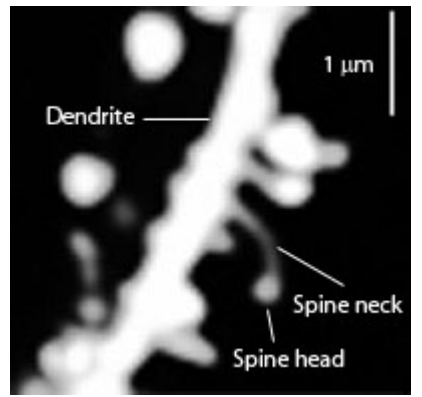


AUTISTIC DENDRITIS (A.D.)



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SYNONYMS

AUTISTIC SYNAPSO-DENDRITIS

TREG AUTISM SYNDROME

HISTORICAL SYNONYMS

KANNER`S SYNDROME

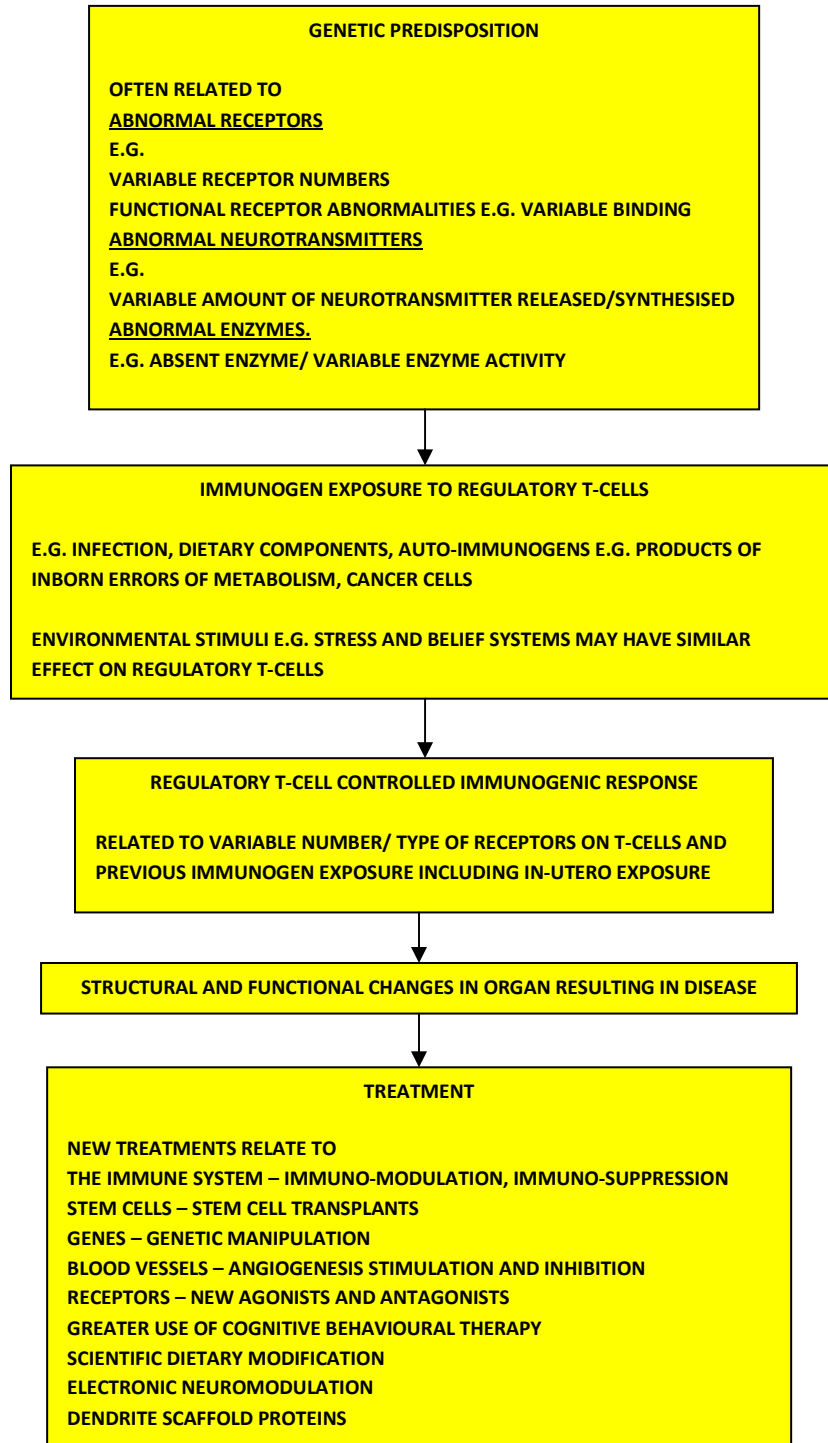
EARLY INFANTILE SYNDROME

AUTISTIC PSYCHOPATHY IN CHILDHOOD (ASPERGER`S SYNDROME)

Ref

PREFACE

The TREG syndrome model for disease, including psychiatric disease, appears to be developing in the following way.



This TREG syndrome model of disease will now be applied to autism.

INTRODUCTION

There have been several theories of autism in the past. This theory encompasses the genetic, immunological, anatomical and clinical features of the disease.

The main underlying pathological abnormality is inflammation of the neuronal dendrites or dendritis.

Dendritis results in abnormalities in the structure and function of dendrites in neuronal circuits in the brain leading to the clinical features of autistic dendritis.

Dendritis is the result of immunological abnormalities in genetically predisposed individuals secondary to immunogen or auto-immunogen exposure.

During the writing of the first two parts of this report series, I realised that

1. The clinical manifestations of the alcohol-drug syndrome overlapped with autism e.g.
 - The hypersensitivity to the predominantly extreme negative thoughts and feelings relating to self-pity, resentment and fear.
 - The extreme thoughts and feelings relating to hypersensitivity to higher and peripheral sensory modalities.
 - The obsessive-compulsive behaviour.
 - The effects on motor function and speech.
 - The hypersensitivity of the autonomic nervous system.

Fetal-alcohol syndrome has a well-recognised association with autism.

Ref

2. There was a possibility that autism may be similarly related to dendritis with changes in the structure and function of dendrites as well as apoptosis which was confirmed.
3. There were possibly immunological and genetic abnormalities in autism suggesting the similar immuno-genetic basis of the disease e.g. elevated C.S.F. T.N.F.-alpha. This was also confirmed.
4. If autism represented a regulatory T-cell (TREG) syndrome then immunological and anti-inflammatory treatment would be required. This was also confirmed e.g. the current trials and treatment with mesenchymal, CD34+ stem cells, oxytocin and minocycline.

These findings have led to the suggestion that the approach to autism should be re-evaluated, and that a new definition would be more appropriate in order to incorporate the above.

Therefore the final part of this book is to draw attention to

1. Autistic dendrititis (A.D.) as an example of a TREG syndrome.
2. The immuno-genetic aetiology of A.D.
3. The dendritic nature of A.D. with the associated
 - Clinical hyper/hyposensitivity to extreme thoughts and feelings and possible deliberate adoption of stoical behaviour in order to reduce emotional pain.
 - Clinical hypersensitivity to higher and peripheral sensory modalities.
 - Clinical hyposensitivity to pain and temperature.
 - Obsessive-compulsive behaviour.
 - Effects on motor and speech development.
 - Clinical hypersensitivity of the autonomic nervous system.

The alcohol-drug syndrome (A.D.S.) immuno-genetic model of dendrititis is used as previously described in the first part of this book.

4. The current immunological and anti-inflammatory drug trials involving
 - Tumour necrosis factor binding proteins and anti- cytokines.
 - Mesenchymal cells/CD34+ stem cells.
 - Minocycline and pyridoxine.
 - Oxytocin.
 - Gene therapy.
 - Hyperbaric oxygen therapy.

This may provide useful information to parents of affected children and adults with A.D. Doctors may develop more of an “organic cause” approach to autism if described as an immunogenetic dendritis.

Autistic disorder and autistic dendritis (A.D.) are used interchangeably in the following text.

TRADITIONAL DEFINITION OF AUTISM VERSUS DEFINITION OF AUTISTIC DENDRITIS

Autistic dendritis (A.D.) is due to the immunogenic response to immunogens or auto-immunogens in a genetically predisposed individual resulting in dendritis due to regulatory T-cells (TREGS) failing to recognize the immunogen or auto-immunogen as “self”. This results in abnormalities in the structure and function of the neuronal dendrites.

The clinical component of A.D. may be defined according to the D.S.M.-IV criteria of autism.

[Ref](#)

The most recent American Academy of Pediatrics Clinical Report on Autism Spectrum Disorders was published in 2007.

[Ref 1](#) [Ref 2](#)

However, when higher-functioning A.D. spectrum patients were interviewed the core symptoms appeared to be

1. Unusual perceptions.
2. Unusual information processing.
3. Impairment of emotional regulation.

These are not mentioned in the D.S.M.-IV definition.

[Ref](#)

“If you listen to the patient they will tell you the diagnosis” – Sir William Osler (1849 – 1919)

Therefore, an alternative definition is required to confirm the diagnosis of A.D. relating to the clinical effects of progressive immuno-genetic dendritic structural and functional changes. This more comprehensive clinical-pathological definition is described below.

DEFINITION

1. **Clinical hyper/hyposensitivity to extreme negative and less frequently extreme positive thoughts and feelings possibly due to the adoption of stoical behaviour.**
2. **Clinical hypersensitivity to higher sensory modalities**
Vision. Hearing. Taste. Smell.
3. **Clinical hypersensitivity to peripheral sensory modalities except pain and temperature.**
Touch. Proprioception. Vibration. Pain. Temperature.
4. **Clinical hyposensitivity to pain and temperature possibly due to deliberate adoption of stoical behaviour.**
5. **Obsessive-compulsive behaviour.**
6. **Gross/fine motor and speech delay.**
7. **Clinical hypersensitivity of the autonomic nervous system.**
8. **History of associated medical TREG syndromes e.g. the “auto- immune” diseases and epilepsy.**
9. **History of associated psychiatric TREG syndromes e.g. attention-deficit hyperactivity disorder (A.D.H.D.).**
10. **Family history of associated medical TREG syndromes e.g. the “auto - immune” diseases.**
11. **Family history of associated psychiatric TREG syndromes e.g. A.D.S.**
12. **Abnormal rate of growth of head circumference within the first three years of life.**
13. **Abnormalities of cell-mediated and humoral immunity in the brain, blood and gastro-intestinal tract.**
14. **Abnormal genotype.**
15. **Abnormal biochemical investigations in the brain and blood.**
16. **Abnormal anatomy including structural and functional changes in neuronal dendrites.**

Although A.D. patients will not satisfy all of the criteria, this alternative definition may be useful in adopting a different approach to autism.

The alternative definition reflects the

1. Need to include the TREG origin of the disease.
2. Importance to include the terms hypersensitivity and hyposensitivity to extreme thoughts and feelings, and higher and peripheral sensory modalities in the definition.
3. Need to include personal and family history of associated medical and psychiatric TREG syndromes in the definition.
4. Need to include recently discovered immune system abnormalities in the definition.
5. Need to include recently discovered genetic abnormalities in the definition.
6. Need to include recently discovered biochemical abnormalities in the definition.
7. Need to include anatomical abnormalities, including neuronal dendrite abnormalities in the definition.

PERVASIVE DEVELOPMENTAL DISORDERS

ALSO KNOWN AS AUTISM SPECTRUM DISORDERS

These are defined according to the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (D.S.M.-IV)

There are five Pervasive Developmental Disorders (PDDs) known as Autism Spectrum Disorders (A.S.D.'s).

299.00 Autistic Disorder

299.80 Pervasive Developmental Disorder, Not Otherwise Specified

299.80 Asperger's Disorder

[YOUTUBE REFERENCE](#)

299.80 Rett's Disorder

[YOUTUBE REFERENCE](#)

299.10 Childhood Disintegrative Disorder

Autistic disorder and autistic dendritis (A.D.) are used interchangeably in the following text.

HYPOTHESIS

A.D. results in immuno-genetic structural and functional changes in dendrites with subsequent changes in synaptic connectivity.

Altered aggregate firing rates of dendrites result in hypersensitivity to thoughts and feelings and obsessive-compulsive behaviour.

Dendrites in central neuronal circuits are segregated or carry segregated impulses for thoughts and feelings in the same way that different neurons carry impulses representing different higher and peripheral sensory modalities.

The central neuronal dendrites carry impulses representing the following ranges of thoughts and feelings

Acceptance – Resentment

Trust – Fear

Gratitude – Self - pity

Honesty – Dishonesty

Increase in aggregate dendrite firing rates results in acceptance, trust, gratitude and honesty.

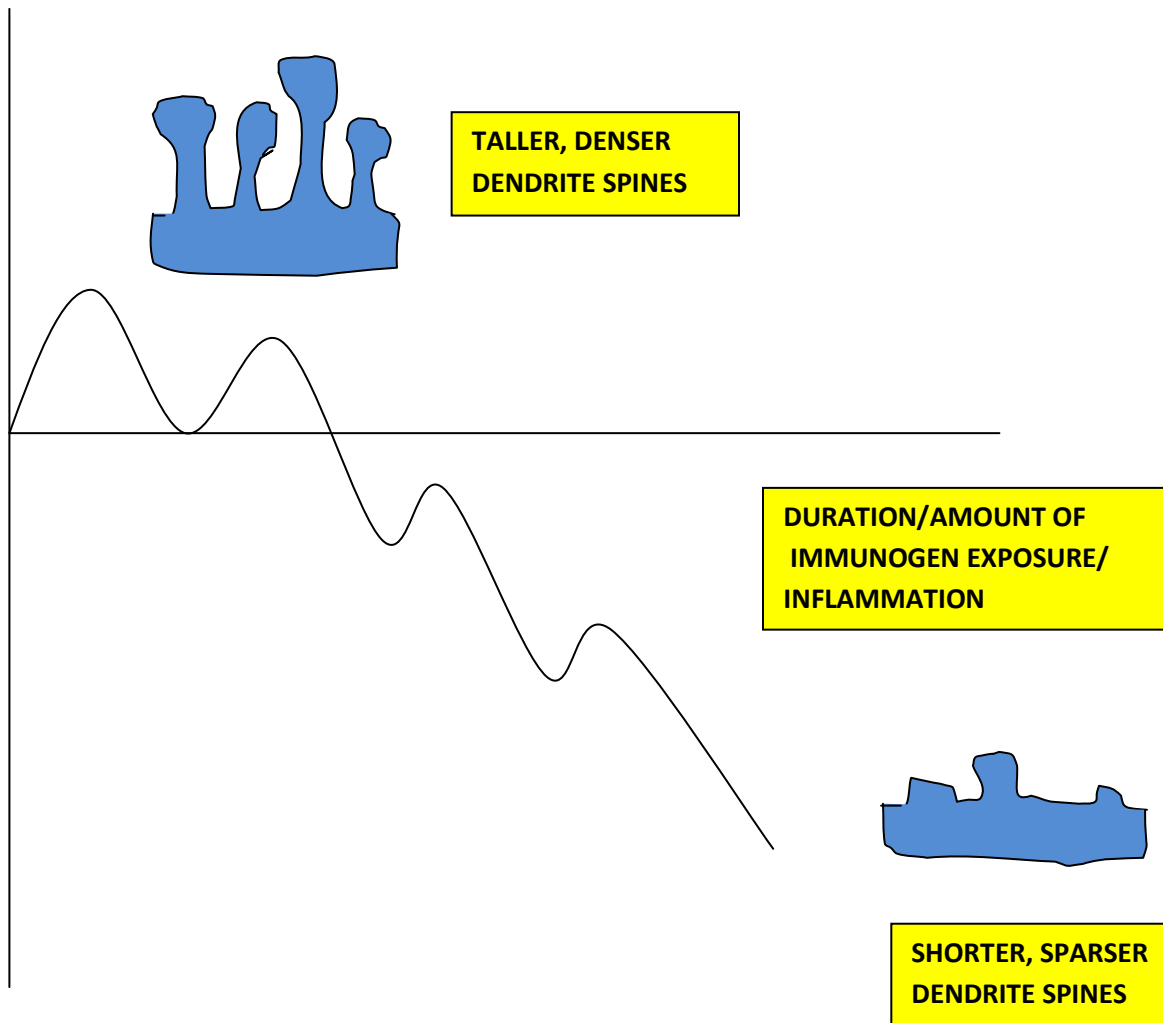
Reduction in aggregate dendrite firing rates results in resentment, fear, self-pity and dishonesty.

