporal (and parietal lobe) damage. (This author would note that this is consistent with the areas of decreased function being seen on NeuroSPECT scans with Dr. Ismael

Mena - clinical research in progress.) It also furthers the evidence that herpes simplex encephalitis can cause an autistic syndrome. In 1975 an article was published in Cortex describing a syndrome similar to autism in adult psychiatry, involving loss of emotional significance of objects, inability to adopt in social relationships, loss of recognition of the significance of persons, and absence of sustained purposeful activity after temporal lobe damage. In 1989 an article appeared in the Journal of Autism and Developmental Disorders, describing a 14-year old boy, with a normal history until the second grade, when he was admitted to the hospital with herpes simplex encephalitis. Later he developed significant language, social, and memory deficits. The research group commented on the cognitive and behavioral deficits caused by temporal lobe damage in herpes encephalitis. While other studies have also implicated the temporal lobes in the pathogenesis of autism, this does not prove a common association between temporal lobe pathology and autism. Research has found a variety of lesions in the brain, particularly the cerebellum. Confusion and differences may be due to the heterogeneity (differences) in possible etiologies or time/duration effects within this varied syndrome we label "autistic". However, since Herpes virus has a predilection for the temporal lobes it is possible to hypothesize that there is an association between temporal lobes and autism, but not necessarily a direct cause and effect relationship. It is equally important to note that failure of development in temporal lobes early in life may produce different symptoms from those arising out of a later destruction of previously normal lobes.

NeuroSPECT scans are becoming extremely informative, as they show blood flow through areas of the brain. Blood flow implies function/activity., As noted, the Autistic children that I have been able to obtain NeuroSPECT scans on (limited by age and affordability), have shown a decrease in blood flow in the temporal (and parietal) areas. Consistent with the reports of temporal lobe dysfunction in Autistic kids, this is a very logical finding. Surprisingly, and without good explanation, is the finding of increased blood flow in the frontal lobes which is consistent with ADD on the hyperactivity end. (Note: While this may explain occasional success in the usage of Ritalin with some Autistic children, Ritalin has the effect of decreasing blood flow on the whole brain. Therefore, while helping the child if there is too much flow in the frontal area, you may not be helping "over all" if you are cutting low in areas that are already low, such as in the temporal or parietal areas).

It is also interesting to note that in my working with Chronic Fatigue Syndrome, "Immune Dysregulation" for the past 12 years, in a recent study (pending publication) we have observed a significant diminution of blood flow in children suffering from CFS/CFIDS in both temporal and, to a lesser degree, the parietal lobes. It is this researcher's opinion that there is a strong connection between various immune dysfunctional/dysregulatory states appearing over the last 12 - 13 years and the emergence of an onslaught of "atypical" autism.

From the Journal of Clinical Immunology and Immunopathology, Singh et al. hypothesized that autoimmunity secondary to a virus infection may best explain autism in some children. Congenital rubella virus and congenital cytomegalovirus have been indirectly involved as causative factors in autism. Researchers found evidence for autoimmunity as a possible mechanism to explain autism, based on a cellular immune

response to myelin basic protein, antibodies against putative brain serotonin receptors, and neuron-axon filament proteins of the nerve cell. About 67% of the autistic sera contained antibodies to NAEP. They were present in almost all patients with abnormal cell-mediated immunity (CMI). An interesting observation was that the sera from household contacts was also positive for anti-NAEP (46% of the siblings or 55% of the parents). Antibodies to NAEP have been previously reported in neurotropic "slow virus" diseases (Kuru and Creutzfeldt-Jacob disease) in man. Other studies of household contacts of patients with degenerative disorders of the brain have revealed anti-NAEP to be highly prevalent, suggesting an association of an infectious agent (i.e. slow virus) in the etiology of these diseases. With this hypothesis, eight patients (six with abnormal CMI and two without the defect) were placed on immunomodulant therapy. In six patients, parameters in T-cell function and defects in AMLR were partially corrected. Improvement was noted in terms of clinical status, speech, sleep, and attention. After 8 weeks they could speak more than one command; after 16 weeks they were able to write a complete sentence; and all had increased attention span and or ability to sleep. The two patients without abnormal CMI were nonresponders.

This research has also shown a significant depression of CD4+ T helper cells and their suppressor-inducer subset, with an increased frequency of the null allele at the complement C4B locus in children with autism. As similar changes have been known to occur in other autoimmune diseases, these researchers postulate that the increase of serum concentrations of sIL-2 (soluble interleukin 2) and sT8 antigens indicates immune activation of a T-cell subpopulation that may be important in the etiology of the disorder in some children with autism. In a fashion similarly proposed for Alzheimer's disease, it is possible that an anatomical alteration in the brain, particularly the hypothalamus (because of its role in controlling emotions and behaviors) of autistic children, may result in a functional disturbance of the neuroendocrine-immune axis. Further investigation is necessary. Many of the Autistic children I have been evaluating have shown very high T-4 and T-8 counts.

