"NOT ALL IN THE MIND" (With Thanks to Dr. Richard Mackarness)

Presentation at AUTSCAPE 2009 by ouinon

Hello, my name is Olivia Clayton; I self-diagnosed as Aspergers two years ago, after someone on an internet forum suggested that I might be an introvert, a description which so surprised me, (because I love spending certain amounts of time with certain people in certain circumstances, ;)), that I looked it up, … and found out about Aspergers, … and I have been using diet for 17 years now, on and off, to prevent depression, hypomania, and frequent headaches, among other things.

Finding out about Aspergers was a revelation, (as finding out about diet had been), because it explained why, although changing my diet had had a positive effect on my mood, particularly depression and hypomania; helped me sleep better, alleviated fatigue, lowered anxiety levels, and reduced frantic-thinking, brain-fog, floaty/spaced-out sensations, irritability, frequency and severity of meltdowns, (though I didn't call them that then), and sensitivity to noise, etc, it didn't have any effect on my literal-mindedness, need for time alone, intense and preoccupying interests, slowness at understanding other people, and disorientating/disconcerting contrasts between ability levels.

How did I get interested in diet and mental health? I had an out of body experience; … after half a day spent battling a terrible headache, being sick, and lying down to rest, I saw my body from a height and it was like looking at a beaten and abused animal; I thought "I wouldn't treat anyone like this", and yet I had, for years. It was an astonishing discovery; for the first time that I could remember I felt compassion, for my body, and shame, and grief at what I had done, and decided then and there to begin looking after my body. I very soon found out the effect that had on my mental health, and began reading about it.

For a long time I depended on books, (mostly from libraries because of lack of funds, mostly out of date too), and on my own dietary experiments, for information. I struggled, got confused, went from one extreme to another, gave up over and over again. The worst aspect of having so little access to authoritative and up-to-date research on the subject was not just that many other people thought that I was exaggerating wildly, or heading for mania again, but that "I" did. So the internet was like the cavalry coming to the rescue. Sometimes the wealth of information is almost shocking; there is so much scientific data now on the connections between diet and mental health, and yet most people still know nothing about it.

In fact before I continue I want to say that the hardest thing about preparing my presentation has been not knowing how much you know about diet already. For instance it is not that unusual on Wrong Planet to find that people don't know the difference between proteins and carbohydrates, or have no idea what gluten is.

Preparing this presentation I have realised even more just how much I am autist. Not only because the physical act of writing it was sometimes almost impossible because my son's father has been home for the holidays the last three weeks, watching television and generally hanging around, and because it has been very hot in France, which seems to fry my brain, but also because I found myself up against two classic autist problems; social dynamics and needing a clear purpose.

I have been struggling with the issue of how to talk to people about my special interest in an engaging/interactive way, so that I don't bore you to death with a monologue, at the same time as being coherent, ie. not losing my train of thought as a result of audience input and questions. And I have also been having trouble understanding the purpose of this presentation; what is it supposed to achieve? Is it just entertainment, creating debate, or might it serve as a guide to healthy eating, help some people overcome mental health problems?

Basically I haven't been able to work out whether this is supposed to be a technical presentation, with scientific papers to support my every remark, or a non-technical guide to exclusion diets for people who know little or nothing about diet and will take my word for it that diet can have a huge effect on mental health.

Who here is expecting, and/or looking forward to hearing, a closely reasoned argument backed up by scientific research?

Who here is expecting, and/or looking forward to, some simple non-technical advice about what to eat to improve your mental health? …

More generally, how many of you are here simply because this presentation supposedly has something to do with effective living?

What is effective living anyway? I think I know what it means, but can't help wondering about it. Can a life ever be more, or less, "effective" than another? I don't think so, but I think that it is possible to "feel" more effective, and I believe that diet can and does in many cases play a very important role in maintaining the kind of connection with one's body and the world which enables this "feeling".

Anyway, with this ambiguity of purpose in mind, I am going to start with a few questions about people's experience of diet and its effect on mental health. After a brief general introduction I'll stop for questions, and then I'll explain in more depth, with quotes from scientific papers, some ways in which food can affect mood and cognitive function.

Where relevant I will include references to metabolic fragilities, or differences, found in many people on the spectrum, and which make us more susceptible/vulnerable to certain foods, dietary deficiencies, etc, but I would like to make it clear that my presentation is about the links between diet and mental health, not about diet and autism.

I will stop after each section so that you can ask questions about anything you haven't understood, or which needs clarifying.

I will then explore the implications of these effects, and what can be done about them, after which you can if you wish ask questions until it is time for the break.

1) How much do you know about diet and mental health?

A great deal? A fair amount? A little? Very little or nothing?

2) How many here already know that diet affects your mental health, (mood and cognitive functioning), have made changes to your diet in consequence, and seen improvements?

3) How many here believe that diet affects your mental health, (mood and cognitive functioning), have made changes to your diet in consequence, but seen no improvement, are still struggling? …

4) How many here already know, as a result of accidental or deliberate exclusion-fasts/dieting, or tests, that diet affects your mental health, but have not yet made any changes, because you are not sure how to start, or don't seem able to? Discuss …

5) How many here think that it's possible that diet has an effect on your mental health, but have done nothing about it because you feel "well", or well enough? …

6) How many think that diet affects some people's mental health but not your own?

7) And how many think it is a heap of crap? …

8) Those of you who think, or know, that diet is a factor in your mental health; what was it that made you consider it?

G.I. symptoms
Tests
Read about it; seemed to fit
Accidental food-exclusion, because of holiday, or illness, had an effect on you
Other

There are many ways in which diet can and does affect mood and cognitive functioning; certain foods more than others. Certain foods have predominantly positive effects, eg. oily fish, green vegetables, and organ meats, and others, particularly the carbohydrates and certain proteins, have predominantly negative ones. And some groups of people are not just more aware of, but also more susceptible to, these effects.

A mistake I made for several years was thinking that I could find a diet which would have no effect on me at all. I became almost obsessed with finding the "zero diet", one which would have no discernable effect on me, on my mental health, and of course I failed, because food is part of our environment, which as most autists know, by painful experience, has an effect on us. 100% "independence", or freedom, from the effects of food and the rest of our environment, is impossible while you are alive. Took me a while to figure out, and accept, that one.

Food is one of the most powerful environmental factors because not only does it come into direct contact with one of our largest and most sensitive, surfaces, that of the gastro-intestinal system, all 300 square meters of it, (our skin is only 2 meters squared), with a Nervous System all to itself, the Enteric system, but because that surface is semi-permeable, food penetrates and becomes part of, our body. Eating is one of the most intimate acts of all.

Interestingly one of the most popular, and powerful, portrayals of "eating" in art and culture is the horror film. Vampires, werewolves, zombies and aliens make a speciality of enslaving, destroying, and using people by "eating" them, and programming them to "eat". Eating is even more scary, or emotionally loaded, than sex, and until very recently we didn't even show people doing it, much anyway, unless it was representing sex (ironically), "or" if the humans had already been transformed into something less than, or non,-human.

eg. John Hurt's character in the film "Alien", who eats more in one scene than you usually see anyone eat in a whole film, and it turns out to be because he is harbouring an alien.

Even the couple of exceptions to this tendency, that I know of; " Babette's Feast" and "Chocolat", definitely not horror films, but which concentrate on food and its effects, present it as transformative, perhaps dangerous, certainly powerful.

How many here experience difficulties with food; are repelled by it, feel consumed by it, resentful of it, unable to control their eating, etc? I think that many of our problems with food are the result of the move towards the post-paleolithic-diet, which accompanied, or may even have been partly responsible for, the Neolithic Revolution, and the almost completely new experience of daily food as something which "transformed" life for the worse.

Archeological research has shown that as soon as humans began eating a diet made up principally of cultivated grains/cereals and pulses their health declined dramatically. Bones show evidence of osteoporosis, dental decay, stunted growth, and other degenerative aswell as infectious diseases, long before there were urban environments in existence to explain these with other factors.

I believe that the post-paleolithic diet puts pressures on the human body to which it is not adapted.

For example, the sweetened stewed fruit, cooked carrot puree, or soft custard that is often spooned into infants at four months as part of weaning, triggers the production of large amounts of insulin which in turn commands the body to "store" the fatty acids that are essential for normal nerve-cell/synaptic growth, cell-wall construction, repair and maintenance, etc, for hard times ahead, "rather" than making them available for use now.

In paleolithic times "sugar" meant fruit, and summer, or thereabouts. Insulin production, (except in response to the "sugar", lactose, in mother's milk, when its production is mediated by food opioid peptides in the milk), was a seasonal affair. Suddenly, with the introduction of cereals to our diets less than 12,000 years ago, we started to call on our pancreas three times a day, all year round. And our bodies cried out for the fats we weren't getting access to anymore. We began to crave food in a way we had never done before.

And then there are auto-immune reaction to foods, most commonly gluten, (in wheat and some other cereals), corn, soya, eggs, and dairy. It is becoming increasingly clear that, although there is a genetic component to this sort of reaction, the full-blown auto-immune response to food, especially certain dietary proteins, is probably triggered by a range of environmental factors, among them a deficiency in the immuno-modulator Vitamin D, (in sunlight and fish oils), and a fragile gut-to-blood barrier, (cell membranes again, thus a possible connection with high-carbohydrate/sugar diet in infancy).