Immuno-genetic dendritic structural and functional changes due to A.D. may initially increase the aggregate firing rates but eventually there is progressive reduction in the aggregate firing rates.

As A.D. progresses there is a reduction in dendritic aggregate firing rates which correlates with the increasing predominance of hypersensitivity to negative thoughts and feelings and obsessive-compulsive behaviour.

(See Graphs 1. and 2.)

INCREASED AGGREGATE FIRING RATES OF DENDRITES IN RESPONSE TO IMMUNOGEN EXPOSURE – ACCEPTANCE, TRUST, GRATITUDE, HONESTY

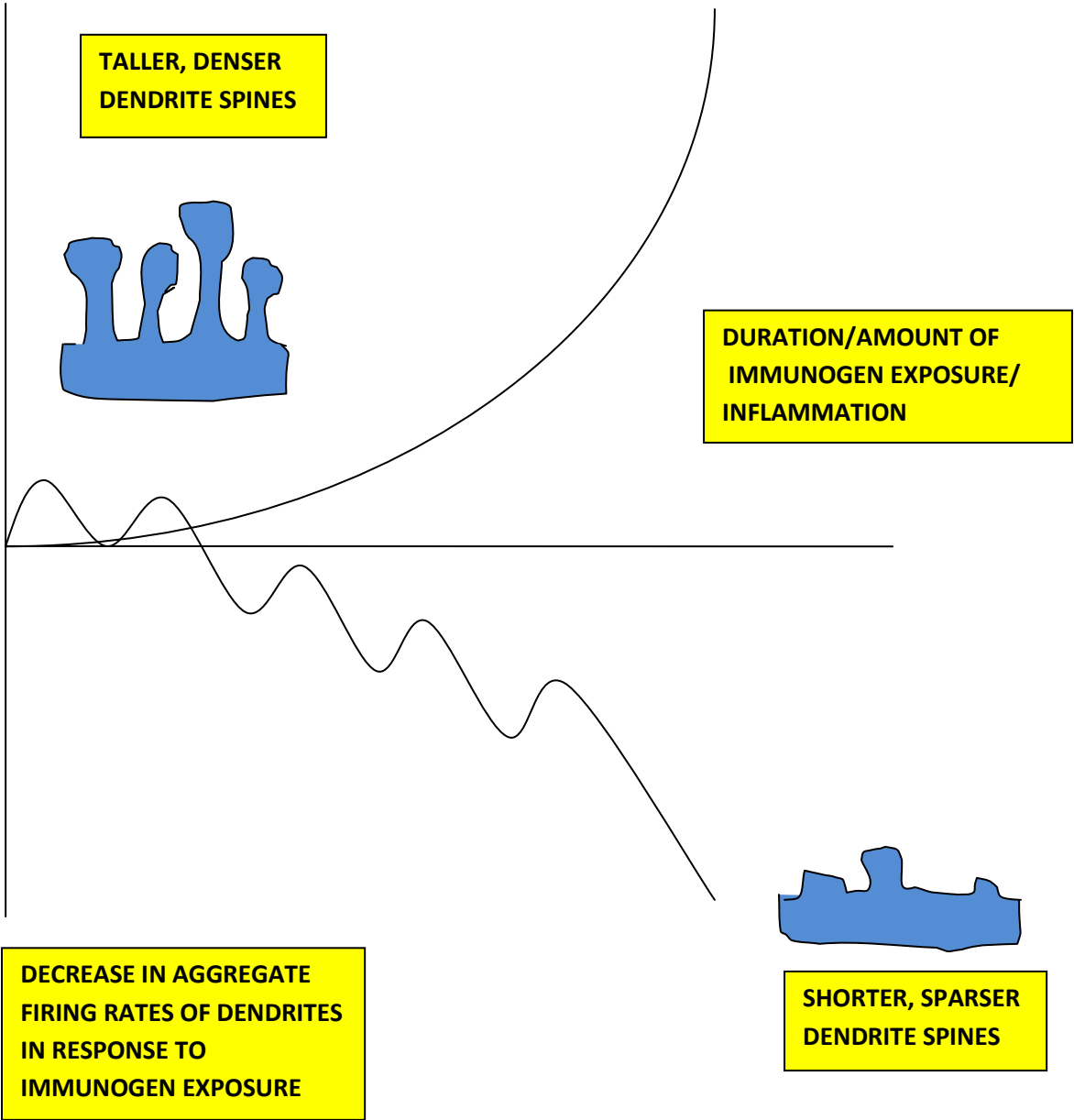


REDUCED AGGREGATE FIRING RATES OF DENDRITES IN RESPONSE TO IMMUNOGEN EXPOSURE – RESENTMENT FEAR SELF-PITY DISHONESTY

**GRAPH 1: HYPOTHESIS
ALTERED AGGREGATE FIRING RATES OF DENDRITES IN RESPONSE TO REPEATED IMMUNOGEN EXPOSURE IN A.D. AND RELATIONSHIP TO DENDRITE SIZE/SHAPE**

INCREASE IN AGGREGATE FIRING RATES OF DENDRITES IN RESPONSE TO IMMUNOGEN EXPOSURE

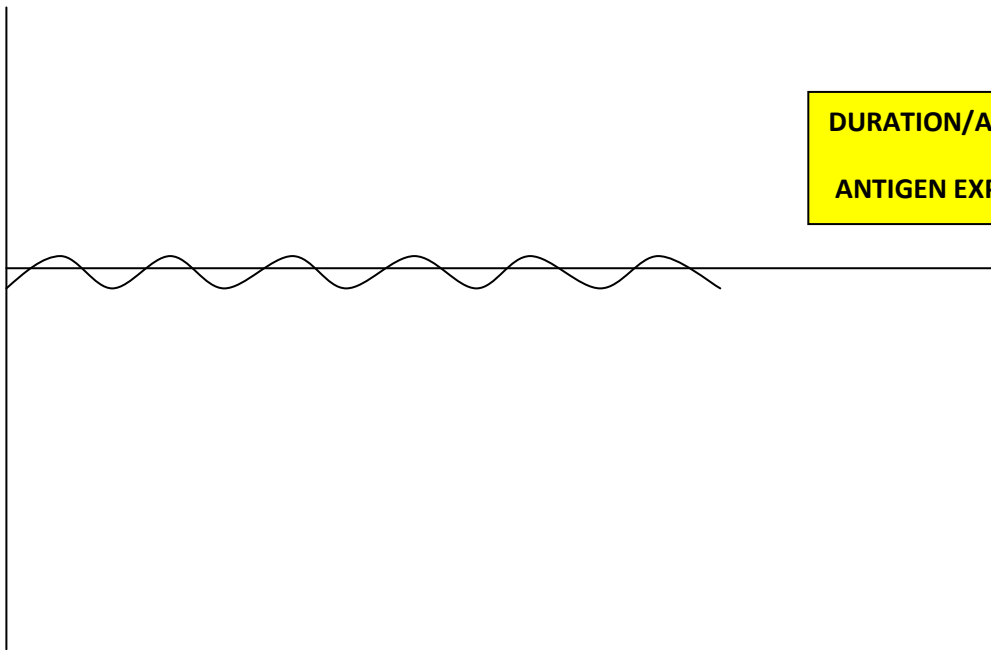
OBSESSIVE-COMPULSIVE BEHAVIOUR



GRAPH 2: HYPOTHESIS. OBSESSIVE-COMPULSIVE BEHAVIOUR IN RESPONSE TO REPEATED IMMUNOGEN EXPOSURE IN A.D. AND RELATIONSHIP TO DENDRITE SIZE/SHAPE

**NORMAL RESPONSE OF AGGREGATE
DENDRITIC FIRING RATES TO ANTIGEN**

**INCREASED AGGREGATE FIRING
RATES OF DENDRITES IN RESPONSE
TO ANTIGEN EXPOSURE**



**DURATION/AMOUNT OF
ANTIGEN EXPOSURE**

**REDUCED AGGREGATE FIRING
RATES OF DENDRITES IN RESPONSE
TO ANTIGEN EXPOSURE**

GRAPH 2

AETIOLOGY

PREVALENCE

Prevalence is variable according to

1. The genotype frequency in the population.
2. The immunogen exposure to the population.
3. The intensity of screening programs.
4. The agreement on the diagnosis.
5. The definition of A.D. spectrum disorder

n.b.

- Autism was first added to the D.S.M. in 1980.
- P.D.D.-N.O.S. was added to the D.S.M. in 1987.
- The criteria for autism was changed (greatly broadened) in 1994.
- Aspergers's syndrome was added to the D.S.M. in 1994.

The following figures are often quoted for A.D. spectrum disorder.

1. 12 in 1000 in 1999. U.S. Department of Health figures.

[Ref 1](#) [Ref 2](#)

2. 1 in 150-300 or even 1 in 75 in some areas more recently.

There was an increase in prevalence of 273% between 1987 and 1993 in California.

There appears to be general disagreement regarding the degree of change in the prevalence of A.D. both historically and at present. Many agree that the trend is upwards, whilst others argue that the prevalence is increasing because of different definitions.

[Ref 3](#) [Ref 4](#)

Further epidemiological studies are awaited.

SEX RATIO

The sex ratio in A.D. may be near parity. Autism spectrum disorder affects 3-4 males to each female affected. Asperger's syndrome affects up to 4 males to 1 female.

Ref

In-utero drug exposure-related A.D. e.g. due to sodium valproate, has an equal sex ratio.

FAMILY HISTORY

1. If one child has A.D. there is a 3-6% chance of the siblings being affected with A.D.

Ref

2. 80-90% of affected monozygotic twins will both have A.D. spectrum disorder suggesting possible in-utero exposure to trans-placental immunogen or early auto-immunogen exposure.
60% of affected monozygotic twins will both have A.D.

3. 10% of affected dizygotic twins will both have A.D.

4. "Healthy" siblings of affected children often have minor autistic-like behavioural changes.

Ref

CLUSTERING

Ref

Clustering will occur

1. In isolated populations or societies where consanguinity more prevalent.
2. In populations where immunogen exposure is increased e.g. to organo-chlorines.
3. In populations where "assortative mating" prevalent.

[Ref 1](#) [Ref 2](#)

EXPRESSIVITY

Expressivity will be variable according to

1. Number of genes inherited.
2. Immunogen exposure.

Ref

LEFT-HANDEDNESS

There may be an association between left-handedness and A.D. although not confirmed.

PARENTAL AGE AT CONCEPTION

Parental age of over 35 years at conception may be associated with A.D. spectrum disorder.

Ref

THE "WESTERN-DIET"

1. Saturated fat, containing omega-6 essential fatty acids, should only make up 10% of total calorie intake e.g. meat, dairy produce, eggs and preserved food. However, the "Western diet" contains more than 10% saturated fat and is pro-inflammatory.
2. Polyunsaturated fat is converted to saturated trans-fats in food processing, which are also pro-inflammatory.
3. The "Western-diet" contains less anti-inflammatory unsaturated fat containing omega-3 essential fatty acids i.e. less oily fish, fruit, nuts and vegetables.
4. There is also reduction in anti-inflammatory mono-unsaturated fat.
5. Omega-3 essential fatty acids reduce the inflammatory cytokines

Interleukin-1 beta.

Tumour necrosis factor-alpha.

Interleukin-6.

[Ref](#)

6. The increase in the omega-6/omega-3 essential fatty acid ratio from a historic ratio of 1:1 to the present 15:1 in the diet has led to enhanced inflammatory activity in the body.

[Ref](#)

7. Non-esterified fatty acids may directly cause cell apoptosis e.g. stearate action on coronary artery endothelium.

[Ref](#)

8. In genetically pre-disposed individuals especially, immunogenic reactions will be more severe on low omega-3, high omega-6 essential fatty acid diet due to the effect on the immune system and steroid metabolism.

OBSTETRIC RISKS

A.D. may be associated with

1. Prematurity.
2. Breech presentation.
3. Low Apgar score at 5 minutes.

[Ref 1](#) [Ref 2](#)

INTELLIGENCE

Intelligence in A.D. may be technically difficult to assess due to the difficulty in achieving the full compliance of the patient, because of the effect on behaviour due to the underlying dendritis.

This may lead to under-measurement. I.Q. results should be regarded with caution.

Ref

The type of test used to measure I.Q. may lead to different measurements e.g. Raven's Progressive Matrices scores can be 30 percentile points higher than Wechsler scales of intelligence scores.

Ref

Mental retardation may be less prevalent than reported in A.D.

Ref

Asperger`s Syndrome may result in exceptional memory for detail i.e. "photographic memory". A.D. may result in the "autistic savant" with "splinter skills" i.e. highly specialised but limited general skills.

Ref

Measurable I.Q often ranges from 35-50 in A.D.

Ref

AGE OF ONSET

A.D. may commence in utero. This may follow trans-placental immunogen or auto-immunogen exposure and could explain the concordance in affected mono-zygotic twins.

Many parents noticed subtle differences in affected children compared to their healthy sibling's development in the first few months of life.

Siblings of A.D. patients who later develop A.D. themselves often have subtle behavioural changes in the first year.

Ref

Head circumference often increases in "spurts" at 2 months of age and thereafter resulting in macrocephaly.

Ref

The increase in rate of head circumference growth may be related to immunogen exposure and immunogenic response representing progressive dendritis if genetically pre-disposed.

A.D. may result in delayed head-turning response by the patient when his or her name is called as seen on home-videos at one year of age. Relative aversion of eye-contact may also be noted in some of the home-videos.

The following delays in achieving developmental milestones may be noticed.

- No babbling by 12 months.
- No pointing/waving by 12 months.
- No single word by 16 months.
- No two-word phrases by 24 months.
- Loss of language or social skills at any age.

Ref

Usually the diagnosis is confirmed by three years of age.

[Ref 1](#) [Ref 2](#)

FAMILY HISTORY OF RELATED TREG SYNDROMES

1. There is often a family history of A.D. or TREG psychiatric syndromes which exhibit immunogenetic abnormalities.

These include

Dyspraxia.

A.D.H.D.

Depression, schizophrenia and mania.

Alcohol-drug syndrome.

Obsessive-compulsive syndromes.

THESE ASSOCIATIONS ARE BEING FURTHER INVESTIGATED.

Ref

2. There is often a family history of TREG medical syndromes which exhibit immunogenetic abnormalities.

These include

Diabetes mellitus.

Rheumatoid arthritis.

Systemic lupus erythematosus.

Hashimoto`s disease.

Multiple sclerosis.

Epilepsy.

Asthma/ Rhinitis/ Eczema.

i.e. includes several of the “auto-immune” syndromes.