While reactions to MMR (measles/mumps/rubella) vaccine are in general mild, cases of meningoencephalitis occurring in the third and fourth week post-vaccination have been reported in the UK and elsewhere. Starting in February of 1990 the British Paediatric Surveillance Unit asked all paediatricians to report all cases with one or more reactions occurring within six weeks of MMR vaccination. Reactions they were asked to look for included neck stiffness (or sign of meningism), extreme irritability, convulsions, altered consciousness, unexplained screaming attacks, motor or sensory deficit, visual disturbance, visual deficit or speech disturbance. In some of these cases mumps virus was cultured from cerebrospinal fluid (CSF).

Nucleotide sequencing of virus isolates has enabled strains of vaccine origin to be separated from wild strains. Definite cases of a vaccine-like strain of mumps virus were cultured from CSF. While there was no sex differences in the cases reported overall, an excess of males (2:1) were reported in the definite or probable categories. Even though mumps occurs equally in both sexes, complications of meningoencephalitis following both mumps vaccination or wild infection has been reported more frequently among males than the females, with ratios ranging from 3:1 to 5:1. One must bear in mind that the natural occurrence of meningoencephalitis following mumps infection is estimated to be 1 in 400 cases. Before the MMR vaccine was introduced in the UK, mumps was

responsible for a fifth of all reported cases of viral meningitis. Mumps vaccine related meningoencephalitis is generally short lived or mild, but some permanent sensorineural deafness has been reported. Published evidence indicates that vaccine reactions are rare and unlike the natural disease, does not lead to permanent sequel.

In this author's opinion, while the UK and Canada have focused on the MMR vaccine, both its mumps component and Rubella, there is much skepticism regarding the "true" incidence of mumps meningoencephalitis as reported above, and vaccine risk remains very doubtful, if existent at all. This country has not experienced or reported any significant problems with the MMR vaccine. While there may be a possible "triggering" factor with Rubella and an immune active state, this remains an unlikely cause of Autism. Unless further research creates a stronger connection, it remains safer to vaccinate a child than not. Consistent with the question of whether there is a peculiar or unusual immune reactivity when a child is younger, waiting till a child is 3 or 4 could not be faulted, but with ongoing measles outbreaks occurring at times, it is not something easy to recommend routinely at this time.

Another difficult position to address, is the possible role of fungi in the pathophysiology of Autistic dysfunction. *Candida albicans* is arguably the single most important fungal pathogen. Because it is a commensal organism present in virtually all human beings from birth, it is ideally positioned to take immediate advantage of any weakness or debility in the host, and probably has few equals in the variety and severity of the infections for which it is responsible. Clinically, there is abundant inferential evidence that both mucocutaneous and systemic candidiasis are typically associated with defects or weaknesses in the cell-mediated immune response. They may reflect specific deficiencies in this context, such as in chronic vaginal candidiasis, or chronic mucocutaneous candidiasis. (One must note, that while one might anticipate neuro-cognitive dysfunction in these states, it is not a primary focus of discussion. Significantly, these states do not account for or induce an "Autistic" state of CNS dysfunction, seeming to negate many metabolic theories that abnormal metabolic products, seen in exceptionally high volume in these type of patients, induce Autism.) Epidemiological studies of *C. albicans* have been hampered by the lack of precise and reproducible methods for identifying isolates. Whatever the ultimate role and pathogenesis of *Candida*, there seems to be no doubt that it can play a role in many pathologic conditions. Yeast is certainly a potential pathogen in any immune dysfunction/dysregulated state. Yeast may be seen as a secondary phenomenon due to a generalized immune dysfunctional state. A yeast "overgrowth" in the GI tract can interfere with nutrient absorption, altering Amino Acid and protein metabolism and thereby altering multiple body functions. I do believe that it is logical, if you are in an immune dysregulatory state, you may get an overgrowth in the G.I. tract. It is likely *Candida* may play a role in what is referred to as the "leaky-gut" phenomena. Some physicians believe you actually have a toxin released by the yeast and absorbed into the body, affecting the nervous system.

Clinical Manifestations

Typical characteristics include:

a) nondeveloped or poorly developed verbal and nonverbal communication skills

- b) abnormalities in speech patterns
- c) impaired ability to sustain a conversation
- d) abnormal social play
- e) lack of empathy
- f) an inability to make friends

Also frequent seen are:

- g) stereotypic body movements
- h) a marked need for sameness
- i) very narrow interests
- j) preoccupation with parts of the body
- k) changes handedness or becomes ambidextrous, as they turn autistic.

