Proposal: To develop a program to screen infants and identify at-risk factors for autism. To development guidelines for the prevention of vaccine injury in susceptible infants. To advance knowledge of treatment options and treatment development for people with autism. To prevent the development of abortion policies in regards to this population.

Max and Sandra Desorgher: Executive director and deputy director of World Community Autism Program, SA
Email desorgher@sai.co.za
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Introduction

The diagnosis and recognition of autism spectrum disorder has risen, according to some, to epidemic proportions. Once considered a rare psychological condition, recent advances and communication have propelled autism to the front headlines in medical journals[1] as well as the news media.[2,3] Funding for research has been slow and provided almost exclusively to genetic studies. Population studies[3] lag behind, with forthcoming information being too little too late for many who have and will suffer the 'lifelong' disability of autism. The cost to family and community for providing lifetime care for individuals with moderate to severe autism, estimated at $2,000,000 per individual, is forcing governments to take a close look at the possible causes for the increase in diagnosis, educational impact and long-term commitment and cost of continued ignorance.[4]

World Community Autism Program was founded in 2002 with the principal aim of redefining autism as a treatable condition, and to develop the program that can bring about improvement and recovery and allow these children to reach their full potential. We have stated many times, that the biological markers that are consistent in this population are measurable and it should be possible to develop a screening program to identify autism as a biological condition, and armed with that knowledge, to give parents the choice not to vaccinate, and to implement dietary and other programs that are known to produce the best outcome for these children. As well as biological markers, a family background of certain 'autoimmune' diseases, metabolic disorders and genetic and chromosomal differences and early signs of feeding disorder, movement disorder, visual disturbance should alert care-givers to a higher risk of the development of autism and the need to screen.

Sara

Our work begins in 1994 when Sara Johnson, an 11 year old girl diagnosed with moderate autism with 19 primary characteristics of autism began a journey of recovery when lutein-containing foods were removed from her diet. She was declassified at the age of 15 by the Marcus Institute in Atlanta, Georgia.

Her adoptive mother, Sandra Johnson (now Sandra Desorgher) was the first to identify the lutein connection. Sandra had suffered from severe food intolerance reactions her whole life. A lifetime search to understand her condition led to the discovery that lutein was the common denominator in her food intolerances. When she adopted Sara in 1989, Sara exhibited severe behavioral problems, hyperactivity, food intolerance, and autism. Sandra's background in food science and nutrition led her first to implement a functional hypoglycemic, gluten and casein-free nutritionally rich diet. Her background in psychology and wide experience in working with special

needs and behaviorally challenged children gave her the tools to help Sara overcome many of her behavioral problems, to the point that Sara could be enrolled in a regular school and made great strides educationally. Sara was already virtually gluten free, limited in her intake of dairy products to dairy fats which are very low in casein, and her diet was additive-free and food dye-free. Nevertheless, at age ten, Sara still exhibited the symptoms and behaviors of autism.

Sandra became aware of the research into food intolerance in autism in 1994, including reports that many children had made great improvements when certain foods were removed from their diets. She also was aware of the work of Rosemary Waring of UK who reported deficiency of PST-P (sulphating) enzyme in autists. After the improvements she experienced in removing the lutein-containing foods from her own diet, she postulated that the same diet restriction might be of benefit to Sara. After attending a conference hosted by Allergy Induced Autism, she decided to try the diet with Sara. She wrote a diet protocol that eliminated lutein and major sources of gluten while providing all known essential nutrients, and implemented it in November 1994.

Within two weeks:
1) Her oppositional behavior dissipated to a normal 11 year old level, flaring only during sibling rivalry.
2) Her inappropriate laughing and giggling subsided except for two 4-hour periods directly corresponding with dietary infractions (wheat).
3) Her sense of danger became measurably increased to typical 11-year-old standards. Her apparent insensitivity to pain became replaced with average complaints to typical discomforts. There have been NO incidents of self-abusive behavior since her diet was changed and NO periods of withdrawal into the autistic psychological state that she previously often entered, in which she was unreachable by our attempts to communicate with her.
4) She initiated interaction with family members and peers, including: sitting next to siblings to watch TV and game playing (checkers and chess). She made us aware of her desire to participate in competitive sports and exhibited skills which indicated she could do so successfully. She has joined the indoor soccer team and is doing great. She is trying to decide between baseball and softball. With her new-found interests she is leaning towards the co-ed baseball, whereas we are pushing towards softball with same-sex typical role models for her to develop friendships in the little time she has left to fill in so many blanks before entering her teenage years.
5) Her use of verbal language became normal and interactive, even to the point of causing her to blush initially when she became embarrassed by her excessive elaborations about daily events and interactions with classmates. Her intonation and expressive capabilities no longer have the mechanical qualities and are spontaneous and original.
6) She voiced concerns over distressful situations for family members and peers.
7) Her autistic gait dissipated within 4 days.
8) She was running and walking in a typical 11-year-old gait.
9) Her perception became clear as did her writing and drawing, replacing the odd distorted drawings and overlapping letters we had become accustomed to.
10) Her rocking decreased greatly and became occasional after 3 months, with 3 to 4 days passing between episodes of brief periods of rocking lasting only minutes. This was the last autistic behavior to dissipate.

She also: voiced preferences using aesthetic choices; increased her assertiveness and began to try things she had refused to attempt prior to the implementation of 'Sara's Diet' with the strict regulation of nutrient intake and removal of the colored fruits and vegetables: rolling her hair; opening a can; coloring for fun; division; fixing her own cereal; choosing her clothes; folding clothes; learning to do dishes; taking out garbage; care for the pets; using the stove, blender and microwave.

In addition to her new skills, she was able to: explain behaviors and events going back to age 2 using specific details and dates, including naming all the children from the develop-mentally delayed program she had attended; recounting field trips with same and even naming the foods the other children had eaten while on these field trips; giving detailed accounts of specific abuses that had created anxiety for her when she was exposed to stimuli that reminded her of those past events, proving to us that, like Temple Grandin states in her accounts of childhood autism experiences and when speaking at conferences: although they do not appear to have reasoning skills nor coherence, they in fact are aware of the world around them and are simply unable to respond to it. Much like a person under the influence of anesthesia. Sara no longer requires a schedule, nor does she approach strangers to ask repetitive questions about birth dates, addresses, or phone numbers.

Additionally, her pulse rate normalized, from 88 to 72 bpm within 4 months. Her blood pressure normalized from 138 over 108 at day one to 94 over 68 at day 120.

From 'The Power of Exile': 'Within two days of removing the pigmented fruits and vegetables, Sara walked into the living room and saw a rainbow reflecting off a glass of water. She said "Awe what a beautiful rainbow". She had never spoke of anything in an aesthetic manner nor had she used such emotional expression previously. On the fourth day of her diet we attended the 'N.C. Conference on Autism'. I packed Sara's special lunch and off we went. I learned many things at that conference, but as much of it came from speaking with other parents as from the lectures. When I picked Sara up from the playroom where she had spent the day with many autistic individuals, I was given some original drawings Sara had done and I was perplexed. One drawing was of an ear of corn, symmetric and outlined, colored perfectly with bright yellow kernels and green leaves. After questioning the care-giver, I was convinced Sara had done the drawing. Sara had never chosen to do an original drawing to the best of my knowledge and she did not like corn. On the way home she talked more freely than I could ever remember. "Mom, I like Fall the best". "Why", I asked. "I like orange leaves" she simply answered as if we had interactive conversations every day. We stopped at a restaurant when we were nearly home. On the walk across the parking lot, Sara grabbed my arm and said "Look Mom, I'm walking like you!" and she was walking like me. Not in the odd roll-off-the-balls-of- her-feet with her elbows as high as her face, hands dangling, bouncy walk. I had been able to spot this child a football field's distance away just by looking for her bounce. Not only had I never thought that she was capable of walking differently, but I was not even aware that she was aware that she walked differently from everyone else." . . . All of the autistic behaviors which caused us so much concern have gone completely. She has done no more self-abuse, her sense of danger is working fine, she is clearly in the present and her perception is great.'

Sara continued to improve, participated in sports, achieved honor roll at school, developed independence and currently lives with us in South Africa, cooks, writes letters, and apart from a little immaturity and occasional rocking, hardly betrays any signs of her former condition.

The news spreads

In 1997, Sandra wrote: 'More phenomenal than Sara's story is the potential to reproduce the results in autistic individuals around the world. For the past 16 months, I have shared 'Sara's Diet' with the parents of autistic individuals willing to implement the protocol. Some of their stories are as amazing as Sara's. . .There have been multiple reports of eye-color change and some of hair-color change after 3 weeks on the diet. 28% were already gluten and casein-free, and in this group 90% reported positive improvements with the additional restrictions. Several have been declassified, and others state their child is now 'symptom-free'. Some have begun the use of verbal language for the first time - the oldest to begin to speak is a man aged 23 after 3½ weeks on Sara's Diet.'

One parent reported:
'Three weeks ago, we started Sara's Diet. Jonathan's eyes went from cloudy to very clear and sparkly. We have seen no adverse responses to food since we started. His speech is much better. Every therapist is thrilled, because his ABA sessions are going so well. We took him for his 6 month standard evaluation at University of Iowa Hospital this past week. The Head of Pediatric Psychology said that Jonathan has caught up in all deficit areas. More importantly, he said he saw NO AUTISTIC SYMPTOMOLOGY whatsoever during the testing. Jonathan (4 years and 3 months) was outgoing, charming, talkative, focused and cooperative for over two hours.'

Sandra also spoke at conferences and wrote a grant application to NIH. She provided free dietary consultations for fifteen hundred families at this time, leading to as many as 100 reports of recovery or declassification. Then, overburdened with the number of parents asking for her help, she withdrew from public autism work in 1997 and continued with research into autism working through private contract in India and in the USA with her new husband Max Desorgher. Contracts included work with children with autism in the United Arab Emirates, work as house parents and nutritional consultants at a training center for adults with autism in Scotland, as teachers at a private boarding school in England and also involvement in transitioning autistic adults who lived in a residential care facility to supported community living - autistic adults who had been housed since early childhood in the institution. During this same time, the work of Paul Shattock (University of Sunderland UK) and a book by Lisa Lewis led to the use of Gluten and Casein-Free diets becoming popular. This approach is based on unusual levels of morphine-like substances in the urine of autists. On removing gluten and casein, these levels drop and some improvements in cognition and behavior are noted. At the same time, increasing food reactions to colored fruits and vegetables were often noticed by parents, and based on the assumption that these were reactions to 'phenols', more foods were eliminated. The lutein-free approach faded into the background. A current review by R. Cocchi, includes that individuals using the gluten and casein free diets would likely be more susceptible to benzoate (phenol) sensitivity. Also at this time, awareness of the problem of Candida yeast overgrowth and other types of unusual gut pathogens increased. Researchers such as William Shaw now of Great Plains Lab and Great

Smokies laboratory in Asheville, N.C. started to provide parents with invaluable information, and anti-candida diets and other treatments began to be used to treat gut dysbiosis. Reports of high levels of heavy metal toxicity, along with the belief by many that mercury containing vaccines were linked to the onset of their child's autism led to chelation protocols being developed and are currently in use. Many children have made great improvements using these and other biochemical approaches to autism treatment, spearheaded by Dr. Rimland and the DAN group of doctors, but the results are tempered by many parents feeling frustrated that their children show improvement at first and then stop improving or deteriorate, that candida overgrowth returns again and again, that chelation therapy only leads to the need for a new round of chelation, that success for a few isn't replicated for the many.

The lutein theory - Gathering the evidence

After the first round of success, Sandra began to focus on explaining why the diet works. As early as 1994, Sandra had postulated that the reaction to lutein was a natural killer immune response. As the substance would likely be too small to produce an antibody, it would not show up in allergy testing. Later, she elucidated this further: 'At the time when the immune system is developing, the first immune cells must select a non-self substance which has crossed the placental barrier and react to this non-self substance in order for the immune system to proliferate. In the developing fetus there is no apparent function for a substance called lutein, a pigment which is used by the human at birth to protect the eyes from ultraviolet light. The immune system is developing just after neural tube closure which has been the time of reference given by some research that corresponds to brain imaging differences that are identified in autists.[5] However, the slightly earlier 'neural tube closure' time frame would likely correlate to a population with co-occurring spina bifida – no such correlation exists. An immune system which identifies lutein as the non-self substance would result in a correlation to Retinopathy of Prematurity - this correlation does exist.[6,7] An immune system reaction of this type could result in a correlation to a disturbance in pterin metabolism - this correlation does exist,[8] and it would result in a correlation to mitochondrial disturbance and again this correlation does exist.[9]'

But why would the immune system make such an error? There are two aspects that are of importance in answering this question – the increase in consumption of carotene-containing foods; and vaccination.