And finally, vitamin and mineral deficiencies, (for example zinc, in fish, meat, shellfish, and eggs), play a role in mental health too, and there is some evidence to suggest that a diet high in carbohydrates increases our need for several of them, including vitamin C.

The mental and physical health problems which can be caused by diet include anxiety/panic attacks, tearfulness, depression, manic-depression/mood disorders, irritability/bad temper, hyperactivity/over-excitability, compulsion to self harm or lash out at objects and other people, cravings for certain foods, eating-disorders, dizzy spells, floating sensations, feelings of alienation/disconnection/unreality, general fatigue/lethargy/exhaustion, disturbed sleep cycles, insomnia, "drugged" sleep, learning disorders, dyslexia, stuttering, poor concentration, poor memory, unsteadiness/bouts of clumsiness, confusion, blackouts, hallucinations/delusions, psychosis/schizophrenia, autoimmune diseases, (of the pancreas, as in diabetes; of the skin as in dermatitis herpetiformis, of the thyroid, pituitary gland, bones and joints, the liver, muscles, and the nerves and CNS as in ataxia and peripheral neuropathy, etc), headaches, neuralgia, hearing loss, tinnitus, hypoglycaemia, weight gain/loss, frequent bacterial and viral infections, candida, hair-loss, premature whitening of hair.

And that is only a selection. I have included a longer list in the handout, and even that is not complete, any more than this presentation is, however much I would like it to be. I have decided to concentrate on just two of the ways in which food can affect mood and cognitive function:

1) Immune-system mediated : food intolerance, particularly to gluten, and "sickness behaviour".

Research suggests that an occasional exclusion diet or fast, (ie. eliminating common offenders for between 5 days and a month), in order to detect food intolerances, which may be lifelong, or acute and caused by illness or other environmental stress, would be of benefit to a significant percentage of the population.

2) Carbohydrates, (both the starchy sort, bread, potatoes, rice, corn, etc, and the "simpler" sugars, such as fructose), and the effect of chronic/frequent insulin production on lipid metabolism, (essential fatty acids etc and the nerve-cells and cell membranes etc that they used for, etc).

Provides support for the hypothesis that a paleolithic or low-carbohydrate diet would be of benefit to a sizeable minority of the population, (and explains why food-combining or the Hay Diet approach may be helpful for many people).

Any questions?

… … …

1) Immune-system mediated: ie. food intolerance, and "sickness behaviour":

The first book I ever read on the subject of diet and mental health was Keith Mumby's "The Food Allergy Plan". It inspired me to try my first ever exclusion-diet, or fast, and the results were so dramatic that although I have often abandoned its principles, out of confusion, lack of support, over-confidence, etc, I have never stopped believing in the connection between food and my state of mind. This belief is summed up by the title of another book on the subject, which was famous in its time, 1976, and is still in print; "Not All in the Mind" by Dr. Richard Mackarness.

Dr. Richard Mackarness was an English doctor born in 1916, who worked as a general practitioner for many years before moving into hospital psychiatry. In 1958 he went to the States to promote his book, "Eat Fat and Grow Slim", and met Theron Randolph, an American "clinical ecologist" who was using diet to treat mental illness in a clinic there. Mackarness was so impressed and inspired by the amazing recoveries he saw, that on returning to England he began using the same principles first in hospital and then in a clinic he set up especially for the purpose. "Not All in the Mind" took him 17 years to write, and was one of the first books, in the modern world, to describe the link between diet, (specifically food intolerance, or sensitivity), and mental health.

The book opens with a quote from Foster Kennedy of Cornell University, 1936:

"Surely the time has come to put away the notion that psychiatry deals just with mind disease … only in Wonderland can we find the grin without the cat".

Dr. Mackarness writes: "The idea that allergy or intolerance to certain foods can cause illness is not new. Centuries before the word allergy was invented it was known that one man's meat could be another man's poison, and the phenomenon is mentioned in the writings of Hippocrates. But it was not until around 1925 that some doctors began to suspect that day-in day-out exposure to certain common foods might be causing chronic illness on a wide scale. It is easy to accept as allergic the rash which appears when a susceptible person eats shellfish or strawberries, but harder to recognise that the bread, milk, or eggs eaten every day may be causing bouts of catarrh, headache, and depression".

The book includes case after case of both chronic and acute illness, mental and physical, cured by food intolerance. The first one, which I will quote at length because it is a perfect example of how diet can affect mental health, concerns a woman who had been variously diagnosed as suffering from "schizophrenia, schizo-affective psychosis, pre-senile dementia, temporal lobe epilepsy, neurotic depression, and anxiety hysteria". I quote:

"At eleven o'clock on Wednesday morning 23 May 1973 Joanna sat in the doctor's lounge of Park Prewett Hospital, her eyes fixed on the floor, too anxious and depressed to say a word. She was being presented at the weekly clinical case conference of the hospital, which is the psychiatric division of the Basingstoke and District General Hospital.

After introductory remarks by the consultant in charge, the registrar or the assistant psychiatrist gives the case history, backed up by reports from the social worker, occupational therapist and clinical psychologist. The audience asks questions, and then the patient is brought in and presented – quite an ordeal for the patient as a rule, though the manic, hysterical, or psychopathic ones seem to enjoy it.Joanna was so tense and nervous that Dr. Lyon let her go back to her ward after less than two minutes.

Joanna's first attack had come in October 1967, after the birth of her third child, when she had become irritable, tense, depressed, unable to feed the baby and occasionally violent towards the two older children. She had been treated for this attack by ECT. At that time she weighed 11 stone, but by now, in 1973, she was over 14 stone. In the interval she had been admitted to Park Prewett Hospital 13 times, often compulsorily because the various psychiatrists called by her GP to see her at home had judged her to be a danger to her children and herself.

In her most disturbed phases she would slash her forearms with any nearby sharp object, not with any suicidal intent, but as a way of relieving, if only temporarily, the unbearable tension and irritability mounting inside her. On one occasion Joanna had knocked her three-year old son unconscious, and on another had thrown her older daughter through a closed window, luckily on the ground floor. Her three children had never shown any resentment towards their mother for their ill-treatment, seeming to realise that she could not help herself and loved them in spite of her repeated violence and neglect.

The hospital social worker who visited Joanna at home reported that the baby was scarcely ever taken out of its pram and its nappy seldom changed. Time after time it was almost decided to take the children into care, but the extraordinary resilience and contentedness of the boy and the two little girls made it seem better to leave them at home. When Joanna was asked at the case conference her ambitions in life, she replied, "To have good health, to go home, to be happy."

After Joanna had left the room with the nurse, Dr Lyon asked the meeting for their opinions. Almost without exception leucotomy was recommended. Repeated stays in the Psychiatric Intensive Care Unit aswell as every known combination of psychotropic drugs and several courses of ECT had had failed to effect any improvement at all. But leucotomy would mean that the three children would have to be taken into care. In this desperate situation I felt nothing could be lost by suggesting that Joanna might be a particularly severe case of food allergy, or intolerance, and asked to be allowed to make an attempt at rehabilitation through diet.

The following letter from Dr. Lyon to her GP, written after Joanna had gone home, summarises the result: "… In May 1973 Joanna was extremely tense, and quite unable to talk about her problems. Her only resort was to inflict injury upon herself, or to rock persistently like a baby. Under the influence of valium she was able to describe her strong feelings of guilt and unworthiness. She was shown at a case conference with a view to considering a leucotomy. It was suggested by Dr. Mackarness that her symptoms could be due to food allergy.

To enquire into this possibility we set up an experiment in which she ate nothing for five days, after which she was given test doses of specified foodstuffs. The fast resulted in a very marked improvement in her condition, and the tests showed extreme reactions to some foods but not to others. As a further test a trial was undertaken on a double-blind basis. … Her condition improved so drastically that we were able to discharge her home on no medication at all. I must admit that such a remarkable response has been a surprise to me. It would be difficult to say that it was due to anything but the dietary changes, especially in view of the double-blind trial."

Three months later Joanna's GP sent me this report:"Since her discharge from hospital in July 1973 Joanna has made a remarkable improvement. She is happy, gay, euphoric, sometimes almost hypomanic in her enthusiastic enjoyment of life, (which is something I experienced after my first experiments in exclusion dieting too). When she eats the "wrong" foods, (something almost everybody does either deliberately or accidentally in the first years of exclusion, because it can be hard to stick to, and "wrong" foods can also crop up in the most unlikely places), she rapidly becomes sullen, morose, apathetic, and withdrawn, and on one occasion hallucinated, seeing a herd of deer in a public park."

Dr. Mackarness remarks; “Deliberate dietary lapses, in the face of certain knowledge that they will bring on a return of mental symptoms, suggest an addictive element in food intolerance, food itself, or both”. This is very common, so common in fact that a fairly reliable sign of food intolerance is somone having to eat a certain food on a frequent, and regular basis. Someone intolerant to eggs for instance may need to have one every morning for breakfast, and feel somewhat less than human until they do, in the same way as an alcoholic has to have their hair-of-the-dog to start the day.