Role of food allergens/sensitivities:

From the Department of Biochemistry, Birmingham University, United Kingdom, Dr. R.H. Waring, along with B.A. O'Reilly, coordinator of the Allergy-induced Autism Support and Self-Help Group is doing some exciting work (pending pub.). They are currently carrying out studies to see if children with known food/chemical sensitivities, along with autism, have a deficiency of phenolsulphotransferase-P enzyme and/or a low capability to oxidize sulfur compounds. From the results they have obtained so far, all 18 children showed to have a low enzyme level, and some had little capacity to oxidize sulfur compounds. Now, after 40 children have been tested, the results show the enzyme is low in every child. This enzyme is necessary to metabolize amines and phenols. So it makes sense that with a reduced level children will not be capable to fully metabolize chemicals and foods that contain phenol. Autistic children typically have adverse reactions to many medications. Sedatives keep children awake, antibiotics woen behavior even anesthesia may be a problem. Equally, a build-up of substances such as dopamine, serotonin, and noradrenaline is possible as amines are also metabolized with the same enzyme. As it is well documented that high serotonin levels are found in some autistic children, if other body chemicals build-up they may be metabolized and produce a substance similar to phytoxins (plant toxins). In unpublished results Dr. Waring ran blood tests on 14 children and found that all had low levels of sulfate (the substrate which is used by the phenol-sulphotransferase-P enzyme). These results show that there may be a fault in the manufacture of sulfate, or it is being used up by an unknown toxic substance the children are producing. [The test for this enzyme is simple; one administers a dose of paracetamol (acetaminophen) followed by a urine collection test for eight hours.] Parents reported feverish, off-color children who's urine output was limited. Moreover, some children were not able to urinate too cse to the eight hour point. [Caretakers should be aware of the potential side effects of this drug on autistic children , as it is given freely for minor illnesses.]

Many autistic children have major allergies or intolerances to many chemicals and foods. The main offenders appear to be wheat, cow's milk, and salicylates. Occasionally these reactions may turn into urticaria or asthma, but in the majority of these children the effect is the worsening of autistic-like behavior. Interestingly, family history reveals eczema, migraines (especially in mothers), hay fever, and asthma. These children crave

the very thing that does them damage. They do this not only with foods, but also non-food items they ingest, mouth suck or chew (e.g. metal, plastic, perfume, soap, plastic, etc.). Nearly all autistic children become picky eaters at the time they "change," eating only a few different foods and both craving some and avoiding some. Some autistic children begin to eat non-foods items with notable immoderation. There has been speculation that diet may effect other factors of the body. In a double blind placebo controlled trial children were put on a restricted diet for a period of three to four weeks. The foods allowed were two meats, two carbohydrate sources, two fruits, a range of green and root vegetables, bottled water, sunflower oil, and milk free margarine. The child's preference was taken into consideration, and suspect foods or foods the child craved were avoided. Worsening of behavior was connected to all relapses with reintroduction of foods, except for four relapses caused by cow's milk and two by cheese, which produced physical symptoms only. This trial proved diet can contribute to behavior disorders in children, and that their parents were able to report on a behavior change caused by food that could be reproduced in a placebo controlled trial. Although the way in which the diet works is not clear, allergic, toxic or pharmacological mechanisms may be involved. It is possible that diet (foods) ght induce changes in brain perfusion similar to those found by Lou et al. reporting on attention deficit disorder. Many parents have commented after just the initial food/dietary phase, that their children had become more manageable and more amenable to reason. Some to the extreme of beginning to talk, that did not talk before. One should not underestimate or ignore the potential reactivity of the immune system, and various foods, proteins, peptides, or other sensitivities. If a parent notices a good effect from a diet elimination, effort should be made to support the family in their search for other "logical" exclusions. Again, unless there is another significant jump, "extremes" are usually not necessary or justified. What I have experienced clinically, is that as a child begins to do better, it is easier to judge what throws him/her off. You should be expecting a continuous upswing and if there is a fall back, try to think what did he/she have to eat before the decline. What was done differently? Stay "tuned-in" that way . It is also useful to keep a diary, particularly tracking "off" times.