1. The World Health Organization (WHO) and Food and Agricultural Organization (FAO), in 1967, determined that humans could obtain their vitamin A from vitamin A precursor foods i.e. beta-carotene.[10] Studies have since shown that whole populations cannot convert precursor beta-carotene to usable vitamin A (retinol).[11,12] Improved agricultural practices allowed foods that had been consumed seasonally (such as colored fruits and vegetables) to become available as year round foods. Prenatal vitamins included the precursor vitamin A (beta-carotene). The amount of pigment produced by a plant depends on many factors but research has shown that lutein production increases when the plant is exposed to direct sunlight, increased sunlight or is under stress. We are consuming more pigments from fruits and vegetables than ever before. At the same time research confirms that vitamin A deficiency continues to result in adverse reactions to vaccination, blindness and death at alarming rates, even in the most developed countries.[14-19]

2. The development of the vaccine and the further development of more vaccines have contributed to evolutionary changes which can be seen in the human population. There are many who believe that vaccination practice over the last hundred years has led to an explosion in 'auto-immune diseases' or conditions that seem to involve an abnormal immune activity. In many of these conditions, it is not clearly understood to what the immune system is reacting. Conditions such as arthritis, celiac disease, diabetes, Chronic fatigue syndrome, Multiple Sclerosis, AIDS and Cancer are among the primary diseases of Modern Civilization. Autism can now be added to this list. The connection to Vaccination is highly controversial, and yet some molecular biologists are beginning to link changes in the human genome to these diseases. 'The molecular biologists, using some of the most advanced tools of modern man, are finding some of the patterns and changes which are taking place in our human population. Some of the most recently studied areas are the 'hypervariable regions' in our DNA and in particular the Human Leukocyte Antigens (HLA), histocompatibility antigens governed by genes of the HLA complex and the human major histocompatibility complex (MHC) – a region on the short arm of chromosome 6 with regions A, B, C and D - the region of our DNA which interacts with our immune system. Immunogenetic (IoGc) research is telling us that how we develop in the womb is not governed solely by our DNA and the environmental insults (impact) that the fetus is susceptible to, but is also due to the response of our own developing immune system. The immune system develops to protect the host and the impact of the immune system during fetal development includes changes which alter our genetic make-up.' What is here suggested is that our immune system is beginning to evolve in response to environmental changes. Of course, modern life exposes us to an avalanche of environmental insults, but vaccination practice is unique in the way it exposes the developing immune system to a barrage of deadly albeit 'attenuated' pathogens introduced directly into the body. But the way vaccinations are developed and cultured raises further questions. Culturing requires that the live virus is grown in a medium, such as egg yolk or agarose gel. The process of attenuation requires that the live virus is passed multiple times through culture mediums so that it loses its potency, such as animal organs. There are many reports that these procedures have led to contamination with other viruses and pathogens. Our concern is that the use of mediums such as agarose gel and egg culture has led to the inclusion of heat shock protein from chloroplast and plastid DNA into the vaccines: 'Our genes are altered to protect us from immune reactions that were unfavorable in the previous generation. Scientific investigation for autism has shown us that the cytokine activity (pre-antibody cells) are different in the autism population. Science is also looking at how this type of immunogenetic response occurs in the animal model. It is finding that using heat shock proteins as vaccine carriers results in an antibody response in the parent and an innate immune response in the offspring, indicating that there are problems with this type of vaccine development which has prevented the development and use of heat shock protein chaperone (carrier) vaccines. However, science has unwittingly been using this model for nearly a century. The agarose gel and egg yolk used to culture vaccines contain the heat shock protein structure. Live viruses alter themselves regularly by incorporating DNA, such as that of the heat shock protein, into their own structure. The heat shock protein crosses all living species. Normally we, as humans, do not get viruses from plant foods. The use of vaccines resulted in the virus (pathogen) and the heat shock protein coming into our body together. The specific heat shock proteins of the xanthophyll (egg yolk) plastid and agarose chloroplast DNA have a 72 kDa mass. The heat shock protein which protects the

chloroplast in plant foods containing chlorophyll b (pre- lutein) is also 72 kDa. It is the protein coating on the outside of the chloroplast which tells the chloroplast about the environment and the cell reacts by producing more or less pigment. In the single-celled organism this is the substance that tells the cell about the environment. The organism reacts, for instance by moving towards or away, or by producing chemicals in response to the stimulus. In the human, this is the structure which tells the immune cell when to react and what to react to. The vaccine inclusion of heat shock protein DNA has caused a dilemma – self or not-self? The pre-immunocyte selection of a substance associated with the heat shock protein 72 kDa cannot be reversed in the individual. The plant substance associated with the 72 kDa chloroplast (agarose gel) or plastid (egg yolk) is chlorophyll or lutein (a xanthophyll pigment), a substance too small to produce an antibody response, it is little more than a vibration.

Autism spectrum disorders – the growing paradigm

Autism research began in 1942 when Leo Kanner reported his findings in an article entitled 'Autistic Disturbances of Affective Contact'. Out of the 11 cases he reported, eight mentioned an unusual relationship to food, or feeding difficulties in infancy and early childhood. Nevertheless, autism was quickly taken over by behavioral psychologists, and became defined as a behavioral disorder diagnosed with a standard checklist of 'autistic behaviors'. The DSM-IV became the standard tool for diagnosing 'strictly defined autism.'

At around the same time, Hans Asperger described a group of children with unusual behaviors. Asperger Syndrome has never been clearly defined, but AS experts Volkmar and Klin have characterized it as follows: 'Proficient verbal skills, overall IQ usually within the normal or above normal range, and a solitary life style often masking outstanding deficiencies observed primarily in novel or otherwise socially demanding situations. It appears that, in the past, many individuals with AS (Asperger Syndrome) were diagnosed as learning disabled with eccentric features, a non-psychiatric diagnostic label that is much less effective in securing services. Others, who were given the diagnosis of autism or PDD-NOS, had often to contend with educational programs designed for much lower functioning children, thus failing to have their relative strengths and unique disabilities properly addressed. Yet another group of individuals with AS are sometimes characterized as exhibiting "Social-Emotional Maladjustment" (SEM)'. [13]
From another recent review from the Journal of Abnormal Child Psychology June, 2001 'Does DSM-IV Asperger's Disorder Exist?', we can see that 'dislike of certain foods' has been set apart from the diagnostic criteria and is included as an associated feature.

Along with Autism and Aspergers, recent years have seen an explosion in the number of children diagnosed with Attention Deficit (Hyperactive) Disorder. Much controversy surrounds this diagnosis, as many speculate that it is being used as a tool to control unruly children through medication, primarily Ritalin. Nevertheless, the clinical and behavioral picture shows considerable overlap with autism. The work of Feingold led to considerable success in treating ADHD with dietary intervention, specifically removal of food dyes and colored fruits and vegetables.

New diagnoses have emerged, from the educational (Pragmatic language disorder) to the behavioral (Oppositional Defiant Disorder) to the regressive (Childhood

Disintegrative Disorder). Medical and (immuno-)genetic conditions are associated with autism or autistic-like characteristics in some or all sufferers: Rett's Syndrome, Angelman Syndrome, Tuberous Sclerosis, Fragile X, Turner Syndrome, Hypomelanosis of Ito, Epilepsy, Congenital blindness, Usher's Syndrome (deafness).

Controversial findings by Dr. Andrew Wakefield link chronic inflammation in the colon and reactive ileal lymphoid hyperplasia, the media coverage has avoided mention of other Wakefield findings including and particularly significantly raised urinary methylmalonic acid as well as a smaller number of the participants presenting also with low haemoglobin in four children, and a low serum IgA. [1] Dr. Goldberg refers to autism as a Neuro-immune Deficiency Syndrome, linking it to conditions such as Chronic Fatigue and Fibromyalgia. Autism has been linked to serotonin abnormalities, sleep disturbances, enzyme deficiencies, CSF markers for immune activity. MRI studies and autopsy reports include consistent findings of Purkinje neuron and granule cell loss and differences in other brain regions including Superior and Inferior Olive, and the amygdala – the emotional learning center of the brain. Lab testing reveal a vast array of seemingly conflicting information, Streptococcus and other gut pathogen levels that in 'normal situations' would lead to symptoms, serious illness or even death, allergy testing that reveals intolerance to a perplexing array of foods, sometimes foods that these young children have never even seen, and the presence of chemical compounds that are not related to any known disease, disorder or condition. Additionally, there are now many cases of autists who have recovered, using dietary intervention, and conversely there are those who develop autism-like behaviors and conditions later in life. The lutein-free approach raises the prospect of symptom-free autists – people with the biochemical markers of autism, or with a history of autism, who present no, or minimal behavioral or biological manifestations of disease.

So we have a very complicated picture, with experts from a diverse array of disciplines trying to understand these 'Autism Spectrum Disorders' from many perspectives - immunological, neurological, behavioral, gastrointestinal, immunogenetic, pigmentary, endocrine and metabolic. So, if we are to develop a screening protocol for infants, we have to find the commonalities. This process of looking for commonalities across the whole spectrum will help us at the same time to determine if we are really looking at a single condition with many presentations, or are really looking at multiple conditions with different causes. Once we have found the commonalities to define the condition, we can begin to look at variations in that picture and try to understand how one condition can present in so many ways.

Part 1 - Explain how this immune error leads to the presentation of autism in all its manifestations.
It is conceivable that autism could be diagnosed as a co-occurring condition with any disease, disorder or condition and yet the available literature is conspicuously lacking in reports of autism with some co-occurring conditions. A thorough review of the literature could be undertaken to identify the predominant medical conditions which do not present in the autism population with any measurable frequency and for which the autism immune system could then be recognized as potentially protecting from these prevalent conditions: i.e. childhood rheumatoid arthritis, HIV-AIDS and various cancers.

An immune system selection of the pigment pathogen entering the neonate from blood sources should result in evidence which correlates the pathogen to the disease presentation. Markers suggesting this evidence exists include disturbance of granule cell dispersion and reduced numbers of granule cells in the brain, reduced number of purkinje neurons, amygdala (fight, fright, flight) disturbance. Elevated GFAP in CSF. Decreased levels of PST-P enzyme activity. Link to Cytochrome P450 immune-metabolic action in pigmentary, pterin, genetic and immune conditions associated with or co-occurring with autism. Elevated levels of bilirubin at birth in a significant percentage of the affected individuals. Visual impairment and blindness. Elevated levels of neopterin, which should correlate to dietary lutein sources entering the neonate and later the infant from breast milk, vitamin supplements and baby foods and treated as pathogen resulting in the macrophage release of neopterin. Elevated neopterin could be a rate limiting factor contributing to disturbed pterin metabolism. Alternatively the immune system of some affected individuals may associate both the yellow carotenoid and yellow pterin (sepiapterin) as non-self. Immune interference in carotenoid elimination could result in abnormal tryptophan metabolism and related serotonin disturbance.
Insects, reptiles and fish species use pterin pigments in coloration. Birds use carotenoids in the coloration of talons, beaks, cock's comb and feathers. In species such as the medaka fish the use of carotenoids in the coloration of the fish is established at the earliest stages of development whereas white varieties of the same species contain no carotenoids at this time. 'Behavior of the Pteridine, Fat and Carotenoid during Xanthophore Differentiation in the Color Varieties' of the medaka species has been painstakingly carried out by Tadao Hama and Hiromi Hasegawa.

At birth, once the infant is exposed to the post-natal environment, the full revelation of the immune choice would result in the immune system adaptations to environmental factors which were not present in the womb. Stress factors should be measured for at risk infants. Amniocentesis coupled with improved methods of identifying the respiratory pigment waste in the amniotic fluid of at risk infants should lead to a better understanding of the underlying cause(s) of autism.