Any food that you need to eat at least once a day, especially if you feel insecure unless you know that you can get to that particular food at any time, may be something that you are intolerant of/sensitive to. I have only just this last week realised, as a direct result of research I came across while preparing this presentation, how much the fruit juice, (apple or grape), with water, that I have been drinking every morning, and through the day, for years now, is not the healthy habit that I have been successfully pretending it is. And how this sugar intolerance accounts for my need to have something to drink available at all times.

The foods which people appear to be most addicted to, however severe the symptoms of intolerance, are gluten, in bread, etc; casein, in dairy, and sugar, (both in starchy carbohydrates and in simple sugars like fructose). It is possible that the food opioid peptides present in casein and gluten, and no other foods, (apart from spinach oddly enough … Popeye !), have something to do with the addiction to bread and cheese, etc, and a weakened glucose metabolism may account for the addiction to carbohydrates, of which more later.

Since the 1970s’, when Mackarness was writing, more and more research has been done into the effects of diet on mental and physical health. For instance, on the subject of gluten intolerance, or sensitivity, there are now hundreds, even thousands, of studies, showing how immune-system reactivity to gliadins, (a part of gluten; in wheat and rye and barley, and many processed-foods nowadays), antibodies to which are found in at least 10 % of the population, can cause a variety of symptoms, both physical and mental, from auto-immune thyroid disorder, and depression, to peripheral neuropathy and ataxia.

An overview of gluten intolerance, from Dr. Kaslow’s site, listed in my handout.

The Celiac Disease of Mental Illness (from a lecture James V. Croxton, M.A. summer 2002)

Professor F. C. Dohan of the University of Pennsylvania was the first researcher to use this concept, beginning in the late 1960’s. He quoted from earlier researchers in his article published in The Biological Basis of Schizophrenia (Hemmings, ed; MTP Press; London, 1980). “Celiac disease may present with psychiatric symptoms, which, in association with other symptoms, may be of diagnostic help... Kaser (1961) described celiac children as showing definite symptoms in all cases. The children are conspicuously quiet, turned, inward, often weepy, often discontented or surly and apparently lack all joy in living. They can take on negativistic and schizoid characteristics and may execute ceaseless stereotyped movements. Paulley wrote in 1959: many (adult celiacs) showed extreme obsessional neuroses, suffering delusions, frequently believing they had cancer. Paranoid ideas *were frequent and many were considered psychotic or near psychotic”*.

In the 1960’s and 70’s it was thought that there were only about five infants out of 10,000 born with this strongly genetic disorder. The idea that that very low frequency could account for many of the large number of schizophrenics in the general population did not appear reasonable.

So the “celiac model” for explaining the development of schizophrenia did not catch on. The incidence of this disease has changed, however, and estimates now are stated to be as high as 1 in 100-250 in the American population. [in fact it is now known that the gliadin antibodies responsible for gluten sensitivity are present in almost 10% of the population].

A different factor in the celiac model emerged in the late 1990’s based on a new appreciation of the role of glial cells in the brain - those cells which make up about one-half of the brain’s mass. Before the last decade the glia were characterized as “support cell” with no clear functions. It is now understood that glia are capable of being activated as immune system agents, and engage in “signaling” activity (sending “messages” to each other and perhaps even to neurons).

Recent successes with two kinds of therapy provide some indirect support for the connection of celiac disease with mental illness. When troublesome proteins, especially alpha-gliadin in gluten and casein in milk are avoided, marked improvement has been reported by a number of individuals with these brain biochemistry disorders. The other therapy is to use essential fatty acids (emphasizing Omega 3, “cold-water fish” oils), because of the importance of phospho-lipid metabolism in regulating immune-system activity and neurological functions.
Many adult celiacs who have not been diagnosed and are not following a strict gluten-free diet have some of the same symptoms as persons diagnosed with schizophrenia and other mental, psychological, or emotional disorders.

Because gluten enteropathy is, in part, an immune system disorder originating in the wall of the small intestine, any amount of gluten from wheat, rye, barley, and oats keeps the immune system activated, which in turn may result in “spreading” of symptoms. It is hypothesized that organ systems not apparently involved during childhood become involved as the child ages. What began in the gut seems to move through the body, affecting lung function, the skin, and even the brain. Again, evidence to support such a theory is based on the effect of gluten avoidance – less mucus and bronchial symptoms, clearer skin, improved cognition, stabilization of mood, etc.

Since the fats and oils we eat become both structural and functional components of the “barrier” membranes in our bodies, such as the cell membranes, gut wall and the blood-brain barrier, another result of lipid malabsorption, [and impaired lipid-metabolism as a result of the high levels of insulin and leptin produced to deal with diets increasingly high in carbohydrates, and whose function is to store fats away rather than make them available for use] could be a less-reliable blood-brain barrier, [among other things].

Another factor is related to the concept “cerebral allergy.” It became increasingly apparent in the 1990s that there are immune system defenses in the brain. Experiments show that microglia can be stimulated to “change roles” and produce a cascade of cytokines, which produce, maintain and increase the immune-system’s inflammation response.

The cerebral allergy concept proposes that brain tissue is subject to “local inflammation” and that this causes unusual or abnormal symptoms. The “allergens” could be proteins in foods such as alpha-gliadin in wheat, volatile gases such as fumes of toluene, certain chemicals in perfumes or cosmetics, and so on. The symptoms could be very diverse: unusual behaviors (paralleling symptoms of toxic psychosis), altered motivations, sudden emotional upsets, etc.

In this hypothesis, celiac disease could be a specific kind of cerebral allergy, with or without ongoing disruption in gut tissue, and increasingly intense and diverse symptoms involving depression, paranoia, hallucinations, etc.

From an informal survey of about 20 people with gluten related sensitivity, >90% reported improvement from a gluten-free diet. All spoke of delayed learning prior to a gluten free diet either in themselves or their children. Some of the physiological, cognitive, and emotional symptoms they reported with dietary avoidance of gluten included:

Improved ability to learn Improved concentration No more meds for depression problems No more avoidance of meeting people Partial, and expected-full recovery of ataxia problems (inability to coordinate muscle movements) Improved gross motor skills (was delayed in some cases) Improved physical growth (was smaller than expected) Went from bottom of class to the top of his class after 3 months on diet Found a "hunger" for learning after avoiding gluten Improved mood with less “crossness” and “crankiness” Improved development to catch up with peers Improved intellect with definite increases in intelligence Grade point average went from 2.5 to 3.9 Came alive academically Improved ability to meet daily challenges Improved speed of learning ("quicker" in her studies) Lots of stories about coming out of withdrawn state socially to an outgoing one -- running for student council, more motivated in doing well and meeting people Increased well-being and better brain chemistry No more "brain fog" Improved in reading (“noticeable”) Improved temperaments in children

Before going gluten-free, students had the following difficulties/complaints:
Daydreaming in school
Difficulty in finishing sentences and finding words
Speech delay
Delays in walking and talking
Delayed puberty including menarche
Vitamin deficiencies
Non-epileptic seizures
Arthritis and osteopenia
Short term and long term memory was not good
Many reports of struggles with school but score high in intelligence
Misdiagnosis of fibromyalgia
Visual and auditory delusions
Anxiety problems, tummy aches
Temporary dyslexia

1. K. Horvath, MD, PhD, et al; Gastroenterology, April 1996: “First Epidemiological Study of Gluten Intolerance in the United States”
2. Etty Benveniste, PhD.; American Journal of Physiology 263, 1992: “Inflammatory Cytokines within the central nervous system: sources, function, and mechanism of action”

Marios Hadjivassiliou and Richard Grünewald
Practical Neurology, 2004, 4, 124–126

Neurological manifestations of gluten sensitivity are a scientific fact, not a theological issue. Whilst the debate continues, we owe it to our patients to screen them effectively for gluten

sensitivity with the simple widely available antigliadin antibody test so that we do not in the meantime deprive them of a harmless but potentially effective treatment.

Gluten sensitivity as a neurological illness 2007
M Hadjivassiliou, R A Grünewald, G A B Davies-Jones

It has taken nearly 2000 years to appreciate that a common dietary protein introduced to the human diet relatively late in evolutionary terms (some 10 000 years ago), can produce human disease not only of the gut but also the skin and the nervous system. The protean neurological manifestations of gluten sensitivity can occur without gut involvement and neurologists must therefore become familiar with the common neurological presentations and means of diagnosis of this disease.

In 1961 Taylor published an immunological study of CD. In his paper he commented that " . . .an obstacle to the acceptance of the immunological theory of causation has been the lack of satisfactory demonstration of antibodies to the protein concerned". He went on to demonstrate the presence of circulating antibodies against gliadin (antigliadin antibodies), the protein responsible for CD. This provided further evidence that CD was immunologically mediated and that the immune response is not confined to the mucosa of the small bowel. Antigliadin antibodies became a useful screening tool for the diagnosis of CD.

In 1966, Marks *et al* demonstrated an enteropathy in nine of 12 patients with dermatitis herpetiformis, an itchy vesicular skin rash mainly occurring over the extensor aspect of the elbows and knees. The enteropathy had a striking similarity to that seen in CD. It was later shown that the enteropathy and the skin rash were gluten dependent but skin involvement could occur even without histological evidence of gut involvement. This was the first evidence that the gut may not be the sole protagonist in this disease.