These associations are being further investigated.

Cancer may also be more prevalent in the relatives.

Ref 1 Ref 2

ASSOCIATED MEDICAL DISEASES

Medical TREG syndromes (vide supra in TREG syndromes) may be more prevalent in A.D. including the following

Diabetes mellitus.

Rheumatoid arthritis.

Systemic lupus erythematosus.

Hashimoto`s disease.

Multiple sclerosis.

Psoriasis.

Epilepsy.

Asthma/ Rhinitis/ Eczema.

i.e. several of the “auto-immune” syndromes.

These associations are being further investigated.

ASSOCIATED PAEDIATRIC NEUROLOGICAL DISEASES

Fragile X syndrome – associated with abnormal dendrite spines and increased T.N.F.

[Ref 1](#) [Ref 2](#) [Ref 3](#)

Tuberous sclerosis – associated with abnormal dendrite spines and increased T.N.F.-alpha.

[Ref 1](#) [Ref 2](#) [Ref 3](#)

Neurofibromatosis – associated with dendrite and T.N.F. abnormalities.

These associations are being further investigated.

ASSOCIATED PSYCHIATRIC DISEASES

Psychiatric TREG syndromes associated with abnormalities of dendrites and the immune system may be more prevalent in A.D., especially the following

Dyspraxia.

A.D.H.D.

Obsessive-compulsive disorder.

Affective and bipolar disorders. Schizophrenia may not be more prevalent.

Tourette`s syndrome.

Encopresis.

Enuresis.

Trichotillomania.

Oppositional defiant and conduct disorders.

These associations are being further investigated.

[Ref 1](#) [Ref 2](#) [Ref 3](#) [Ref 4](#) [Ref 5](#) [Ref 6](#)

PATHOLOGY

DENDRITES AND DENDRITIS

Greek: Dendron, tree

Dendrites are the parts of neurons which receive information from the axons of surrounding neurons. The dendrites are tree-shaped structures which transmit information to the cell body of the neuron. The axon transmits information away from the cell body to other neuronal dendrites.

Dendrites divide from primary dendrites into secondary, tertiary dendrites etc. The terminal segments of dendrites are at the ends of each dendrite.

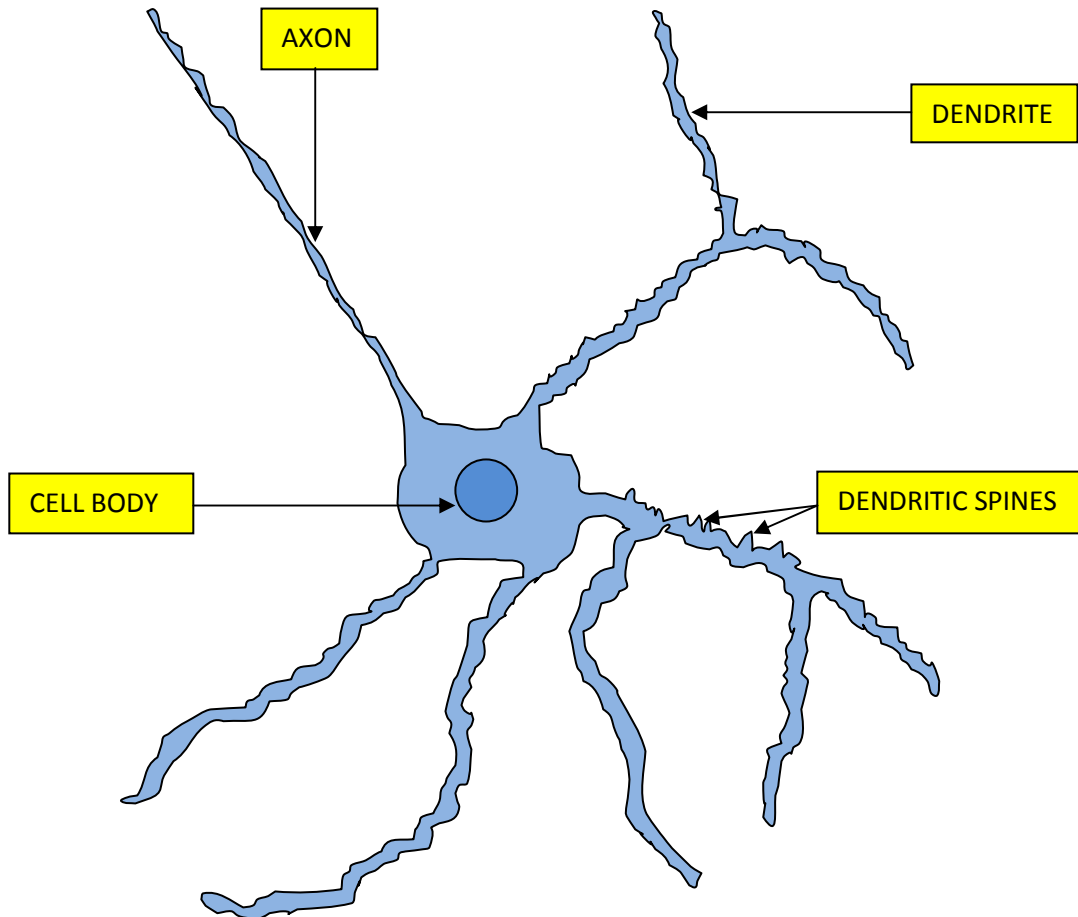
Some dendrites are smooth edged, but others have appendages called spines.

A.D. is the result of progressive inflammation of the terminal segments of dendrites or dendritis. This results in the following

1. Altered spine density of dendrites.
2. Altered spine size of dendrites.
3. Abnormal dendritic interconnectivity.
4. Abnormal dendritic firing rates.

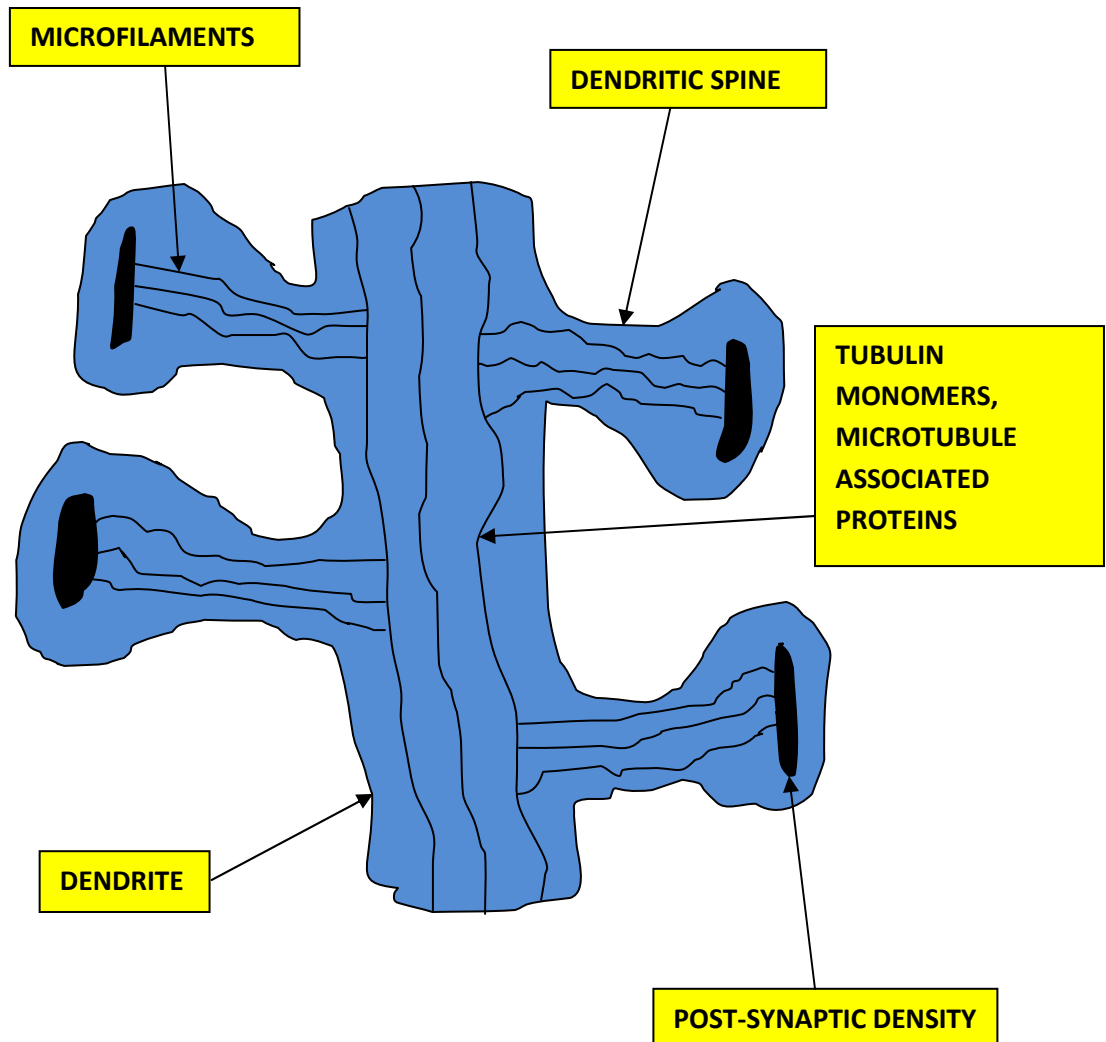
[Ref 1](#) [Ref 2](#)

(See schematic illustrations below.)



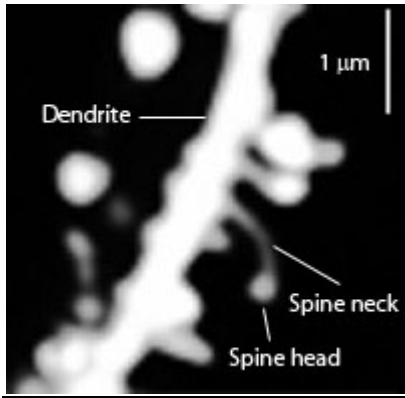
SCHEMATIC ILLUSTRATION OF NEURON INCLUDING NEURONAL AXON, DENDRITES AND DENDRITIC SPINES

[Ref 1](#) [Ref 2](#)



SCHEMATIC ILLUSTRATION OF DENDRITE AND DENDRITIC SPINES

[Ref 1](#) [Ref 2](#)



SPINY DENDRITE OF A STRIATAL MEDIUM SPINY NEURON

[Ref 1](#) [Ref 2](#)

IMMUNE SYSTEM

DEFINITION OF ANTIGEN AND IMMUNOGEN.

ANTIGEN – any substance that binds to an antibody or T cell receptor.

IMMUNOGEN- any substance which induces a humoral and/or cellular response.

ALL IMMUNOGENS ARE ANTIGENS BUT NOT ALL ANTIGENS ARE IMMUNOGENS. AN AUTO-IMMUNOGEN IS AN ENDOGENOUS IMMUNOGEN SYNTHESISED BY THE BODY.

Ref

The failure of the regulatory T-cells to identify antigen as “self”, in genetically pre-disposed individuals, results in an immunogenic response and the development of A.D.

THE IMMUNOGENIC RESPONSE AFFECTS THE DENDRITES. THE INFLAMED DENDRITES HAVE DIFFERENT STRUCTURES AND FIRING RATES FROM NORMAL DENDRITES. THE INFANT'S DENDRITES ARE STILL DEVELOPING RESULTING IN INCREASED SUSCEPTIBILITY TO DENDRITIC INFLAMMATION.

The immune system comprises of

1. T-cells.

These cells are divided into

I. Regulatory or suppressor cells.

[Ref](#)

These cells suppress activation of the immune system. Suppressor cells include

a. Those expressing CD4+,CD25+ and Foxp3 cells or “naturally occurring regulatory T-cells” (TREGS). TREG activity is affected by the mammalian target of rapamycin (mTOR) pathway and heat-shock protein (HSP) 60.

[Ref 1](#) [Ref 2](#)

b. Those expressing CD8+ T cells.

c. Other T-cells which are immuno-suppressive.

Reduction in suppressor TREG T-cell activity may result in “auto-immune” or “atopic” disease due to failure to distinguish “self” from “non-self”.

TREG T-cells may be

- Up-regulated by HSP60. Increased by acetyl-1-carnitine.
- Down-regulated by the mTOR pathway, which is in turn affected by leucine and arginine, which decrease TREG T-cell activity, and glutamine, which increases TREG T-cell activity. Rapamycin is a macrolide antibiotic which inhibits the response to IL (interleukin)-2 and reduces lymphocyte proliferation.

Quite recently the following have also been shown to affect the regulation of TREG T-cell activity.

- GATA-3

[Ref](#)

- p110 delta

[Ref 1](#) [Ref 2](#)

II. Helper T-cells or CD4 cells.

[Ref 1](#) [Ref 2](#) [Ref 3](#)

These cells recognize antigen on the surface of a cell. There are the following types of response.
(See Diagram 1)

Th (T helper) 1 response.

The Th1 response results in release of tumour necrosis (T.N.F.)-beta and interferon-gamma. Macrophage killing and macrophage/dendritic cell release of IL-12 is increased. CD8+ cytotoxic killer T-cell proliferation is stimulated.

IL-12 stimulates further interferon-gamma release and positive feedback to the Th1 response. Interferon-gamma inhibits IL-4 also preserving the Th1 response. The Th1 response is associated with “auto-immune” disease.

Th (T helper) 2 response.

The Th2 response results in release of IL-4, IL-5, IL-6, IL-10 and IL-13. B-cell immunoglobulin and IgE production are stimulated. IL-10 inhibits IL-2, IL-12 and interferon-gamma. The Th2 response is associated with “atopy”.

Th (T helper) 17 response.

Transforming growth factor (T.G.F.) beta 1 stimulates TREG cells and reduces inflammation. However, in the presence of IL-6 and IL-23, T.G.F. beta-1 stimulates the pro-inflammatory Th17 T-cell subset which releases IL-17 and other chemokines and cytokines. Vitamin A regulates the T.G.F. beta-1 response and increases TREG cell proliferation.

Th (T helper) 3 response

The Th3 response results in release of T.G.F.-beta and IL-10 which inhibit helper cells. The Th3 response suppresses activity of most of the immune system, but possibly not the activated Th2 response.

III. Killer T-cells, CD8 cells or cytotoxic cells.

These cells recognize antigen on the surface of a cell and kill the cell.

2. B-cells

Produce immunoglobulin.

3. Other components include.

i. Macrophages/dendritic cells.

ii. Complement.

iii. Mast cells.

iv. Leucocytes.

