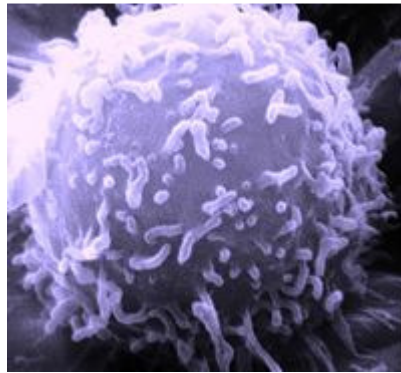


THE REGULATORY T-CELL (TREG) SYNDROMES

BY DR. M.E. VINCENT



FROM WIKIPEDIA

Copyright © Dr. M.E. Vincent

**The right of Dr. M.E. Vincent to be identified as the author of this work has been asserted in
accordance with the copyright laws.**

**All rights are reserved. No part of this publication may be reproduced in any way manner or form
without the written permission of the copyright owner.**

PREFACE

In the second part of this report series I describe the importance of regulatory T-cells (TREGS) in disease. It appears that enhancing or reducing TREG activity may affect disease progression.

CONTENTS

INTRODUCTION	6
DEFINITION	13
AETIOLOGY.....	16
PATHOLOGY	18
INVESTIGATION	39
PREVENTION	42
TREATMENT	43
CONCLUSION.....	59
SOME QUESTIONS ARISING FROM THIS BOOK.	60

SYNONYM

THE TREG SYNDROMES

INTRODUCTION

Following on from the first part of this report series (the alcohol-drug syndrome or A.D.S.), it became apparent that the regulatory T-cell immuno-genetic disease model for A.D.S. could be applied to many other diseases which

1. Were of unknown origin. These are usually described with the pre-fix “essential, idiopathic, primary or degenerative” including cancer.
2. Had become epidemic in the 20th century.

“40% OF CANCERS ARE PREVENTABLE BY FEASIBLE DIETARY MEANS”.

AMERICAN CANCER SOCIETY

Ref

I now believe that most of these diseases will eventually be treated with expensive drug therapies which will alter and partially heal the abnormal immunogenic response to environmental immunogens or auto-immunogens in genetically predisposed individuals, as it unlikely that diet will change in the immediate future. There appears to be a need for a new group of professionals who will have to focus on changing our diet from an early age, as these diseases start at conception. Genetic investigation at birth in the future may be able to predict which environmental immunogens to avoid.

THE AGE OF PERSONALISED MEDICINE OR PREDICTIVE MEDICINE IS HERE

Ref

Unfortunately, there are

1. Limited finances to create such designated groups of professionals.

Current newborn screening programmes vary widely. More molecular genetic investigations are expected to become available in the near-future. Increasing numbers of counselors will be required.

At present counselors are

- i. Sub-specialist physicians.
- ii. Specially trained nurses.
- iii. Trained Counselors.
- iv. General Practitioners.

Trained counselors are felt to offer better advice than General Practitioners although there are currently few measurements of quality assurance. In the near-future the Human Genome Project will result in the ability to investigate the newborn for an increasing number of diseases. Decisions will have to soon be made as to who will be counseling the parents. Trained genetic counselors appear to offer superior advice but there are limited finances for training.

[Ref](#)

The demand on immunology and genetic services will continue to increase as more immunological and genetic investigations are requested. Without increased investment the system will soon be saturated.

[Ref](#)

2. Limited finances to perform comprehensive genetic testing for genetic susceptibility at birth, even if the technology becomes available.

The Human Genome Project will result in more molecular investigations becoming available for a greater variety of diseases

There is uncertainty as to who will finance the increasing number of molecular genetic investigations.

i) Individual payments

U.S.A. 1994 Figures

The cost of complex family studies involving linkage analysis: \$500 - \$4,000.

Direct D.N.A. testing of individuals: \$50-\$900, but the cost for six or more D.N.A. tests was anticipated to decrease to \$50-\$150.

These estimated costs do not include genetic counselling, interpretation and education.

ii) Government and insurance companies

Government and insurance companies will have to decide on who has

- Single-gene testing
- Genetic polymorphism (D.N.A. sequence variation) testing

There are concerns that poor patients and those who live in remote areas will be increasingly disadvantaged with regard access to these investigations.

[Ref](#)

3. Limited finances to treat everybody with the new immunological treatments.

New treatments relating to the immune system are very expensive. The National Institute of Clinical Excellence has had to amend several decisions on immuno-modulatory treatment after patients have taken their Health Authorities to court and won.

[Ref](#)

Here are some examples of the cost of the new drugs affecting the immune system.

IMMUNOSUPPRESSANTS

SIROLIMUS

Sirolimus is a potent non-calcineurin inhibiting immunosuppressant.

1 mg, 30-tab pack = £90.00; 2 mg, 30-tab pack = £180.00

Initially 6 mg, after transplant surgery, then 2 mg once daily (dose adjusted according to blood-sirolimus concentration) in combination with ciclosporin and corticosteroid for 2–3 months (sirolimus given 4 hours after ciclosporin); ciclosporin should then be withdrawn over 4–8 weeks

BASILIXIMAB AND DACLIZUMAB

Basiliximab and Daclizumab are monoclonal antibodies that prevent T-lymphocyte proliferation

BASILIXIMAB

20 mg within 2 hours before transplant surgery and 20 mg 4 days after transplant surgery

DACLIZUMAB

5 mg/mL, 5-mL = £223.68

1 mg/kg within the 24-hour period before transplantation, then 1 mg/kg every 14 days for a total of 5 doses

RITUXIMAB

Rituximab is a monoclonal antibody which causes lysis of B lymphocytes.

10mg/mL, 10mL = £174.63, 50-mL = £873.15

Rheumatoid arthritis (in combination with methotrexate), 1g, repeated 2 weeks after initial infusion

CYTOKINE MODULATORS

Adalimumab, etanercept, and infliximab inhibit the activity of tumour necrosis factor alpha (TNF- α).

ADALIMUMAB

40mg = £357.50.

Rheumatoid arthritis

40 mg on alternate weeks; if necessary increased to 40 mg weekly in patients receiving adalimumab alone

ETANERCEPT

25mg = £89.38; 50mg = £178.75.

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, adult over 18 years, 25 mg twice weekly *or* 50 mg once weekly

INFLIXIMAB

100mg = £419.62

Rheumatoid arthritis 3 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks.

RANIBIZUMAB

10 mg/mL, 0.3-mL vial = £761.20

Macular degeneration.

Initially 500 micrograms once a month for 3 months into the affected eye, thereafter monitor visual acuity once a month; if necessary subsequent doses may be given at least 1 month apart

TRASTUZUMAB

Monoclonal antibody that acts on the Human Epidermal growth factor Receptor 2 (H.E.R.2)/neu (erbB2) receptor.

150mg vial = £407.40

ABATACEPT.

Prevents the full activation of T-lymphocytes.

250mg = £252.00

Rheumatoid arthritis. Body-weight 60–100 kg, 750 mg repeated 2 weeks and 4 weeks after initial infusion, then every 4 weeks.

OTHER IMMUNO-MODULATING DRUGS

INTERFERON BETA

300microgram = £39.78.

30micrograms once-weekly

Multiple sclerosis.

GLATIRAMER ACETATE

20 mg = £16.00

20mg once a day

Multiple sclerosis

NATALIZUMAB

20mg/mL, net price 15-mL vial = £1130.00

300 mg once every 4 weeks.

Multiple sclerosis.

SUTENT (SUNITINIB)

The latest novel drug to be involved in controversy is Sutent (sunitinib malate). Sutent is used to treat advanced renal cell carcinoma.

Sutent is a receptor tyrosine kinase (RTK) inhibitor.