At the Autism conference in Las Vegas, July 1994, Dr. Luke Y. Tsai presented information on neurotransmitters and psychopharmacology in autism. While identifying and looking at different neurotransmitters, neuroscientists have also found different problems with too much or too little of one or the other. Too much dopamine in the brain's limbic system ( the brain's emotion center) , and too little in the cortex (the seat of reason), may cause suspiciousness and an inability to process the information in the rhythms and cues of social interaction. Inhibited children may have excessive levels of norepinephrine. In people with too much norepinephrine everything is pumped up; every stimulation demands a response. The other side of the coin is that a shortage of norepinephrine seems to rob people of the ability to know what's important. Working memory (the part that stores information while the mind considers if it is worth keeping and where to file it) fails without enough dopamine. Altered central dopanergic function in the midbrain has been implicated in the pathogenesis of Tourette's Syndrome. Shortage of serotonin in the frontal lobes and in the brain's limbic system (where emotions come from) seems to relate to impulsivity; the person may not be able to connect disagreeable consequences or what provoked them Obsessive-compulsive

symptoms may be caused by a serotonergic defect involving the basal ganglia. Several drugs which either enhance or block the action of neurotransmitters have been looked at in Autism and other neuro-processing disorders. Haloperidol (Haldol) is a dopaminergic blocking agent Diphenylbutylpiperidine (Pimozide or Orap) is a dopamine antagonist Methylphenidate (Ritalin) may enhance CNS catecholamine (dopamine and norepinephrine) release from sympathetic nerve terminals and cause inhibition of re-uptake in the caudate nucleus Clonidine (Catapres) is a alpha-adrenergic agonist Tricyclic antidepressants inhibit the uptake of neurotransmitters at adrenergic nerve terminals - this results in an increase of monoamine neurotransmission. Clomipramine (Anafranil) and Fluoxetine (Prozac) are selective inhibitors of serotonin re-uptake in the CNS Naltrexone - an opiate antagonist

Also at the Las Vegas conference, Dr. E. Gene Stubbs hypothesized that interferon alpha (INF), a product of many cells, but especially cells of the immune system, may be a major factor in the cause of autism. When INF is given in large doses to children with cancer, the result is that they withdraw and become noncommunicative. These are primary symptoms of autism. Also, children with autism have higher pain thresholds, and elevated endorphins in their cerebral spinal fluid. INF can activate endorphin receptors and is a potent analgesic. In addition, INF has been reported to contribute to autoimmune disorders and allergies. An increased incidence of antinuclear antibodies has also been reported in these children. Children with autism frequently have an impaired immune function: high levels of INF could impair the immune function.

In a preliminary study, 10 autistic children were tested for their level of serum INF. All 10 children with autism had a higher incidence of serum INF than the control adults. Normally, levels of INF are not detectable unless one had an infectious disease or illness. While the levels of the autistic children were high, they were not as high as expected. (Note: My experience thus far has shown inconsistent/scattered levels, with some Autistic children being high, while others are low or normal. Interferon could possibly be a potential marker to distinguish different groups, but is routinely subject to multiple influences.) Other preliminary evidence suggests that a subgroup of autistic children have elevated levels of other cytokines (INF is considered a cytokine, a soluble substance that is secreted by cells that affects other cell functions). It is this author's opinion, that the "true" pathophysiology lies in these other cytokines, rather than alpha interferon. Research is urgently needed to sort these factors out and open new doors for potentially dramatic therapeutic changes within the next year or two, longer if not pursued urgently and correctly now.

William Shaw, Ph.D., presented Organic Acid testing which showed abnormal metabolites in the urine of autistic children. Closely resembling normal products of metabolism, these metabolites are presumably toxic and may interfere with normal cellular energy production. Also, an increase in the yeast-specific sugars arabinose and arabinitol has been found.

Several explanations are possible:

a) These metabolites are due to a metabolic block caused by a new inborn error in



metabolism analogous to PKU.

b) These abnormal metabolites are produced by systemic or gastrointestinal yeast in the human host due to yeast overgrowth caused by a deficiency in cellular immunity and/or extensive antibiotic use. If so:

1. These metabolites are toxic and may be involved in causing autism and/or worsening some of its manifestations .
2. These abnormal metabolites are produced by yeast in the host but are nontoxic and their presence is insignificant.

c) The abnormal metabolites are fake due to yeast or microbial contamination of urine. (This last possibility is not very plausible because the normal children only excreted very minute quantities of these compounds in their urine.)

Dr. Shaw's test may prove valuable in the diagnosis and/or treatment choices in autism. THIS AUTHOR'S CURRENT POSITION ON AUTISM: It has been my direction to "backdoor" into working with Autistic children (and other learning disorders). While ADHD (Attention Deficit Disorder) caught my interest in medical school and during my Pediatric training in the mid-seventies, we had very few answers, and very little objective data to make decisions on within the field. Therapy was very "symptomatic" with little understanding or knowledge of the physiologic events occurring within the brain. During this time, Autism was considered a psychiatric disorder, with most children assumed to be "untrainable" or "barely" trainable, to have low IQ's, and little reason, if any, for optimism in the future.