<u>Visual impairment:</u>
"Ten autistic children, 6 girls and 4 boys, underwent a complete ophthalmologic examination in the Department of Pediatric Ophthalmology at the Hospital La Timone, Marseilles, France. Their age ranged from 1 to 14 years (mean = 8.5 +/- 3.8). RESULTS: Refraction showed:

- Hypermetropia (far-sighted) in 7 cases (70%);
- Astigmatism (Unequal curvature of the refractive surfaces of the eye, hence a point source of light cannot be brought to a point focus on the retina, but is spread over a diffuse area) in 6 cases (60%)
- Strabismus (deviation of the eye which the patient cannot overcome) was present in 6 cases (60%)

CONCLUSION: Ophthalmologic findings in autistic children appear to be mainly unilateral or bilateral astigmatism and binocular vision troubles. They can lead to **amblyopia** (chronic visual disorders) with the risk of functional loss of vision. **Early diagnosis of visual problems in autistic children is also essential** in order to be able

to propose adequate psychological and educational cares for the children and their family." [Ophthalmologic signs in children with autism; Denis D et al; 1997]

"A comparison between the 15 blind children who had IQs over 70 and 10 sighted children group-matched for age and verbal ability revealed that a number of autistic-like features were more common in the blind. When the nine blind children who had IQs less than 70 were compared with nine group-matched autistic children, the picture that emerged was of substantial overlap in clinical presentation, despite subtle differences on clinical impression. Similar results were obtained when blind subgroups were reconstituted according to the children's non-autistic or autistic-like clinical presentation, rather than IQ." [6]

"Children with blindness due to retinopathy of prematurity (ROP)—who are at greatly increased risk of cerebral damage - have been noted to have a high rate of autistic symptoms, but systematic controlled studies have been lacking. A controlled population-based study was performed; one group was blind due to ROP (N=27) and the other was congenitally blind due to hereditary retinal disease (N=14). Fifteen of the 27 children with ROP had autistic disorder." [7]

Brain differences, visual impairment, stress as food is treated as a pathogen and related immune system symptoms which occur in response to pathogen(s) entering the human body would result in the individual immune system adaptation. Identical twins with the same genetic information still have individual immunogenetic differences which make us each unique individuals. Immune and genetic (IoGc) development in the womb and during immune system maturation after birth result in the specific individual ways in which our immune systems respond to pathogens. These adaptations will contribute to the specific enzyme alterations in the individual and individuals with similar immune and genetic histories should present with similar markers which can be identified and used to develop and apply treatment options. Similarities can be found for immune system activity in some disease presentation which is known to co-occur with autism. Similarities can be found for immune system activity and immunogenetic weaknesses among preserved populations who are predisposed to these same conditions which co-occur with autism. A wider array of immune system activity is anticipated for people from diverse ancestry and who have disease presentation which co-occur with autism. These differences could be compared to data gathered for those with autism who have the same diseases and who are from diverse cultural backgrounds as well as those who are from the same ancestry where significant immune response information is known. Thus looking at disease presentation for common and rare conditions in preserved populations can result in finding information which might be overlooked when research includes the general population in studies.

Epidemiology

Small studies which identify subjects with autism in preserved populations and for whom family history does not contain immune phenomena compared to those with family history who do contain immune phenomena and also present with autism should result in some usable information. Statistical information which already exists identifying common immune markers should be re-evaluated including newly gathered information.

Autism genome studies include genetic information which identifies the most common co-occurring conditions. These conditions have generally been studied and immune system as well as biochemical markers have been set forth. Studies establishing comparative data for people with autism who have also these co-occurring genetic conditions should be carried out.
It has been suggested that the presentation of a genetic condition may be less severe for some conditions when autism is also diagnosed (MRC, UK 2001 Review of autism). Comparative data for individuals with autism and a common co-occurring condition should be provided. Establishing how an immune system evolution relates to survival of the species in response to environmental factors could produce information which may be of value for the increasing numbers of the human population who are reflecting IoGc changes.
Prevalence information which establishes ancestry and mixed ancestry comparative epidemiology information in the autism population needs to be addressed. Prevalence information which establishes presentation of autism in children who are from immune compromised family backgrounds compared to those who are birthed in families with no apparent immune illnesses needs to be forthcoming. Severity of presentation for individuals with autism who have both family history of immune illness and mixed ancestry has been significantly worse than for those who are from stable ancestry and for whom no immune conditions are reported in the family history. Overlap of ancestral diversity and immune illness appears to result in the more severe presentation. How this correlates to those with also genetic conditions needs to be addressed.
Co-occurring genetic conditions have been studied and the specific information related to these conditions and particularly viability of the fetus needs to be evaluated to determine the incidence and frequency of spontaneous abortion and male to female ratio. This information could be used in establishing whether some genetic conditions which co-occur with autism are more prevalent in the female population. This information could establish a different set of statistical comparative information which re-evaluates the current understanding of male to female ratio of autism for the overall autism population and speculation that this ratio is a result of purely genetic influence. A lower female ratio may reflect an increased frequency of spontaneously aborted females. How this information correlates to the disease manifestation during fetal development needs to be evaluated and particularly as related to luteal phase activity and re-production. The RPE and reproductive systems are developing later than the suggested time period during fetal development when the predisposing factors that lead to autism are set in motion. These systems would be at war with the immune system for competing availability of lutein. Immunogenetic changes would likely result in response to this competition. Thus the individual presentation would be expected and the consistency of findings related to pigment metabolism, endocrine metabolism and visual disturbance would be anticipated.

Mercury

Currently the focus is on vaccination as a causal factor for autism. Certainly we do not disagree with this hypothesis. We are not convinced that toxins in the vaccines are the main culprit and suspect the use of vaccines for mass population vaccine campaigns have led to the current autism epidemic in affluent countries. We are situated in South Africa and specifically in the heart of the Zulu nation. Here the indigenous people are not yet aware of autism although another immune disease is prevalent, HIV-AIDS. Autism is still at the level of a very rare disorder in South Africa, only 1000 cases

have been recorded in a population of 43 million people. Additionally, the native Zulu peoples have been criticized for including mercury in pregnancy tonics and active measures are being sought to prevent continuing these practices. "Registration of traditional medicines- new bill", Healthlink, Issue No 37, October 1998. Note that mercury tonics have been included in tribal tradition for decades and possibly centuries and still the diagnoses of autism is virtually unheard of here. Epidemiology and medical studies here in South Africa could produce valuable information as to the influence of mercury toxicity on the development of autism. There is no debate that mercury is a toxin that should never have been included in vaccines. 'The report, the federal government's second comprehensive assessment on children's health that weighs environmental and biological factors has defined asthma, developmental I.Q. deficits and motor skill dysfunction linked to mercury.' (Jennifer Lee, Schafer Autism Report, February 20, 2003). Debating the cause of autism as an evolutionary step in response to vaccination can be taken a step further. Whereas autism is still considered a rare condition in South Africa, HIV-AIDS is prevalent and at the heart of government, medical and international agendas. Still the literature lacks any reported cases of both autism and HIV-AIDS. The original argument against the potential for someone with autism to develop HIV-AIDS were based on lack of social interaction, lack of sexual exposure and no use of illicit drugs. Four decades later there are now HIV positive and HIV-AIDS victims birthing babies and some of these infants have a later diagnoses of autism. There are anecdotal reports from mothers that include their child who later was diagnosed with autism was born sero-positive and later converted with onset of autistic symptomology. Whereas the mechanisms of MMR, HIV-AIDS and autism have some similarities outlined nicely by Dr. Barbara Brewitt PhD (Autism, MMR Vaccine, HIV Similarities and Growth Factor Cell Signaling, Biomed Comm Inc., Seattle WA USA) it is probable that vaccination further exacerbates the immune response and immunogenetic development of the autistic metabolism present at birth and continuing to be influenced during early childhood development. Denying the relevance of this possibility is also denying the positive aspects of this same evolutionary response - a population which apparently has greater protection from cancer, rheumatoid arthritis, SLE and in a significant percentage (perhaps 39%) of the autism population have the same immune system markers which have been found to result in a natural immunity to the HIV-AIDS 'virus'. [20]

Biomedical testing

Invasive and dangerous procedures which involve looking at the CFS should not be considered as the resulting potential for damage is too great. Testing to determine PST-P enzyme deficiency (Waring, R. and Ngong) has not resulted in the development of a cost effective test however, Metallothionein (MT) dysfunction has more recently been reported on by Walsh and a test kit is now available. Stress factors including evidence of immune activity responding to pathogens can be obtained from urine samples i.e. neopterin and CD4/CD8 levels. Family history should be obtained prior to considering vaccination and particularly relevant are history of immune disease, diverse ancestry, genetic and allergic conditions. Allergy testing to rule out particularly egg and gelatin allergy should be a primary consideration. Eye abnormalities are associated with neurodevelopmental delay and severe delay disorders, eye screening could produce evidence for a predisposition to weakness and recommendation to at least delay vaccination until further information could be obtained. Abnormal metal and sulfur metabolism, Cytochrome P450 enzyme metabolism markers could be discerned and the specific areas of disturbance would

need to be determined based on ancestry and family history information or genetic and metabolic screening. Thus different test kits could be recommended for infants with identified areas of potential weakness. Once identified these findings could be used to include treatment recommendations for diet, supplements and pharmaceuticals which address the underlying conditions and which may prevent the infant from developing the full impact of the conditions to which he or she is immunogenetically predisposed. An estimated 12 to 25 percent of people with an autism diagnosis present with elevated levels of antibodies to gluten and or casein. Screening for gluten and casein antibodies should always be considered if a diagnosis of autism is suspected; people of Irish ancestry are reported at increased risk of celiac disease. Seizures and epilepsy are reported in as few as 8 percent and as many as 40 percent of the autism population. No statistics are as yet available on the male to female ratio of seizure disorders in the autism population. Seizures should be included as a reason to screen also for autism. Wood's lamp screening should be provided for all infants.
The first biochemical marker identified in the autism population was abnormal blood serum serotonin levels, this finding has remained consistent. Abnormal serotonin and tryptophan metabolism can be indicative of B vitamin metabolism insufficiency and this can be supported with moderate supplementation, adequate fatty acid intake, digestive enzyme support and avoidance of soy protein. Soy protein contains genistein which acts to force the conversion of tryptophan to neurotoxic kynurenines. Evidence can be obtained from lab work which shows normal kynurenine levels prior to inclusion of soy protein foods or products and increased abnormal levels of kynurenines after soy protein inclusion in the diet. Whereas soy protein is generally a problem soy bean oil, a source of vitamin K is generally beneficial. G6PD needs to be assessed before including sources of vitamin K above the recommended daily intake. Developing protocols to prevent the severe manifestation of disease presentation in autism is certainly needed. However, the epidemic level of disease presentation also demands rapid advancement in treatment options and application. For those suspected to have suffered further injury through vaccination or exposure to environmental toxins or childhood illnesses then a review of the available therapies offered, resulting in useable information to support parents and care providers, is desperately needed. Including a review of homeopathic treatments such as homeopathic growth factor and EPD, use of natural substances: antivirals, antibacterials, antifungals and their pharmaceutical counterparts to more invasive therapies including but not exclusive to blood cleansing, IVIG and chelation. Continuing research should lead to pharmaceutical options which could replace or be used in conjunction with some currently used therapies i.e. galanin hormone in place of deep pressure massage or to reduce SIB and improve sleep. TENS therapy and galanin hormone to improve sleep and reduce SIB.