Sutent has direct anti-proliferative effects and anti-angiogenic properties by inhibiting

- Platelet-derived growth factor receptors (PDGF-R alpha and beta)
- Vascular endothelial growth factor receptors (VEGFR1-3).
- Stem cell factor receptor (KIT).
- Fms-like tyrosine kinase-3 (FLT3).
- Colony stimulating factor receptor (CSF-1R).
- Glial cell-line derived neurotrophic factor receptor (RET).

The cost of Sutent is in excess of £2,000 per month, but is now the gold-standard of treatment for advanced renal cell carcinoma .

The annual rate of increase in the cost of these drugs appears to be out-stripping that of traditional drugs. The drug companies are subject to criticism but defend their position by explaining that money is needed for research and development.

[Ref](#)

Several million pounds have to be set-aside when these new drugs such as Sutent are approved by authoritative bodies dealing with the economical aspects of giving doctors permission to prescribe them e.g. the National Institute of Clinical Excellence.

[Ref](#)

Neo-natal genetic predictive testing will also have implications affecting

1. INSURANCE

Some patients who are deemed “high-risk” on neo-natal genetic testing will possibly request greater life-insurance, whilst “low-risk” individuals may not see a need for life-insurance. Problems are anticipated if a patient receives genetic test results which place him/her in the “high-risk” strata but does not inform the insurance company. Insurance-companies may not wish to insure patients who are at high-risk of Alzheimer`s disease. Employers may decide to employ people on the basis of their neo-natal genetic tests.

[Ref](#)

2. CLINICIAN DECISION-MAKING

Clinicians will have to make increasingly more difficult decisions regarding the allocations of funding with the myriad of discoveries from the Human Genome Project.

[Ref](#)

This next section of the report series is once again written from a General Practitioner's perspective.

DEFINITION

1. Regulatory T-cell (TREG) syndromes are due to
 - The failure of TREGS to recognise environmental antigens or auto-immunogens as “self”.
 - The failure of TREGS to recognise cancer cells as “non-self”.
2. The immunogenic response results in clinical inflammation and may progress to cancer.
3. Any organ in the body may be affected.
4. Underlying genetic abnormalities result in the immunogenic response
5. The immunogenic response may commence in utero due to trans-placental antigen exposure.
6. TREG syndromes are often associated with each other.
7. There is often a family history of the same TREG syndrome.
8. TREG dendritis results in hypersensitivity to extreme thoughts and feelings and obsessive-compulsive behavior due to dendritic inflammation.

GENERAL COMMENT

"40% OF CANCERS ARE PREVENTABLE BY FEASIBLE DIETARY MEANS"

AMERICAN INSTITUTE FOR CANCER RESEARCH

Ref

TREG syndromes are responsible for many of the 21st century diseases described as having "primary, idiopathic, essential or degenerative" aetiology or cancer.

All of the syndromes are associated with each other to varying degrees depending on which organs respond to the environmental immunogen involved.

The multiple organ immunogenic responses in some syndromes result in some patients on multiple treatments. Other patients devoid of these syndromes continue through life without treatment and die of infection, senility or trauma. They often achieve great longevity and have the following characteristics

1. Family history of great longevity.
2. Thin body habitus.
3. Low blood pressure.

These characteristics may be related to

1. Genotype e.g.

Extra copies of the SIR2 gene increases longevity in other species e.g. fruit flies.

Ref

Genes related to the mammalian target of rapamycin pathway which is known to down-regulate regulatory T-cell activity.

Ref

2. The relative lack of immunogen exposure.
3. "Spirituality" - currently being researched in the U.S.A.

Ref

4. Increased regulatory T-cell tolerance.

Ref

5. Dehydroepiandrosterone levels.

[Ref](#)

The syndromes are increasing in prevalence due to

1. Exposure to different, distant but historically old environmental immunogens due to increased international travel and food transport.
2. Exposure to historically new often synthetic environmental immunogens, which are often less than 150 years old. The new immunogens are increasing in number especially in the last 50 years.
3. Prolonged exposure to local old environmental immunogens due to increased longevity related to improved basic nutrition, antibiotics and immunisations.

In bygone times and even now in rural parts of the Earth humans died/die of

1. Infection.
2. Malnutrition.
3. Trauma.
4. Alcohol-related and tobacco-related TREG syndromes e.g. A.D.S.
5. Senility.

Old immunogens were mainly infection, alcohol and tobacco. Diet had been unchanged for centuries. People travelled infrequently and international food transport was only just developing on a large scale. Transport was slow and expensive. Immunogens were relatively old and localised. People had often died of infection and malnutrition before immunogenic activity, which is usually slow and progressive, had the opportunity to cause any inflammation or cancer. There were often teleological advantages in having susceptible genotypes i.e. may confer protection against infection.

However with improved nutrition, public health and antibiotic development longevity has increased.

The increasing exposure to new, different and old immunogens over a longer period has resulted in epidemics of these syndromes in Western civilisation. Doctors will have to re-adjust their approaches to the diseases of the 21st century and focus more on reducing the implicated old, new or different immunogen exposure from an early age instead of simply patching up the results of decades of inflammation and cancerous change later on – usually at great expense.

Teachers will have to incorporate prevention into the school curriculum.

Already in some States in the U.S.A. schools prohibit “junk food”.

The food and pharmaceutical industries in association with politicians are aware of the cause of the epidemics already. Profitability is so great that the development of new dietary immunogens is likely to continue e.g. genetically modified food is expected to be next.

AETIOLOGY

FAMILY HISTORY

1. Often positive for the same organ affected as the index case
e.g. coronary artery disease, breast cancer. Often increased in certain H.L.A. types.
2. If chromosomal or genetic abnormalities are identified in the index case the chances of positive family history affecting the same organ are increased.
e.g. breast and ovarian cancer and BRCA genes.

CLUSTERING

Occurs in

1. Geographical locations where exposure to immunogen is prevalent e.g. in certain diets, in localised industrial activities using particular immunogens i.e. occupational diseases. Trans-global migrant workers and their families are at greater risk if immunogen e.g. dietary intake is radically different from area of origin e.g. epidemic of coronary artery disease and diabetes mellitus in Indian sub-continent immigrants in the U.K.
2. In areas where consanguinity more prevalent i.e. in isolated communities or societies where consanguinity more frequent.

EXPRESSIVITY

There is variable expression which is related to

1. The abundance of the incriminating genes in the individual.
2. The exposure to immunogen.

This may explain "skip generations".

AGE OF ONSET

Earlier onset if

1. Associated genetic/chromosomal abnormalities.
2. Family history strongly positive.
3. Earlier immunogen exposure.
4. Severe immunogen exposure.

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
 - i. Interleukin-1 beta.
 - ii. Tumour necrosis factor-alpha.
 - iii. 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.

PATHOLOGY

DEFINITION OF ANTIGEN AND IMMUNOGEN

1. ANTIGEN – any substance that binds to an antibody or T cell receptor.
2. IMMUNOGEN- any substance which induces a humoral and/or cellular response.

ALL IMMUNOGENS ARE ANTIGENS BUT NOT ALL ANTIGENS ARE IMMUNOGENS.

Ref

IMMUNE SYSTEM

The immune system comprises of

1. T-cells.

These cells are divided into

i) REGULATORY OR SUPPRESSOR CELLS.

Ref 1 Ref 2

These cells suppress activation of the immune system. Regulatory 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”. Increased suppressor TREG T-cell activity may result in cancer.