SUMMARY OF T HELPER CELL RESPONSES TO IMMUNOGEN

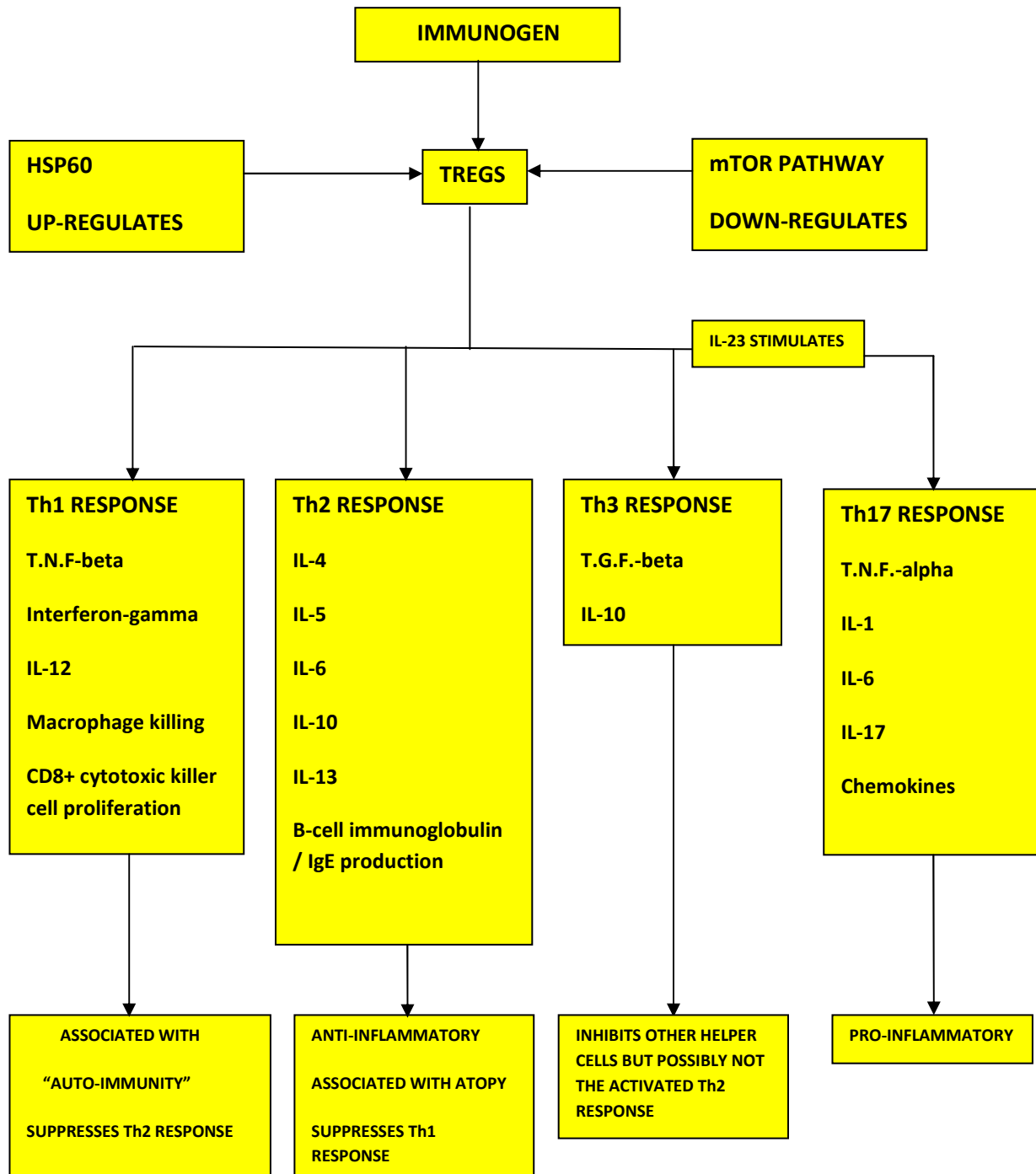


DIAGRAM 1

GENERAL COMMENT

- 1. A.D. is a disease due to the failure of TREGS to recognise**
 - i. Certain environmental antigens and/or their metabolites**
 - ii. auto-antigens**
 - as "self" i.e. the antigens or auto-antigens become immunogens or auto-immunogens.**
- 2. This results in an immunogenic reaction by the immune system.**
- 3. There is an imbalance in the Th1/Th2/Th3/Th17 response.**
- 4. This is truly an allergic or hypersensitive reaction.**
- 5. The immunogenic reaction is primarily in the brain i.e. dendritis but may affect other organs in the body e.g. the gastro-intestinal tract.**
- 6. The brain may appear macroscopically normal initially, but is already different at cellular level prior to immunogen or auto-immunogen exposure due to predisposing genetic abnormalities yet to be discovered.**
- 7. The dendrites or the message-carrying components of neurons become inflamed with subsequent structural and functional changes.**

MACROPHAGE FUNCTION

1. The macrophages engulf the environmental antigen or their derivative molecule and phagocytosis occurs.
2. The macrophages express processed antigen or their derivatives in major histocompatibility complex on cell membrane. The macrophages are now known as antigen-presenting cells.
3. In normal individuals, the environmental antigen may be accepted as “self” or “near-self” by the TREGS.
4. In A.D. there is activation of T-helper cells and B-cells due to environmental antigens or their derivatives becoming immunogens instead of antigens i.e. due to being recognised as “non-self”.
5. The inflammatory response results in the following.

- Further T-cell activation.
- Auto-reactive immunoglobulin release.
- Cytokine release – including T.N.F., interferon, and interleukins.
- Blockage of activation of tissue growth factor.
- Release of metallo-proteases.
- Fibroblast activation.
- Development of tissue specific immunoglobulin e.g. anti-tissue transglutaminase immunoglobulin.
- Disorganisation of tissues leading to clinical inflammation manifesting primarily as dendritis.

ABNORMALITIES OF CELL-MEDIATED AND HUMORAL IMMUNITY IN THE BRAIN

The following observations have been confirmed at autopsy of A.D. patients.

Abnormalities of cell-mediated immunity in the brain. Includes

1. Decreased T-lymphocyte CD4 population.
2. Imbalance of Th1/Th2/Th3/T17 towards Th2.

Abnormalities of humoral immunity in the brain. Includes

1. Auto-antibodies to the brain.

Myelin-based protein antibody.

Neuron-axon filament protein antibody.

Glial fibrillary acidic protein antibody.

2. Increase in pro-inflammatory chemokines.

Macrophage chemoattractant protein in brain and C.S.F.

3. Increase in anti-inflammatory and modulatory chemokines.

T.G.F. - beta-1.

4. Increased T.N.F. - alpha. Measurable in the C.S.F.

5. Increased interleukin 1-beta, interleukin-8 and interleukin - 10.

6. High nitric oxide levels.

7. Increased number of Toll-like receptors.

[Ref 1](#) [Ref 2](#) [Ref 3](#) [Ref 4](#)

Macrophage dysfunction may be associated with A.D. Macrophages in the brain are known as dendritic cells, but do not confuse this term with neuronal dendrites which are quite separate.

[Ref 1](#) [Ref 2](#) [Ref 3](#) [Ref 4](#) [Ref 5](#) [Ref 6](#)

Decreased IgA and abnormal numbers of CD3 T-cells may result in reduced gastro-intestinal protection and increased pathology affecting the gastro-intestinal tract, which is well-recognised in A.D.

[Ref](#)

(See Diagram 2.)

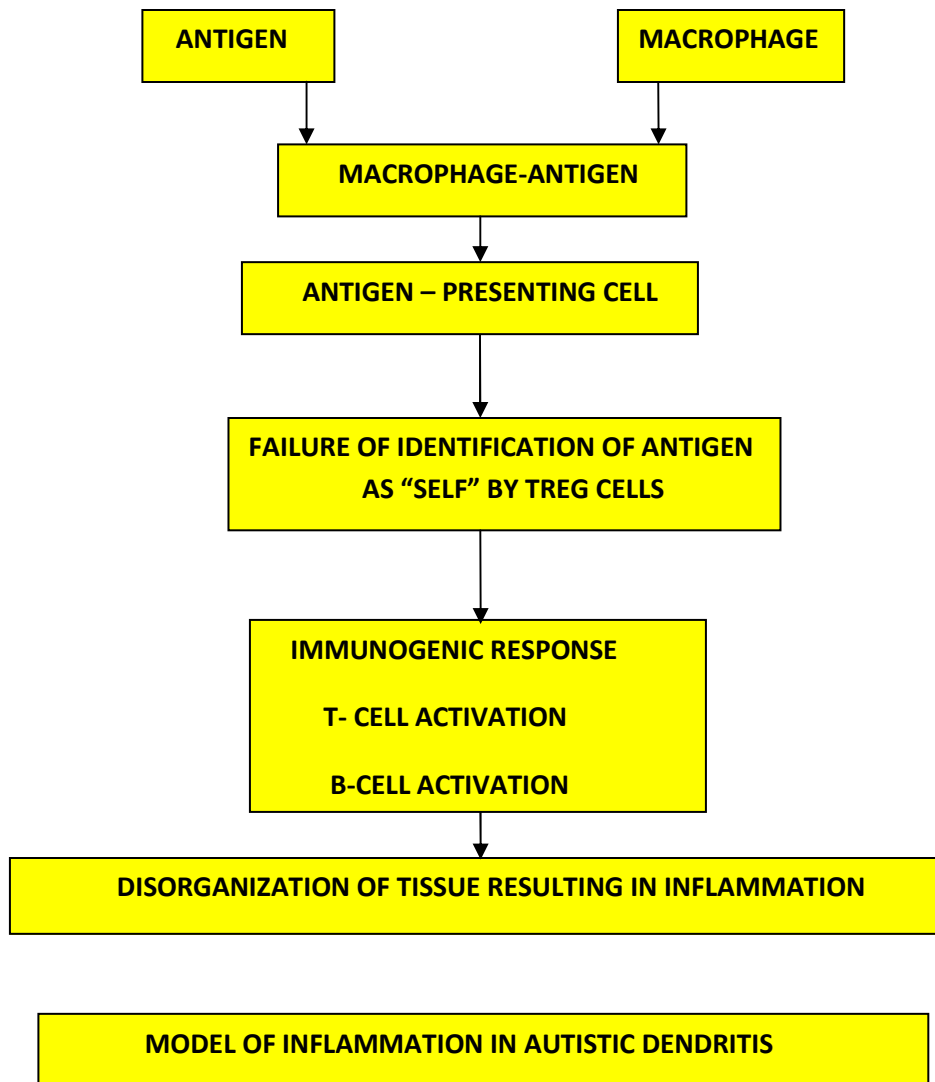
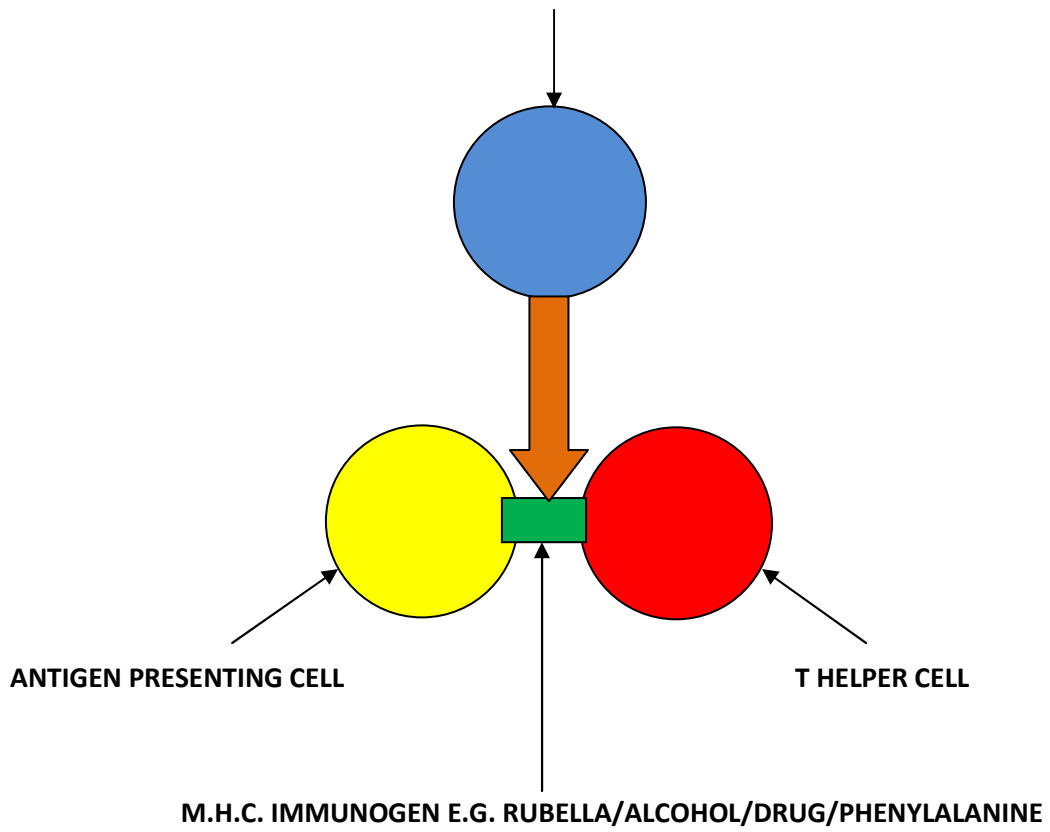


DIAGRAM 2

SUMMARY

THE REGULATORY T-CELL SUPPRESSES THE IMMUNOGENIC RESPONSE OR ALLOWS THE IMMUNOGENIC RESPONSE TO PROCEED



ABNORMAL GENOTYPE

There are up to 100 genes contributing to the abnormal genotype. There are associated chromosomal abnormalities.

The following are more prevalent in A.D.

CHROMOSOMAL ABNORMALITIES

These have been noted at the following sites

2q37.

7q.

[Ref](#)

22q13.

[Ref](#)

Maternal Duplications of Chromosome 15 q11-13

Present in 1-3% of A.D. patients. Also present in Angelman's syndrome.

[Ref](#)

FRAGILE X SYNDROME AND A.D.

Fragile X syndrome is associated with autistic clinical features and abnormalities of T.N.F. expression.

Fragile X mental retardation 1 results in REDUCED dendritic firing rates.

Mutation of the gene PAK which codes for p21 activated kinase results in INCREASED dendritic firing rates. Insertion of PAK gene mutation led to improvement in autistic behavior in fragile X mental retardation 1 in animal studies.

Although a different but associated disease these findings suggest that gene therapy to increase dendritic firing rates may be helpful in improving A.D.

[Ref](#)

GENETIC ABNORMALITIES

These have been noted on the following site

FOXP2 mutation on chromosome 7q.

Associated with autosomal dominant speech and language disturbance.

Ref

Rett's Syndrome is associated with mutations of methyl-CpG-binding protein 2 gene. There are associated dendrite and T.N.F. abnormalities.

Ref 1 Ref 2

Mutations of the methylenetetrahydrofolate reductase gene (MTHFR) involving folate metabolism are also being investigated.

Ref

Macrophage migration inhibitory factor gene abnormalities may be associated with A.D.

Ref

There may be associations with

Abnormal oxytocin genotype.

Ref

H.L.A.-DRB1 and H.L.A.-DR4.

Ref

RECEPTOR ABNORMALITIES

Receptor abnormalities have also been described in A.D.

Ref

BIOCHEMICAL ABNORMALITIES

These include

FREE SULPHATE

Low levels of free sulphate have been noted in A.D. and may be precipitated by ingestion of citric acid and chocolate. Magnesium sulphate (Epsom salt) baths developed to restore sulphate balance but causes skin irritation.

Ref

HYPERSEROTONINAEMIA

Hyperserotoninaemia has been noted in up to 25% of A.D. patients. Hyposerotoninaemia may also occur. Neurotransmitters may be affected by hyperserotoninaemia. Serotonin transporter genes may also be abnormal.

Ref 1 Ref 2

METHYLATION

Abnormal methylation may be associated with A.D.

Ref 1 Ref 2

ACCUMULATION OF VERY LONG CHAIN FATTY ACIDS IN CELL MEMBRANES

The accumulation of very long-chain fatty acids in cell membranes in A.D. may be related to carnitine deficiency.

Ref 1 Ref 2

ABNORMALITIES IN TESTOSTERONE METABOLISM

Abnormalities in testosterone metabolism have been reported in A.D. but dehydroepiandrosterone (DHEA) and DHEA – S are not consistently elevated in A.D.