In 1966 Cooke published a landmark paper on 16 patients with neurological disorders associated with adult CD. A striking feature was the loss of Purkinje cells with atrophy and gliosis of the cerebellum.

Systematic screening of 143 patients with "idiopathic sporadic ataxia" showed that 41% had gluten sensitivity as defined by the presence of circulating antigliadin antibodies. Alhough the ataxia tends to be slowly progressive, in some cases it can take a very rapid course with the development of cerebellar atrophy within a year of the onset of the illness .Up to 40% of patients also have a sensorimotor axonal peripheral neuropathy that can often be subclinical.

Peripheral neuropathy is the second commonest manifestation of gluten sensitivity. Prospective screening of 101 patients with idiopathic peripheral neuropathy has shown the prevalence of gluten sensitivity to be 40%. The commonest type of peripheral neuropathy we encountered is sensorimotor axonal (26) followed by mononeuropathy multiplex (15), pure motor neuropathy (10), small fibre neuropathy (four) and mixed axonal and demyelinating (two). The neuropathy is usually chronic and of gradual progression. Patients with a pure motor neuropathy may progress to involvement of sensory fibres.

We have recently identified a subgroup of patients with gluten sensitivity who complained of episodic severe headache often with transient neurological deficit and extensive white matter abnormalities on MRI. Some of them also had ataxia or neuropathy. Their headache resolved with the introduction of a gluten free diet though the MRI abnormalities persisted at least for

the short follow up period. We have also found a higher incidence of gluten sensitivity in patients with systemic vasculitis and neurological involvement, perhaps reflecting the autoimmune nature of gluten sensitivity. There is a well known association of CD with other autoimmune diseases (for example, diabetes, thyroid disease). Some researchers think that prolonged exposure to gluten in a gluten sensitive person may be the trigger for the development of other autoimmune disease.

Where there is intestinal mucosal damage in coeliac disease it is the result of both humoral and T cell mediated inflammation. Inflammation is not, however, confined to the gut, as activated HLA restricted gliadin specific T cells and antigliadin antibodies are found systemically. Antigliadin antibodies are also found in the CSF, primarily in the white matter of the cerebellum. There was also marked but patchy Purkinje cell loss. We have also found antibodies against Purkinje cells in patients with gluten ataxia. Our research suggests that IgG antigliadin antibodies cross react with epitopes on Purkinje cells from human cerebellum.

Gluten sensitivity is best defined as a state of heightened immunological responsiveness in genetically susceptible people. ... which does not imply bowel involvement. That gluten sensitivity is regarded as principally a disease of the small bowel is a historical misconception. Early diagnosis and removal of the trigger factor by the introduction of gluten-free diet is a promising therapeutic intervention. IgG antigliadin antibodies should be part of the routine investigation of all patients with neurological dysfunction of obscure etiology.

Prevalence and clinical presentation of subclinical/silent celiac disease in adults : An analysis on a 12-year observation

TURSI Antonio; GIORGETTI Gianmarco; BRANDIMARTE Giovanni, et al.

In recent years, an increased incidence of subclinical/silent celiac disease has been reported. Here we describe the prevalence and the clinical presentation of subclinical/silent celiac disease in 252 consecutive diagnosed celiac patients. Methodology: From 1988 to 1999 we diagnosed 252 celiac patients (74M and 178F, mean age: 27.9 yrs; range: 15-65 yrs, F/M ratio: 2.4). 144 patients were referred to us due to gastrointestinal symptoms, while 108 were referred to us from other specialists due to unexplained or unresponsive disease.

All patients underwent both total immunoglobulin A and antigliadin antibodys antiendomysium antibody and evaluation, followed by gastrointestinal endoscopy with duodenal histological examination. Results: 144 (57.14%) patients showed classic celiac symptoms, and 108 (42.86%) patient showed subclinical/silent celiac disease, respectively.

The most frequent extraintestinal marker of subclinical celiac disease were iron-deficiency anemia (27.77%), alopecia and dermatitis berpetiformis (11.36%), osteoporosis (6.81%) and recurrent aphtous stomatitis (5.68%), while first-degree relatives (30%), Basedow's disease (25%) and insulin-dependent diabetes (20%) were the most frequent in silent celiac disease.

Conclusions: This study confirms the extremely polymorphic nature of this condition that can affect several organs and apparatus without gastrointestinal symptoms. However, a more precise description of subclinical/silent celiac disease can only emerge from screening studies on general populations.

Silent celiac disease: exploring the iceberg in the school-aged population

Cilleruelo Pascual ML, Román Riechmann E, et al

Epidemiological studies have shown a high prevalence of silent celiac disease (CD) among unselected pediatric populations and a low ratio of diagnosed to undiagnosed CD. OBJECTIVES: To quantify the prevalence of silent CD, to assess the clinical features of subclinical CD and to determine the total prevalence of CD (silent plus symptomatic cases). METHODS: We determined total serum IgA, IgA antiendomysial antibodies (EMA) and IgG antigliadin antibodies (IgG AGA), if IgA deficiency was found, in schoolchildren aged 10-12 years from health district IX in Madrid. RESULTS: A total of 3,378 schoolchildren (47.8 % of the eligible population) were studied. Fifteen were EMA-positive and one child with IgA deficiency was IgG AGA-positive. CD was confirmed by intestinal biopsy in 12 children, representing a prevalence of undiagnosed CD of 1/281. Of these 12 children, 7 showed clinical features of CD. The most frequent symptom was iron-deficiency, followed by recurrent aphthous stomatitis and mild malnutrition. Before the start of this study, CD had been diagnosed in seven children from the same population, which would increase the total prevalence of the disease to 1/220 with an estimated ratio of diagnosed to undiagnosed CD of 1 to 3.5. CONCLUSIONS: We confirm the high prevalence of silent celiac disease among the school-aged population. Greater awareness of the minor symptoms of CD would reduce the number of patients with undiagnosed CD.

The immunology of gluten sensitivity beyond the intestinal tract

Aristo Vojdani, Ph.D., M.T.1*; Thomas O'Bryan, D.C., C.C.N., D.A.C.B.N.2

Gluten sensitivity, celiac disease (CD) and gluten-sensitive enteropathy are terms that have been used synonymously to refer to a disease process affecting the small bowel and characterized by gastrointestinal symptoms and malabsorption. However, since 1966 scientific evidence has been accumulated demonstrating that gluten sensitivity can exist even in the absence of enteropathy. For example, patients with dermatitis herpetiformis and presentation of blistering skin do not have any gastrointestinal symptoms but have elevated gliadin antibody in the blood which improves on a gluten-free diet. Additionally, associations of CD with other organs such as the central and peripheral nervous systems also go as far back as 1966. However, until recently, this phenomenon of immune reaction against neural tissue, in particular the cerebellum, was attributed to vitamin deficiencies and not to immunological pathogenesis. During the past five years, based on overwhelming evidence of immune pathogenesis involving organs other than gut and skin, many scientists have begun to re-evaluate the notion that gluten sensitivity is solely a disease of the gut. Other organs suspected of involvement include: the joint, the heart, thyroid, bone, the brain cerebellum and the neuronal synapsins which are summarized below. Although it is believed that the prevalence of CD is one in one hundred, for every symptomatic patient with CD there are eight patients with CD with no GI symptom. In addition 10% of the apparently healthy population have significant elevation in gliadin antibody but no obvious classic disease manifestations. In our laboratory, when the blood of these individuals is tested against different tissue antigens (joint, myosin, endothelial cell, bone antigens, myelin basic protein, cerebellar and synapsin peptides) more than 90% of them exhibit elevation in IgG, IgM and IgA antibodies against one or all these organ-specific antigens.

A3. Association between gluten sensitivity and neuroautoimmunity

During the past two decades, gluten sensitivity and CD has been recognized as a multisystem autoimmune disorder. A growing body of distinct neurologic conditions such as cerebellar ataxia, epilepsy, myoclonic ataxia, chronic neuropathies, and dementia have been reported. However, recent studies suggest that the variability of neurologic disorders that occur in gluten sensitivity is broader than previously reported and includes “softer” and more common neurological disorders, such as chronic headache, depression, developmental delay, hypotonia, and learning disorders or ADHD.

The evidence for gluten ataxia as a disease entity is now overwhelming.The disease is characterized by ataxia, the presence of anti-gliadin antibodies, the HLA haplotype (DQ2, DQ8) asociated with gluten sensitivity, the presence of anti-Purkinje cell antibodies, the presence of high levels of the interferon-g-inducible chemokine CXCL10 and often oligoclonal bands in the cerebrospinal fluid (CSF) and the presence of inflamamtory pathology of the cerebellum at postmortem. Perhaps even more compelling is the evidence of a clinical response in the form of improvement of ataxia after a gluten-free diet, even in the absence of an enteropathy. This was demonstrated in the largest control study ever to be published indicating the relationship between gluten, cerebellar antibody and the presence of ataxia.

What is the pathogenesis of neurological dysfunction in gluten sensitivity? In the sera of patients with gluten ataxia there is evidence of additional antibodies targeting Purkinje-cell epitopes, (cerebellar peptides).