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

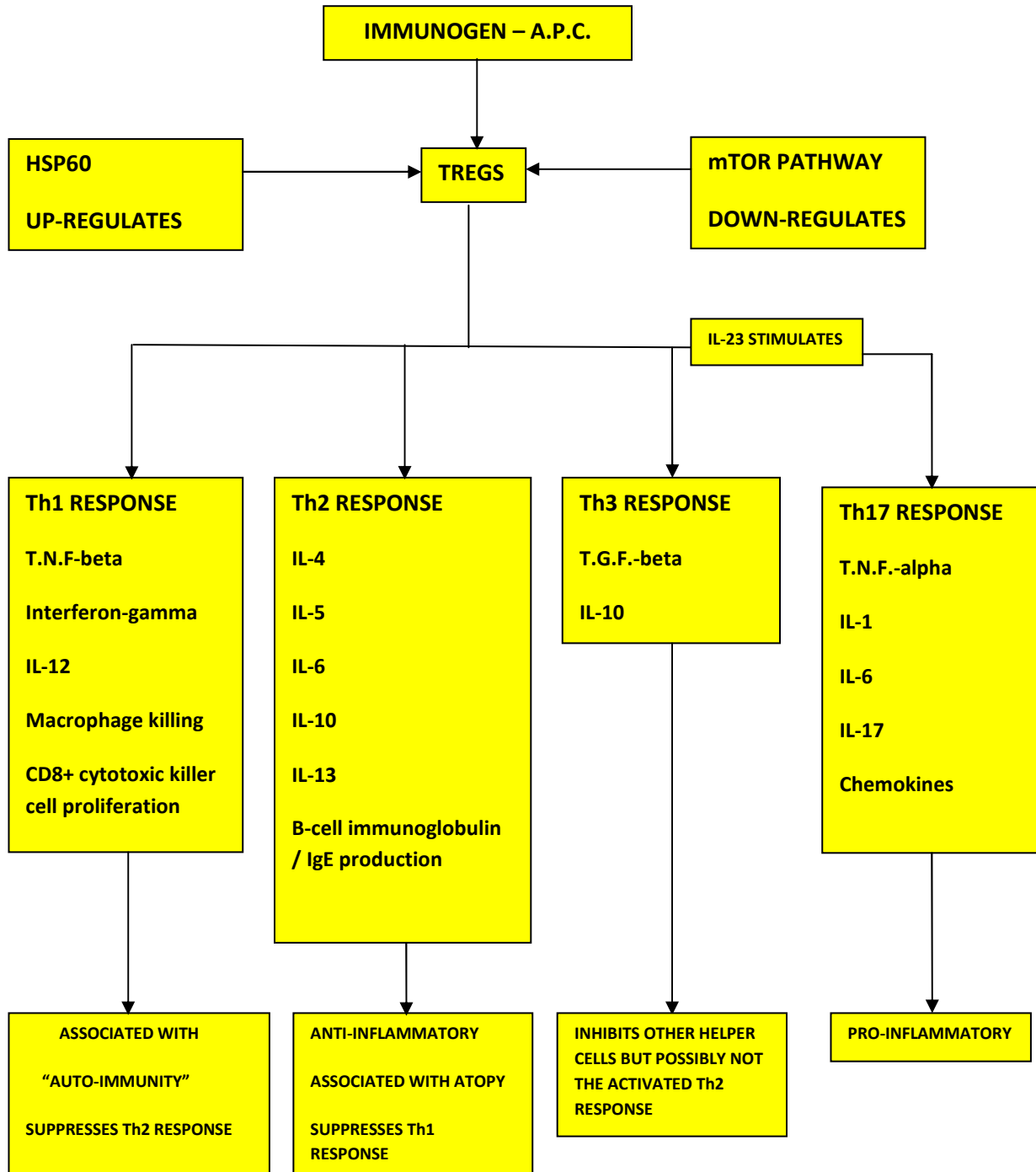


DIAGRAM 1

TREGS are involved in the initiation of the inflammatory response. Antigens are not recognized as “self” by TREGS. This results in abnormalities of

1. CD4+ T-cells, CD8+ T-cells and CD4+/CD8+ ratio.
2. Th1, Th2, Th3 and Th17 balance
3. Interferon-gamma.
4. Interleukins IL-1, IL-6, IL-10, IL-12.
5. Tumour necrosis factor.
6. Macrophages, peripheral mast cells, leucocytes and complement factors.
7. Immunoglobulins.

[Ref 1](#) [Ref 2](#) [Ref 3](#) [Ref 4](#) [Ref 5](#) [Ref 6](#) [Ref 7](#)

MACROPHAGE AND DENDRITIC CELL FUNCTION

Dendritic cells (D.C.) are macrophage-like cells or antigen-presenting cells in the nervous system, peripheral blood, skin and gastro-intestinal tract.

Ref 1 Ref 2 Ref 3 Ref 4

The macrophage/dendritic cell (D.C.) engulfs the antigen molecule and phagocytosis occurs. The macrophage/D.C. expresses processed antigen or their derivatives in major histocompatibility complexes on the cell membrane. The macrophage/D.C. is now known as the antigen-presenting cell. In normal individuals, the antigen may be accepted as “self” or “near-self” by the TREGS. In TREG syndromes there is activation of T-helper cells and B-cells due to the antigen or their derivatives becoming immunogens i.e. due to being recognised as “non-self”. The inflammatory response results in the following.

1. Further T-cell activation.
2. Cytokine release – including tumour necrosis factor, interferon, and interleukins.
3. Blockage of activation of tissue growth factor beta-1.
4. Auto-reactive immunoglobulin release.
5. Release of metallo-proteases.
6. Fibroblast activation.
7. Development of tissue specific immunoglobulin e.g. anti-tissue transglutaminase immunoglobulin.
8. Complement activation.
9. Disorganisation of tissues leading to clinical inflammation, predominantly dendritis, and cancer.

(See Diagram 2)