In reality so little useable information is provided to the general population during the course of receiving public education that people are not armed with information necessary to support their own nutritional needs. A review of the food guide pyramid quickly reveals unrealistic recommendations for protein foods which if followed would result in substantially elevated intake of protein, nearly 3 times the RDI. Little information on the wide variety of fats and healthy fats are included. Grain foods are associated by the general population and I dare say some of the medical community as many selections of gluten containing grains when indeed there are many healthy non-glutenous grain foods which do not reach the public attention. Celiac disease and gluten intolerance was reported as 1 in 300,000 in the 1960's, rising to 1 in 30,000 by

1980 and now reported at 1 in 150 in the general population and in some research 1 in 50 in the autism population. We cannot continue to support a population of ignorant people who rely on advertising and media for their news on nutrition. The health food industry will take full advantage of current research to develop products and promote them as healthy for everyone. Regulating the industry is not the answer, the answer lies in educating the public and the medical community. In South Africa efforts to match pharmaceutical dollars spent on product representation through representatives, literature and product samples are being matched with nutritional campaigns to include education, literature, product samples and improve health care services, policies and delivery. In effect they are trying to avoid mistakes made by more affluent countries adopting health care policies. South Africa is determined to include natural as well as allopathic treatment and prevention in medicine. Not throwing out the baby with the bath water so to speak. Interestingly the pharmaceutical companies and researchers often look to Africa for new products based on tribal tradition in an area of the world that has not yet been fully stripped of her natural resources.

Always the dietary acetylcholine precursors, vitamin and mineral status, fatty acid sources and protein sources should be evaluated and if insufficient then recommendations to supplement should be provided:
Acetylcholine is a brain chemical that is active in biological processes. It is suggested that acetylcholine is active in verbal speech development in humans (Koelle). It is a chemical that helps the other brain chemicals to do their jobs balancing the molecules of emotion and immune influence. We see and respond to our environment with chemical reactions to words, music, noises, textures. These responses are a combination of immune responses and emotional responses. Feels good and is good for me to feels bad and is not good for me. Foods also contribute to the chemicals our bodies produce which make us feel good or feel bad. The acetylcholine name is quite scientific but it is just a word that describes the substance which is made from a combination of foods. The substance itself is very important because if we do not have all of the dietary foods needed to produce this acetylcholine then things go wrong. The acetylcholine substance relies on five primary dietary food substance precursors. It helps me to think of it as a puzzle with a changing picture. You can buy these as developmental toys in the form of six blocks. Each of the blocks has six sides and when you put all of the blocks together correctly you get a picture. Turn all the blocks to a different square and you get a different picture using the same blocks.
Acetylcholine can be pictured as the substance which cleanses the toxin known as gliadin which comes from mainly wheat and rye. In the past century wheat particularly has been altered by science and farming practice and use of wheat has increased in our human diet. It comes in from breads, cereals, cookies, biscuits, pasta and as additives in other foods. Some forms of wheat contain also lutein i.e. durum wheat and spelt. Wheat made with yeast to make breads rise is particularly addictive. The fermentation in the gut after ingesting foods made with yeast as rising agent can contribute to alcoholic addiction, makes the individual crave alcohol. If our foods are being used to manufacture acetylcholine for cleansing gluten-gliadin wastes then we are at greater risk of B vitamin deficiencies, fatty acid deficiencies and digestive enzyme deficiencies. Avoiding foods which contain wheat eliminates temptations which also contain the live yeast and often food dyes, preservatives and which are often made into food stuff with little nutritional value. In a population for which wheat was not a natural grain there is a greater chance of wheat intolerance

which causes gut damage, mood changes and can result in B vitamin deficiencies which can be irreversible.
Acetylcholine can be pictured as the substance which is needed by the body to produce the enzyme which break down the milk protein casein, called rennin. Casein can also be broken down by Streptococcus bacteria. A diet deficient in acetylcholine precursors can or appears to contribute to strep overgrowth. This overgrowth can also be related to ingestion of dairy protein. Dairy is also a primary source of riboflavin, a B vitamin. Many do well with dairy fat foods such as butter, ghee and cream or cream cheese.
Acetylcholine can be pictured as the substance which is used to make the enzyme which regulates blood pressure called renin. In a family where blood pressure irregularities exist paying close attention to the acetylcholine precursor foods can prevent the development of problems and can reduce or alleviate existing problems.
Acetylcholine can be pictured as the substance used to produce enzymes in saliva called sialic acid which kill bacteria and germs coming in through the mouth and nose. Used also to break down simple sugar to gases so these do not feed gut pathogens such as candida albicans (yeast infections).
Acetylcholine is also a brain chemical acting and interacting with other brain chemicals which contribute to feelings of satisfaction, satiation (fullness after eating), elation, happiness, sadness, fear, anxiety. Acetylcholine is associated to the arachidonic acid cascade whereby waste matter is moved through the gut by smooth muscle contraction.
If all of the acetylcholine precursors are not supplied in the diet then food substances such as choline can be converted to betaine and the body must use alternative detoxification methods - seen as profuse sweating and increased thirst.

The dietary precursors of acetylcholine include:
1. Choline. Choline is supplied in the human diet primarily from apple, banana, butter, cauliflower, oats, peanut or peanut butter, ginger, beef liver, tomato, cucumber, lettuce, potato.
2. Soy lecithin. Vitamin E from soy bean oil.
3. Arachidonic acid. Sources: Beef liver, safflower oil, egg yolk or Evening Primrose oil.
4. DMG (N,N, dimethylglycine). Food sources: Brown rice (unpolished dark rice) and yam (Egyptian or African white sweet potato), raw cabbage, sunflower seeds and bee pollen. AND, adequate intake of all essential B vitamins.
5. Complex sugars: A combination of * simple sugar and starch * root vegetable * vegetable * fruits and berries. Food combinations ultimately providing glycoproteins.
If food sources of nutrients are impossible to obtain whether from self-limited (self-protective), restricted diets re: food allergies, or food intolerances then adequate supplementation must be provided to meet nutritional requirements. If the diet supplies the essential nutrients from foods and adequate digestion is taking place then supplements are expensive waste products using not only monetary resources but also valuable detoxification pathways.

Looking at these food sources it is easy to see that the human diet naturally provides ample food sources for a normal metabolism. Most people ingest choline food sources regularly. Most people can produce lecithin from beans or lentils (dhal). Egg yolk is widely used in the human diet and many using a strict vegan diet use safflower oil (India). DMG was included more in the diet from rice before wheat

processing and distribution and yam (sweet potato) was a staple root vegetable which was stored for year round use in most cultural diets. Use of honey has largely been replaced with processed sugar.

Genetics part I

Chromosome 1q: Dermatitis, deafness, family history of Porphyria cutania tarda or Parkinsonism should result in recommendation for fatty acid profile and assessed need for essential arachidonic acid supplementation.

Chromosome 2q: Deafness, hypopigmentation, family history of disturbed cholesterol regulation, any of the suspected predisposing factors to a diagnosis of autism. Test for urinary neopterin level and methylmalonic acid level. Test for digestive enzyme sufficiency, support with digestive enzymes if indicated. Proceed with lutein free diet and fish liver oil supplementation. Homeopathic growth hormone treatment.

Chromosome 6q: Family history of retinitis pigmentosa or Refsum's disease. Identify IgA levels. Supplement with cod liver oil, proceed with carotenoids restricted diet. Stool analysis and OAT test to determine enzyme sufficiency. L-glutamine and folic acid supplementation with digestive enzymes if warranted.

Chromosome 7q: Family history of diabetes. Family history of Hemochromatosis. Check vitamin status: folic acid, vitamin K, iron, B12, vitamin C. Support with purine controlled diet, folic acid supplementation, B12 if indicated, support for the iron metabolism i.e. diet (brown rice) or phytic acid supplement, regulated intake of vitamin C, supplemental vitamin K after screening for G6PD. Diabetic diet format if indicated. Carotenoids restricted diet. TENS therapy.

Chromosome 13q, Wilson's disease, Jaundice. Referral for copper restricted diet monitoring and zinc supplementation. Carotenoids restricted diet. Test for urinary neopterin level and methylmalonic acid level. Proceed with lutein free diet and fish liver oil supplementation.

Chromosome 16p diagnosis of Tuberous sclerosis. Test for elevated neopterin. Assess amyloid deposition differences in autism population with also TS. If subject presents with differences associated with autism and TS as opposed to the characteristic presentation without also autism then further recommendatios can be produced which may include a lutein restricted diet. TENS therapy. Substantial nutritional support with particular attention to the acetylcholine precursor foods or supplemental sources.

Chromosome 18q, Family history of cancer, Epstein Barr virus. Cancer screening. Support with non-carotenoid antioxidants including vitamin C, pycnogenol and vitamin E.

Chromosome 16q, suspected Bartter syndrome, screen for Gitelman syndrome. Homeopathic growth hormone treatment. Calcium and magnesium assessment.

Chromosome 19p, Visual impairment screen for Fucosyltransferase deficiency. Purine controlled and carotenoids restricted diet. Enzyme support.

Chromosome 15, FRAXA or Turner syndrome with suspected autistic symptomology or markers. Lutein free diet. Adequate nutritional support: cod liver oil, acetylcholine precursor foods and or supplements. Homeopathic growth hormone treatment.

Chromosome 15q. Angelman's Syndrome. Prader-Willi. Molybdenum supplement. Fatty acid profile. Test for urinary neopterin level and methylmalonic acid level. Proceed with lutein free diet and cod liver oil supplementation.

Chromosome 4q. Parent with Piebaldism. Chronic constipation screen for defect on chromosome 4q 'Circadian Locomotor Output Cycles Kaput' CLOCK (Ref. Steeves et al 1999). Support with natural stool softeners (magnesium source from Epsom salt

baths, supplement and iodized sea salt). Support also with cascara segrada to relieve constipation.
Chromosome 10q. PKU. Test for neopterin levels. If suspected autism then PKU diet with also Purine restriction, lutein free diet. Supplementation with vitamin A as cod liver oil, trials with SAMe and DMG. Support with vitamin supplementation or liquid nutritional support as determined. Pharmaceutical support, strict doctor supervision.
Chromosome 17q. café-au-lait macules, (co-occurring condition – asthma); Autosomal dominant retinitis pigmentosa (ADRP), (Inglehearn CF et al). Sanfilippo (sulfate sulfatase deficiency and sulfamidase deficiency). Molybdenum sources from diet or supplement. Avoid also citrus. Supplement with vitamin E. Lutein restricted diet if autism is determined.
Chromosome 21, not included in the genome screen Down Syndrome is cited in the literature as co-occurring with autism. Down syndrome infants should be screened for autism. Interestingly Down Syndrome individuals with also autism may present with less severe medical conditions generally associated with Down Syndrome.
Chromosome 22q. Adenylosuccinate lyase deficiency. Eye screening. Hearing screening. Purine restricted diet. Test for urinary neopterin level and methylmalonic acid level. If autism is determined then additionally carotenoids restricted diet and cod liver oil supplementation. Homeopathic growth hormone treatment.
Chromosome 5p. Heterotopic calcification. Calcium regulated diet. Also restricted oxalate intake: avoid - chocolate, coffee, tea, pecans and rhubarb, dark green leafy vegetables. Controlled intake of vitamin C. If autism is determined also lutein restricted diet.
Chromosome X include: FRAXA, Incontinentia pigmenti (IP) (usually lethal prenatally in males): Hypomelanosis of Ito (HI). Screen for also Bartter syndrome and more rare type Gitelman syndrome. Strict carotenoids free diet. Nutritional and particularly anti-oxidant support with vitamin E, pycnogenol and adequate vitamin C. Homeopathic growth hormone treatment.

<u>Genetics part II</u>
Summary of Most Significant Regions of Linkage for Autism from Whole Genome Screens includes the greatest agreement for chromosome 7q, but it should be noted that the regions identified by each group are not precisely the same.
Elucidation of autism probability regions and their relation to other diseases, conditions and disorders
[NB: Information provided on Cytochrome P450 (CYP) has been obtained from the website of the 'National Center for Biotechnology Information']
1p
[The value given for 1p (Risch et al.,1998) is 2.15 and this measure - of the probability that an identified region is of association - is a score below 3 and is in a region not identified in the other cited studies.]
Defects of chromosome 1p include: Cytochrome P450: CYP2J2 arachidonic acid epoxygenase deficiency; CYP4B1 Parkinsonism. Porphyria cutania tarda, light sensitive dermatitis and associated excresion of uroporphyrin; hypertrichosis and hyperpigmentation also occur. Waardenburg syndrome (WS) type 2B sensorinural hearing loss, heterochromia irides, white forelock and early graying.
Oligodendrogliomas: $_{21}$ Autists often present with symptoms characteristic for screening of this type of benign brain tumor: ataxia, visual impairment, seizures. [NB: The selection process resulting in a 1p abnormality as opposed to the 1q abnormality

on the opposite loci, which contains the gene for Chediak-Higashi syndrome (CHS), indicates the evolutionary direction of species survival whereas CHS would be in the evolutionary direction of species extinction. 'Chediak-Higashi syndrome (CHS) is an autosomal recessive disorder characterized by hypopigmentation or oculocutaneous albinism and severe immunologic deficiency with neutropenia and lack of natural killer (NK) cell function. Most patients die in childhood from pyogenic infections or an unusual lymphomalike condition.'] [22]

2q

[The values given for 2q IMGSAC,1999 0.52 and Phillippe et al.,1998 0.64 are scores below 3 but is in a region cited in more than one study.]