Ref 1 Ref 2

ABNORMALITIES IN GROWTH-RELATED HORMONES

Abnormalities in I.G.F.-1, I.G.F.-2, I.G.F.B.P.-3 and G.H.B.P. may contribute to the abnormal rate of head circumference growth.

Ref

ABNORMALITIES IN GLUTAMINE METABOLISM

Abnormalities in glutamine metabolism have been described in A.D. Glutamine dietary supplementation is often recommended.

Ref

ABNORMALITIES IN VITAMIN D METABOLISM

This may explain the increasing prevalence in A.D. with increasing latitude possibly related to reduction in sunlight exposure.

Ref

ANATOMICAL ABNORMALITIES

Many of the findings are inconsistent.

The brain stem is often smaller which may reflect inflammation.

Ref

The third ventricle volume is often enlarged which may reflect inflammation.

The brain parenchymal volume is often enlarged which may reflect inflammation.

Ref

The degree of macrocephaly is correlated with the severity of A.D.

Ref

There are increased numbers of neurons in various areas of the brain.

There are usually abnormalities of the minicolumns of the brain which contain dendrites. The minicolumns are up to 50% narrower than normal.

The reduction in minicolumn width is not associated with neuronal apoptosis.

Ref 1 Ref 2

The severity of the localised reduction in brain grey matter in areas belonging to the mirror neuron system, are correlated with the severity of A.D.

Ref 1 Ref 2

HIPPOCAMPUS

Hippocampal neurons in A.D. are smaller in the perikaryon area and dendritic branching neurons are reduced compared to normal.

Ref

Hippocampal shape may be abnormal. The shape abnormality may be related to the severity of A.D.

Ref

The changes in hippocampal shape and volume may be asymmetrical.

Ref

However, the results of hippocampal shape and volume measurements are inconsistent.

Ref

There may be associated amygdala abnormalities.

[Ref](#)

GASTRO-INTESTINAL TRACT

There are also frequently found abnormalities affecting the gastro-intestinal tract e.g. gastritis/duodenitis possibly related to reduction in IgA, T-cell e.g. CD3 and interleukin abnormalities as described above. Digestive enzyme abnormalities may also be contributory.

[Ref 1](#) [Ref 2](#)

IMMUNOGENS AND DEFICIENCY-STATES

Several immunogens and deficiency-states have been linked with A.D.

PROVEN AND POTENTIAL IMMUNOGENS

1. Infection (including prions) e.g. congenital rubella – **PROVEN**.
2. Alcohol – **PROVEN**.
3. Drugs
 - Thalidomide, sodium valproate – **BOTH PROVEN**.
 - Unproven – antibiotics, hormones in medicine and in the food industry. 50% of manufactured antibiotics enter food chain at food industry level. Drugs are often found in the water supply.
2. Inborn errors of metabolism e.g. phenylketonuria – **PROVEN**.
3. Tobacco.
4. Gluten.
5. Casein.
6. Pesticides – organochlorines.
7. Herbicides.
8. Fertilizers.
9. Sweetening agents.
10. Refined sugar, sugar-milk, and milk – contains milk protein butyrophilin.
11. Added salt.
12. Aluminium – from tin-cans, cooking utensils, deodorants, water.
13. Rape pollen near large centres of population.
14. Environmental pollutants e.g. car-exhaust.
15. E-numbers.
16. Soya.
17. Occupational immunogens.
18. Immunisations.
19. Radon.
20. Electro-magnetic field radiation.
21. Talc.
22. Manganese.
23. Mercury.
24. Lead.
25. Homocysteine.

DEFICIENCY-STATES

- 1. Folic acid.**
- 2. Vitamins A, C, D, E and vitamin B complex.**
- 3. Trace metals – copper, zinc, selenium, magnesium and manganese.**
- 4. Carnitine.**

EXAMPLE OF A SWEETENING AGENT

ASPARTAME

The aspartame theory in the causation of A.D. provokes controversy.

[Ref](#)

CONSTITUENTS

1. Phenylalanine – 50%.
2. Methanol or wood-alcohol – 10%.
3. Aspartic acid – 40%.

Hyperphenylalaninaemia which occurs in phenylketonuria is associated with autistic symptomatology.

The recommended daily intake of methanol is up to 7.8 mg. One litre of soft drink contains 56 mg of methanol.

Aspartic acid, if taken in the free form, results in increased blood glutamate and aspartate. Aspartate is an EXCITOTOXIN.

EXCITOTOXINS

Excitotoxins

- Are usually secreted by the nervous system microglial immune cells.
- Cause T.N.F. mediated myelin oligodendrocyte apoptosis and the break-down of the blood-brain barrier.

Dietary sodium monoglutamate is used as a food additive for improving the taste of food.

When combined with aspartame in the diet there is a marked increase in aspartate excitotoxin blood levels.

FOODS CONTAINING ASPARTAME

Aspartame is widely-used in

1. Cereals and desserts.
2. Coffee, tea and cocoa preparations.
3. Juices, milk-shakes and soft drinks.
4. Vitamin and pharmaceutical tablets/capsules.
5. Sugar-substitutes used in cafes, restaurants etc;

IMMUNOGENS CAUSING A.D.

THALIDOMIDE

Children of mothers who were treated with thalidomide in pregnancy had an increased frequency of A.D. Thalidomide affected angiogenesis and decreased brain blood flow during embryogenesis. However thalidomide also affects TREG cells directly resulting in altered immunogenic response to “non-self” antigen and may be used for treating inflammatory bowel disease n.b. stem-cell treatment of A.D. with mesenchymal stem cells and CD34+ T-cells aims to stimulate angiogenesis and improve blood flow to the brain as well as suppressing inflammation.

Ref 1 Ref 2

ORGANOCHLORINES

Maternal exposure to organochlorines during pregnancy may result in a 6-7 fold increase in A.D. the evidence is very preliminary.

Ref

SODIUM VALPROATE

Sodium valproate is more likely to be associated with A.D. than other anti-convulsants.

Ref

CONGENITAL RUBELLA

Congenital rubella is associated with A.D.

Ref

PHENYLKETONURIA

Phenylketonuria is associated with A.D. The hyperphenylalaninaemia may act as an auto-immunogen.

Ref

IMMUNISATIONS

Historically, the simultaneous administration of measles and varicella immunisation possibly increased the risk of developing sub-acute sclerosing panencephalitis. The measles, mumps and rubella (M.M.R.) immunisation and the infant's increasingly multiple immunisation programme have recently been brought into question in relation to the development of A.D. and gastro-intestinal disease including inflammatory bowel disease. On-going studies have not yet proven any causative effect.

Previously, because the M.M.R. immunisation caused the significant complication of encephalitis, the Urabe strain of the mumps virus had to be changed. There was some suspicion that the U.K. Government were aware of the problem earlier on.

[Ref 1](#) [Ref 2](#) [Ref 3](#)

Quite recently, the U.S Government awarded compensation to a patient who had developed autism with an immunisation history, and after extensive investigation was later discovered to have a rare mitochondrial disease. The decision was criticized by Paediatricians as sending out the wrong message to parents regarding the safety of immunisation of their children. Paediatricians argued that the mitochondrial disease would have manifested itself eventually with or without an immunisation history.

Ref

However, this may suggest that for a certain small sub-group of children predisposing genetic abnormalities results in them having an abnormal immunogenic response to childhood immunisations. Screening for mitochondrial disease is prohibitively expensive and mitochondrial disease is rare.

The immune response to immunisations has been found to be abnormal in A.D. The immune system is also frequently abnormal in the intestinal mucosa in A.D. e.g. abnormal IgA and numbers of CD3 T-cells are subject to continuing investigation. This may explain the development of the proposed immunization-related colitis if genetically predisposed.

Ref

The three questions on which the public need reassurance are

1. Is there an association between immunisations and A.D.?
2. Is there a positive correlation between immunisations and A.D.?
3. Do immunisations have a causative effect in A.D.?

The area remains highly controversial. The medical intelligence of the public is increasing with media exposure and Internet access. Any uncertainty in the answer "definitely no" to these three questions obviously will result in continued speculation by the public, especially when their children's lives are at stake and there is a suggestion of historical ineptitude by government and secrecy surrounding the release of some drug trial results by the pharmaceutical industry.

CEREBRAL HYPO-PERFUSION

Cerebral hypo-perfusion has been noted in A.D. and may be primary or secondary to the inflammatory process. Thalidomide affected in-utero angiogenesis and was associated with the development of A.D. Hyperbaric oxygen therapy aims to improve oxygenation of the hypo-perfused areas. Stem cell therapy promotes angiogenesis.

[Ref 1](#) [Ref 2](#)

PRE-NATAL STRESS

Pre-natal stress may be associated with

1. Abnormal postnatal behaviors that resemble the defining symptoms of A.D.
2. Other abnormalities that have elevated rates in AD, such as learning deficits, seizure disorders, peri-natal complications, immunologic and neuro-inflammatory anomalies, and low postnatal tolerance for stress.

[Ref](#)

Stress is known to reduce the density of dendritic spines.

Stress hormones e.g. corticotrophin releasing factor can also contribute to the reduction in the number of dendritic spines.

[Ref 1](#) [Ref 2](#)

FEVER

Fever has been associated with improvement in the clinical features of A.D.

[Ref](#)

CLINICAL FEATURES

The initial observation is that the children appear healthy and are thriving physically. They have been described as “sweet, funny, smart and beautiful”.

The clinical features are as described in D.S.M. - IV criteria for autism. An alternative description may be based on the A.D.S. model of dendritis which results in

1. Hyper/hyposensitivity to extreme thoughts and feelings and sensory perception.
2. Obsessive-compulsive behaviour.

The clinical features of A.D. may be defined as

1. Hyper/hyposensitivity to extreme thoughts and feelings.
2. Hypersensitivity to higher sensory modalities.
3. Hypersensitivity to peripheral sensory modalities.
4. Hyposensitivity to peripheral sensory modalities of pain and temperature.
5. Obsessive-compulsive behaviour.
6. Delayed motor and speech development.
7. Hypersensitivity of the autonomic nervous system.
8. Abnormal rate of growth in head circumference possibly related to the underlying dendritis.

The patient often appears hypersensitive to thoughts and feelings from higher and peripheral sensory stimuli except temperature and pain e.g. not crying with painful stimuli such as falling over. Patients with A.D. may be attempting to deliberately suppress the response to these painful thoughts and feelings which result in behavioural changes seen in A.D.

The behaviour in A.D. may be related to extreme “stoicism”.

The lack of empathy and imitation with the associated self-obsession may be related to the reduced thickness of the mirror neuron system in the cerebral cortex.

STOICISM

Stoicism in modern usage is defined as:

“An ancient Greek School of Philosophy which taught that it is wise to remain indifferent to changes of fortune and to pleasure and pain” (Compact Oxford English Dictionary)

[Ref](#)

Stoicism results in self-control as a means of overcoming negative thoughts and feelings. This may result in improvement in emotional pain.

In summary, apparent hyposensitivity to pain may be the result of stoical suppression of negative thoughts and feelings secondary to hypersensitivity to sensory modalities i.e.

1. Vision.
2. Hearing.
3. Taste.
4. Smell.
5. Touch.
6. Proprioception.
7. Vibration.

MIRROR NEURONS

A mirror neuron is a neuron which fires both when an animal acts and when the animal observes the same action performed by another (especially conspecific) animal. The neurons may be important in the development of empathy and imitation. Mirror neuron failure may contribute to the development of self-obsession.

[Ref 1](#) [Ref 2](#)

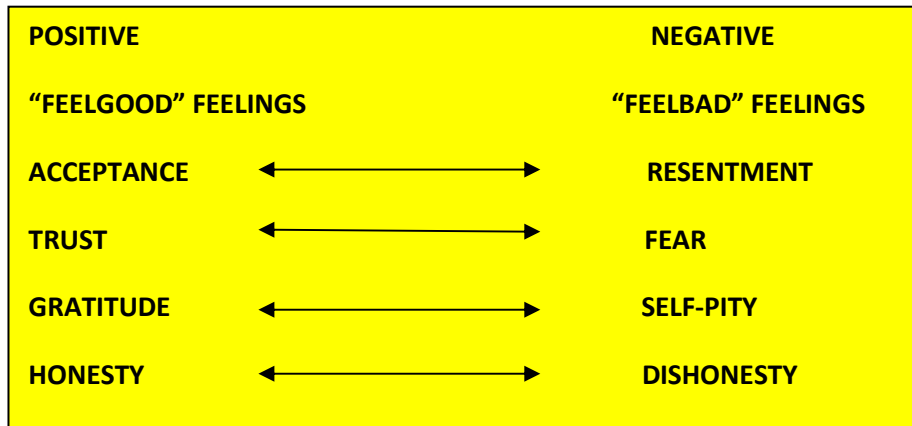
Self-obsession may result in not responding to the name when called, in addition to apparent deafness due to hypersensitivity to sound.

[Ref](#)

[YOUTUBE REFERENCE](#)

HYPERSENSITIVITY TO EXTREME THOUGHTS AND FEELINGS

There are four main groups of feelings. These feelings have ranges.



The feelings are defined as

GRATITUDE – the state of being grateful/thankful.

ACCEPTANCE – the act or process of accepting.

TRUST – firm reliance on the ability or character of a person/thing.

HONESTY – the quality or condition of being honest.

RESENTMENT – extreme displeasure caused by insult or slight.

SELF-PITY – pity for oneself especially exaggerated or self-indulgent pity.

FEAR – feelings of agitation and anxiety caused by the presence or imminence of danger.

DISHONESTY – lack of honesty or integrity. Departure from what is legally, ethically and morally correct.

Increased aggregate dendritic firing rates result in feelgood thoughts and feelings.

Decreased aggregate dendritic firing rates result in feelbad thoughts and feelings.

Normal children/adults have thoughts and feelings midway between the extremes. A.D. results in extreme thoughts and feelings nearer the end of each spectrum due to dendritic inflammation.

A.D. results in considerable emotional pain due to the preponderance of hypersensitivity to extreme negative thoughts and feelings.

The later stages of the disease result in self-obsession and derealisation.

The extremities of thoughts and feelings can be categorised under the headings of the main positive and negative feeling equivalents.

EXAMPLES OF HYPERSENSITIVITY TO EXTREME THOUGHTS AND FEELINGS

POSITIVE

ACCEPTANCE

PERFECTIONIST

“AUTISTIC SAVANT” “SPLINTER SKILLS”

YOUTUBE REFERENCE 1

YOUTUBE REFERENCE 2

NEGATIVE

RESENTMENT

RUDE

**E.G. INTERRUPTS CONVERSATIONS/WALKS
OVER PEOPLE**

RAGES, SCREAMING, TANTRUMS

DEMANDS

STUBBORN

ACUTE EPISODES OF VIOLENT BEHAVIOUR

REFUSES TO SPEAK

ABUSIVE TO CARERS

GRIMACING

IMPATIENT WITH SHORT ATTENTION SPAN

POSITIVE

TRUST

EXCESSIVE LOVING/BEING LOVED

WANTS TO BE HUGGED – BUT
HYPERSENSITIVE TO TOUCH, INAPPROPRIATE
SEXUAL BEHAVIOUR

OVER -FAMILIARITY

GULLIBLE

LACK OF FEAR E.G. RUNNING INTO ROAD

NEGATIVE

FEAR

DIFFULTY LOVING/BEING LOVED

SHY – AVOIDS EYE CONTACT

YOUTUBE REFERENCE

DIFFICULTY MIXING WITH OTHERS

“LOOKS THROUGH PEOPLE”

“SAMENESS” DISLIKES CHANGE – AVOIDS
CHANGE TO ROUTINE E.G. CHANGE OF TOYS,
INITIAL SCHOOL ATTENDANCE,CHANGE OF
SCHOOL

SUSPICIOUS

OF LOSS OF CONTROL E.G. PUSHING PEOPLE
AWAY

OFTEN PARALYSED WITH FEAR E.G. OF
HEIGHTS, CARS, DOGS, SHOPS, OF WATER
PROJECTING E.G. THINKING CARS ARE
MONSTERS AND WILL EAT PATIENT E.G. OF
VACUUM CLEANERS

YOUTUBE REFERENCE

ANXIETY

YOUTUBE REFERENCE

POSITIVE

TRUST

NEGATIVE

FEAR

NIGHT-MARES, NIGHT TERRORS

“HOARDING” BEHAVIOUR

AVOIDS CONFRONTATION

POSITIVE

GRATITUDE

INCREASED ACTIVITY – A.D.H.D.