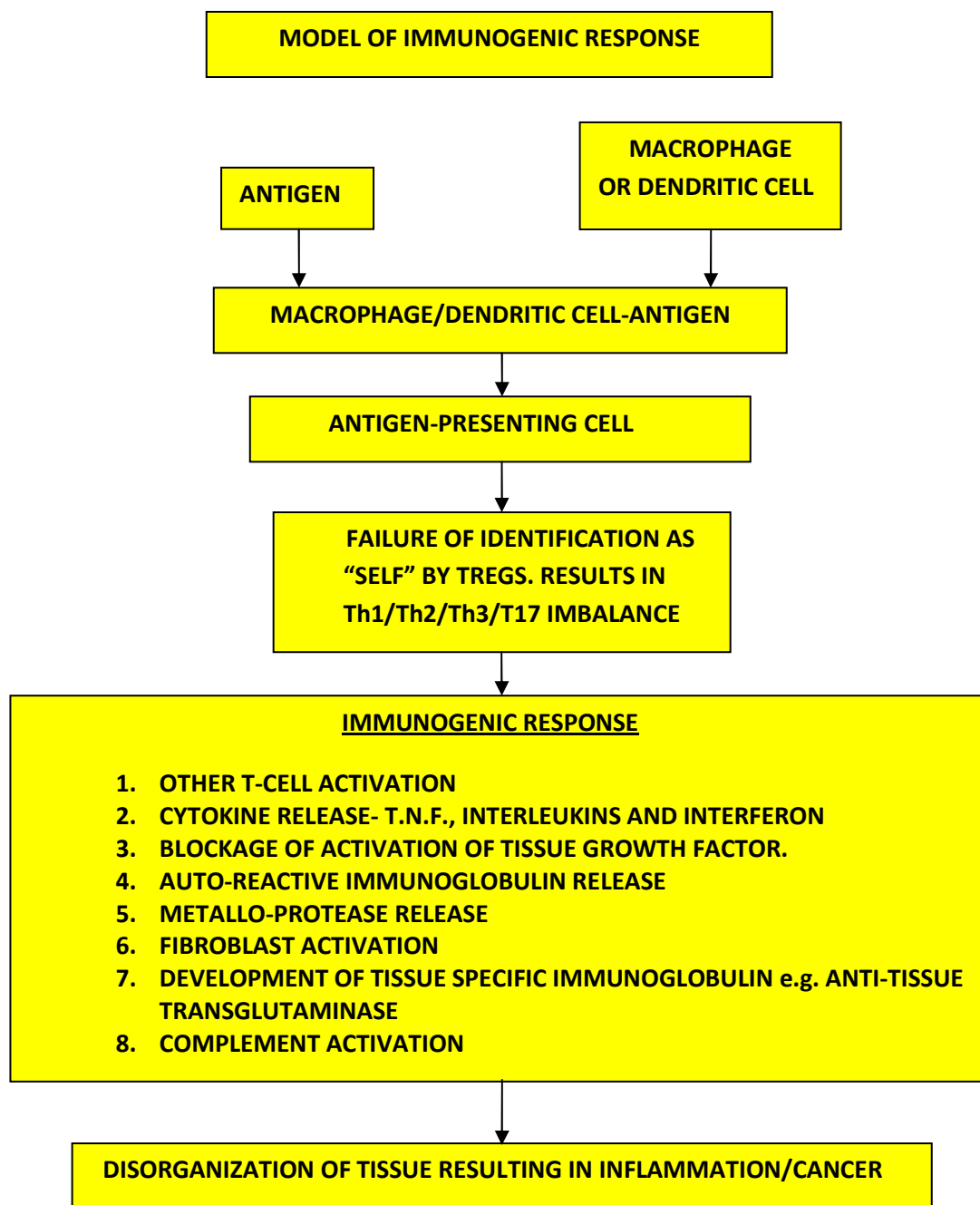


DIAGRAM 2

Tumour necrosis factor may correlate with severity of tissue inflammation and measurements may represent the degree of disease activity.

[Ref](#)

Expression of transcription factor Fox p3 may also be useful in measuring disease activity and has already been able to distinguish between dogs without cancer and dogs with cancer.

[Ref](#)

There is functional evidence of a significant increase of TREGS in the peripheral blood of cancer patients.

[Ref](#)

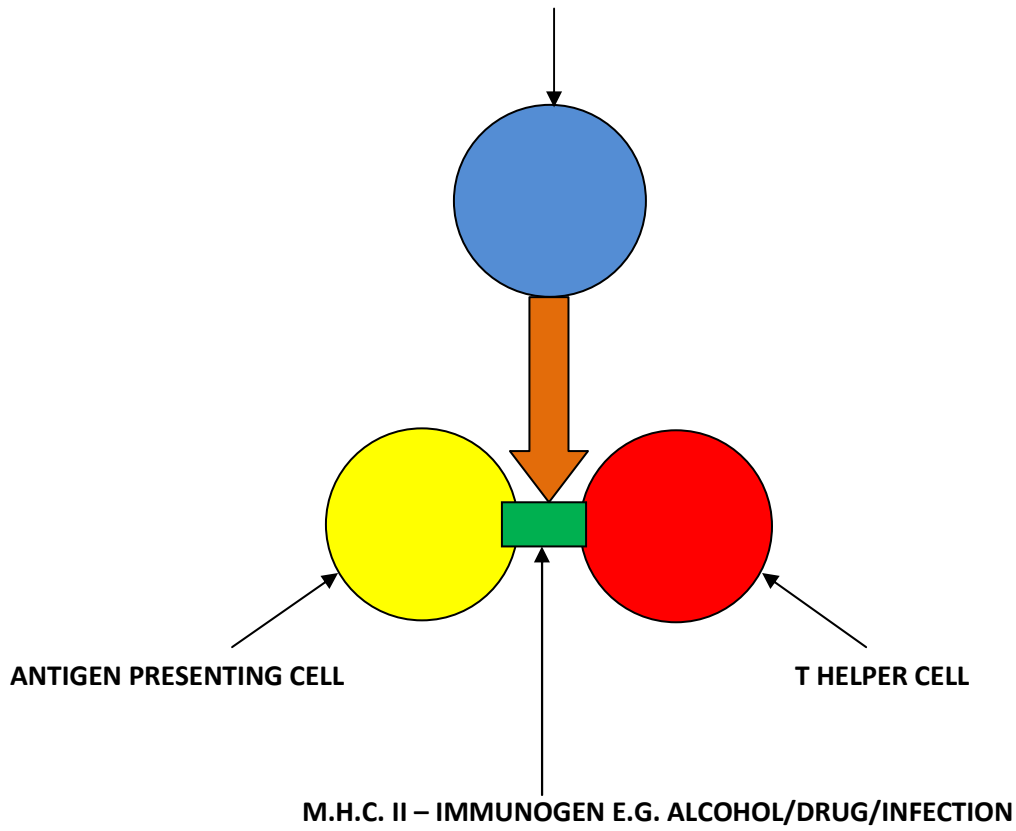
Foetal exposure to immunogens may also be contributory.

Histocompatibility lymphocyte antigen (H.L.A.) types may also predispose to the severity of the immunogenic response.

SUMMARY

Ref

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



TISSUE DISORGANIZATION

The immunogenic reactions result in the surrounding cells becoming disorganised. The disorganisation is greater if

1. There are associated chromosomal/genetic defects in these cells.
2. The cells have more rapid turnover.
3. The cells have greater immunogen exposure.

SEVERE CHROMOSOMAL/GENETIC ABNORMALITIES IN CELLS

In these cases, the syndrome often develops in childhood and is more likely to progress to cancer. Even if the cancer is successfully treated the risk of developing a second cancer is greatly increased due to the increased genetic pre-disposition.

ORGANS MORE LIKELY TO BE AFFECTED

a) ORGANS WITH RAPID CELL TURNOVER

1. Respiratory system.
2. Gastro-intestinal system.
3. Uro-genital system.
4. Skin.
5. Bone marrow
6. Vascular endothelium.
7. Breast.

b) ORGANS WITH GREATER IMMUNOGEN EXPOSURE

1. Respiratory system.
2. Gastro-intestinal system.
3. Uro-genital system.
4. Skin.
5. Bone marrow
6. Vascular endothelium.

IMMUNOGENS THAT MAY BE ASSOCIATED WITH TREG SYNDROMES

1. Infection including prions.
2. Alcohol.
3. Tobacco.
4. Drugs including antibiotics, hormones in medicine and in food industry. 50% of antibiotics produced enter food chain at food industry level.
5. Gluten.
6. Pesticides.
7. Herbicides.
8. Fertilizers.
9. Sweetening agents.
10. Monosodium glutamate.
11. Refined sugar, sugar-milk.
12. Added salt.
13. Aluminium - tin-cans, cooking utensils, deodorants.
14. Rape pollen near large centres of population.
15. Environmental pollutants e.g. car-exhaust.
16. E-numbers.
17. Soya.
18. Occupational immunogens e.g. petro-chemicals.
19. Immunisations.
20. Radon.
21. Electro-magnetic radiation.
22. Talc.
23. Manganese.
24. Mercury.
25. Lead.
26. Homocysteine.

DIETARY DEFICIENCIES MAY ALSO CONTRIBUTE

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

TYPES OF TREG SYNDROMES

INFLAMMATION

- 1.Mild.
- 2.Moderate.
- 3.Severe.

MAY PROGRESS TO CANCER

- 1.Mild grade.
- 2.Moderate grade.
- 3.Severe grade.

The following diseases may be due to TREG cells

- Incorrectly not identifying normal antigens as “self” e.g. “auto-immune” diseases.
- Incorrectly identifying abnormal antigens as “self” e.g. cancer cells.

with the consequential abnormal immunogenic response resulting in inflammation and cancer. They may be associated with each other. Immunogenic response may accelerate pre-existing pathology. TREG activity may be abnormally increased or decreased.