Defects of chromosome 2q include: Cytochrome P450: Cyp27 (Sterol 27-hydroxylase): 'bile acid synthesis' and cerebrotendinous xanthomatosis, cerebral cholesterinosis (CTX). Waardenburg syndrome (WS): an inherited disorder often characterized by varying degrees of hearing loss and changes in skin and hair pigmentation: 'Many specific gene products are sequentially made and utilized by the melanocyte as it emigrates from its embryonic origin, migrates into specific target sites, synthesizes melanin(s) within a specialized organelle, transfers pigment granules to neighboring cells, and responds to various exogenous cues. A mutation in many of the respective encoding genes can disrupt this process of melanogenesis and can result in hypopigmentary disorders'.[23] 'Following are examples highlighting this scenario. A subset of neural crest derived cells emigrate from the dorsal surface of the neural tube, become committed to the melanoblast lineage, and are targeted along the dorsal lateral pathway. The specific transcription factors PAX3 and MITF (microphthalmia transcription factor) appear to play a regulatory role in early embryonic development of the pigment system and in associated diseases (the Waardenburg syndromes). During the subsequent development and commitment of the melanoblast, concomitant expression of the receptors for fibroblasts growth factor (FGFR2), endothelin-B (EDNRB), and steel factor (cKIT) also appears essential for the continued survival of migrating melanoblasts. Lack or dysfunction of these receptors result in Apert syndrome (a new mutation), Hirschsprung syndrome and piebaldism, respectively. Once the melanocyte resides in its target tissue, a plethora of melanocyte specific enzymes and structural proteins are coordinately expressed to form the melanosome and to convert tyrosine to melanin within it. Mutations in the genes encoding these proteins results in a family of congenital hypopigmentary diseases called oculocutaneous albinism (OCA). The tyrosinase gene family of proteins (tyrosinase, TRP1, and TRP2) regulate the type of eumelanin synthesized and mutations affecting them result in OCA1, OCA3, and slaty (in the murine system), respectively. The P protein, with 12 transmembrane domains localized to the melanosome, has no assigned function as of yet but is responsible for OCA2 when dysfunctional (15q). There are other genetically based syndromes, phenotypically resembling albinism, in which the synthesis of pigmented melanosomes, as well as specialized organelles of other cell types, is compromised. The Hermansky-Pudlak syndrome (HPS) and the Chediak-Higashi syndrome (CHS) are two such disorders. Eventually, the functional melanocyte must be maintained in the tissue throughout life. In some cases it is lost either normally or prematurely. White hair results in the absence of melanocytes repopulating the germinative hair follicle during subsequent anagen stages.'[22]

6q

[The value given for 6q (Phillippe et al. 1998) is 2.23 and this measure - of the probability that an identified region is of association - is a score below 3 and is in a region not identified in the other cited studies.]
Defects of chromosome 6q include: Congenital adrenal hyperplasia (CAH) is an inherited recessive disorder of adrenal steroidogenesis caused by mutations in the steroid 21-hydroxylase gene (CYP21) in more than 90% of affected patients. Retinitis Pigmentosa (RP) also found on chromosomes 1p, 1q , 9q and 10p. [24, 25, 26] A clotting of the pigment in the choroid structure of the eye. Retinitis pigmentosa is reported in more than a coincidental number of families (parent or grandparent) who have a child or grandchild with autism., 'Immunodeficiency and IgA deficiency are related disorders, susceptibility to which is determined by a gene(s) within or near the MHC class III gene region on chromosome 6'. [27] IgA deficiency has been reported in autism. [28] [NB: 6p and 10p: Refsum's disease (treatment with a chlorophyll free diet – Eldjarn, L. et al 1966) is characterized as a syndrome with RP and nerve deafness, ichthyosis, cerebellar ataxia and polyneuritis.]
7q
[The values given for 7q (IMGSAC 1999 2.53, Phillippe et al. 1998 0.83, Risch et al.1998 0.93, CLSA 1999 2.20) are scores below 3 but is in a region cited in all 4 of the studies.] Defects of chromosome 7q include: Cytochrome P450: Nitric Oxide Synthase 3 (NOS3), endothelial nitric oxide synthase (ENOS). 'The unexpected recognition of the substrate Larginine at the H4B (tetrahydrobiopterin) site indicates that this site is poised to stabilize a positively charged pterin ring and suggests a model involving a cationic pterin radical in the catalytic cycle' Raman et al (1998); CYP3A4, CYP3A43 'Xenobiotic' metabolism; CYP51, sterol biosynthesis, cholesterol biosynthesis; CYP5, thromboxane A synthase, bruises, nosebleeds, defective platelet aggregation. Speech Language disorder (also occurring on 19q and 16q). Hemochromatosis (HFE3); [29, 30, 31, 32] a disorder due to deposition of hemosiderin in the parenchymal cells, causing tissue damage and dysfunction of the liver, pancreas, heart, and pituitary. Other clinical signs include bronze pigmentation of the skin, arthropathy, diabetes, cirrhosis, hepatosplenomegaly, hypogonadism, and loss of body hair. Idiopathic Hemochromatosis: an autosomal recessive disorder of iron metabolism associated with a gene tightly linked to the A locus of the HLA complex on chromosome 6.[33] Hemochromatosis is also linked to Crystal Deposition Disease: 'CPPD crystal deposition disease may be classified as hereditary (autosomal dominant), sporadic (idiopathic), or associated with other metabolic diseases, such as hyperparathyroidism, hemochromatosis, hypothyroidism, or even gout itself. The acute pseudogout syndrome is characterized by an abrupt onset of acute inflammatory gout-like arthritis affecting one or more joints, most commonly the knee. Among other clinical manifestations, about 50% of patients with CPPD deposit disease present with progressive degeneration of multiple joints, usually the knees, ankles, wrists, elbows, hips, or shoulders. The initiating event for CPPD crystal deposition within joints is not well understood. The pathogenesis of the acute inflammatory changes in the joints are attributed to the uptake of CPPD crystals by polymorphonuclear and mononuclear phagocytes, followed by release of degradative enzymes, inflammatory mediators, and chemotactic factors, very much as in gouty arthritis.' [34] In the autist, the typical presentation of these iron deposition disorders is not found. Nevertheless, autists do often have problems with iron metabolism, and even when anemic, supplementing with iron can result in an unexpected drop in iron level. Likewise, supplementing with Vitamin C has an unexpected negative outcome for some autists.

VITAMIN C

‘Vitamin C is also known as ascorbic acid, L-ascorbic acid, dehydroascorbic acid and the antiscorbutic vitamin. Chemically, it is called L-xyloascorbic acid and L-threo-hex-2-uronic acid g-lactone. The very highest concentrations of vitamin C are found in the adrenal and pituitary gland. High levels are also found in liver, leukocytes, brain, kidney and pancreas. Most of the vitamin C is found in liver and skeletal muscle because of their relative size to the rest of the body. The best characterized function is the synthesis of collagen connective tissue protein at the level of hydroxylation of prolyl and lysyl residues of procollagen. Vitamin C also plays important roles in the synthesis of neurotransmitters, steroid hormones, carnitine, conversion of cholesterol to bile acids, tyrosine degradation and metal ion metabolism. This vitamin also may enhance iron bioavailability. The role of ascorbic acid as a biological reducing agent may be linked to its prevention of degenerative diseases, such as cancer and cardiovascular diseases.

Clinical uses: The only established use of vitamin C is in the prevention and treatment of scurvy. Studies investigating possible effects on wound healing, blood pressure, colds and immune function have often employed other antioxidants in addition to ascorbic acid and, in most cases, the results have been unremarkable, conflicting or inconsistent.

Toxicity: Megadoses of vitamin C of 1000-2000 mg have commonly been associated with gastrointestinal disturbances (nausea, abdominal cramps and diarrhea). In general, megadoses of vitamin C should be avoided in individuals with a history of renal stones due to oxalate formation or hemochromatosis or other diseases related to excessive iron accumulation. Excess vitamin C may predispose premature infants to hemolytic anemia due to the fragility of their red blood cells. In healthy individuals, it appears that megadoses of vitamin C are well tolerated and not associated with any consistent adverse effects.’ [35, 36, 37]

Some individuals carry a gene which increases Fe storage. For these, adequate vitamin C in the diet is preferred over supplementation according to Victor Herbert MD of Mount Sanai Medical School, who states that it can become pro-oxidant when interacting with Fe of the genetically predisposed individuals. Vitamin C thus might increase the dangerous oxidation of LDL cholesterol which when oxidized are pulled in by the monocyte/macrophage cells which have been linked to plaque build-up in disorders such as Alzheimers.

Vitamin C supplementation in excess of the RDA is not always a good idea for people with ASD.

13q

[The values given for 13q (Risch et al.1998 0.68, CLSA 1999 03.00) are scores below 3 but is in a region cited in more than one study. The CLSA, 1999 score of 3.00 borders on the strength of probability cited in one of the 2 studies which referenced findings for the 13q area. That only 2 of the 4 studies referenced the 13q diminishes the finding somewhat.]

Defects associated with chromosome 13q include: Wilson’s disease (potentially resulting in jaundice), copper-transporting P-type ATPases copper transport, Mutations of ATP7B. Currently NIH is funding studies to clarify the association between Wilson’s disease and autism. In our experience we have encountered an autistic female who presented with yellow eyes and also encountered many ASD females who exhibited yellow eye color especially at or near the onset of menstruation. Phylloid pattern of pigmentary disturbance (Ribeiro Noce T

et al). Hirschsprung disease type 2: Puffenberger et al. (1994) presented evidence that Hirschsprung disease type 2 (HSCR2; 600155), an apparently multigenic disorder, is due to mutation in the endothelin-B receptor gene. EDNRB was a candidate gene because it mapped to the same region of chromosome 13 as did HSCR2. Among the Mennonites, at least 5 megacolon patients did not seem to carry the specific EDNRB mutation trp276 to cys (W276C) present in most of the affected members. This suggested the existence of as yet undiscovered HSCR susceptibility genes. Among the affected Mennonites, HSCR was associated with nonenteric phenotypes in several: bicolored irides (6.3%), hypopigmentation (2.5%), sensorineural hearing loss (5.1%), and white forelock (7.6%), reminiscent of the Shah-Waardenburg syndrome [see also 22q] Puffenberger et al. suggested that these nonenteric features represented pleiotropic effects of the W276C mutation. This and other findings indicated that interaction of EDN3 with the endothelin-B receptor is essential to the development of neural crest-derived cell lineages.[38]

16p

[The values given for 16p (IMGSAC 1999 1.51, Phillippe et al. 1998 0.74) are scores below 3 but is in a region cited in more than one study.]

Defects associated with chromosome 16p include the differential diagnosis of the guttate leukoderma of TSC (Tuberous Sclerosis), also found on chromosome 9q and includes several clinical entities such as idiopathic guttate hypomelanosis, [39] disseminated hypopigmented keratoses, and dyschromic amyloidosis. [40, 41, 42, 43]

18q

[The values given for 18q (Phillippe et al. 1998 0.62, Risch et al. 1998 1.00) are scores below 3 but is in a region cited in more than one study.]

Defects associated with chromosome 18q include Erythropoietic Porphyria. B-Cell CLL/Lymphoma (unknown inhibitor of apoptosis) dominant white-spotting; ‘B-cell lymphomas and polyclonal B-cell lymphoproliferative disorders are related to Epstein-Barr virus (EBV) activation.’[44]

19p

[The values given for 19p (IMGSAC 1999 0.99, Phillippe et al. 1998 1.37) are scores below 3 but is in a region cited in more than one study.]