NEGATIVE

SELF-PITY

ISOLATION – PREFERS TO BE ALONE

DIFFICULTIES WITH CONVERSATIONS/

**IMPAIRED SOCIAL INTERACTION E.G.
FRIENDSHIP**

SELF-HARM IN 30%

EASILY CRYING WITH SADNESS

DEPRESSION

APATHY

ANHEDONISM

NEGATIVE DELUSIONS

LOW SELF-ESTEEM

**SLEEP DISTURBANCE E.G. EARLY MORNING
AWAKENING, DIFFICULTY GETTING TO SLEEP,
INTERRUPTED SLEEP**

POSITIVE

NEGATIVE

HONESTY

DISHONESTY

HIGHER FUNCTIONING PATIENTS ARE

LYING

VERY HONEST OFTEN TO THEIR OWN

DETRIMENT IN ADULTHOOD (VIDE INFRA)

LACK ABILITY TO DLIBERATELY DECEIVE

EXAMPLES OF HIGHER SENSORY MODALITIES AFFECTED BY HYPERSENSITIVITY

POSITIVE

NEGATIVE

VISION

SPINNING OBJECTS APPEALING

PHOTOPHOBIA – HYPERSENSITIVE TO LIGHT

RUBS EYES

SQUINTS EYES

DISLIKES COLOURS, MOVEMENT

“LOOKS THROUGH PEOPLE”

**ALTERED VISUAL PERCEPTION E.G. OF
HEIGHTS, OF TUNNELS**

ALTERED VISUAL PERCEPTION

E.G. OF HEIGHTS, OF TUNNELS

APPEARS BLIND/ NIGHT BLINDNESS

PLEASANT VISUAL HALLUCINATIONS

UNPLEASANT VISUAL HALLUCINATIONS

**DIFFICULTY SEEING LIGHT-DARK SHADING IN
DAYLIGHT**

DILATED PUPILS

DIFFICULTIES WITH ORIENTATION

YOUTUBE REFERENCE

POSITIVE

HEARING

PLEASANT AUDITORY HALLUCINATIONS

SMELL

PLEASANT OLFACTORY HALLUCINATIONS

NEGATIVE

PHONOPHOBIA – HYPERSENSITIVE TO SOUND

YOUTUBE REFERENCE

GRIMACES WITH SOUND

APPEARS DEAF

ANXIETY WITH ODD VOICES

DOES NOT RESPOND TO NAME WHEN CALLED

UNPLEASANT AUDITORY HALLUCINATIONS

HEARS VERY DISTANT SOUNDS WHICH MAY ANNOY PATIENT

DISLIKES PLEASANT SMELLS

MAY PREFER FAECAL SMELL

TENDS TO MOUTH-BREATHE

UNPLEASANT OLFACTORY HALLUCINATIONS

POSITIVE

TASTE

NEGATIVE

PREFERS BLAND FOOD

PREFERS SAME FOOD

OFTEN DISLIKES SWEET FOOD

UP TO 75% OF A.D. PATIENTS HAVE EATING DISORDERS. SUGGESTED THE DIAGNOSIS A.D. IN THE PAST

EXAMPLES OF PERIPHERAL SENSORY MODALITIES AFFECTED BY HYPERSENSITIVITY

POSITIVE

NEGATIVE

TOUCH

INCREASED INTIMATE ZONE

DISLIKES HUMAN TOUCH

DISLIKES FEEL OF CLOTHES

DISLIKES MASTURBATION

DISLIKES PROLONGED SITTING

**DISLIKES HAND CONTACT E.G. WRITING, DIRT
ON HANDS**

DISLIKES WALKING ON GRASS BAREFOOTED

PAIN

APPARENT HYPOSENSITIVITY TO PAIN. DOES NOT CRY WITH PAINFUL STIMULI

POSITIVE

NEGATIVE

POSITION

DOES NOT LIKE SITTING STILL

ODD POSTURES

DIFFICULTY MANIPULATING SMALL OBJECTS

TEMPERATURE

APPARENT HYPOSENSITIVITY TO TEMPERATURE, RISK OF SUNBURNS, HYPOTHERMIA

VIBRATION

DISLIKES VIBRATORY MOVEMENT

POSITIVE

NEGATIVE

MOTOR SYSTEM

INCREASED ACTIVITY E.G. A.D.H.D.

**DIFFICULTIES WITH
STANDING, WALKING, GRASP, FINE
MOVEMENTS. HYPOTONIA**

TOE WALKING

**POOR EYE-HAND CO-ORDINATION (EXCLUDE
HYPERMETROPIA)**

TICS

SPEECH

INAPPROPRIATE LAUGHTER

MONOTONOUS VOICE

ECHOLALIA- REPEATED WHAT JUST HEARD

SPEECH DELAY

DIFFICULTY EXPRESSING NEEDS

REPETITIVE SPEECH

YOUTUBE REFERENCE

JARGON – NEW WORDS OR NEOLOGISMS

YOUTUBE REFERENCE

AUTONOMIC NERVOUS SYSTEM

POSITIVE

NEGATIVE

RESPIRATORY SYSTEM

AIRWAY DIAMETER MAY DECREASE

DYSPNOEA

CARDIO-VASCULAR SYSTEM

HEART RATE MAY INCREASE

BLOOD PRESSURE MAY INCREASE

CHEST PAIN, PALPITATIONS

GASTRO-INTESTINAL SYSTEM

INCREASED APPETITE

DECREASED APPETITE

WEIGHT GAIN

WEIGHT LOSS

DIARRHOEA

CONSTIPATION, ABDOMINAL PAIN

75% OF A.D. PATIENTS HAVE EATING DISORDERS

POSITIVE

NEGATIVE

URO-GENITAL SYSTEM

INCREASED RISK OF URINE RETENTION

VASO-MOTOR SYSTEM

COLD CLAMMY SKIN

ENDOCRINE

**REDUCED SENSITIVITY TO INSULIN,
THYROXINE, CORTISOL, ERYTHROPOEITIN**

OBSESSIVE-COMPULSIVE BEHAVIOUR

VARIOUS BEHAVIOURS HAVE BEEN DESCRIBED:

- **“ROCKING” MOVEMENTS.**

YOUTUBE REFERENCE

- **HAND WRINGING OR FLAPPING.**

YOUTUBE REFERENCE

- **PLAYING WITH THE SAME TOY.**

YOUTUBE REFERENCE

- **SPINNING.**

YOUTUBE REFERENCE

- **HAIR-TWIRLING.**
- **FOLLOWING THE SAME ROUTE IN THE HOME OR OUTDOORS.**
- **HEAD ROLLING.**
- **DRESSING RITUALS.**
- **ARRANGING OBJECTS IN THE SAME WAY.**
- **PERFORMING SAME BEHAVIOUR AT SAME TIME EVERY DAY.**
- **STACKING TOY CUBES OR LINING UP TOYS.**

YOUTUBE REFERENCE

- **SUSTAINED ODD PLAY.**
- **REPEATED DRAWING PATTERNS.**
- **WRITING THE SAME STORIES, WORDS OR ENDING OF STORIES.**

THERE ARE MANY OTHER VARIATIONS OF THE REPETITIVE BEHAVIOUR.

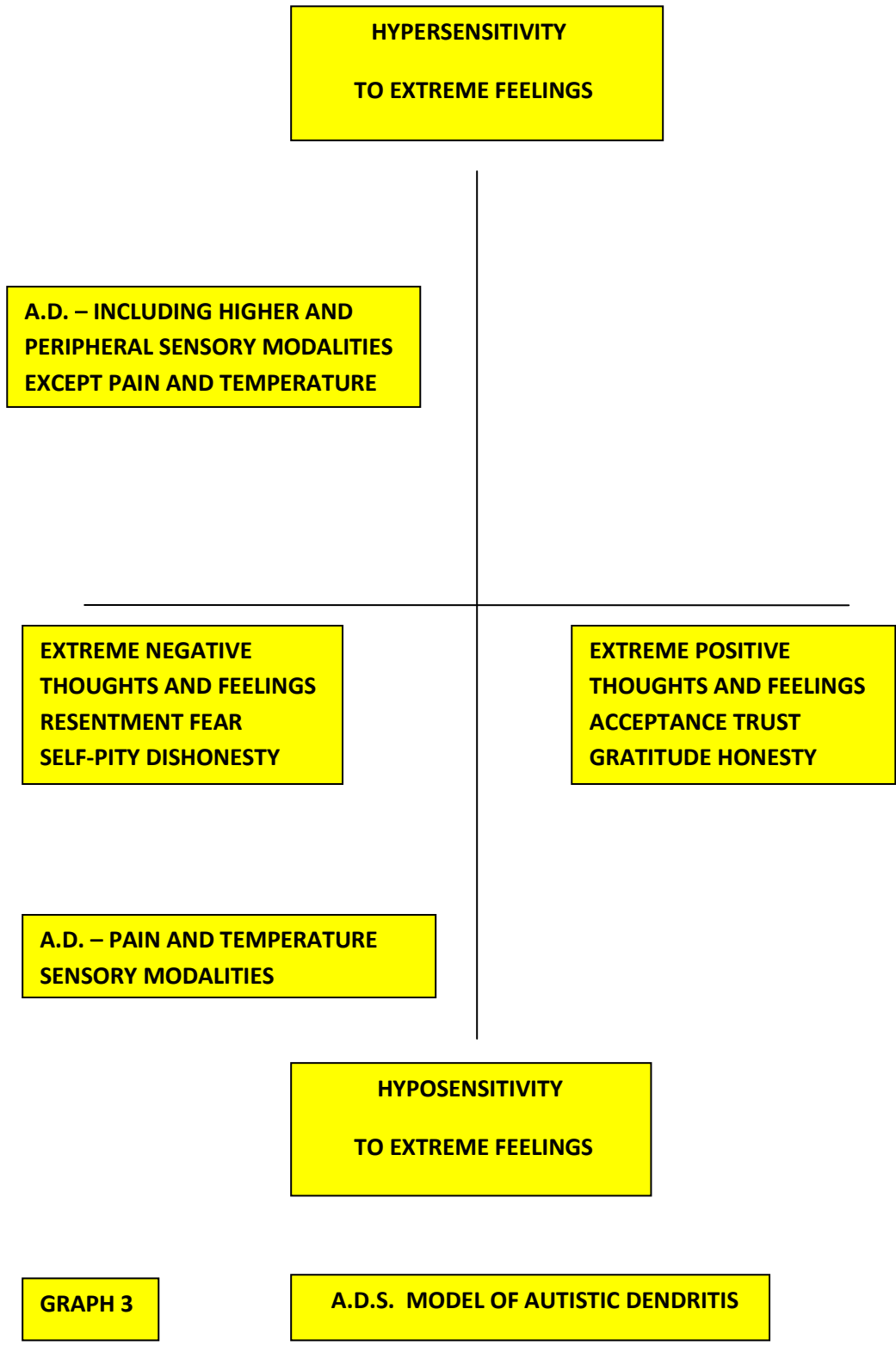
GENERAL CLINICAL FEATURE SITES ON YOUTUBE

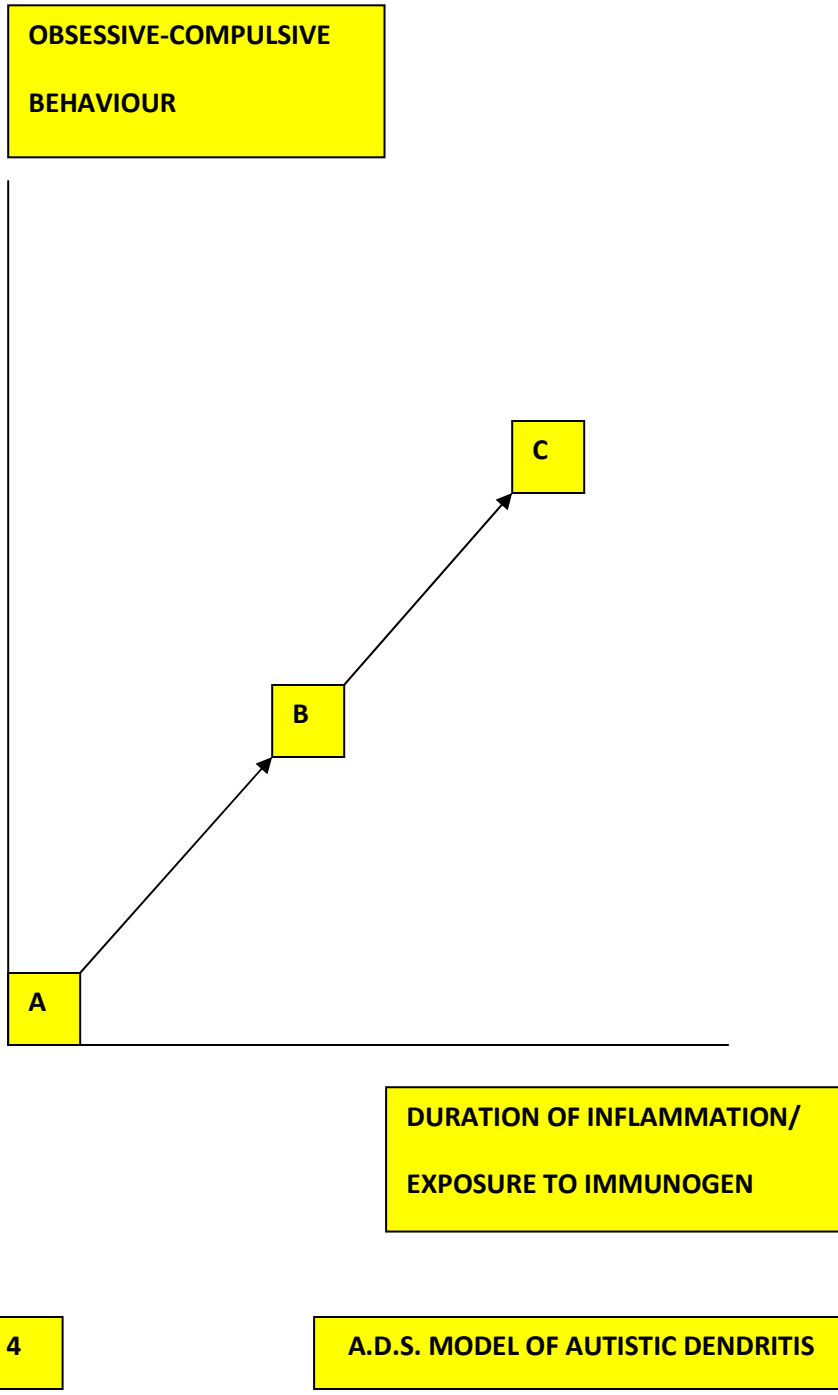
YOUTUBE REFERENCE 1

YOUTUBE REFERENCE 2

YOUTUBE REFERENCE 3

(See Graphs 3. and 4.)