The following diseases may well be TREG syndromes. There are some references to recent studies confirming the potential importance of TREG cells in these diseases where available. It is anticipated that many more of these diseases will be subject to studies assessing TREG function in the near-future.

NERVOUS SYSTEM

1. Alzheimer`s disease.

TREGS are increased in Alzheimer`s disease.

[Ref](#)

2. Multiple sclerosis.

TREG development and function are disturbed in multiple sclerosis.

[Ref](#)

3. C.V.A./T.I.A.

TREGS may play a protective role in the progression of atherosclerosis.

[Ref](#)

4. Parkinson`s disease.

TREGS mediate neuro-protection through suppression of microglial responses to stimuli. Cytokine abnormalities are also present.

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

5. Motor neurone disease.

TREG activity relates to progression of loss of motor function.

[Ref](#)

6. Migraine.

7. Idiopathic epilepsy.

8. Central pontine myelinosis.

9. Spongiform leucoencephalopathy.

10. Huntingdon`s disease.

11. Brain tumours.

High number of TREGS permits the aggressive growth rate seen in malignant brain tumors.

[Ref](#)

12. Peripheral neuropathy.

During the progressive or the relapsing phases of chronic inflammatory demyelinating polyradiculoneuropathy, the number of TREGS was reduced, and the suppressive function of them decreased.

[Ref](#)

13. Chronic fatigue-immune dysfunction syndrome.

TREG abnormalities have been noted.

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

14. A.D.S. (Alcohol-dependency and drug-dependency).

15. Guillain-Barre syndrome.

There are abnormalities of circulating TREGS in Guillain-Barré syndrome.

[Ref](#)

16. Myasthenia gravis

Increasing the number of TREGS may suppress disease activity.

[Ref](#)

CARDIO-VASCULAR SYSTEM

1. Arteriosclerosis including coronary artery disease.

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

2. Congestive cardiomyopathy.

3. Cardiac rhythm diseases – atrial fibrillation, tachy-brady syndrome, S.V.T., V.F.

4. Pericarditis.

5. Aortic aneurysm.

[Ref](#)

6. Deep venous thrombosis.

7. Sudden adult death syndrome.

8. Valvular heart disease.

RESPIRATORY SYSTEM

1. Asthma.

[Ref](#)

2. Emphysema.

[Ref](#)

3. Bronchiectasis.

[Ref](#)

4. Lung cancer.

5. Fibrosing alveolitis.

6. Sarcoidosis.

[Ref](#)

7. Mesothelioma.

[Ref](#)

GASTRO-INTESTINAL SYSTEM

1. Oesophagitis/cancer oesophagus.

2. Peptic ulcer/stomach cancer.

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

3. Coeliac disease /duodenal lymphoma.

4. Crohn`s disease/ulcerative colitis.

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

5. Colon cancer.

[Ref](#)

6. Diverticulosis.

7. Haemorrhoids.

PANCREAS

1. Pancreatitis.

[Ref](#)

2. Pancreatic Cancer.

LIVER

1. Fatty inflammation.

2. Hepatitis – acute/chronic.

3. Cirrhosis- Including primary biliary cirrhosis.

4. Chronic active hepatitis.

5. Hepato-cellular carcinoma.

6. Cholangiocarcinoma.

7. Haemochromatosis.

[Ref](#)

ENDOCRINE

1. Obesity.

It is anticipated that 86% of men will be overweight in 15 years and 70% of women will be overweight in 20 years.

2. Diabetes mellitus types 1/2.

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

3. Addison`s disease.

4. Cushing`s syndrome.

5. Adrenal cancer.

6. Hashimoto`s disease.

7. Graves`s disease.

[Ref](#)

8. Thyroid cancer.

9. Hyper/hypoparathyroidism.

10. Metabolic syndrome.

URO-GENITAL SYSTEM

1. Glomerulo-nephritis.

2. Kidney cancer.

[Ref](#)

3. Interstitial cystitis.

4. Bladder cancer.

5. Chronic pelvic pain syndrome.

6. Non-specific urethritis.

7. Prostate cancer.

[Ref](#)

8. Orchitis.

9. Testicular cancer.

10. Pelvic inflammatory disease – non-infective type.

11. Polycystic ovarian disease.

12. Idiopathic infertility.

13. Ovarian cancer.

[Ref](#)

14. Uterine cancer.

15. Endometriosis.

16. Cervical cancer.
17. Cancer of vulva.
18. Premature menopause.

DERMATOLOGY

Ref

1. Psoriasis. [Ref](#)
2. Dermatitis.
3. Alopecia.
4. Pemphigus/pemphigoid. [Ref](#)
5. Acne rosacea.
6. Acne vulgaris.
7. Basal cell carcinoma.
8. Squamous cell carcinoma.
9. Melanoma – explains why increasing number of cases affecting palms and soles although not exposed too much sun-light. [Ref 1](#) [Ref 2](#)
10. Behcet`s disease.
11. Vitiligo.

HAEMATOLOGY

1. Myelodysplastic syndrome. [Ref](#)
2. Aplastic anaemia. [Ref](#)
3. Leukaemia. [Ref 1](#) [Ref 2](#)
4. Idiopathic thrombocytopenic purpura. [Ref](#)
5. Thrombasthenia.
6. Lymphoma. [Ref](#)
7. Myeloma.
8. Erythrophagocytic disease.
9. Haemolytic anaemia.
10. Leucopenia.
11. Paroxysmal nocturnal haemoglobinuria.
12. Porphyrin.

BONE

1. Osteoporosis.
2. Osteomalacia.
3. Avascular necrosis.

RHEUMATOLOGY

1. Osteo-arthritis.
2. Rheumatoid arthritis. [Ref](#)
3. "Collagen" diseases – including S.L.E., P.N., dermatomyositis, temporal arteritis, scleroderma and Wegener's disease. [Ref 1](#) [Ref 2](#)
4. Dupuytren's contracture.
5. Gout.

ORAL

1. Dental decay. [Ref](#)
2. Oral carcinoma.
3. Sjogren's syndrome.

EAR, NOSE AND THROAT

1. Chronic secretory otitis media.
2. Meniere's disease.
3. Laryngeal /naso-pharyngeal dysplasia/cancer.

OPHTHALMOLOGY

1. Macular degeneration.
2. Cataract.
3. Sicca syndrome. [Ref](#)
4. Glaucoma.
5. Retinal haemorrhage/detachment.
6. Optic neuropathy.

BREAST

1. Fibroadenosis.
2. Fibroadenoma.
3. Breast cancer. [Ref](#)

PREGNANCY – immunogenic response to paternal immunogens in foetus /placenta accelerated by other immunogens. [Ref](#)

1. I.U.G.R.
2. Miscarriage.
3. Prematurity.
4. Abruptio placentae.
5. Pre-eclamptic toxæmia.
6. Choriocarcinoma.

PAEDIATRICS

The following may be more prevalent in the early years of TREG syndrome patients.

1. Paediatric cancer
2. Congenital defects.
3. Sudden infant death syndrome.
4. Dyspraxia.
5. Autism.
6. Immunisation reactions.
7. Attention deficit hyperactivity disorder.
8. Night terrors.
9. Childhood depression, schizophrenia, mania, hysterical conversion reaction
10. Para-suicide.
11. School refusal/truancy.
12. Stool withholding.
13. Kawasaki syndrome.

These lists are not comprehensive.

INVESTIGATION

These may be performed in a general health screen.

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. Vitamin B12, folate and iron/total iron-binding capacity.
8. Uric acid.
9. Prostate-specific antigen.
10. CA-125.
11. Chest radiograph.
12. Electrocardiograph.
13. Faecal occult bloods.