In 1983 my wife came down with an undefined illness, marked by recurrent flu symptoms, fatigue, sore throat, cervical lymph glands, and, as was ultimately noted by researchers studying my wife and other adults with this disorder, cognitive dysfunction, characterized by short-term memory loss and decreased "processing" ability. While desperately trying to figure out how to help my spouse, and by that time other "mothers" and children within my practice, I took a strong look at the principle of nutritional supplementation and amino acid metabolism. During this time, some Autistic children were referred in from West LA. To my surprise, upon testing they had "Candida" titers higher than most patients I was evaluating at the time, and Amino Acid profiles with many similarities to those I was seeing in other patients, with this "mysterious" new phenomena. As I was already beginning to view this phenomena as "immune system" related, it made no sense based on all previous teaching, What did Autism have to do with the Immune system?

As I began attending and taking part in conferences looking at advanced work on neuro-cognitive dysfunction, NeuroSPECT, other advanced neuro imaging techniques and newer quantitative measurements, there was/is an emerging understanding of the Neuro-Immune axis and the concept of PsychoNeuroImmunology (the rapidly developing field concerned with complex multi-dimensional interactions between the immune system and the central nervous system). These discussions and presentations raised the idea within me what if a more extreme version of this was "Autism"? The idea of Autism being linked to a severe Neuro-Immune Cognitive Dysfunction is logical, one can say more than probable, at this point.

In addition to the articles noted above, there are many papers already in the literature, noting various immune abnormalities or potential markers. With each passing day, there is less reason to doubt the potential significance of this for "Autistic" syndrome children (?? all or some) and probably other cognitive learning disorders. While metabolic factors certainly play a role in these children, and need to be approached and understood far better than they are now, it is extremely unlikely that the origin of this dysfunction lies in a metabolic/genetic defect as we currently understand them. At this time, I would propose that these metabolic abnormalities are secondary to a dysfunctional body. [ A process affecting the mitochondria (energy factories) of potentially all cells in the body.] It seems likely that the linkage here is a dysregulated immune system, and the effects created by "out of control" cytokines. As noted above, the ultimate origin or etiology may lie anywhere from genetic factors, a "genetic disposition", to viral, retro-viral, or "other" environmental factors. The good news is that patients do not need to wait years for these answers to emerge, and then years longer for testing of potential agents to develop/occur and gain approval; thanks to research of the last 10 - 12 years there are agents developed as "immune-modulators" which can "adjust" various cytokine levels and other factors. However, these newer, generally extremely safe pharmaceutical agents, cannot be used without first establishing a "justified" population to try them with. While the literature and my personal experience and observations supports without question the concept of an "Immune Dysregulatory" dysfunction within Autism, there exists no solid, medically valid publication, showing "controlled" differences in Autistic Syndrome children. Within my own practice, in running a series of tests including Immune markers and general function, viral titers/exposure, general chemistry and metabolic markers, one sees informally the branching of this group of children labeled "autistic" into at least 3 patterns, maybe more. It is important to define appropriate metabolic and immunologic markers/parameters, so that we might better separate and understand children's different response to therapy, etc.

In reality, most "antedotal" reports of "successful" therapies for autistic children can be understood through the concept of a dysregulatory Immune System and/or altered metabolic sensitivities and dysfunction. In fact, I would dare say that the only unanswered question in this concept is whether one will be able to correct all neuro and metabolic abnormalities via "Immune-Modulator Therapies", or whether there will be a need for combined Immune and Metabolic approaches over time.

Seeing children make dramatic cognitive progress on modified Elimination diets, anti-fungal therapies, and anti-viral/immune active therapy heightens the urgency to move forward into controlled trials with definable markers. With the recent recognition of the fact that if the brain "misses" certain stages of development, you may never make that up fully in the future, the urgency of helping these children can not be overstated. As noted above, we can "accelerate" the medical/therapeutic process greatly, but only if approached with the correct resources and manner. In the meantime, there is some logic worth following in approaching a child therapeutically at this time.

To start with, it's always best to start with the concept of removing "negatives", clearing away "debris". In that position, removing potential food sensitizing agents makes sense, is any agent/protein stimulating a negative immune reaction in the body will create more CNS dysfunction, via the Neuro-Immune pathways. It is logical to attempt to normalize a

child's nutritional state, and often, since one is looking at a "stressed" body, there is logic in providing extra nutritional supplements.