RATE OF GROWTH OF HEAD CIRCUMFERENCE

The rate of growth of head circumference is intermittently increased within the first three years of age. Often the increased rate of growth is initially noticed at two months of age. The degree of macrocephaly is related to severity of A.D.

Ref

YOUTUBE REFERENCE

ADULTHOOD

33% achieve partial independence. Employers are often unaware of the symptoms of A.D. and may need to have further information e.g. from a "job-coach".

YOUTUBE REFERENCE

Adults with A.D., especially Asperger`s Syndrome may have an increased risk of criminal convictions because of their behaviour e.g. following or "stalking" people simply to gain friendship. During interrogation they are very honest and do not realise the legal implications of their confessions. Unfortunately, if they are imprisoned they may end up as being used as "punch-bags" by other prisoners. The legal profession and police are becoming increasingly aware of these cases and their inappropriate treatment.

Ref 1 Ref 2

Up to 50% never gain the ability to talk.

Spontaneous recovery may occur. Further studies are awaited.

Ref

INVESTIGATION

The yield for these investigations is quite low i.e. 2-10% and other clinical indications e.g. dysmorphic features are recommended before applying such a battery of investigations.

Ref

These may include:

1. Full blood count +/- coagulation.
2. Urea and electrolytes including calcium.
3. C-reactive protein.
4. Liver function test.
5. Fasting plasma glucose, high-density lipoprotein, low-density lipoprotein and total cholesterol.
6. Urine analysis for glucose, blood and protein.
7. Thyroid function test, prolactin, 9 a.m. cortisol, testosterone and oestradiol.
8. Vitamin B 12, folic acid and iron/total iron-binding capacity.
9. Uric acid.
10. Amino-acid chromatography.
11. Wood`s light examination.
12. M.R.I. , C.T., P.E.T. head scans.

Ref

13. Blood gas analysis and ammonia level.
14. Infection screen including "T.O.R.C.H."
15. Chromosomal analysis e.g. F.I.S.H. testing for 15q duplications.

Ref

16. Genetic analysis. Usually negative unless family history positive and/or dysmorphic features present e.g. macrocephaly. Negative results are reassuring to some degree if considering another pregnancy.

Ref

FURTHER INVESTIGATIONS MAY INCLUDE

1. Electroencephalogram. This is often unrewarding.

[Ref](#)

2. Immunology

There are many abnormalities which are often inconsistent.

[Ref 1](#) [Ref 2](#) [Ref 3](#)

- i. Regulatory T-cells.
- ii. Cytokines.
- iii. Macrophages.
- iv. Immunoglobulins.
- v. Auto-immune profile including tissue transglutaminase.
- vi. Tissue-specific immunoglobulins e.g. auto-antibodies to basic myelin protein and oligodendrocyte glycoprotein.

[Ref](#)

- vii. Circulating Immune complexes.
- viii. Lumbar puncture – there are many immunological abnormalities including
C.S.F. T.N.F-alpha, C.S.F. nerve-growth factor and beta-endorphins in Rett`s syndrome.
C.S.F. insulin-like growth factor-1 in A.D.
C.S.F. cytokine analysis remains a research investigation at present. The children also have to often be sedated for the procedure.

[Ref 1](#) [Ref 2](#) [Ref 3](#) [Ref 4](#) [Ref 5](#)

3. Urine opioids.
4. Free sulphate.
5. Serotonin level.
6. Carnitine level.
7. Trace metal levels.

8. Lead level.
9. Family chromosomal/ genetic analysis. Usually negative unless family history positive.
Reassuring to some degree if considering further pregnancies.

COMMENT.

C.S.F. T.N.F.-alpha may best represent inflammatory activity and be used to assess the effects of immunological treatment.

[Ref](#)

There are some laboratories already offering extensive investigations of the above.

[Ref](#)

PREVENTION

1. Pre-implantation genetic diagnosis (P.G.D.) of I.V.F. embryos.

Ref

2. Genetic screening of parents if positive family history. Usually negative.

Ref

3. Genetic screening of neonates for genetic predisposition.

Some commercial enterprises already exist.

Ref

4. Reduction of immunogen exposure during pregnancy i.e. avoid alcohol and smoking completely. Avoid sweetening agents and monosodium glutamate if possible.
5. Vitamin/mineral supplementation in pregnancy. However, recently excess folic acid has been discovered to impair natural killer cells.

Ref 1 Ref 2

6. Discussion of risk of immunisations to subsequent siblings i.e. consider mercury-free immunisations.

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of modification of immunisations.

Ref

7. Discussion of dietary changes for subsequent siblings i.e. casein-free, gluten-free diet.

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of prophylactic dietary modification.

SCREENING

Early diagnosis may improve long-term outcome. Use of screening is limited e.g. “Checklist for autism in toddlers” or “C.H.A.T.” has 38% sensitivity and 98% specificity.

Ref

Consider diagnosis if

- No babbling 12 months.
- No pointing/waving 12 months.
- No single word 16 months.
- No two-word phrases 24 months.
- Loss of developmental skills at any age.

YOUTUBE REFERENCE

TREATMENT

“A nice adaptation of conditions will make any hypothesis fit with the phenomena. This will please our imagination but does not advance our knowledge”

Joseph Black. Chemist Lectures of the elements of chemistry 1803

Treatments to be discussed are as follows

- 1. Reduction of immunogen exposure.**
- 2. Dietary supplementation.**
- 3. Secretin.**
- 4. Chelation.**
- 5. Methylation.**
- 6. Applied behaviour analysis programme.**
- 7. Music therapy.**
- 8. Massage therapy.**
- 9. Of associated psychiatric TREG syndromes.**
- 10. Of associated TREG epilepsy syndromes.**
- 11. Of other associated TREG medical syndromes.**
- 12. Melatonin.**
- 13. Anti-inflammatory treatment.**
- 14. Hyperbaric oxygen.**
- 15. Stem cell treatment.**
- 16. Immuno-suppressive, disease-modifying treatment.**
- 17. Intra-venous immunoglobulin.**
- 18. Cognitive behavioural therapy.**
- 19. Drugs with serendipitous effects on the immune system.**
- 20. Electronic screen media aids and robotic aids.**
- 21. Gene therapy.**
- 22. Astrocyte and microglia suppressants.**
- 23. Cypin.**
- 24. Snapin.**
- 25. MEP2.**
- 26. SHANK.**

There is a distinct lack of randomized, double-blind, placebo-controlled trials of the following treatments which is surprising when the prevalence of A.D. is 1 in 150 children.

REDUCTION OF IMMUNOGEN EXPOSURE

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of immunogen avoidance. However, there are anecdotal reports of improvement in behaviour.

[Ref 1](#) [Ref 2](#) [Ref 3](#)

Discuss dietary changes with dietician.

Reduce or avoid the following

- Casein
- Gluten-free diet.
- E-numbers.
- Caffeine.
- Citric fruits.
- Chocolate.
- Aspartame.
- Monosodium glutamate.
- Passive smoking.
- Pesticides.
- Herbicides.
- Fertilisers.
- G.M. food.
- Atmospheric pollutants.
- Electro-magnetic radiation –
microwaves, mobile telephones.
- Aluminium – in anti-perspirants.
- Hair dyes.

Beware of calcium and vitamin D deficiency with milk-free diets. There may be an association between A.D. and reduced bone density.

[Ref](#)

NUTRITIONAL SUPPLEMENTATION

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of nutritional supplementation. However, there are anecdotal reports of improvement in behaviour.

[Ref 1](#) [Ref 2](#)

Nutritional supplementation should ideally be initiated for proven nutritional deficiency. However, full nutritional screens are rarely performed except in clinical studies. The following nutritional supplements and “alternative” oral therapies have been used with some success, but individual response is variable.

- Increasing omega-3 essential fatty acid in diet.

[Ref](#)

- Vitamin B12.
- Carnitine.
- Vitamins A, C and E.
- Vitamin B complex including niacin.
- Folic acid.
- Zinc, selenium, magnesium and manganese. Magnesium sulphate baths may irritate the skin.
- Reducing leucine and arginine in diet. Consider increasing dietary glutamine.
- “Ketogenic diet” – low in carbohydrate.
- “Candida” diet.
- Echinacea.
- Cat`s claw.
- Dandelion.
- Lysophilus.

COMMENTS ON DIET

The following information may prove helpful.

[Ref](#)

OILS/FOOD HIGH IN OMEGA-3 ESSENTIAL FATTY ACIDS – TRY TO INCREASE

Flaxseed oil	53.3g per 100g
Linseed oil	53g per 100g
Linseeds	14g per 100g
Walnut oil	11.5g per 100g
Rapeseed	9.5g per 100g
Soya oil	7g per 100g
Walnuts	5.5g per 100g
Polyunsaturated margarine	2g per 100g
Soya beans	1.5g per 100g
Olive oil	0.5g per 100g
Sunflower oil	Trace
Almond nuts	Trace
Brazil nuts	Trace
Cashew nut	Trace

OILS/FOOD HIGH IN OMEGA-6 ESSENTIAL FATTY ACIDS – TRY TO REDUCE

Safflower oil	74g per 100g
Grapeseed oil	68g per 100g
Sunflower oil	63g per 100g
Walnut oil	58g per 100g
Soya oil	51g per 100g
Corn oil	50g per 100g
Sesame oil	43g per 100g
Polyunsaturated margarine	34g per 100g
Groundnut oil	31g per 100g
Walnuts	29g per 100g
Brazil nuts	23g per 100g
Rapeseed oil	20g per 100g
Linseed oil	15g per 100g
Soya beans	10.5g per 100g
Almonds	10g per 100g
Linseeds	6g per 100g

FISH WITH HIGH OMEGA-3 ESSENTIAL FATTY ACID

Mackerel – contain the most omega-3 essential fatty acid.

Anchovies

Sardines

Salmon

Tuna

RECOMMENDED DAILY ALLOWANCES OF VITAMINS AND MINERALS

AGE- RELATED

	UNDER 1 y.o	1-4 y.o	4-10 y.o	10-15 y.o	Adult
A (mg)	0.5	0.6	0.7	0.9	1.0
Retinol					(4,000 I.U.)
Adult therapeutic dose is 25,000 I.U.					
B1 (mg)	0.3	0.6	1.0	1.3	1.3
Thiamine					
Adult therapeutic dose is 2-10 mg					
B2 (mg)	0.3	0.7	1.0	1.2	1.5
Riboflavine					
Adult therapeutic dose is 2-10 mg					
Niacin (mg)	3.0	7.0	10	15	17
Nicotinamide					
Adult therapeutic dose is 100-300 mg					
B6 (mg)	0.2	0.4	0.6	1.2	1.4
Pyridoxine					
Adult therapeutic dose is 10 mg					
Folic Acid	70	200	300	400	400
(micrograms)					
Adult therapeutic dose is 400 micrograms					
C (mg).	50	60	70	90	100
Ascorbic acid					
Adult therapeutic dose is 100- 150 mg					
D.	10	5	5	5	5
(micrograms)					
(400 I.U.)					
Adult therapeutic dose is 5,000 I.U.					
E (mg)	4	6	10	10	15
Adult therapeutic dose is 30 I.U.					
Vitamin K	6	15	25	45	65
(micrograms)					
Calcium (g)	0.4	0.6 - 0.8	1.0	1.2	1.2

NORMAL ADULT REFERENCE RANGES

- Vitamin A: 28-94 micrograms/dl
- Thiamine: 9-44 nmol/l
- Vitamin B₆: 7-52 ng/ml
- Vitamin B₁₂: 200-1100 pg/ml
- Folate : 3.1-18.0 ng/ml
- Riboflavin: 6.2-39 nmol/l
- Vitamin C : 28-84 mg/dl
- Vitamin D (25-hydroxycholecalciferol): 25-50 ng/ml
- Vitamin K: 80-1160 pg/ml

NON-AGE RELATED

	<u>Milligrams/day</u>
Chromium	0.003 (3 µg)
Cobalt	0.002 (2 µg)
Copper	1.0
Fluoride	2.9
Iodine	0.2 (200 µg)
Iron	15
Magnesium	300-400
Manganese	2.5
Molybdenum	0.05 (50 µg)
Nickel	0.025 (25 µg)
Selenium	0.06 (60 µg)
Zinc	15

n.b. much higher doses than recommended daily requirement may be required to achieve therapeutic benefit, the analogy being the high doses of levodopa required to obtain clinical improvement in Parkinson's disease. Excessive dosages of vitamins may also be detrimental to health.

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of the following nutritional supplementation. However, there are anecdotal reports of improvement in behaviour.

CARNITINE

Acetyl-1-carnitine up-regulates TREG cells by increasing HSP60. Carnitine may improve attention-deficit hyperactivity disorder.

Ref

ARGININE

Down-regulates the mTOR pathway. Avoid the following high arginine containing foods – spinach, crab, lobster, soya products, turkey and sesame products.

LEUCINE

Down-regulates the mTOR pathway. Avoid the following high leucine containing foods – beef, pork, fish and soya products. Fruit and vegetables contain only small amounts of leucine.

GLUTAMINE

Up-regulates the mTOR pathway. Dietary supplementation of glutamine has been used in several adult TREG syndromes. The use of glutamine in A.D. is controversial, in view of the excitotoxic action of glutamate.

SECRETIN TREATMENT

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of secretin treatment. However, there are anecdotal reports of improvement in behaviour.

Treatment became popular following improvement in symptoms after secretin injection for investigation of gastro-intestinal symptoms. Secretin is derived from pigs and there is a risk of allergic reaction. The dose and frequency of injections required has not been confirmed in scientific studies. There is the possibility that the improvement was related to other concurrent therapies or spontaneous in nature. Results of further investigations are awaited.

Ref 1 Ref 2

CHELATION TREATMENT

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of chelation treatment. However, there are anecdotal reports of improvement in behaviour.

Mercury poisoning due to mercury in teething powder caused Pink disease or acrodynia in the 1800`s. Pink disease is characterized by social withdrawal and reduced communication skills. Ethyl mercury is present in childhood immunizations. The number of immunizations in the childhood immunization programme is increasing. The theory of chelation therapy is to increase mercury excretion from the body. Chelation therapy may be administered orally, intra-venously or as a cream. ONE PATIENT DIED AS A RESULT OF INTRA-VENOUS THERAPY. Anecdotal clinical improvement has been reported. There is the possibility that the improvement was related to concurrent therapy or spontaneous in nature. A randomized double-blind placebo-controlled chelation trial using D.M.S.A. was in phase II. The trial provoked controversy regarding the ethical issue of subjecting children to potentially lethal D.M.S.A. and has now been discontinued.

Ref 1 Ref 2 Ref 3

METHYLATION TREATMENT

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of methylation treatment. However ,there are anecdotal reports of improvement in behaviour.

Ref

APPLIED BEHAVIOUR ANALYSIS PROGRAMME

40 hours/week is recommended but less time may be as equally effective. Further studies are awaited.

MUSIC THERAPY

There are no randomized, double-blind, placebo-controlled clinical trials which confirm the statistical significance of music therapy. However, there are anecdotal reports of improvement in behaviour.

Music therapy may improve episodes of social engagement. Results of further investigations are awaited.