FURTHER CLINICAL AND RESEARCH INVESTIGATIONS MAY INCLUDE

RADIOLOGY

1. Ultrasound.
2. Full/partial body M.R.I. scan or C.T. scan.

ENDOSCOPY – respiratory tract/gastro-intestinal /uro-genital tract.

IMMUNOLOGY

1. T-Cell subsets, regulatory T-cells including transcription factor Fox p3.
2. Interleukins e.g IL-2.
3. T.N.F-alpha.
4. Immunoglobulins – including immunoglobulin E, specific antibodies i.e. alcohol and drug antibodies, R.A.S.T. e.g. to milk.
5. Auto-immune profile including tissue transglutaminase.
6. Tissue specific immunoglobulins e.g. auto-antibodies to basic myelin protein, oligodendrocyte glycoprotein and annexin IV, anti-chondrocyte antibodies.
7. Anti-serotonin immunoglobulins.
8. Circulating immune complexes.

GENETIC ANALYSIS

1. Chromosomes.
2. Genetic analysis – blood/bone marrow aspirate.
3. H.L.A. typing.

BIOCHEMISTRY

1. Alpha-fetoprotein.
2. Human chorionic gonadotrophin.
3. Atrial natriuretic peptide.
4. Prolactin, 9 a.m. cortisol, testosterone and oestradiol.

HISTOPATHOLOGY

1. Cytology.
2. Biopsy.

NEUROLOGICAL

1. Electro-encephalogram.
2. Lumbar puncture – including TREG cells, macrophage and cytokines.

NUTRITIONAL SCREEN – vitamins, minerals, trace metals.

N.B. elevated C.R.P. is associated with active inflammation.

T.N.F. measurement will probably become more popular in the future replacing C.R.P.

Expression of transcription factor Fox p3 can already distinguish between dogs with cancer and dogs without cancer.

PREVENTION

1. School education regarding risks of immunogen exposure and the “Western-diet “.
2. School dietary changes
 - Increased omega-3 essential fatty acids.
 - Reduced omega-6 essential fatty acids.
 - Reduced immunogens e.g. E-numbers, aspartame and monosodium glutamate.

Some States in the U.S.A. have made “junk food” illegal in schools. “Energy drinks” may be associated with cigarette smoking, illicit drug use and violence.

Ref

3. Fortification of food with folic acid – but there are risks e.g. to elderly with B12 deficiency.
4. Reduce incriminating immunogen exposure listed above.
5. Genetic screening pre-conceptually, at birth or in childhood – in the future.
6. Avoiding dietary immunogens in pregnancy e.g. alcohol, nicotine, aspartame and monosodium glutamate.

TREATMENT

DIET

Increasing dietary omega-3 essential fatty acids and reducing omega-6 essential fatty acids. “Junk food” is now illegal in schools in several states in the U.S.A.

Consider increasing vitamins A, B vitamins including folic acid, C, D, E, zinc, selenium, glutamine, carnitine and vitamin B17 in diet if proven deficiency.

D.H.A. supplementation of the diet may be effective in protecting against TREG syndromes developing.

COMMENTS ON DIET

Aim for the following recommendations by the World Cancer Research Fund (2007).

Five portions of fruit or vegetables per day including wholegrains and pulses.

Avoid sugary drinks

Limit red meat to 500g cooked weight per week.

Limit salt consumption.

If consumed at all limit alcoholic drinks to 2 for men and 1 for women per day.

Do not use supplements to protect against cancer.

Do not smoke or chew tobacco.

It is best for mothers to breast-feed exclusively for up to six months.

The following dietary information may be helpful.

[Ref](#)

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

Flaxseed oil	53.3g per 100g
Ref	
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.

CARNITINE

Acetyl-1-carnitine up-regulates TREG cells by increasing HSP60.

[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.

DISCONTINUING ALCOHOL INTAKE.

ALCOHOL IS A CARCINOGEN.

DISCONTINUATION OF SMOKING TOBACCO.

TOBACCO IS A CARCINOGEN.

EXERCISE/WEIGHT CONTROL.

One hour of brisk walking per day.

One hour of vigorous exercise per week.

Maintain body mass index between 18.5-25.

SPECIFIC MEDICAL TREATMENT

e.g. coronary artery angioplasty.

ANTI-INFLAMMATORY TREATMENT.

Includes

a) Aspirin.

Aspirin is probably underused in TREG syndromes. There are regular often unexpected reports related to the anti-inflammatory effect of aspirin e.g. a recent study confirmed that aspirin reduced the risk of newly diagnosed adult-onset asthma in a large, randomized clinical trial of apparently healthy, aspirin-tolerant men by 22% and has to be repeated.

[Ref](#)

However most physicians will be loathe considering aspirin in asthma due to perceived risk. "Old habits die hard".

Other preliminary studies suggest that aspirin may also be considered for the prevention of

- Parkinson`s disease.

[Ref](#)

- Cancer e.g. colon cancer.

[Ref](#)

- Primary cardio-vascular disease in all men and women without diabetes above the ages of 48 and 57 years respectively.

[Ref](#)

These studies have to be repeated but perhaps most of the population in the "West" should take aspirin if there are no contra-indications .

n.b. mesalazine, a derivative of aspirin, is being used to treat diverticulosis.

[Ref](#)

b) Statins.

Statins reduce all-cause mortality in ostensibly cardio-vascular clinical trials probably due to their effect on TREGS. Certain types of cancer may be less frequent which is being investigated further. One could argue that following on from this observation that statins should be used for many of the TREG syndromes listed above.

The statin effect on reducing cardio-vascular events may be more likely to be related to anti-inflammatory properties on the endothelial TREGS rather than reduction in the cholesterol "number". Patents have recently been awarded for the assessment of the effect of statins on TREG cells.

[Ref](#)

The effect of statins on TREG cells in several other diseases is being assessed.

Renal

[Ref](#)

Age-related decline in lung function.

[Ref](#)

Perhaps most of the population in the “West” should take statins if there are no contra-indications.

- c) Many drugs may serendipitously affect TREG function and the immunogenic response. This may result in measurable improvement in immune function e.g. reduction in T.N.F. levels. These effects have resulted in the drugs having unexpectedly beneficial results in treating diseases which they were not initially licensed to treat. This is expected to become an increasing area of study.

Including

- Tetracycline – e.g. minocycline in multiple sclerosis , schizophrenia and autism, doxycycline in osteo-arthritis.

Ref 1 Ref 2 Ref 3 Ref 4

- Clarithromycin – e.g. in severe asthma.

Ref

- Metronidazole – e.g. in inflammatory bowel disease.

Ref

- Digoxin – e.g. reduced the frequency of cancer in cardio-vascular trials. Now used in lung cancer trials.

Ref

- Warfarin – e.g. reduces the frequency of cancer.

Ref

- Heparin – e.g. reduces the growth in certain cancers.

Ref

- Beta-blockers – e.g. in cardiomyopathy.

Ref

- Angiotensin II antagonists and angiotensin converting enzyme inhibitors– e.g. in myocardial ischemia.

Ref 1 Ref 2

- **Flecainide – e.g. in multiple sclerosis.**

Ref 1 Ref 2

- **Amlodipine – e.g. in heart failure.**

Ref

- **Spironolactone – e.g. in animal corneal graft survival.**

Ref 1 Ref 2

- **Metformin – e.g. in polycystic ovarian syndrome.**

Ref 1 Ref 2

- **Anti-psychotics – e.g. phenothiazines – known to protect against infection for decades.**

Ref 1 Ref 2

- **Anti-depressants including fluoxetine, amitriptylene and bupropion – e.g. Bupropion used in psoriasis, systemic lupus erythematosus and inflammatory bowel disease. Amitriptylene is used extensively by Pain Clinics.**

Ref 1 Ref 2 Ref 3 Ref 4

- **Anti-Parkinsonian drugs including L-dopa and selegiline – e.g. Selegiline may be effective in human immunodeficiency virus infection. Levodopa is used for restless legs syndrome.**

Ref 1 Ref 2

- **Anti-convulsants e.g. carbamazepine, sodium valproate and topiramate. Topiramate is used for psoriasis.**

Ref 1 Ref 2

- **Thalidomide. Used in inflammatory bowel disease and non-solid tumours.**

Ref

- Dapsone. Used in various non-infectious dermatologic diseases e.g. dermatitis herpetiformes.