A4. Binding of anti-gliadin antibody to neuronal synapsin.

Synapsin is a neuronal phosphoprotein involved in the regulation of neurotransmitter release. Celiac disease is also characterized by systemic manifestations that contribute to a complex clinical presentation. Neurologic deficits, including axonal neuropathy and cerebellar ataxia, are among the most common extraintestinal symptoms associated with celiac disease which were discussed earlier.

[Based on these neurological manifestations of gluten sensitivity, a different study looked into the cross-reactivity of anti-gliadin humoral immune response with neural tissue.31 It was shown that both human and animal anti-gliadin antibodies can cross-react with synapsin I, a cytosolic phosphoprotein found in most neurons of the central and peripheral nervous systems. The anti-gliadin antibodies bound to both isomers of synapsin I, a and b, which have very similar amino acid sequences. In the human serum samples, antibody to synapsin I was detected in several patients with gluten sensitivity, while control specimens without anti-gliadin antibody did not exhibit significant anti-synapsin antibody reactivity. The patient data also clearly demonstrated that anti-gliadin antibody levels do not necessarily correlate with antisynapsin antibody reactivity and that only certain subsets of anti-gliadin antibodies crossreact with synapsin I. Because of the large number and heterogeneous nature of gliadins, as well as the high diversity of wheat phenotypes, the anti-gliadin immune response is likely to involve a sizeable repertoire of antigenic determinants. Therefore, varying degrees of cross-reactivity to synapsin I can be expected in different patients with gluten sensitivity. Such differences in the anti-gliadin antibody cross-reactivity in different patients may reveal clues

about the potential pathogenic role of the antibody and its association with specific extra-intestinal complications. Although pathogenic antibodies typically target antigens in the extracellular matrix or on the cell surface, there is evidence that antibodies to intracellular antigens can also cause disease. As synapsin I is associated with synaptic vesicles, it might be similarly targeted by antibodies taken up from the extracellular compartment. Therefore, it is conceivable that, in some patients with gluten sensitivity, the anti-gliadin antibody response would affect synapsin I activity, thus interfering with neurotransmitter release and resulting in neurologic dysfunction. Immune cross-reactivity may also lead to tissue damage through T cell-mediated mechanisms. Among the celiac patients in this recent study, anti-synapsin antibodies were present in subjects with neurologic disease, as well as those without. This implies that, like other autoimmune disorders, antibody reactivity is only one piece of the puzzle in the pathogenic mechanism of the neurologic complications of celiac disease. Therefore, the potential pathogenic role of antisynapsin immune cross-reactivity in the neuropathy or CNS manifestations is likely to depend on a number of additional factors, including the type and fine specificity of the immune response, local integrity of the blood-nerve or blood-brain barrier, and presence of proinflammatory factors.]

Key concepts and clinical implications:
· Antibody against gliadin from patients with gluten sensitivity reacts with myelin basic protein, neurofilaments, and cerebellar peptides.
· Antibody against gliadin from patients with gluten sensitivity reacts with neural protein called synapsin I.
· Presence of anti-synapsin antibody in some patients with gluten sensitivity can affect synapsin I activity, interfere with neurotransmitter release, and result in neurologic dysfunction.
· Patients with abnormal levels of neurotransmitter, and signs and symptoms of neurological disorders should be tested for neuroimmunology of gluten sensitivity, celiac disease, and associated autoantibodies, including neural cell antibodies.

I have concentrated on gluten intolerance because it is one of the most common, most researched, and apparently most devastating, of the food sensitivities, but it is possible to be seriously intolerant of almost any food; eg. casein in dairy, sugar, soya, corn, bacon, yeast, potatoes, onions, and eggs aswell as carbohydrates in general.

A food-intolerance is more often than not invisible. You very likely would not know that you had one, unless you go on an exclusion diet, (or fast), to expose it, because regularly eating a food tends to disguise its “real” effect, until it has exhausted your body’s adaptive capabilities, and you experience a kind of slow or sudden breakdown, (physical and/or mental).

There are a couple of reasons why people on the spectrum may be more likely than most people to find a gluten-free diet useful; a very large, recent, study by Eaton et al, (listed in my handout), showed that children of mothers with celiac disease are three times more likely to be autist than children of mothers without an auto-immune disease. (eg. Avignon meet: eight autists; one celiac, one with family history of celiac, and one with gluten intolerance)

This suggests that gluten-intolerance, or sensitivity, may be more common among autists, indicating that a gf diet is more likely to be useful for someone on the spectrum than in the population at large. And there are several studies which show that autists have higher levels of gliadin (the offending bit of gluten), and other anti-bodies, (to various dietary proteins aswell as bacterial endotoxins/lipopoylysaccharides), than the general population. I have listed one, by Vojdani, in my handout, but here is another:

"Higher Plasma Concentration of Food-Specific Antibodies in Persons With Autistic Disorder in Comparison to Their Siblings"

Vladimir Trajkovski Aleksandar Petlichkovski et al. Institute of Immunobiology and Human Genetics, Faculty of Medicine, University Ss. Kiril and Metodij, Skopje

Specific IgA, IgG, and IgE antibodies to food antigens in 35 participants with autistic disorder and 21 of their siblings in the Republic of Macedonia were examined. Statistically significant higher plasma concentration of IgA antibodies against alpha-lactalbumin, beta-lactoglobulin, casein, and gliadin were found in the children with autistic disorder. Plasma concentrations of IgG antibodies against alpha-lactalbumin, beta-lactoglobulin, and casein in participants with autistic disorder were significantly higher. IgE-specific antibodies (alpha-lactalbumin, beta-lactoglobulin, casein, and gluten), as well as plasma concentration of total IgE, also were statistically significantly higher in the participants with autistic disorder. Gender differences were found for select IgA, IgG, and IgE (but not for total IgE) food-specific antibodies (kU/L) in the participants with autistic disorder and their siblings".

But anyone can have a food intolerance. Anyone at all. …

Someone suffering from a food intolerance produces inflammatory cytokines every time they eat that food, and research has now found a link between immune-system activity, (especially the inflammatory cytokines), and depression, brain-fog, confusion, and other cognitive dysfunction. Anyone with an auto-immune system disease for example, (whether of the thyroid, bones and joints, skin, respiratory system, the pancreas, or pituitary gland, aswell as gastro-intestinal), produces more inflammatory-cytokines.

It is probably the explanation which Mackarness, Randolph, and the other researchers into food-intolerance, in the first 60 years of the last century, were looking for.

Any questions?

Cravings?
Favourite food?
Breakfast now?
Breakfast as a child?
What foods/meals do yoy remember from childhood?

SICKNESS BEHAVIOUR: http://biopsychiatry.com/immunesystem/index.html
Source: New Scientist Date: 16 June 2001 A Mind Under Siege by Phyllida Brown

Could an overactive immune system be the trigger for some people's life-threatening depression?

A FIFTY-year-old woman living in Japan is infected with a potentially fatal virus, hepatitis C. Doctors bombard her body with a powerful drug to boost her immune response. The drug beats back the virus, but has horrific side effects. She becomes inexplicably moody, rapidly sinking into a depression so savage that the woman douses herself in oil and sets herself alight. Fortunately, her suicide attempt fails and she recovers fully. But the woman's terrifying experience is not unique.

Over the past few years, there's been a steady trickle of bizarre reports of people becoming suicidal after taking alpha interferon and interleukin-2, two popular immune-boosting drugs. Hundreds of others have become seriously depressed. But the terrible suicidal urges are turning out to have a silver lining. They are awakening interest in one of the most promising new avenues in depression research since Prozac.

Most of us associate depression with being run down and having poor immunity to infections. The startling side effects of the immune-boosting drugs turn that notion on its head. They suggest that some people who are depressed may actually be suffering from an over-heated immune system, and that damping down inflammation could offer a brand new way to treat routine clinical depression. It's a theory that recasts depression--one of the great plagues of our time--as a chronic inflammatory disease like rheumatoid arthritis.

In an inflammatory attack, immune cells rev each other up by pumping out substances known as inflammatory cytokines. Drugs like interferon are simply artificial versions of these substances. That's why they boost immunity so well--and why, according to the new "immune theory" of depression, they also induce such dark moods in some patients.

"At the beginning I was very reluctant to get into this question because depression is such a can of worms," says neurobiologist Robert Dantzer of France's national medical research agency INSERM at the University of Bordeaux 2. "But when we saw the way these drugs affected patients, it made me sure that it was worth it."

The first inkling of a connection between mood and inflammation came around 1990. Michael Maes, a psychiatrist now at the University of Maastricht in the Netherlands, was investigating claims that depressed people are unusually vulnerable to infections and cancer, a theory that could be explained by a lacklustre immune system. But when Maes looked at immune cells from depressed people such as natural-killer cells, monocytes and macrophages, he found instead that the cells were more active than normal, and spewed out more inflammatory cytokines. "We had expected to find just the opposite," admits Maes.

The surprise results did fit in with some other vague hints that depression and inflammation are entwined. Depressed people tend to have slightly raised temperatures, which suggests that they are suffering from some chronic inflammation. They are also three times as likely to die

of heart disease--often caused by arteriosclerosis, itself an inflammatory condition of the linings of arteries.