Defects of chromosome 19p include: Cytochrome P450: CYP4F3, Leukotriene B4 omegahydroxylase (LTB4H) bioactive compounds that play roles in such processes as inflammation. Fucosyltransferase deficiency (co-occurring condition - enzyme deficiencies) potentially relating to purine and pyrimidine biosynthesis. Oligodendrogliomas (tumors associated with ataxia, visual impairment and seizures) [45, 46] [See also 1p]

Regions not cited in the whole genome studies but with literature to support the connection to ASD:

Chromosome 15 ‘The strength of evidence supporting claims of a specific association between genetic /chromosomal disorder and ASDs is very variable. The strongest evidence of a causal association is found for tuberous sclerosis, fragile X and inverted duplications of chromosome 15. While fragile X Syndrome used to be thought to affect as many as 25% of males with ASDs, Fombonne, in his review estimated a far lower figure (0.75%). The symptoms shown by those with this disorder may be more properly described as ‘autism like’ or fitting only within the broader spectrum. An association between duplications and triplications of part of the long arm of chromosome 15 of maternal origin has been found with ASDs, often accompanied by severe mental retardation. This is of some interest as genetic studies of ASD have

identified loci on the long arm of Chromosome 15. The role of mental retardation in the association needs to be investigated. In addition, sex chromosome abnormalities (Turner syndrome) have been linked to ASDs. Some 5% of females with Turner syndrome have either ASDs or features that may fall within the broader ASD phenotype. In all confirmed cases the normal X chromosome was maternal in origin. It is possible that there is increased vulnerability to ASDs in females who lack a normal paternally derived X chromosome. Untreated phenylketonuria is nowadays so rare that the evidence for an association stems from very early studies that were undertaken before the use of well developed and validated diagnostic criteria, although the evidence from the early reports is quite persuasive. The frequency of single gene disorders or chromosomal abnormalities in population based and clinic samples of individuals with ASDs is low and amounts to at most 5-10% of the population.' (MRC, UK 2001 Review of Autism).

Additional defects associated with chromosome 15 include: Cytochrome P450 'aldehyde dehydrogenase', 'retinaldehyde dehydrogenase 2'. Chromosome15 syndrome of inv. dup. (inversion-duplication) characterized by macrogenitalia, seizures and autism. [47]

15q

Defects associated with chromosome 15q include: Cytochrome P450 'molybdenum cofactor deficiency' molybdenum cofactor is essential to the function of 3 enzymes: sulfite oxidase, xanthine dehydrogenase and aldehyde oxidase. Molybdenum cofactor (molybdopterin) deficiency is characterized by developmental delay, seizures, lens dislocation and often early infantile death; CYP19: 'estrogen synthetase', induced by follicle stimulating hormone; CYP450 'polycystic ovary syndrome'; CYP1A2 (deficiency: porphyria cutania tarda); CYP11A, cholesterol side chain cleavage; CYP1A1: (XRE's) xenobotic response elements. Oculocutaneous albinism type 2 (OCA2), 'Xanthism type (OCA3) found on chromosome 9q', ['The P protein, with 12 transmembrane domains localized to the melanosome, has no assigned function as of yet but is responsible for OCA2 when dysfunctional'[22]] pink protein, melanosomal membrane. [48, 49, 50, 51, 52, 53] Angelman Syndrome 'light pigmentation' and Prader-Willi characterized by obesity, round face, almond shaped eyes, obsessive compulsive eating and often with scratching and itching.

4q

Defects associated with chromosome 4q include Cytochrome P450 'Circadian Locomotor Output Cycles Kaput' CLOCK (Steeves et al 1999). Piebaldism: congenital patches of white skin and white hair, principally located on the scalp, forehead, chest and abdomen and on the limbs; several patients report lifelong severe constipation; a hierarchical correlation has been elaborated between severe or mild phenotypic traits and the associated KIT mutations; in a few patients with interstitial deletions mental retardation and congenital anomalies have been also described etiology: defective melanoblasts proliferation, survival and migration from the neural crest during development and defective migration of enteric-plexus ganglion cells from the neural crest to the gut pathology : white spotting in human piebaldism results from the absence of melanocytes from the nonpigmented patches of skin and from hairbulbs in the white patches of hair; occasionally, individuals lack ganglion cells of the intestinal enteric neural plexus, which like melanoblasts, are derived from the neural crest, melanoblast migration signal Mutations of KIT. 'Subcellular defects of hypomelanosis in tuberous sclerosis (TS) (28 subjects) were compared by light and electron microscopy with other forms of congenital

circumscribed hypomelanosis that occur in nevus depigmentosus (ND) (8 subjects) and in piebaldism (PB) (4 subjects), respectively. On the light microscopic level in both TS and ND, the population density of functioning melanocytes was normal but each perikaryon was small, and dopa activity was decreased. On the ultrastructural level, the hypomelanotic skin and hair of TS were associated with a decrease in the synthesis, melanization, and size of melanosomes; the decrease in the size of melanosomes resulted in the aggregation of melanosomes (i.e., a melanosome complex) in the keratinocytes in all the specimens examined. In ND, there were no obvious changes in the size and melanocytes. the hypomelanosis of ND is related to the decreased synthesis and also, perhaps, abnormal transfer of melanosomes. In PB the hypomelanosis of the skin and hair results from the absence of functional melanocytes. The hypermelanotic areas of PB, however, characteristically contain melanocytes that synthesize abnormal (sperical and granular) as well as normal (ellipsoidal and lamellar) melanosomes.' [43]

We have within our case histories an adult male age 40 who was diagnosed with Down Syndrome, ASD and piebaldism. He was quite high functioning and generally healthy. He did exhibit the characteristic self-limited diet of the Down Syndrome-ASD group. His diet mainly consisted of pork sausages, mashed potato, fruit yogurt, wheatabix cereal with milk, hot tea with milk and occasionally mashed cauliflower, fish or chocolate. When hungry enough he could be coerced into eating the mashed potato with pureed vegetable (usually peas, carrots or broccoli). After these meals he would become withdrawn and complain of headache this might be followed by a period of one or more days when he would refuse food altogether. He was childlike and mildly mischievous. He attended some special college courses, participated in some social activities and was adapting to a supported living arrangement. His medical history was conspicuously lacking any reference to other medical conditions which often co-occur with Down syndrome. He also had the wide gap between the first and second toes (big toe and long toe) characteristic for Down Syndrome [54] and prevalent in autism. Twenty nine of the 35 children we saw in India had this wide gap between the toes. 10q Defects associated with chromosome 10q include: Cytochrome P450: (RBP) retinal binding protein; CYP2E (ethanol-inducible P450); CYP45026A2, CYPP450RAI2 (retinoic acid inactivating) capable of converting all-trans RA to polar metabolites. Retinoic acid (RA) plays an important role in regulating gene expression during embryonic development; CYP2C19, mephenytoin-4-Pime-hydroxylase; CYPC17, 'congenital adrenal hyperplasia' due to 17-alpha hydroxylase deficiency; CYP2C9, CYP2C8, CYP2C18 (gene expression). Oligodendrogliomas 'pterin-4-alpha-carbinolamine dehydratase' (PCBD) leads to mild PKU 'hyperphenylalaninemia', hyperphenylalaninemia with premapterinuria (increased ratio of neopterin to biopterin). Hermansky Pudlak syndrome: Hermansky-Pudlak Syndrome (HPS) is a genetic metabolic disorder which causes albinism, visual impairment, a platelet dysfunction with prolonged bleeding, and progressive symptoms including pulmonary fibrosis, inflammatory bowel disease and kidney disease. The severity of HPS ranges from very mild with few symptoms to severe and disabling., membrane protein lysosome/melanosome structure/function. Hermansky-Pudlak syndrome is characterized by oculocutaneous albinism, a storage-pool deficiency, and lysosomal accumulation of ceroid lipofuscin, which causes pulmonary fibrosis and granulomatous colitis in some cases. [55]

17q Defects associated with chromosome 17q include: café-au-lait macules (co-occurring condition – asthma); [23] Café-au-lait macules are commonly reported by parents among the many types of pigment anomalies described for ASD children.

Autosomal dominant retinitis pigmentosa (ADRP) (Inglehearn CF et al). Sanfilippo (sulfate sulfatase deficiency and sulfamidase deficiency).
Chromosome 21, (not included in the genome screen cited in the table) Down Syndrome (trisomy 21) is estimated by the University of Goteberg, Sweden, to co-occur with ASD at 5 to 9% and by Kennedy Kreiger at 5 to 7 % which also cites Down Syndrome co-occurring with epilepsy at 10%. [72, 73] These figures, rarely cited in the literature, indicate that as many as 2% of the autism population also have Down syndrome.
22q
Defects associated with chromosome 22q include: Cytochrome P450: 'peroxisome proliferator-activated receptor-alpha' (PPARA); CYP2D, 'xenobiotic metabolism', 'thyroidlupus autoantigen'; CYP3A7, 'Polypeptide 7', CYP3A5 gene constitutes the major genetic determinant of polymorphic activity in humans. (Paulussen, A et al, 2000). Adenylosuccinate lyase deficiency. Waardenburg-Shah Syndrome: Dystopia canthorum (lateral displacement of the inner canthus of each eye) Pigmentary abnormalities of hair, iris, and skin (often white forelock and heterochromia iridis); Sensorineural deafness. The combination of recessively inherited WS type II characteristics with Hirschsprung disease has been called Waardenburg-Shah syndrome or WS type IV, SRY-box containing gene 10 transcriptional activator, Mutations of SOX10. Hearing impairment. [56, 57] See also 2q (Hirschsprung is also associated with chromosome 13 and 20)
Xp Defects of chromosome X include: FRAXA (Fragile X Syndrome); Cytochrome P540 'granulomatous disease', chronic CGD (lack of metabolic burst). Ocular albinism type 1, Gprotein-coupled receptor signal transduction Mutations of OA1, pinkeyed-dilution (p). [48, 58, 59] Incontinentia pigmenti (IP) (usually lethal prenatally in males): [60] 'We show the complications observed in a large series of children with Hypomelanosis of Ito (HI) or incontinentia pigmenti achromians, studied in a neurology service over 30 years. Of the 76 patients, 35 were male (46%) and 41 female (54%) with ages ranging from newborn to 10 years at the time of the first visit. Mental retardation was observed in 43 cases (57%) of whom eight (10%) showed autistic behavior; 16 (21%) were borderline and only 17 (22%) had a normal mental level (IQ > 85). Thirty-seven patients (49%) had seizures, consisting of infantile spasms in six cases (8%). Twelve cases showed macrocephaly and coarse facies, six had microcephaly, and 14 showed hypotonia with pes valgus and genu valgus. Three cases of cerebellar hypoplasia, another of intracranial arteriovenous malformation and another of distal spinal muscular atrophy were observed as well. Some other anomalies, such as syndactyly, clinodactyly, abnormalities of the skeleton, asymmetry of the facies, ears, body and/or extremities, gynecomastia and asymmetrical breasts, short stature, oral alterations, congenital cardiopathies and genital anomalies, were also occasionally found. Three children died, but necropsy was performed only in one. Anatomical and histological studies did not disclose specific findings.' [61] 'This case report presents a thirteen year-old boy who was diagnosed as having Hypomelanosis of Ito. The developmental history includes severe failure to thrive, and moderate atypical autism as well as diverse clinical and neuropsychological symptoms.' [62] 'Hypomelanosis of Ito (HI) also called Incontinentia pigmenti achromians, is the third most frequent neurocutaneous disorder. The abnormal skin lesions are more evident under Wood's lamp and consist of hypopigmented areas with irregular borders, streaks, whorls or patches which are usually distributed on the trunk or on the limbs. Non-cutaneous abnormalities, particularly of the central nervous system, eye, teeth and skeleton, have been reported in 76-94% of patients. We report