As a pediatrician, I feel it is very important and logical to provide and replenish the bodies basic nutrients. However, at present, parents must approach this area with skepticism and caution. There are no controlled trials showing appropriate dosing or long term safety of many "harmless" agents. While there is logic in the concept of nutritional, "supportive" approaches, there are dangers and there are product concerns (re absorption, purity, over-dosage, etc.). Any nutritional manipulation in children is open to dangers or new/induced metabolic problems, vs. potential gains. It has been this authors experience that megadosages usually seem to provide little if any gain vs. risk, and that any "extreme" is subject to many problems in children.

Basic replenishment certainly includes a good basic vitamin / mineral / fluoride supplement, additional Iron, Ca<sup>++</sup>, Mg<sup>++</sup>, Zinc<sup>++</sup> as indicated, a diet high in protein (the source of natural amino acids, the "building" blocks of the body), low in sugar, good nutritional value, but for the concerns of allergy reactions or sensitivities, best to avoid whole wheat, whole grains, "health-food" store eating. A product such as Nu-Thera, while antedotal, has been evaluated and observed in a reputable manner, such that it seems a good supplement for most children, with a general caution not to dose at maximum dosing.

The area that a lot of mistakes have been made in, is that of Candida or yeast. Yeast is not the answer to this problem/syndrome. or perhaps any clinical syndrome it is frequently associated with, but seems an opportunistic organism, that can create or accentuate problems in an already dysfunctional host or immune system. You can help a child by treating them for yeast overgrowth or infection, but it and all current therapy should be viewed as a step along the way of getting them better, it is not an answer to the whole problem.

As diet plays a large role in the control of Candida, reducing sugars, wheat products, and other yeast promoting foods is logical within reason. In general, I do not see enough clinical gain to justify "extreme" approaches via diet. There are some children in which "extreme" diet eliminations or adjustments may be logical. Once basic diet needs are met, there seems good logic, although again very little "hard" medical data, in looking at some type of anti-fungal/anti-Candida approach. (Tests that are being developed may help monitor therapy progress with quantifiable markers in the future.) I prefer a trial of Nizoral (Ketoconazole), using as indicated Diflucan, oral Amphoterecin B, and occasionally Nystatin. While logical to continue if clinically successful, care must be taken to monitor these medicines appropriately, and likely "rotate" around, not stay on any individual medication for too long a time period. Along with medication, it is obviously beneficial to avoid sugar loads (e.g.. fruit, fruit drinks, candies, sugar containing soda, etc.), but, as noted, I do not believe it is necessary or overall beneficial to go to "extreme" diets. Again, follow an approach of common sense. Solving the "yeast" problem is not the answer to Autism, and yet in some children it may be very helpful. Therefore, a therapeutic trialchanging one variable or treatment approach at a time - a critical concept for all therapeutic changes or steps for any child) is justified per the above discussion.

Until "controlled" groups are identified and therapies evaluated, any therapy is antedotal. I encourage each parent to look upon their child as their own control. It is critical to be patient and allow enough time to thoroughly evaluate an agent for "gains" or "losses" (to this author, one should not continue using any agent which introduce "negative" and should avoid or approach with great caution, any agent with potential negatives). With the appropriate urgency to want to help these children, it is nevertheless a great mistake not to "organize" your approach and proceed logically, with time for appropriate judgments along the way. I would again stress the need to remove identifiable "negatives" if one expects to adequately evaluate "positives". While there have been many "metabolic" approaches and remedies discussed over the years, there must be a far greater effort at controlled trials before any "special" approach or product can be endorsed. If a parent can be sure of no harm, then cautiously trying some of the products or supplements out there may be useful, but must be evaluated closely on an individual basis.

I have great hope for the possibility of what are called "Immune-modulators". The antedotal reports of success with DMG (an apparently good product at "low" dosing) and Isoprinosine (?? Success) are examples of agents working via the immune system. Zovirax, an anti-viral agent I have used with some children positive for Herpes viral titers, may be successful via an anti-viral effect, or an unrecognized immune-modulatory effect. As noted, most successful antedotal therapies are explainable or understandable through the immune system. With acceleration of efforts, it is this author's hope that "controlled" trials with newer, medically developed "immune modulators" might be possible in the near future. Until that point, an overall approach, looking at maximizing the health and function of any individual patient, remains helpful to many children.

While always feeling the overall approach is far more constructive by eliminating negatives, and "positively" helping the body via supplement or immune modulators; once one has done the best possible at present with what is available and useful, there are existing "medications" that may offer help, some of it/them perhaps even "positive" metabolically.