Still, Maes's results languished in obscurity, being contradicted by other studies almost as often as they were confirmed--until, that is, Dantzer decided to take a second look at some old rat studies he had done in the late 1980s.

When you inject rats with parts of bacterial cell walls called lipopolysaccharides, their temperatures rise, their sleep patterns change, they become less sociable and stop eating. And it isn't the bits of bacteria that trigger this so-called "sickness behaviour", but the immune response to those bits. An injection of the cytokine interleukin-1 (IL-1), which marauding macrophages produce when they meet bacteria, makes the animals behave in exactly the same way. In other words, the rat studies showed that inflammatory cytokines directly influence behaviour.

"Sickness behaviour is like fear--it is a state that makes the animal reorganise its priorities." Just as the sight of a predator makes animals release hormones that drive the "flight-or-fight" response, infection triggers the release of cytokines, which make the animal rest and conserve its resources to fight the infection.

At first, researchers were puzzled at how the cytokines could affect behaviour. How could great big molecules like IL-1 get across the barrier that protects the brain from all the potentially dangerous chemicals sloshing around in the blood?

It turned out they didn't need to. The exact mechanism is still a mystery, but it seems that another set of far smaller signalling molecules, such as nitric oxide and prostaglandins, tell the brain that a part of the body is inflamed. Once in the inner sanctum, these molecules instruct the brain's glial cells to make their own supplies of inflammatory cytokines. These cytokines act on receptors in areas of the brain such as the hippocampus, the cerebellum, and--crucially--the hypothalamus, which is involved in regulating both mood and temperature. "The brain builds a representation of the disease in the body," says Dantzer.

By the mid-1990s, Dantzer was wondering whether sickness behaviour wasn't in some way comparable with depression, and, if so, whether antidepressants could prevent sickness behaviour. After all, some of the symptoms are similar to depression-- disturbed sleep, for instance, or a lack of interest in food or sex.

Dantzer's results were dramatic. He injected rats repeatedly with the antidepressant tianeptine, before treating them with pieces of bacterial wall or IL-1 (Psychopharmacology, vol 24, p 50). The antidepressant sharply reduced the sickness behaviour created by the treatments. What's more, the rats' brains made much smaller amounts of their own IL-1, and much larger amounts of another cytokine, IL-10, which soothes inflammation. "It looks like some antidepressant drugs are working like some anti-inflammatory agents," concludes Dantzer.

The next piece in the puzzle was to take a closer look at those people who get depressed while taking immune-boosting drugs. From about 1996 onwards, study after study showed that about one-third of patients taking cytokine drugs get depressed, sometimes seriously. The trouble is that they also have life-threatening illnesses such as cancer or hepatitis so it's hardly surprising they should feel despair.

To get around that problem, Dantzer's PhD student Lucile Capuron assessed the psychological state of patients with advanced skin or kidney cancers before and during treatment with interleukin-2 (IL-2) or alpha interferon. The results, which appeared last year in the Journal of Clinical Oncology, left Dantzer in no doubt.

Both drugs appeared to induce depression, but there were also some clear differences. The patients on alpha interferon developed symptoms after a few weeks, while people on IL-2 took only a few days. More subtly, the patients taking alpha interferon tended to have slower reaction times, while patients on IL-2 were more likely to have memory problems. To Danzter, such differences are a telling sign that the depression is a specific side effect of the drugs, rather than simply general despair at being ill. (The New England Journal of Medicine, vol 343, p 1594).

Interferons, serotonin and neurotoxicity
by Menkes DB, MacDonald JA Dunedin School of Medicine, New Zealand.
Psychol Med 2000

Interferons are a class of cytokines profoundly affecting immune function. Several interferons are now synthesized and used clinically, notably for viral diseases and cancer. In addition to their desired immune effects, interferons cause a number of toxicities, including prominent effects on the nervous system.This literature review focused on the incidence of depression associated with interferon treatment. Possible neurochemical mechanisms and remedial strategies were also considered. * Interferon treatment, particularly with the alpha subtype, is unquestionably linked with depression, but the strength of association is uncertain because of erratic ascertainment and pretreatment co-morbidity. A likely pathogenic mechanism has been described, involving interferon suppression of serotonin synthesis. Controlled treatment trials of interferon-induced depression are not yet available. * Neurotoxicity substantially limits the use of interferons. At least some of the risk of depression appears to derive from their anti-serotonergic effects, consistent with the large body of evidence pointing to a general link between serotonin and affective illness. Vigilant detection and aggressive treatment of depression is necessary to optimize interferon treatment of many patients.

Cytokines and the Brain: Implications for Clinical Psychiatry
by Kronfol Z, Remick DG
Am J Psychiatry 2000 May 1;157(5):683-694

This article reviews recent developments in cytokine biology that are relevant to clinical psychiatry.METHOD: The authors reviewed English-language literature of the last 15 years that pertains to the biology of cytokines with emphasis on central nervous system effects in general and psychiatric disorders in particular.RESULTS: Growing evidence suggests that, in addition to providing communication between immune cells, specific cytokines play a role in signaling the brain to produce neurochemical, neuroendocrine, neuroimmune, and behavioral changes. This signaling may be part of a generalized, comprehensive mechanism to mobilize resources in the face of physical and/or psychological stress and to maintain homeostasis. The clinical implications of these findings are far-reaching and include a possible role for cytokines in the pathophysiology of specific psychiatric disorders such as major depression, schizophrenia, and Alzheimer's disease. The effects of cytokines in the central nervous system may provide a possible mechanism for the "sickness behavior" of patients with severe infection or cancer, as well as for the neuropsychiatric adverse effects of treatment with interferons and interleukins.CONCLUSIONS: A better understanding of the role of cytokines

in various brain activities will enhance knowledge of specific psychobiological mechanisms in health and disease and provide opportunities for novel treatment interventions.

Further evidence for the depressive effects of cytokines: Anhedonia and neurochemical changes:
by Anisman H, Kokkinidis L, Merali Z. Institute of Neuroscience,
Life Science Research Building, Carleton University, Ottawa, ON, Canada
Brain Behav Immun 2002 Oct;16(5):544-

Although human studies have emphasized a role for IL-2 in depressive illness, limited attention has been devoted to the behavioral and neurochemical effects of this cytokine in animal studies. The present review assesses the behavioral effects of IL-2 in rodents, in counterpoint to the effects of interleukin-1beta (IL-1beta), necrosis factor-alpha (TNF-alpha) and endotoxin challenge. Unlike IL-1beta, systemic IL-2 provokes modest effects on hypothalamic-pituitary-adrenal (HPA) functioning, and does not provoke marked signs of illness or anxiety. In some respects, however, IL-2 elicits effects reminiscent of traditional stressors, including anhedonia (diminished pleasure gained from otherwise rewarding stimuli). Additionally, when chronically administered, IL-2 may impact on cognitive processes, including spatial working memory. While IL-2 may induce depressive-like symptoms, the available data are sparse, have hardly considered the impact of chronic cytokine treatment, only assessed behavior in a narrow range of tests, and it remains to be established whether the effects of IL-2 are modifiable by antidepressant treatments. Finally, as the effects of IL-2 on CNS processes vary in a biphasic fashion, and may also engender neurotoxic effects, further analyses are necessary to discern under what conditions this cytokine provokes depressive-like behavioral outcomes.

The vagus nerve mediates behavioural depression, but not fever, in response to peripheral immune signals; a functional anatomical analysis
by Konsman JP, Luheshi GN, Bluthe RM, Dantzer R
INSERM U394, Neurobiologie Integrative, Institut Francois Magendie,

Cytokines act on the brain to induce fever and behavioural depression after infection. Although several mechanisms of cytokine-to-brain communication have been proposed, their physiological significance is unclear. We propose that behavioural depression is mediated by the vagus nerve activating limbic structures, while fever would primarily be due to humoral mechanisms affecting the preoptic area, including interleukin-6 (IL-6) action on the organum vasculosum of the laminae terminalis (OVLT) and induction of prostaglandins. This study assessed the effects of subdiaphragmatic vagotomy in rats on fever, behavioural depression, as measured by the social interaction test, and Fos expression in the brain. These responses were compared with induction of the prostaglandin-producing enzyme cyclooxygenase-2 and the transcription factor Stat3 that translocates after binding of IL-6. Vagotomy blocked behavioural depression after intraperitoneal injection of recombinant rat IL-1beta (25 microg/kg) or lipopolysaccharide (250 microg/kg; LPS) and prevented Fos expression in limbic structures and ventromedial preoptic area, but not in the OVLT. Fever was not affected by vagotomy, but associated with translocation of Stat3 in the OVLT and cyclooxygenase-2 induction around blood vessels. These results indicate that the recently proposed vagal link between the immune system and the brain activates limbic structures to induce behavioural depression after abdominal inflammation. Although the vagus might play a role in fever in response to low doses of LPS by activating the ventromedial preoptic area, it is likely to be

overridden during more severe infection by action of circulating IL-6 on the OVLT or prostaglandins induced along blood vessels of the preoptic area.

Cytokine-induced changes in mood and behaviour: implications for 'depression due to a general medical condition', immunotherapy and antidepressive treatment
by Pollak Y, Yirmiya R. Department of Psychology, The Hebrew University of Jerusalem, Israel.