two cases of Hypomelanosis of Ito in two female girls with facial coarse features. In the first case the psychomotor development was normal. Segmental dilatation of the colon, precocious puberty, abnormal periventricular white matter hypersignal on MRI and nodular mass on left caudate nuclei were also present. In the second case a severe developmental delay and autistic behaviour were the prominent features.' [63] 'A pair of monozygotic and a pair of dizygotic twins with autism and hypomelanosis of Ito: skin abnormalities are described. These observations are further evidence of the frequent association between these two conditions, already demonstrated in the literature, and suggest a possibly higher incidence of single gene associations among cases of autism with known genetic basis.' [64] 'Two girls and a boy showing autistic behaviour and fulfilling the criteria for autistic disorder, Asperger syndrome or atypical autism were diagnosed as having hypomelanosis of Ito syndrome. It is suggested that skin changes indicating underlying neurocutaneous disorders be meticulously looked for in all cases with autism and autistic-like conditions.' [65] 'Subcellular defects of hypomelanosis in tuberous sclerosis (TS) (28 subjects) were compared by light and electron microscopy with other forms of congenital circumscribed hypomelanosis that occur in nevus depigmentosus (ND) (8 subjects) and in piebaldism (PB) (4 subjects), respectively. On the light microscopic level in both TS and ND, the population density of functioning melanocytes was normal but each perikaryon was small, and dopa activity was decreased. On the ultrastructural level, the hypomelanotic skin and hair of TS were associated with a decrease in the synthesis, melanization, and size of melanosomes; the decrease in the size of melanosomes resulted in the aggregation of melanosomes (i.e., a melanosome complex) in the keratinocytes in all the specimens examined...' [43] 'We studied a boy with macrocephaly, hypotonia, pigmentary retinopathy, unilateral whorled hypopigmented skin lesions, and seizures. Skin biopsy confirmed the clinical diagnosis of Hypomelanosis of Ito. Postmortem examination at age 22 months revealed a severe neuronal migrational defect that altered the cerebral cortex architecture of white matter. Embryologic migration of both melanoblasts from neural crest and cortical neurons occurs in the second trimester, suggesting a common mechanism for the developmental pathology of skin and brain.' [66] 'We studied 34 Spanish children with hypomelanosis of Ito. This disease has an incidence of 1 per 1000 new patients consulting a paediatric neurological service, or 1 per 8000-10,000 unselected patients in a children's hospital. About 94% of our patients show noncutaneous abnormalities. Mental retardation (IQ below 70) was present in 64.7%; another 14.7% had an IQ between 70 and 90, usually associated with poor school performance. Four children exhibited autistic behaviour. Seizures of various types were present in 53% of cases. Other skin alterations in addition to the typical hypomelanosis were observed in 38% of our cases: café-au-lait spots, angiomatous nevi, nevus marmorata, nevus of Ota, Mongolian blue spot, heterochromia of the iris or hair, and other nonspecific pigmentations. Other associated disorders occur inconsistently and include macrocephaly, microcephaly, hémihypertrophy, kyphoscoliosis, coarse facial features, genital anomalies, inguinal hernia, congenital heart disease, hypertelorism, and abnormalities of the teeth, feet and eyes. Autosomal dominant inheritance is demonstrated in some but not all cases.' [67] 'In this report we describe an 8-year old boy of Algerian origin with profound sensorineural deafness and skin pigmentation anomalies consistent with the diagnosis of hypomelanosis of Ito.' [68] 'The case of a female child with a unique generalized congenital dyschromia is reported. She had hypopimented skin, with hypomelanosis and hypomelanocytosis, and many pigmented macules, which consisted of epidermal and dermal hypermelanosis without hypermelanocytosis. Biochemical investigations revealed

normal catecholamine metabolism but abnormal tryptophan metabolism, including a decrease in blood serotonin and melatonin. A slight platelet storage pool disease was demonstrated, and a recurrent megaloblastic folate-related anemia occurred...' [69]

Mitochondrial DNA region

Four adjacent loci, C4A, 21-OHA, C4B, and 21-OHB located in the class III region of the major histocompatibility complex (MHC) In this region, known as the hypervariable region or the mitochondrial DNA region, the 21-OHB gene is generally inactive. The C4A gene abnormalities are reported to be more common in the parents of autistic offspring and particularly the mothers. The C4B gene null allele is more frequent in the autism population and appears to increase immune reactivity to viral pathogens, toxins, molds, pollens and other hapten substances. The immune system evolution to include plant pigments as pathogens has likely been exacerbated by the use of plant substance in vaccines. Likewise, there is evidence that the autistic population cannot make enzymes from plant foods in the normal way. In the human body bacteria such as e-coli, candida and fungi species produce these substances (carotenoids) for us. It appears that people who have anomalies among these four adjacent loci are the population referred to as having immune system disorders. Offspring from families who have these anomalies have a greater chance of being diagnosed with autism. It also appears that in autism, enzyme deficiencies without any corresponding genetic anomaly is a prevalent finding. 'In view of evidence suggesting vitiligo is an autoimmune disease, we investigated whether vitiligo is associated with inherited deficiencies of the fourth (C4) and second (C2) component of complement and with certain human leukocyte antigens (HLA). Analysis of functional activities of C4 and C2 in sera of patients with vitiligo (n = 42) showed that 17% of them had a heterozygous C4 deficiency and 5% had a heterozygous C2 deficiency. In the normal control group (n = 30), 3% had a heterozygous C4 deficiency and none had a C2 deficiency. C4 typing by Western blot analysis showed the frequency of the C4A*Q0 allele in the vitiligo patient group to be close to normal. However, the frequency of one C4B*Q0 allele was three times higher, and that of two C4B*Q0 alleles five times higher in the vitiligo patient group than the reported frequencies in normal control groups. …These results suggest that abnormalities of the C4B gene and the above-mentioned associations with HLA antigens may be some of the risk factors in vitiligo.'[70]

'Genes encoding several serum complement components and the gene(s) for steroid 21-hydroxylase (21-OH) have been located in the class III region of the major histocompatibility complex (MHC). All these genes are highly polymorphic in man, and these polymorphisms have been used to draw conclusions about the structure and function of these genes. For example, electrophoretic polymorphisms of the fourth component of complement (C4) have been shown to be controlled by two closely linked genes, which also control expression of the red cell antigens. (Rodgers and Chido) Steroid 21-OH deficiency (D) can occur in several forms which differ in severity, and because of genetic linkage disequilibrium with different HLA antigens the inheritance of these forms is consistent with the existence of several alleles at a single locus. When severe 21-OH D occurs in association with the HLA haplotype A3;Bw47;DR7, there is a simultaneous null allele at one of the C4 loci. This was hypothesized to result from a single deletion or rearrangement affecting the 21-OH and C4 loci and perhaps the HLA-B gene as well. These experiments showed that at least one structural gene for the cytochrome P450 specific for 21-hydroxylation is located in the MHC, probably very near the C4 genes, and a mutation in this gene

results in 21-OH D. Cosmid clones have been used to locate the 21-OH genes both in man and mouse. In both species, there are two 21-OH genes, each located immediately 3' of one of the two C4 genes, and oriented in the same direction as the C4 genes. In man, the gene located 3' of the C4B gene is deleted in 21-OH D on the Bw47 haplotype, but the gene 3' of the C4A gene is deleted in hormonally normal individuals on the A1;B8;C4AQO;C4B1;DR3 haplotype. Thus the 21-OH B gene is normally active in man, but the 21-OH A gene is not.' [56]

4p

Defects of chromosome 4p include: Hermansky-Pudlak syndrome (HPS). Wolf-Hirschhorn syndrome: Clinical features include mental retardation, seizures, distinct facial appearance, and midline closure defects. [38] Parkinsonism.

5p

Melanin-concentrating hormone (MCH) gene (Viale A et al). Defects of chromosome 5p include: Primary ciliary dyskinesia, left-right asymmetry (Olbrich H et al). 'The spectrum of heterotopic calcification or ossification is expanding because of the reports of several kindreds with calcium pyrophosphate deposition disease, apatite deposition disease, and others with less common syndromes associated with extracellular matrix calcification, such as fibrodysplasia ossificans progressiva and related syndromes.' [22]

Calcification

Although calcification problems have been identified to coexist with autism i.e. tuberous sclerosis and PKU, the genetic findings would indicate a probable predisposition to arthritic conditions, and yet these have not been reported in the literature. Potentially the immune system involvement in purine and pyrimidine disturbances includes removal of formed crystals via the skin rather than deposition, possibly to protect the kidneys. The findings of an association of chromosomes 5p (calcification) and 7q (hemochromatosis) in autism research (7q in multiple genome studies) would tend to support the findings of a pilot study 'Preliminary study of altered skin temperature at body sites associated with self-injurious behavior in adults who have developmental disabilities,' (Frank J. Symons, Kelly A. Sutton, and James W. Bodfish, American Journal on Mental Retardation, Vol. 106, No.4, 2001.) The article includes 'skin temperature changes can be indicative of neuropathy . . . For each participant the body site targeted most frequently for self-injury may itself change skin temperature, evidence from other animal studies suggests that neuropathy can lead to self injury. For Instance, they note, self-mutilation is a common finding in animals with dysesthesia, or abnormal sensations caused by lesions of the sensory nerve pathways. In addition, cases of intellectually normal individuals who targeted self-injury toward areas with neuropathy and altered skin temperature have been documented. 'The researchers suggest that self-injury may provide temporary relief of neuropathy caused pain or discomfort (as when a child scratches at a scab or chicken pox lesion), but may lead in the long term to more irritation that in turn generates more self-injury. We suggest that, in autism, the pain and discomfort is caused not by sensory neuropathy but by the immune system removal of calcium and other crystals as well as other breakdown products of lutein (formic acid, epoxy residues) through the skin. The researchers note that all four of their subjects responded well to naltrexone, a substance that blocks opioid receptors and alters perception of pain. They suggest that further studies examine whether naltrexone treatment, although it has no known effect on neuropathy itself, is more effective in individuals with skin temperature differences at self-injury sites. In

addition, Symonds and colleagues say, “one clinical implication of a pain related model of self-injurious behavior (SIB) is that treatments for peripheral neuropathies may provide an effective treatment option for some subset of SIB cases.” They note that several studies show decreased self-injury during treatment with transcutaneous electrical nerve stimulation (TENS), a treatment that blocks peripheral pain signals.”’

Our paper ‘Autism – The vaccine connection’ explores more deeply how the human immune system could make this error and how this relates to gut dysbiosis and disturbances in immune recognition and treatment of viral, fungal and bacterial pathogens. An evolution of the immune system which is capable of treating a food substance as a pathogen. The shortened version is included here. The full text version is available on our website:

http://www.saras-autism-diet.freeservers.com/literature/connection.pd

More information about World Community Autism Program can be found on our website: http://www.saras-autism-diet.freeservers.com/

Part 2 – The biochemical markers

a. measurable at birth
b. measurable at onset of autistic symptoms
c. common across all autism spectrum disorders
d. specific to various types of autism
e. markers that respond to dietary intervention
f. markers that respond to other interventions

Part 3 – Immunological markers

g. measurable at birth
h. measurable at onset of autistic symptoms
i. common across all autism spectrum disorders
j. specific to various types of autism
k. markers that respond to dietary intervention
l. markers that respond to other interventions

Part 4 – Environmental toxins - contributing factors

m. vaccination
n. pollution
o. aluminum cooking pots, food wrappers, beverage cans
p. fluoride, chloride poisoning
q. bismuth from over the counter medicines and make-up
r. baby crib mattresses and flame retardant pajamas
s. cleaning products
t. dry erase markers, nail polish, perfumes, hygiene products

Autism – the vaccine connection

Evolution of the immune system

Current research shows that there are many substantiating factors to consider vaccination as the causal factor for autism. The time line for human vaccination coincides with the first descriptions of autism, at first a rare disorder. A current report by the National Autism Society UK reports teachers state 1 in 89 primary school

children in England and Wales have autism. The literature identifies this condition to have been recognized by Leo Kanner in 1938 “Since 1938, there have come to our attention a number of children whose **condition differs so markedly and uniquely from anything reported so far**, that each case merits - and, I hope, will eventually receive - a detailed consideration of its fascinating peculiarities.” [1] The subjects ranged in age up to 11 years at the time of the 1942 publication suggesting that autism was affecting the human population at least as early as 1930. These could have been among the first children born of parents who received several vaccines. The most significant characteristic among the children as related by Kanner were that most were born with feeding problems. Historically one of the most intriguing developments during this time period was the scientific advances being made in vaccine research and application.