As controversial a term as it might be, Prozac, at low dosages, may have a very beneficial effect on cognitive functioning and sleep cycle (off in so many of these children) via its serotonin mediated effects and by increasing blood flow , particularly in the temporal lobe/limbic system areas. Paxil and Zoloft are in this class of SSRI's (Serotonin Re-uptake Inhibitors) which may be particularly useful in the child who seems to space out a lot, loose focus. On the other hand, the child who comes across as very hyper, if continuing to be so after dietary trials and therapy approaches noted above, may do very well with the help of Catapres (preferably via the patch rather than tablets), or the older children with a low dose of Cylert. Opioid blockers such as Naltrexone may play a constructive role in some patients, but have not been investigated or pursued much by this author to date. While the goal must be "normalization" of the body by directed therapy, some of these agents can be useful if used judiciously and appropriately.

It has been my privilege and pleasure to see many children improve substantially by the above measures. This has only increased and emphasized the need to take these approaches into controlled trials, and to hopefully make possible the introduction of new agents in a very short time. In the meantime, work with a physician or therapist that will work with you and your child. Go slowly, with a concept that when things are better, it takes time for the brain and body to change physiologically. Look for combining and building upon safe approaches and your child's "positive" clinical responses, being careful not to create "negative" effects or to act too quickly to document changes. Any parent's anxiety and desire "to find the answer for their child" is understandable and commendable, but at this point, slow/progressive clinical observation and trial is the best probability of success, while we hopefully speed up the day of new therapy's and understanding. I might add that this is not a "pipe" dream or need be 5 - 10 years off. Agents exist now that may have tremendous potential to help. They can become available for trial, as soon as medically credible protocols and justification exist. There are a lot of us trying to make this happen.

We all know it is time, we all know it should happen. We need to make it happen, for all of you as parents, physicians, and children.

Michael J. Goldberg, M.D.

Addendum:

Literally, as each day and month passes, we are losing children who by all recent indications, are both "savable", and likely "recoverable" if dealt with soon enough. At a critical time like this, there is a general slowness in approach, with debate raging louder between Immune and Metabolic schools of thought, and the "no" medical problem thinking of most of "Academics" still. Sadly, much of the accelerated attempt of funding patients are fighting for, will be spent pursuing "more of the same" rather than looking at the new possibilities for the future. At a time like this, with technology and new biomedical advances at our disposal, there is only one way to succeed (I define "succeed" as make advances in therapy for "autistic" syndrome children). If we do not make use of tools and techniques that have evolved in the last five to seven years appropriately, and at academic, peer-reviewable levels, we will never succeed in changing the pace of therapy for these children. Happily, as I know word is beginning to circulate, I am attempting to initiate a controlled cytokine project, in an attempt to open the door for major therapeutic change within twelve to eighteen months (sooner if resources mobilize faster).

There are many advances possible now, but they will NOT occur/succeed unless data and studies are done at a peer-reviewable level (clinically designed and coordinated to speed up the emergence of new ideas, new concepts). Any other efforts will ultimately be more "spinning of wheels".

At the DANN conference in Dallas, January 1995, there was a wonderful coming together of ideas and exciting new directions, but a sad split between "metabolic" and

"immune" camps. Also evident was the absolute "distaste" for the mention of academics. I stand strongly behind the convictions expressed above. I would politely challenge anyone to produce a model that has succeeded for any disease in the past, without ultimate evolution and definition by defined studies, acceptable at Academic levels.

Without objectivity, no therapy can be appropriately evaluated, nor will new therapies (already in existence) become accessible. While metabolic vs. immune discussions are interesting, the only major change on the near horizon, will be if the idea of immune-modulators (agents already in existence, but for which we must provide an objective basis to open the doors to their usage) can be tried, and is optimistically successful (many researchers I have been involved with over the last five to ten years, believe success is likely, but remain skeptical till proven). While we "debate" other ideas and options, I believe it is urgent to accelerate efforts to make possible testing of these agents in autistic syndrome children as soon as possible! As noted, with increased discussions already appearing relating to "auto-immune", "inflammatory", origins for "sub-populations" of children, I would propose without hesitation, that "immune-modulating" agents if effective, will be far safer than steroids or other agents nodiscussed, and needless to say, a better alternative than discussing surgery or severe behavior therapies for these dysfunctional children.

Examining the last ten to twelve years, it has become obvious we are looking at new patterns of disease and illness, that do not fit previously described syndromes, etc. Attending conferences over the last 7 years, being exposed to many "cutting edge" technologies and ideas, one trend emerges. We are looking at a process, appearing to decrease flow/function in the temporal lobe of the brain (other areas may be affected, but the temporal lobe I would propose is the key and common denominator in this process) affecting individuals differently based on their age, and maturation of their immune system.

The common denominator making sense through these discussions has been the immune system and a state of "dysregulation".