Several lines of evidence indicate that cytokine-mediated communication pathways between the immune system and the brain are involved in the pathophysiology of depression: (1) Depression is highly prevalent in various medical conditions, including infectious, autoimmune and neurodegenerative diseases. This clinical association cannot be attributed solely to psychological distress, and it probably reflects direct activation of illness-induced physiological processes. (2) Experiments in humans and in animals demonstrate that exposure to cytokines induces depressive-like mood and behavioural alterations. (3) Cytokine immunotherapy in cancer and hepatitis patients elicits a major depressive episode in a large percentage of the patients. (4) Several types of depression that are not directly associated with a physical disease (e.g. major depression, melancholia, dysthymia) were also associated with cytokine hypersecretion. (5) Antidepressant drugs possess anti-inflammatory characteristics, which may partly account for their therapeutic effect. Congruently, antidepressants were found to reverse cytokine-induced major depression in humans and depressive-like behaviours in animals. (6) Cytokines affect brain systems that were implicated in the aetiology of depression, including the hypothalamus-pituitary-adrenal axis and monoaminergic systems. These conclusions strongly suggest that during medical conditions elevated levels of cytokines directly contribute to the induction of depression. Therefore, illness-associated depression should not be underestimated (in terms of prevalence and severity), and should be treated with antidepressant drugs, which may act on the specific physiological mechanisms of this disorder.

The immune system, depression and the action of antidepressants
by Leonard BE. Pharmacology Department, National University of Ireland, Galway.
Prog Neuropsychopharmacol Biol Psychiatry 2001

The hypothalamic-pituitary-adrenal axis (HPA) is activated by both external and internal stressors which result in the hypersecretion of adrenal glucocorticoids. In major depression the prolonged elevation of the glucocorticoid concentration leads to a desensitisation of the central glucocorticoid receptors and probably those receptors located on macrophages. These changes may account for the observation that many aspects of cellular immunity are activated in depression (for example, the increased release of pro-inflammatory cytokines from activated macrophages in the periphery and brain, and the increased release of acute phase proteins from the liver) even though other aspects of immunity (for example, natural killer cell activity and T-cell replication) are depressed. Evidence is provided that the consequences of the hypersecretion of glucocorticoids and pro-inflammatory cytokines result in the malfunctioning of noradrenergic and serotonergic neurotransmission in the brain, changes which are reflected in the major symptoms of depression. Support for this view is provided by observations of the effects of some of these cytokines in non-depressed individuals being treated with pro-inflammatory and related cytokines for cancer. This has led to the hypothesis that depression is a form of sickness behaviour which forms the basis of the macrophage theory of depression. The review concludes with a discussion of the role of antidepressants in attenuating the adverse effects of glucocorticoids and pro-inflammatory cytokines on central

neurotransmission. Although the precise mechanisms whereby antidepressants these changes is uncertain, there is evidence that they reduce the release of pro-inflammatory cytokines from activated macrophages and thereby facilitate the feedback inhibition of the HPA axis; this results in a reduction in the release of glucocorticoids from the adrenal glands. In addition, many antidepressants have been shown to increase the release of endogenous cytokine antagonists such as interleukin-1 receptor antagonist and interleukin-10. Evidence is also presented to show that different classes of antidepressants act as cyclooxygenase inhibitors which, by lowering the concentration of inflammatory prostaglandins in the brain, reduce the detrimental impact of the inflammatory changes on neurotransmitter function. An advantage of the macrophage hypothesis is that it extends the biogenic amine hypothesis of depression to take account of changes in the endocrine and immune systems which also play a crucial role in the aetiology of depression.

Neurotransmitter changes by interferon-alpha and therapeutic implications
by Schaefer M, Schwaiger M, Pich M, Lieb K, Heinz A. Department of Psychiatry and Psychotherapy, Charite - University Medicine Berlin, Germany. *Pharmacopsychiatry*. 2003

Interferon alpha (IFN-alpha) is a cytokine that is widely used for the treatment of chronic viral infection or malignant disorders. During treatment with IFN-alpha, severe neuropsychiatric syndromes may occur such as depression with suicidal ideation, paranoid psychoses or confusional states. The neurobiological correlates of these side effects are widely unknown. Besides induction of other cytokines and hormonal changes, IFN-alpha has been shown to modulate the opioid, serotonin, dopamine and glutamate neurotransmitter system. Positive therapeutic effects of antidepressants such as selective serotonin-reuptake-inhibitors (SSRI) or of opioid receptor antagonists support the hypothesis that neurotransmitter changes play an important role in the development of IFN-alpha associated neuropsychiatric side effects. We review recent research about IFN-associated neurotransmitter changes in the central nervous system and discuss treatment strategies.

Activation of the inflammatory response system:
A new look at the etiopathogenesis of major depression
by van West D, Maes M. Clinical Research Center for Mental Health (CRC-MH), Antwerp, Belgium. *Neuroendocrinol Lett* 1999;20(1-2):11-17

Major depression is accompanied by various direct and indirect indicators of a moderate activation of the inflammatory response system (IRS). Increased production of proinflammatory cytokines, such as interleukin-1 (IL-1), IL-6 and interferon (IFNgamma), may play a crucial role in the immune and acute phase response in depression. Lower serum zinc and changes in the erythron are indirect indicators of IRS activation in depression. The reciprocal relationships between IRS activation and hypothalamic-pituitary-adrenal (HPA)-axis hyperactivity, alterations in HP thyroid (HPT)-axis function and the availability of tryptophan to the brain led us to hypothesize that these neuroendocrine changes in depression are indicators of IRS activation and that a combined dysregulation of the IRS, the turnover of serotonin (5-HT) and the HPA-axis is an integral component of depression. The IRS activation model of depression provides an explanation for the psycho-social (external stress) as well as organic (internal stress) etiology of major depression. Antidepressive treatments with various antidepressive agents, including SSRIs, tricyclic and heterocyclic antidepressants, have in vivo and in vitro negative immunoregulatory effects, suggesting that their antidepressant efficacy may be attributed, in part, to their immune effects.

The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans
by Wichers M, Maes M. Department of Psychiatry and Neuropsychology, Maastricht University, 6200 MD Maastricht, The Netherlands.
Int J Neuropsychopharmacol 2002 Dec;5(4):375-88

Administration of the cytokines interferon-alpha and interleukin-2 is used for the treatment of various disorders, such as hepatitis C and various forms of cancer. The most serious side-effects are symptoms associated with depression, including fatigue, increased sleepiness, irritability, loss of appetite as well as cognitive changes. However, great differences exist in the prevalence of the development of depressive symptoms across studies. Differences in doses and duration of therapy may be sources of variation as well as individual differences of patients, such as a history of psychiatric illness. In addition, sensitization effects may contribute to differential responses of patients to the administration of cytokines. In animals administration of pro-inflammatory cytokines induces a pattern of behavioural alterations called 'sickness behaviour' which resembles the vegetative symptoms of depression in humans. Changes in serotonin (5-HT) receptors and in levels of 5-HT and its precursor tryptophan in depressed people support a role for 5-HT in the development of depression. In addition, evidence exists for a dysregulation of the noradrenergic system and a hyperactive hypothalamic-pituitary-adrenal (HPA) axis in depression. Some mechanisms exist which make it possible for cytokines to cross the blood-brain barrier. Pro-inflammatory cytokines such as IL-1beta, IFN-alpha, IFN-gamma and TNF-alpha affect the 5-HT metabolism directly and/or indirectly by stimulating the enzyme indoleamine 2,3-dioxygenase which leads to a peripheral depletion of tryptophan. IL-1, IL-2 and TNF-alpha influence noradrenergic activity and IL-1, IL-6 and TNF-alpha are found to be potent stimulators of the HPA axis. Altogether, administration of cytokines may induce alterations in the brain resembling those found in depressed patients, which leads to the hypothesis that cytokines induce depression by their influence on the 5-HT, noradrenergic and HPA system.

http://www.hedweb.com/bgcharlton/depression.html

Bruce G Charlton MD Department of Psychology University of Newcastle upon Tyne
Medical Hypotheses "The malaise theory of depression: Major depressive disorder is sickness behavior and antidepressants are analgesic"

Introduction - deficiencies in current understanding

The diagnostic syndrome of major depressive disorder (MDD) is traditionally classified as an 'affective disorder' - that is, as an illness *primarily* of mood. But the nature of the depressive mood state remains elusive. Many MDD patients deny that they feel sad or miserable, and the diagnostic schemas (such as DSM-IV and ICD-10) specify a variety of 'characteristic' mood states such as hopelessness, 'anhedonia' (reduced or absent capacity to experience pleasure), anxiety, distress and irritability. This variety of dissimilar moods in MDD seems excessively imprecise to constitute a primarily 'affective' diagnostic category.

It has proved difficult to conceptualize how 'sadness' could constitute an illness, and even harder to imagine how ingesting a simple chemical could specifically alleviate sadness and restore normal 'euthymic' mood. The conceptual inadequacy transmits itself to patients who cannot understand the rationale for drug (or ECT) treatment, except to suppose that these are euphoriant 'happy pills'. But antidepressants are not euphoriants in the manner of amphetamine or cocaine, nor do they intoxicate, nor are antidepressants considered to be addictive or

dependence-inducing and recreational abuse is very rare (Healy, 1996). What antidepressants do not do is therefore well established - yet their positive psychological action remains obscure.