Ref

- Biphosphonates. Used in myeloma and breast cancer. Also affect arteriosclerosis by macrophage suppression in atheromatous lesions.

Ref

- Pentoxifylline. Used to suppress human immunodeficiency virus replication.

Ref 1 Ref 2 Ref 3

- Drugs used for A.D.S. e.g. disulfiram in trials of lung cancer treatment.

Beware of variable clinical responses possibly related to unexpected immunological responses e.g. L-dopa has recently been noted to cause excessive spending incurring debts by patients with Parkinson`s disease possibly due to suppression of the dendritic pathology and increased aggregate dendritic firing rates leading to hypersensitivity to extreme positive thoughts and feelings. Physicians have been advised to warn patients of this when commencing L-dopa preparations. Variable responses may be related to different genetic polymorphisms resulting in higher or lower blood plasma levels with the same dose. Early rise in T.N.F. may predict adverse drug reactions i.e. weight gain with mirtazepine.

Genetic testing may guide the type of anti-depressant and dosage

Ref

IMMUNO-SUPPRESSIVE TREATMENT

CANCER AND IMMUNO-THERAPY

Ref

RAPAMYCIN

Ref 1 Ref 2

PREDNISOLONE

Prednisolone is used with great trepidation at higher dosage by physicians because of severe adverse reactions. However, there are few studies of long-term low-dose i.e. 1-2 mg per day in TREG syndromes e.g. progressive primary osteo-arthritis instead of current trials of long-term doxycycline therapy.

CHEMOTHERAPY

Methotrexate is being used more frequently for TREG syndromes causing inflammation e.g. psoriasis, rheumatoid arthritis. Generally speaking, methotrexate is well-tolerated and the adverse drug reaction of hepatic fibrosis is infrequent, but can be fatal.

CYTOKINE/MONOCLONAL ANTIBODY THERAPY E.G. ANTI-T.N.F, IL-2 TREATMENT

Gradually being used or being considered for use more frequently for all of the above TREG syndromes often unexpectedly e.g. for pre-menstrual tension and unexplained infertility, but is prohibitively expensive and has led to several court cases between affected patients and Health Authorities who refused to provide treatment, particularly for cancer patients. Will probably lead to the need for Health Insurance because of incredible cost of treatment covering the whole population and further health inequalities e.g. the cost of monoclonal antibody to integrin-alpha 4 for multiple sclerosis and Crohn`s disease is \$2184.62 per vial. One patient reported the actual cost for one year`s treatment for multiple sclerosis amounted to \$108,000 including hospital admission and infusion equipment costs.

Ref

HEAT- SHOCK PROTEIN

H.S.P. affects TREG function. H.S.P. is being assessed in the treatment of multiple sclerosis.

[Ref](#)

MESENCHYMAL/CD34+ STEM CELL TREATMENT

Mesenchymal cells and CD34+ stem cells

- Improve blood flow by promoting angiogenesis in areas of low oxygenation in the body.
- Affect TREG cell activity and reduce inflammation.

Currently being used for the following e.g. at the Institute Of Cellular Medicine in Costa Rica. There are several legal restrictions on use in the U.S.A.

- Motor neurone disease.
- Spinal injuries.
- Autism.
- Auto-immune disease.
- Multiple sclerosis.
- Type 2 diabetes mellitus.
- Cerebro-vascular accidents.
- Parkinson`s disease.
- Rheumatoid arthritis.

Clinical trials with stem cell therapy have commenced in the U.S.A. for the following.

- Crohn`s disease.
- Graft versus host disease.
- Cardiac failure.

12- STEP PROGRAMME.

Consider 12-step programme and “meetings” with similarly affected individuals if TREG dendritis is causing hypersensitivity to thoughts and feelings and obsessive-compulsive behaviour e.g. TREG dendritis due to smoking and sweetening agents resulting in obsessive-compulsive over-consumption and weight gain.

AVOID HYPERGLYCAEMIA.

Tends to accelerate cancer. Aim for persistent normoglycaemia with small regular uncooked meals i.e.”grazing”.

COMPLEMENTARY MEDICINE

The following unlicensed complementary treatments affect the immune system.

- St. John`s Wort.

Depression.

- Chondroitin sulphate 1 gram per day and glucosamine 1200 milligrams four times per day.

Osteo-arthritis. Reduces T.N.F.

- Feverfew.

Migraine.

- Butterbur.

Hay fever.

- Curcumin.

Curcumin in turmeric e.g. curries reduces macrophage immunogenic activity and leads to increased sense of “well-being”.

- Echinacea. Affects TREG cell activity.

Ref 1 Ref 2

- Cat`s claw.

Affects TREG cell activity.

- Dandelion.

Affects TREG cell activity.

- Mistletoe.

Breast cancer.

IMMUNISATION.

Immunisations have been developed for

Cervical cancer.

Alzheimer`s disease.

Multiple sclerosis. Neurovax for multiple sclerosis stimulates the FOXP3+ TREG cells.

[Ref](#)

PLACEBO RESPONSE.

Placebo may have a 30% beneficial response, but is probably under-used. The medical knowledge of the public is considered to have increased substantially in the past ten years and placebo prescriptions are now regarded as unethical. Obecalp i.e. the reversal of the word “placebo” is now being used in the U.S.A.

ILLICIT DRUGS.

Drugs which are regarded as illicit may have beneficial effects in certain diseases related to their action on the immune system.

CANNABIDIOL OR HU-320.

HU-320 is synthetically derived from cannabidiol. HU-320 reduces lymphocyte proliferation and tends not to cause the unwanted psychological symptoms of cannabis, the parent source. May be effective in multiple sclerosis.

[Ref](#)

“ECSTASY”.

May improve the symptoms of the tremor and bradykinesia of Parkinson`s disease by anti-immunogenic activity, but also causes unwanted psychological symptoms.

CONCLUSION

The involvement of TREG cells in

- Idiopathic disease
- Essential disease
- Primary disease
- Degenerative disease
- Cancer

which are now epidemic in Western civilisation, is becoming increasingly recognised.

The TREG syndromes will be treated increasingly with novel and probably very expensive therapies. It is likely that only a small percentage of the population will be able to afford them. Prevention will prove less expensive. The question is

Will Government be able to convince the electorate that

1. Often more expensive healthier eating, immunogen avoidance and regular exercise will reduce chronic inflammation and subsequent cancer when Doctors themselves are unaware that apart from infection, trauma, senility and malnutrition most of the diseases they are diagnosing and treating are due to TREG syndromes related to diet and life-style and are not “primary, idiopathic, essential or degenerative”. Doctors continue to treat the end-stages of TREG syndromes i.e. inflammation and cancer, but the illnesses are starting decades earlier. Many of the TREG syndromes are under-treated unknowingly due to lack of awareness of the immunogenic aetiology.

There is also an increasingly popular philosophy amongst patients that there is “a pill for everything” with over-reliance on drug therapy.

“One of the first duties of the physician is to educate the masses not to take medicine”. Sir William Osler (1849 – 1919).

Minimal advice is given to school-children regarding TREG syndromes in order that they have some choice regarding their future health. Some States in the U.S.A. have already made “junk food” illegal in schools.