I would propose to all of you, that while many metabolic and other phenomena, make sense when thought of in a state of or propensity for immune activation/dysregulation, no known pediatric or adults metabolic process makes sense as a model for a "primary" metabolic defect in these children and related patients. Therefore, while we may to some degree help the body metabolically, develop new markers, and even answer some very interesting questions over the next ten years, we are unlikely to make major medical changes or even approach a cure while focusing on and dealing with what appears to be "secondary" metabolic phenomena, explainable fully by altered cellular metabolism (a fact brought out in many respectable articles over the last 5 years, and accepted at NIH/Academic levels, etc.). This is a dysfunction that is logical secondary to altered cellular mitochondria and immune reactive phenomena. In this light, why are many physicians and researchers trying to "reinvent the wheel", when there are models and evolving technologies explaining all we are discussing logically and with more and more factual physiology. Because, there are still gaps in the above physiologic

understanding, basic science will still take (if left alone) probably five to ten years to get into any meaningful therapy discussions. These children do not have "years" to wait. Dr. Gupta and Dr. Nancy Klimas (Univ. of Miami), are ready to finish and proceed with a protocol to do a controlled study of cytokine levels in "Autistic" syndrome children. These are professors, who if the study is successful, would be unchallenged at the NIH, Academic levels, many have come to disdain. And yet, as I tried to say at the DANN conference and in many other discussions, if we do not move at "Academic" levels, few will listen, and little will really be done. If we do not unite as physicians and patients to speed up funding for at least the basic cytokine project, we are as guilty as the "establishment" at slowing up, rather than speeding up this process.

Potentially worse, as this "epi-phenomena" has grown, there are more and more desperate parents and suffering patients. As noted above, sadly, while there is the potential to bring into play safe, essentially non-toxic medical agents, physicians and researchers are turning to "old" ideas, (i.e. steroids and other potentially toxic metabolic agents) instead of looking at newer and safer ways to treat this phenomena in children (and adults). In addition, while agents like Prozac and Paxil have the ability to actually help the brain if used physiologically (at low dose they can increase temporal blood flow, and work as very mild immune modulators), physicians, as has been done in the past, are using medications at non-physiologic dosages and accepting multiple side effects or partial results, because something seems like a good idea. As much as I have become an advocate of Prozac and Paxil, this has come only after understanding that they could serve a role in normalizing CNS function, and were very safe class agents if continued. However, I do not believe this or any other currently available agent is going to be successful without an "overall" sound metabolic, nutritional, and immune approach prior to its usage. Likewise, even with the potential emergence of immune modulating agents for therapy, I am not sure whether they will be effective by themselves (as implied by some) or need to be used in a "combined" approach, something that could be designed into controlled trials, if we have the right input and "control" (this is not the usual way Academic's or Drug companies have wanted to design or fund trials in the past).

Watching this "epi-phenomena" for the last ten to twelve years, other factors are obvious. If patients are not appropriately identified by scientifically validated markers, we will never sort out or be able to understand the reasons why different patients respond to different agents (pharmaceutical, nutritional, metabolic, etc.). The truth is what we call Autism, ADHD, CFIDS, etc. are all "heterogeneous" populations, in which any drug or therapy trial appears doomed to frustration and failure, without newer, appropriate "objective" markers. At the Dann conference, the idea that we needed to pursue Academically acceptable studies at peer-reviewable levels, was met with very mixed feelings, and some open hostility. Without this approach, I challenge anyone to tell me how we are going to have significant impact for patients on the medical establishment. In fact, unlike the past, the situation with "restricted" medicine and "fixed guidelines" by HMO and insurance companies, is going to deny care to these children and unless we all help prove the system wrong. Unlike the past, there are ways to do that now that did not exist.

As noted, parents are desperate, reaching for straws, and may be directed or advised into long-term negatives, rather than gain. A metabolic dysfunction by altered cellular metabolism and immune dysfunction, is not likely to correct by any excess of agents introduced to the serum of the bodies. A backup of these agents, may, as noted, be in themselves toxic. Along with others, I have been looking at the idea of an agent called Trental. In theory, it could be an excellent temporary agent, but I have yet to be able to get an answer, regarding long term safety for children. Any therapy proposed must be safe without a doubt. Many of the physicians at the DANN conference had questions with respect to some current therapy usage, and many of us are aware that while some agents may be helpful, some can be toxic, even those called nutritional or metabolic.

To all of you reading this, I apologize for the "personalized" emotion of this last entry, but it has become obvious that with time, many of the negatives expressed above are happening to children, and if appropriate steps do not begin, the future remains ominous for most of these children. While much of "mainstream" medicine remains convinced that many of these children are retarded, it has become evident that at least currently, most of these children are very bright, and their dysfunction is likely a medical problem, unlike any routine disease process in the past, but just as logical, and optimistically, just as treatable