Ref 1 Ref 2

MASSAGE THERAPY

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of massage treatment. However, there are anecdotal reports of improvement in behaviour.

Results of further investigations are awaited.

TREATMENT OF ASSOCIATED PSYCHIATRIC TREG SYNDROMES

The following drugs have been approved by the F.D.A. for other psychiatric diseases which are often associated with A.D.

Most of these drugs are anti-inflammatory reducing T.N.F. levels i.e. reducing dendritis. Up to 45.6% of A.D. patients are treated with psychotropic medication.

Ref

ANXIETY/DEPRESSION AND OBSESSION-COMPULSIVE BEHAVIOUR

Fluoxetine for 7 years old and over

OBSESSIVE-COMPULSIVE BEHAVIOUR

Sertraline for 6 years old and over.

Fluvoxamine for 8 years old and over

Clomipramine for 10 years old and over.

BEHAVIOURAL PROBLEMS

Haloperidol

Thioridazine

Fluphenazine

Chlorpromazine

INATTENTION-HYPERACTIVITY

Methyl Phenidate

CURRENT ON-GOING TRIALS FOR BEHAVIOURAL PROBLEMS

Risperidone

Olanzapine

Ziprasidone

Risperidone is the only drug licensed for use in A.D. Risperidone inhibits pro-inflammatory cytokines and microglial inflammatory reactions.

[Ref 1](#) [Ref 2](#)

TREATMENT OF TREG EPILEPSY SYNDROMES

Epilepsy occurs in 25% of patients.

Most of these drugs are anti-inflammatory affecting cytokine e.g. T.N.F. levels.

Carbamazepine.

Lamotrigine.

Topiramate.

Valproic Acid.

TREATMENT OF ASSOCIATED MEDICAL TREG SYNDROMES

i.e. of the “auto-immune” diseases as above.

MELATONIN

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of melatonin treatment. However, there are anecdotal reports of improvement in behaviour.

Melatonin is anecdotally effective for sleep disturbance in A.D., but is still not licensed for use. Melatonin has anti-inflammatory properties in animal studies. Results of further investigation are awaited.

[Ref 1](#) [Ref 2](#)

ANTI-INFLAMMATORY TREATMENT

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of anti-inflammatory treatment. However, there are anecdotal reports of improvement in behaviour.

a) Minocycline combined with Pyridoxine.

Trials of minocycline combined with pyridoxine have commenced. Minocycline, used for the treatment of acne vulgaris, has a serendipitous neuro-protective effect by acting on TREG cells. There has already been improvement using tetracyclines in other TREG syndromes e.g. with minocycline for multiple sclerosis and doxycycline for osteo-arthritis. Tetracyclines can stain dental enamel in childhood. Results of further investigations are awaited.

[Ref](#)

b) Oxytocin.

Oxytocin e.g.nasal spray trials have commenced. The oxytocin genotype may be abnormal in TREG autism syndrome. Oxytocin has anti-inflammatory effects equal to dexamethasone in animal studies. Results of further investigations are awaited. Oxytocin has recently been found to be released by dendrites of hypothalamic neurons.

[Ref 1](#) [Ref 2](#) [Ref 3](#)

c) Anti-viral and anti-fungal treatment.

Anti-viral and anti-fungal treatments have led to clinical improvement, perhaps related to their effects on the immune system rather than eradicating specific infections.

[YOUTUBE REFERENCE](#)

HYPERBARIC OXYGEN

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of hyperbaric oxygen treatment. However, there are anecdotal reports of improvement in behaviour.

Has been used in A.D. and is anecdotally effective. The results of multi-centre clinical trials are awaited. The safety of ozone therapy is currently being assessed in clinical trials in Italy.

[Ref](#)

[YOUTUBE REFERENCE](#)

[YOUTUBE REFERENCE](#)

MESENCHYMAL /CD34+ STEM CELL TREATMENT

The results of trials and treatments are awaited. The aim is to improve blood perfusion in the brain by stimulating angiogenesis and suppressing immuno-genetic dendritis. The initial treatments are clinically impressive but are being treated appropriately with caution by sceptics. The cost is an estimated \$ 15,000-\$ 20,000 e.g. at the Institute of Cellular Medicine in Costa Rica at the time of writing. There is no federal funding in the U.S.A to treat autistic dendritis with mesenchymal/CD34+ therapy at present due to legislation. Costa Rica, India and China are leading the field of treatment. In animal studies the risk of tumour development may be increased.

YOUTUBE REFERENCE

Some early anecdotal results appear promising. Results of further investigations are awaited.

YOUTUBE REFERENCE

IMMUNO-SUPPRESSIVE, DISEASE-MODIFYING TREATMENT

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of immuno-suppressive and disease-modifying treatments. However, there are anecdotal reports of improvement in behaviour.

a) Prednisolone.

Prednisolone treatment is anecdotally effective. The dosage of 2mg/kg for 8 weeks followed by a further 8 weeks of dosage reduction has led to clinical improvement within the first 2 weeks of treatment on several occasions. The patients often developed weight gain, acne vulgaris, hirsutism, transient hypertension and behavioural changes. However, these adverse reactions were reversible with discontinuation of prednisolone therapy. One child seems to have made a complete recovery from autistic dendritis. Perhaps all children with autistic dendritis should be considered for a 4 month therapeutic trial of prednisolone therapy after diagnosis with early discontinuation if there is no obvious clinical improvement e.g. at 2 weeks.

[Ref](#)

b) Methotrexate.

There do not appear to be any reports of the use of methotrexate in autistic dendritis.

c) Gold.

One patient who had gold treatment for juvenile rheumatoid arthritis noticed clinical improvement in autistic dendritis. This further suggests the TREG basis of the dendritis.

[Ref](#)

d) Cytokine antagonists.

These include T.N.F. – alpha antagonists and IL-1 antagonists.

Patents were issued in 2006. The results of trials are awaited.

[Ref](#)

INTRA-VENOUS IMMUNOGLOBULIN

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of intra-venous immunoglobulin treatment. However, there are anecdotal reports of improvement in behaviour.

Intra-venous immunoglobulin has been anecdotally effective. However the cost-effectiveness was prohibitive. Clinical deterioration to the pre-treatment state may occur after cessation of treatment. Results of further investigations are awaited.

[Ref](#)

COGNITIVE BEHAVIOURAL THERAPY

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of cognitive behavioural therapy. However, there are anecdotal reports of improvement in behaviour.

[Ref](#)

DRUGS WITH SERENDIPITOUS EFFECTS ON THE IMMUNE SYSTEM

NALTREXONE

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of naltrexone treatment. However, there are anecdotal reports of improvement in behaviour.

Naltrexone may improve hyperactivity, agitation, irritability, temper tantrums, social withdrawal, and stereotyped behaviors. There may be improvement in attention and eye contact. Transient sedation was also noted.

[Ref 1](#) [Ref 2](#)

CLONIDINE

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of clonidine treatment. However, there are anecdotal reports of improvement in behaviour.

Clonidine may suppress C.S.F. T.N.F.-alpha. There may be a reduction in sleep initiation latency and night awakening, and to a lesser degree improvement in attention deficits hyperactivity, mood instability and aggressiveness. Results of further investigations are awaited.

[Ref 1](#) [Ref 2](#)

PIOGLITAZONE

Pioglitazone is a peroxisome proliferator activated receptor gamma agonists, a nuclear hormone receptor which modulates insulin sensitivity.

Pioglitazone induces apoptosis in activated T-lymphocytes and has an anti-inflammatory effect on glial cells.

Pioglitazone may be useful in reducing irritability, lethargy, stereotypy, and hyperactivity.

Results of further investigations are awaited.

[Ref](#)

RAPAMYCIN

Rapamycin has improved memory and learning in animals with tuberous sclerosis, which is associated with autistic behaviour.

[Ref](#)

ELECTRONIC SCREEN MEDIA AND ROBOTIC AIDS

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of robotic aid treatment. However, there are anecdotal reports of improvement in behaviour.

Electronic screen media and robotic aids are being considered as treatment. Results of further investigations are awaited.

[Ref 1](#) [Ref 2](#) [Ref 3](#)

GENE THERAPY

There are no randomised, double-blind, placebo-controlled clinical trials which confirm the statistical significance of gene therapy. However, there are anecdotal reports of improvement in behaviour in mice studies.

Although a different disease, the autistic features of Fragile X mental retardation 1 improved after introduction of genetic mutation of the PAK gene which codes for p21 activated kinase. The dendritic firing rates increased in the animal studies. Previously the dendritic firing rates were decreased in Fragile X mental retardation 1.

[Ref](#)

ASTROCYTE AND MICROGLIA SUPPRESSANTS

Astrocyte and microglia suppressants are being considered for treatment in animal studies.

[Ref 1](#) [Ref 2](#)

OTHER TREATMENTS AFFECTING DENDRITE STRUCTURE AND FUNCTION

Several enzyme and structural protein abnormalities of dendrite spines have been discovered and correction of these abnormalities may offer therapeutic options in the future.

CYPIN

Cypin affects dendrite microtubule assembly and the number of dendrite branches in the areas of the brain related to learning and memory. Dendrite branching correlates with the enzymatic activity of cypin.

[Ref 1](#) [Ref 2](#) [Ref 3](#)

SNAPIN

Snapin regulates dendrite numbers in developing neurons by modulating cypin-promoted microtubule assembly and affects dendrite patterning.

[Ref 1](#) [Ref 2](#)

MYOCYTE ENHANCER FACTOR 2 (MEF2)

MEF2 is a protein which affects genes that are involved in dendritic remodeling. MEF2 may stimulate or inhibit dendrite branching.

[Ref](#)

SHANK

SHANKS are post-synaptic scaffold proteins present in the postsynaptic density of the dendrite. Shanks promote the growth of dendritic spines.

Mutations in SHANK 3 have been associated with abnormalities in communication, social interaction, verbal skills and behaviour.

Mutations in SHANK 1 result in reduction in the size and density of dendrite spines. These changes were associated with increased fear and impaired memory in animal studies.

[Ref 1](#) [Ref 2](#)

COST OF CARE

Each patient will require \$ 3,000,000 worth of care in their lifetime.

The U.S.A. spends \$ 35,000,000,000 on care for A.D. per year. Novel treatments will increase the expenditure further.

[Ref](#)

As one mother said of the cost of her son`s care:

“We keep on sending Daniel to Harvard every year for the rest of his life”

CONCLUSION

A.D. is due an abnormal immunogenic response to an environmental immunogens or auto-immunogens in a genetically pre-disposed individual resulting in dendritis. There are structural dendrite spine abnormalities and dendrite firing rates are abnormal. The dendritis results in measurable immune system abnormalities. Genetic and immunological abnormalities are the subject of intense investigation. C.S.F. T.N.F.-alpha may be the best measurement of dendritic activity at present. T.N.F.-alpha antagonist and other anti-cytokine treatment is currently being assessed.

Mesenchymal/ CD34+ stem cell treatment is currently being used in Costa Rica, India and China in clinical trials and treatment and seems to offer the best chance of clinical improvement with apparently few short-term adverse reactions. However, it is uncertain if these are randomized, double-blind, placebo-controlled trials.

Minocycline combined with pyridoxine trials and oxytocin trials have just started.

Hyperbaric oxygen clinical trials are also in progress.

There is an on-going prednisone clinical trial.

There do not appear to be any controlled clinical trials proposed for methotrexate or gold therapy.

A randomised, double-blind, placebo-controlled trial of D.M.S.A. chelation treatment is in phase II and has attracted controversy regarding subjecting these children to potentially lethal treatment.

Gene therapy and astrocyte/microglia suppressant therapy have commenced in animal studies.

If autism were compared to childhood cancer it is unlikely that such haphazard investigation and treatment would be allowed in this era. Centralised, randomised, double-blind, placebo-controlled trials would be arranged. It would appear that there are enough patients being diagnosed globally each year to commence such trials. Perhaps child psychiatrists should organise trial designs using the collaborative model that paediatric oncologists employ.

AUTHOR'S COMMENT

Following the completion of this thesis I feel that there should be more investment in multi-centre randomized, double-blind, placebo-controlled trials e.g. of the following

Gluten-free diet – the gluten-free diet is difficult to adhere to and may be unpleasantly restrictive.

Casein-free diet – the casein-free diet is difficult to adhere to and may be unpleasantly restrictive.

Hyperbaric oxygen treatment

Stem cell treatment

Minocycline treatment

T.N.F. – alpha antagonist treatment

Immunoglobulin treatment

Prednisolone treatment

Cognitive behavioural therapy

Oxytocin treatment

Methotrexate treatment

in order to clarify the efficacy of the treatments, and provide scientific information to parents of children with A.D. Until the Child Psychiatrists start to collaborate on a global scale – which is not too difficult to arrange in this era – the treatment of A.D. will remain confused, which is surprising for such a prevalent disease.

The following quote from a satirical magazine seems to summarise the current state of the treatment of autism:

"I am unmoved by these findings. The amount of scientific evidence I've made up in my mind is too significant to refute."

Fortunately, Child Psychiatrists are now in the process of developing a unified, scientific approach.

“Under the direction of Dr. Martha Herbert, assistant professor at Harvard University, the objective of ASA’s Treatment-Guided Research Initiative (TGRI), established in 2006, is to support a new generation of treatment-based research that will bring early and effective treatment to all people with autism. “We need both to help those who need it now, and to learn more about providing the most effective help,” states Dr. Herbert in her article *Treatment-Guided Research: Helping People Now with Humility, Respect and Boldness* (Autism Advocate, First Edition 2008). “Ideally, this should mean a marriage of research with treatment, with research improving

treatments and treatment responses informing the direction of research.” From The Autism Society Of America.

QUESTIONS ARISING FROM THIS BOOK

During the writing of this book I considered the following questions

- Was Einstein perhaps the most famous higher functioning case of A.D?
[YOUTUBE REFERENCE](#)
- Is Bill Gates another higher functioning case of A.D?
[YOUTUBE REFERENCE](#)
- Why are autistic dendritis patients hyposensitive to pain and temperature but hypersensitive to higher sensory and peripheral modalities?
- Will autistic dendritis embryos always be aborted when genetic diagnosis is available in the future?
- Will earlier diagnosis and immunological treatment of autistic dendritis result in improved outcomes?
- Should autistic dendritis patients continue to be subjected to unproven and unpleasant dietary regimes without results of randomized, double-blind placebo-controlled trials?
- Should autistic dendritis patients be subjected to trials of potentially lethal treatments without preliminary animal studies?
- Is autistic dendritis related to low oxytocin levels in inflamed dendrites?
- Will all autistic dendritis patients have a trial of T.N.F.-alpha antagonist therapy in the future?
- Will all autistic dendritis patients have a trial of hyperbaric oxygen treatment in the future?
- Will all autistic dendritis patients have a trial of stem cell therapy in the future?
- Will childhood stem cell treatment have long-term complications in adulthood?
- Could electrical neuro-modulation be effective in autistic dendritis?

When will the multi-centre, possibly trans-global randomized, double-blind placebo-controlled clinical trials begin?

ABOUT THE AUTHOR

Born in London, England.

Following qualification in Medicine from St. Bartholomew`s Medical College, London University qualified as a General Practitioner.

After General Practitioner training spent further five years in Paediatrics including experience at Great Ormond Street Hospital for Sick Children.

Became General Practitioner in Esher, Surrey and then moved to General Practice in Jersey, Channel Islands.

Proposed “dendritis” and the “dendritides/dendropathies” for entry into the Oxford English Dictionary 2008.