2. Health Insurance will be needed in the very near future in order to pay for expensive cytokine and mesenchymal stem cell treatment e.g. the cost of treating advanced colo-rectal cancer has increased from \$500 in 1999 to \$250,000 at present.

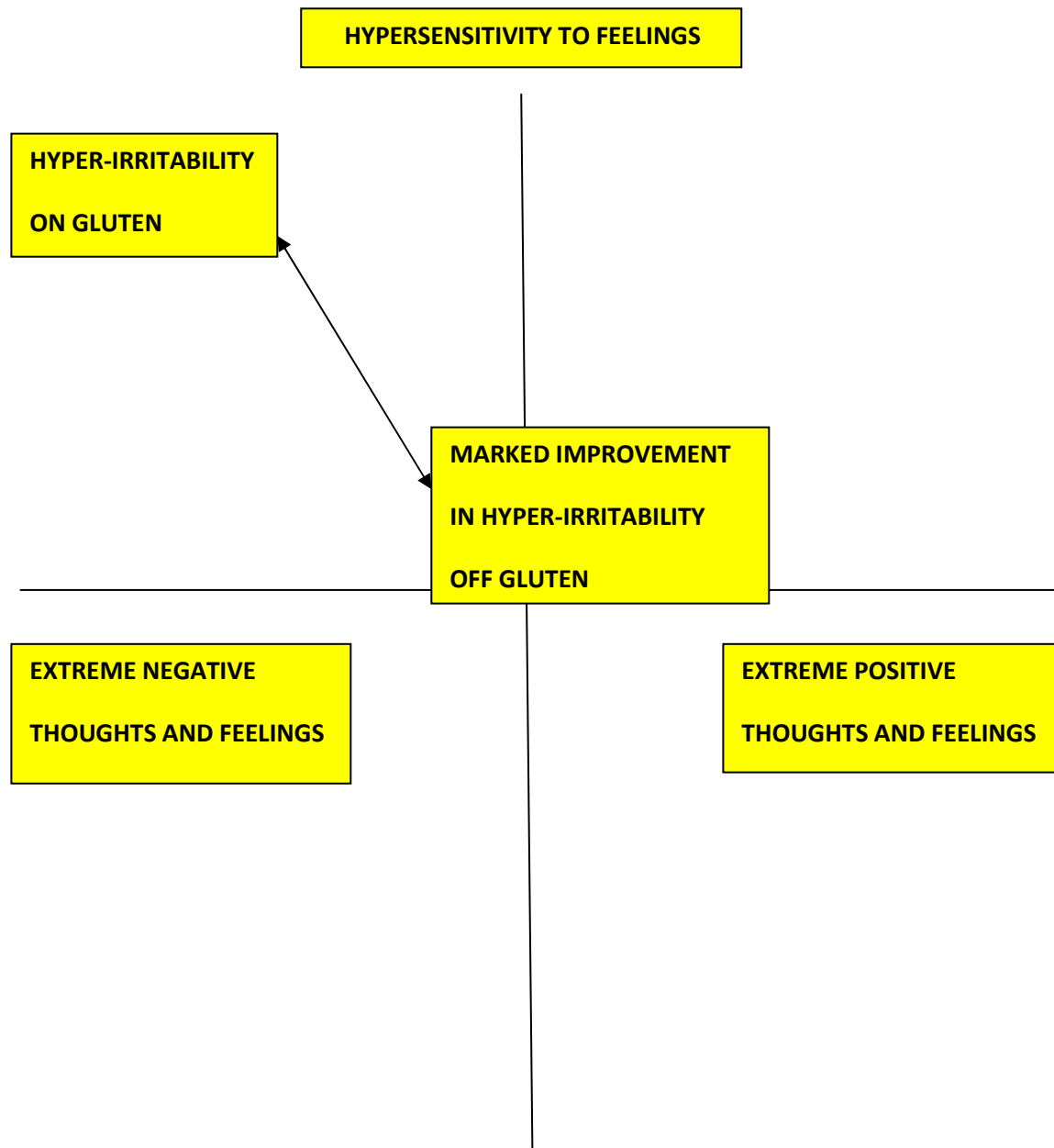
“The future is today”. Sir William Osler (1849 – 1919).

The regulatory T-cell syndromes are set to run and run. Do not hold your breath as doctors are unlikely to use the “N” (nutrition) word as their training in nutrition is minimalistic at medical school and the regulatory T- cell concept of 21st century diseases is all new– it is not their fault!

SOME QUESTIONS ARISING FROM THIS BOOK.

These are some of the questions that I considered during the writing of this book.

1. Do sweetening agents and monosodium glutamate increase the risk of developing or cause TREG syndromes?
2. Should genetic analysis ideally be performed on all patients with TREG syndromes?
3. Does the hyper-irritability of coeliac disease relate to hypersensitivity to negative thoughts and feelings which convert to positive thoughts and feelings with cessation of gluten intake. This may be due to improvement in the associated dendritis and M.R.I. white matter brain lesions which may occur in coeliac disease.(see graph below)



POSSIBLE MODEL FOR CLINICAL IMPROVEMENT IN HYPER-IRRITABILITY IN COELIAC DISEASE ON GLUTEN-FREE DIET ESPECIALLY IF WHITE MATTER BRAIN LESIONS ARE PRESENT ON M.R.I. SCAN

4. Do young men who travel excessively have a higher prevalence of lymphoma TREG syndromes because of multiple different immunogen exposure e.g. infections?
5. Should patients with osteo-arthritis embark on trials of immuno-suppression therapy e.g. long-term low dose prednisolone / low dose methotrexate therapy instead of trials of long-term antibiotic therapy e.g. doxycycline therapy which are on-going?
6. Should aspirin and statins be prescribed for most patients with TREG syndromes?

7. Should patients with genetic abnormalities and strong family history of cancer be prescribed aspirin and statins prophylactically?
8. Should methotrexate be used more extensively and earlier e.g. for severe pre-cancerous TREG syndromes?
9. Should the 21st Century “poly-pill” contain the following: aspirin, statin, vitamins A, C and E, omega-3 essential fatty acid, low-dose prednisolone and low-dose methotrexate?
10. Are cases of adult sudden death syndrome genetically normal?
11. Should hypertension be treated more frequently with prolonged non-drug therapy initially e.g. cognitive behavioural therapy?
12. How should persistently elevated C.R.P, uric acid or “tumour markers” in otherwise healthy patients be investigated and how frequently?
13. Should octogenarians continue with medication for TREG syndromes commenced decades earlier, in view of the fact that the immunogenic response declines with age?
14. Should the teaching about anti-lympho-proliferative “alternative” remedies, which have been used for centuries, be included in the medical school curriculum?
15. Is the epidemic of congestive cardiomyopathy in the U.S.A. related to statin therapy prolonging lives due to anti-inflammatory action?
16. Does isolated elevation of cholesterol as a risk factor always result in accelerated arteriosclerosis?
17. Do oestrogens reduce coronary artery disease prevalence prior to the menopause due to anti-inflammatory action on the endothelium?
18. Do changes in oestrogen levels i.e. pre-menstrually, post-natally and peri-menopausally result in increased immunogenic brain inflammation and altered hypersensitivity to negative thoughts and feelings?
19. Can TREG antigen tolerance and immunogenic responses be affected by the conscious mind or religious beliefs?
20. Why are there not more studies on the effects of praying for patients to get better by friends and relatives?
21. Should the measurement of the expression of transcription factor Fox p3 be made more available to regularly assess patients for cancer as studies in dogs confirm different levels between dogs affected with cancer and those without cancer?
22. Is “cheap labour” from Third World countries offset by the cost of medical care of the epidemic of “Western” diseases affecting this work-force often at an earlier age due to dietary changes?

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.