By 1930 agarose gel had become a standard tool which had moved from the kitchen (gelling agent) to the science laboratory. [2] Red algae and plant species (Urtica) from which science obtains the agarose gel also contain chloroplast DNA and Porphyridium chromatin. [3, 4] Science has developed additional ways to cultivate vaccines and this includes the use of egg yolk (contains the phosphoprotein ovovitellin and xanthophyll). Xanthophyll or lutein is derived from chlorophyll b (plant foods which contain chlorophyll) and is formed in chloroplasts or plastids. Vaccine cultures grown on egg or agar often also contain animal blood. Animal blood contains the by-products from the foods the animals are eating. So the human immune system has been faced with a combination of viruses, blood products, carotenoids, chloroplasts and human immune cells when given a vaccine or vaccines.

Vaccines were developed for polio, diptheria, pertussis, measles, mumps and rubella which are routine and treated as mandatory for entrance to public school. It is my theory that these substances have been brought together by science and have entered the human body in an unnatural combination which resulted in an evolution of the immune system. This evolution can be measured in population studies which is being done by molecular biologists. [5-11] The findings confirm that a percentage of the human population has been genetically altered, with vaccination practice a likely cause, and this includes people with autism. [12, 13] In autism the evolution of the immune system has been in the area of complement-initiated, complement-mediated immune response - the bridge between innate and learned immunity. Modulation of innate and acquired immunity is said to involve the heat shock protein (hsp or HSP) specifically HSP-72 kilodalton (kDa) beginning with the simplest organisms [14] and is consistent throughout the plant and animal kingdom also extending to humans [15, 16.] This is consistent with findings that indicate autism is an immune response involving the bridge between innate and learned immunity. [17]

The hsp which protects the chloroplast or plastid (cells containing chlorophyll or xanthophylls) is hsp-72 [18] and this protein and associated plant pigment crossing the placental barrier could have been made an immune target and as a result of subsequent vaccination which combined plant substance and pathogens this immune response or evolution would have been exacerbated. The literature additionally identifies a high incidence of immune-compromised parents of autistic offspring, parents who are themselves effected by diseases, disorders and conditions impacted by vaccination practice. [12, 13]

‘Heat shock proteins (HSP) or stress proteins are produced by prokaryotic and eukaryotic cells in response to a variety of environmental stressors. The heat shock response is one of the most universal reactions known and heat shock proteins are among the most conserved molecules in phylogeny. Recent findings concerning the

immune response to heat shock proteins are discussed especially with respect to the role of HSPs postulated in septic disease and inflammation, in anti-pathogenic immunity and in the induction of autoimmune diseases. Results and speculations considering a relationship between HSPs and gamma/delta T cells or polyreactive antibodies, possibly as part of a phylogenetic old immune system, are critically reviewed.' [19] 'Among microbial antigens implicated in autoimmunity induced by molecular mimicry, hsp may play an exclusive role. Homology between hsp from the pathogen and the host confronts the immune system with the dilemma of distinguishing self from foreign. Poor expression of self-hsp peptides in the thymus could allow T cells specific for self-hsp to evade selection. In the periphery, elevated expression of conserved epitopes from pathogen-derived hsp could break tolerance and activate immune reactions against self-hsp determinants.' [20]

WARNING

'Use of either foreign or self-hsp as carrier molecules for antigenic determinants provides a basis for applying hsp in conjugate vaccines. However, due to immunogenicity and sequence similarity to self hsp, the potential of foreign hsp when used as carrier molecules to induce cross-reactive immune responses against self must be carefully evaluated.' (Max-Planck-Institute) [20]

It appears that **this warning comes a little too late** as this is exactly what has been happening with hsp-72 kDa from agarose gel, egg yolk (xanthophylls) and the hsp-70, hsp-72, hsp-74 derived from a variety of pathogens from which the vaccines are made [18] or to which immune cells react including smallpox, yellow fever, typhoid, diptheria, tuberculosis [21, 22] tetanus [23], cholera [24, 25], pertussis, influenza [26] polio, measles [27], mumps, rubella, or that these pathogens directly affect the hsp-70, hsp72 and hsp74 mechanics. Additionally the susceptibility to certain pathogens e.g. rotavirus [28], to immune-related inner ear disease [29], to cytomegalovirus [30, 31, 32] and medical conditions such as ear inflammation [33] can be associated with abnormal hsp activity. Inflammatory bowel disease has also been linked to autism, vaccine and hsp [34, 35] as well as the potential for dietary influences to affect disease outcome. [36] Heat shock protein 70-kDa has also been shown to enhance candida albicans. [37]

Autism and GOD (Generation of Diversity)

The evolution of the immune system: immunity for the human 'herd' leads us to a modern day dilemma. It is the strength of the adaptability of the organism which results in it's capacity for survival. We are at the threshold of great changes taking place in our human development. Some of these changes are a direct result of man's creative ingenuity and the fight for survival. At the scientific level this has included vaccination. The development of the vaccine and the further development of more vaccines have contributed to evolutionary changes which can be seen in the human population and will likely be seen in the future generations in ways which we cannot yet begin to comprehend.

The evolutionary changes of modern man are seen first and are most evident in the ethno-culturally diverse populations. The areas of our chemical design are most vulnerable when two different types of people come together and this vulnerability can be additionally impacted by a dramatic change in location for which either or neither individual is biologically prepared resulting in offspring who exhibit the wide range of variation some of which is seen in modern day disease etiology. Areas of our chemical design which are most vulnerable are not exclusive to ethno-culturally

diverse populations; in isolated populations where there is little change in genetic and environmental input the weakness of the population can also be seen as diseases which are prevalent in that culture. Add to this scenario the innovations of modern science which include the development of vaccines, genetic engineering of our food, the use of food additives and chemicals, crop spraying and artificial fertilizers, seasonal foods now used for year round consumption, electricity, motor transport, industry, television, computers, cell phones and then look at the available information which indicates how we, as humans, are reacting to these changes.

The molecular biologists, using some of the most advanced tools of modern man, are finding some of the patterns and changes which are taking place in our human population. Some of the most recently studied areas are the 'hypervariable regions' in our DNA and in particular the Human Leukocyte Antigens (HLA) histocompatibility antigens governed by genes of the HLA complex and the human major histocompatibility complex (MHC) – a region on the short arm of chromosome 6 with regions A, B, C and D - the region of our DNA which interacts with our immune system. Immunogenetic (IoGc) research is telling us that how we develop in the womb is not governed solely by our DNA and the environmental insults (impact) that the fetus is susceptible to, but is also due to the response of our own developing immune system. The immune system develops to protect the host and the impact of the immune system during fetal development includes changes which alter our genetic make-up. Some of the terms used to describe these processes are so far called transduction and frameshifting.

How modern day man is reacting to the environment, including everything from the womb experience to the bustling life in the city, impacts our chemical design. When we are reproducing, the chemistry of our bodies further impacts the new lives we create; even our emotional state contributes to chemical information which influences the developing fetus. At the basic level of this scenario lies the fact that, although we are different as organisms from plants and other animals, we do share much common genetic material. Genetic research is engineering ways to look at the human genome more closely as well as the genomes of more simple plants and animals. This research has led to the available techniques being used today to determine things such as paternity and is also beginning to look at the ways in which we are being altered as a result of drug use, vaccination, agricultural practice and food distribution. Food distribution is becoming more important for research because most human populations no longer have to go to the food source, nor do most of us participate in the growth and manufacture of food sources. Additionally, organizations such as the World Health Organization make decisions that affect us globally based on what they collectively think is good for the world population, but often do not account for individual practices within that population, or variables such as food intolerance within human populations or the metabolic, genetic and environmental differences that make for differences in food and nutrition needs.

Research is showing us that in addition to the ethnically diverse populations such as those found in the UK and the USA the ethnically stable populations react to the same modern day influences in ways that can be measured as a response which is specific or unique for that population. What molecular biology is finding is that the impact of modern life is resulting in and exacerbating the diseases of modern man: gout, arthritis, cancer, heart disease, immune deficiency, psychological illness, and diseases relating to reproduction and aging. What we want to know is how does this impact us individually, at the family level and at the community level. We need to understand these things because individually we might choose to take measures which

could positively impact the outcome for ourselves and our families and communities. A healthy human can be more productive, a better parent and a better mate for life. A sick human takes a lot of resources, particularly in the more developed countries. A sick human is not there to care for the parents or the grandchildren, is not a good parent or a good spouse and cannot be productive in the community.

One of the modern day diseases which has made an impact on humanity is autism. Autism is said to be a lifelong disability with as yet no agreed treatment protocol. For more than 60 years autism has remained in the psychological paradigm with early work blaming the mother's parenting for the condition. Dispelling the poor parenting theory did little towards identifying an alternative causal factor. Nearly forty years ago biochemical evidence began to emerge indicating that autism was more than a psychological illness with the publication of Dr. Bernard Rimland's work 'Infantile Autism; The syndrome and its implications for a Neural Theory of Behavior' in 1964. As the field of immunology developed, additional insight into the metabolism of the autistic population was gained but still little scientific effort was applied to utilizing the new information. Therapies began to be offered: ABA (Applied Behavioral analysis, such as Lovaas); Vitamin therapy (particularly the work of Dr. Rimland at Autism Research Institute), AIT (Auditory Integration Therapy based on the work of Tomatis and Guy Berard), Transfer factor (Fudenberg), IVIG (Dr. Singh), Diet (Reichelt, Shattock, Lewis, Crook, Rapp, Braly), EPD and multidisciplinary approaches (Kotsanis), Irlen lenses, Prism lenses, Relaxation techniques such as Biofeedback, Sensory Integration, the 'Squeeze machine' (Grandin) and a multitude of massage therapies: Cranio-Sacral (Andrea Axt), Indian head massage, metamorphic technique, Alexander method, shiatsu as well as physiotherapy and others. In the past decade we have seen millions of dollars of research funding poured into genetics to try to find a genetic abnormality that was assumed must lie at the basis of autism. After extensive research with more still to come it has been determined by a major autism review (Medical Research Council 2001) that the genetic involvement in autism is very variable and affects 5 to 10% of the autism population.[101] Of this 5 to 10% approximately 2% have co-occurring Down syndrome, nearly 1% have Fragile X Syndrome and the additional 2 to 7% of the autism population present with a chromosomal or genetic defect which are markers for conditions such as tuberous sclerosis (TSC), phenylketonuria (PKU), Turner syndrome, Blindness, Deafness and hypopigmentary as well as hyperpigmentary diseases, disorders and conditions. Whereas these diseases, disorders and conditions may not appear at first glance to have much in common, a closer look reveals that the type of disease and presentation in the autism population reveals a pigment factor which supports the immunological information which has been gathered for this population. Sex chromosome disorders which co-occur with autism include Fragile X and Turner syndrome, while pigmentary or pterin disorders include PKU, TSC, Retinopathy of prematurity (ROP), blindness, deafness, Hypomelanosis of Ito and vitiligo. Autism is most easily understood as an immune system adaptation to the genetics of the individual and a response to the environment. Changes have occurred rapidly as a result of the introduction of the vaccine in the form of a live attenuated virus being introduced together with chloroplast DNA at the turn of the twentieth century. At the turn of the 19th century when Jenner's smallpox vaccine was being used widely, the first descriptions of Down syndrome followed the vaccine trail as has been described by Gerhard Buchwald. [38]

Recently therapies for autism have been introduced such as the lutein-free diet (Johnson, Desorgher), Secretin (Beck), and Vitamin A from fish liver oil (Megson,

Johnson, Desorgher) which address the impact of the immune system involvement on the biochemical metabolism of the autist. These therapies do not undermine or invalidate the already existing treatment options (AIT, Specialized lenses, Squeeze therapy and massage, EPD and immune therapies, restrictive diets or behavior therapy). However, the lutein-free diet (nutrient balanced and provided according to ethnocultural diversity and preference requirements), vitamin therapy which is scientifically investigated (vitamin A - fish liver oil) and enzyme therapy are beginning to treat the cause. We are well past hope that science will be able to agree on a causal factor for autism. We are well past expecting that science will acknowledge a role in creating this epidemic. At this point we can only hope that science will investigate and validate the treatment options and provide medical guidance for the members of the medical profession who are under the burden of providing care for this ever increasing population.

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