MDD is sickness behavior

The evolutionary function of the behavioral pattern of major depressive disorder can be elucidated by a comparison with other animals. MDD turns out to be near-identical with the adaptive state termed sickness *behavior* (SB) in animals. Sickness behavior was first described by a veterinarian as a physiological and psychological adaptation to acute infective and inflammatory illness in many mammalian species (Hart, 1988). The characteristic pattern of sickness behavior comprises pyrexia, fatigue, somnolence, psychomotor retardation, anhedonia (lack of ability to experience pleasures such as eating and sex) and impaired cognitive functioning (Kent *et al*, 1992). In other words the syndrome of SB is almost exactly the same as the standard diagnostic descriptions of MDD (Hickie & Lloyd, 1995; Yirmaya, 1997). The only apparent differences - somnolence and pyrexia - are explicable given that daytime somnolence typically leads to secondary insomnia with nocturnal sleep disruption, and that the presence of pyrexia has not yet been evaluated in MDD.

The evolved function of SB is to act as an energy-conserving, risk-minimizing, immune-enhancing state appropriate for a body mounting a short-term, all-out attack on an invading micro-organism (Hart, 1988; Kent *et al*, 1992).

Cytokines as mediating factors of sickness behavior

Mediating factors for the syndrome of MDD seem to involve hyper-activity of the immune system in response to 'non-self' antigenic challenge (for example, inflammation due to infection, carcinoma or 'autoimmune' disease). The chemical factors responsible for mediating sickness behavior appear to be the class of immune active agents known as *cytokines* (eg. interleukins and interferons (Hart, 1988; Kent *et al*, 1992; Hickie & Lloyd, 1995; Yirmaya, 1997). Indeed, SB is best considered as an integral and adaptive part of the pyrexial response; it is the behavioral change that assists in the generation and maintenance of raised body temperature, and produces a diminution of activity appropriate to immune activation.

Mood changes secondary to sickness behavior

Although animals demonstrate sickness behavior mediated by cytokines in the same way as humans, only conscious animals such as humans can suffer from the distinctive 'existential' state of depression, with feelings such as nihilism, worthlessness, guilt and suicidal ruminations. The state of malaise which prevails in sickness behavior interacts with memories of the past and anticipations of the future such that a demotivated, exhausted and profoundly dysphoric state of malaise fills and colors past, present, and the anticipations of future mental life.

Prolonged sickness behavior therefore creates a nihilistic mental state where life seems devoid of gratifying possibilities (ie. pessimism) because emotional feedback registers a physiological state that is locked-into sickness behavior, and unresponsive to the usual appetites (ie. a state of anhedonia). Another factor is that the sufferer from SB does not know that they are sick, and often interpret their lack of energy, lack of motivation, and poor concentration as a *moral* failure - leading to feeling of guilt and unworthiness. Given the nature of this subjective mental landscape, the high rate of suicide in MDD is unsurprising.

Traditionally (eg. in DSM-IV) it is supposed that depressed people complain of tiredness and aching limbs because they are miserable - whereas the malaise theory suggest that they are miserable because they are tired and have aching limbs. Eventually chronic misery imposes itself on incoming perceptions, these associations are learned, and the depressive cognitive style becomes habitual so it may persist even after resolution of the hyper-immune state that originally caused SB.

To emphasize the physical symptomatology of the depressive is more of a re-emphasis than a novel discovery. Most comprehensive textbooks of psychiatry or psychopathology describe a range of typical 'depressive' physical symptoms such as exhaustion, washed-out feelings, aching, heaviness, or pain in the head, trunk or limbs.

Antidepressants are analgesic

There is considerable evidence to support the idea that tricyclic antidepressants are analgesics when tested in both human and animal models (Lee & Spencer, 1977; Portenoy & Kanner, 1996; Xia *et al* 1996). Furthermore, tricyclics are increasingly used in the management of chronic pain, neurogenic pain, migraine, chronic fatigue, cancer pain, and arthritis (Panerai, 1991; Portenoy & Kanner, 1996; McDaniel *et al*, 1995; Holland *et al*, 1998) .I suggest that analgesia is not just a fortuitous side-effect of tricyclics, but the primary effect of any specifically 'antidepressant' drug. The analgesic effects of non-tricyclic classes of antidepressant are less clearcut - but there is some evidence that fluoxetine and phenelzine are also analgesic (Holland *et al*, 1998; Portenoy & Kanner, 1996).

The most striking aspect of the malaise theory of depression is that it is about the body and not the brain.

... … Any questions? … … …

PART II. Carbohydrates, (both the starchy sort, bread, potatoes, rice, corn, etc, and the "simpler" sugars, such as fructose), and the effect of chronic/frequent insulin production on lipid metabolism, (essential fatty acids etc and the nerve-cells and cell membranes etc that they used for, etc).

Earlier this year I posted a thread on Wrong Planet called "Starch, or the Decline and Fall of the Autistic Organism". I had been reading about and experimenting with the paleolithic, or low-to-no carbohydrate diet, and was feeling so well, so bursting with energy, (that's when I applied to do this presentation ;)), that I wondered if carbohydrates might be inherently stressful for autists.

I based my argument on a few metabolic differences particularly frequent in autists, our lower levels of starch and disaccharide digesting enzymes, and an immune-system hyper-reactivity to bacterial endotoxins, specifically lipopolysaccharides, (which are produced by the bacteria which proliferate in our guts in the presence of undigested sugars). This would create the kind of chronic, if low-level, cytokine-triggered inflammation, and "sickness behaviour", which I have already referred to.

I was just hypothesising, but it did seem to me that carbohydrates were perhaps responsible for more than "just" obesity, erratic blood-sugar levels, diabetes, vitamin B deficiency, and zinc depletion, (all of which, immediately or eventually, have effects on mental health; either mood or cognitive function or both).

Sometime after my thread had vanished into the oblivion that most threads on diet seem to vanish into, on WP, I found out that between 30% and 40% of people in Europe suffer from fructose malabsorption, (fructose is a simple sugar, or carbohydrate), which, in addition to encouraging the proliferation of pathogenic bacteria in the gut, (causing various G.I. symptoms), putting a heavy load on the liver, (non-alcoholic liver disease), also inhibits tryptophan absorption, thus lowering serotonin levels, which can lead to depression.

And then, this last couple of weeks, while scouring the internet for scientific papers on the connections between diet and mental health, I began to find evidence for a link between high-carbohydrate diets, glucose metabolism, insulin production, etc and disturbances in lipid metabolism.

The crucial role of lipids is demonstrated by the many neurological disorders, including schizophrenia, bipolar disorder, severe depression, alzheimers, cognitive impairment in the areas of attention, executive function, and memory, aswell as autism, that involve deregulated lipid metabolism.

D.F. Horrobin and C.N. Bennett Publ. in "Prostoglandins Leukostines etc" 1999

"In all of these conditions there is now evidence of impaired phospholipids metabolism, and impaired fatty-acid related transduction."

"Abnormalities of fatty-acid and membrane phospholipids metabolism play a part in a wide range of neurodevelopmental and psychiatric disorders".

Gordon Bell 2002 "Abnormal Fatty Acid Metabolism in Autism and Aspergers Syndrome"

Richardson A. J. and Ross M. A. "Fatty Acid Metabolism in Neurodevelopmental Disorders: a New Perspective on Associations Between ADHD, Dyslexia, Dyspraxia, and the Autistic Spectrum". … etc etc etc

I don't refer to these because I think that eating a zero or low carbohydrate diet could cure autism but simply because it is clear that our lipid metabolisms are particularly fragile, that lipids are a crucial part of cognitive functioning and mood, (aswell as a healthy immune system), and that alleviating pressure on, or even supporting the functioning of, this metabolic system is likely to have a beneficial effect on our mental health.

Cellular membranes are composed of phospholipids, cholesterol, and fatty-acids, and the Central Nervous System has the highest lipid concentration next to adipose tissue. Phospholipids have a central role in neuronal and synaptic growth and remodelling. Cholesterol is not only one of the most important regulators of lipid organisation, and a precursor for Vitamin D, but a deficiency of it is associated with depression, … and fatty-acids keep inflammatory cytokines under control, ie. they have an immuno-modulatory effect.

I started reading about insulin and glucose metabolism because of cholecystokinin, which induces tolerance to opioids, helps with protein and fat digestion, and affects sleep, sexual maturation, and memory, among other things. Insulin blunts/blocks the CCK response. I thought this was interesting. ;) … And I began to find things like this:

Insulin Inhibits Peroxisomal Fatty Acid Oxidisation in Isolated Rat Hepatocytes
By Frederick G Hamel and Robert G. Bennett et al. Publ. in Endocrine Journals 2001

“Insulin exerts control over a wide variety of cellular functions, including glucose, protein, and lipid metabolism. Although attention has focussed on glucose turnover, the primary metabolic derangement associated with diabetes may pertain as much to alterations in lipid metabolism as to glucose control.”

And this: Caren E. Smith, Katherine L. Tucker, et al. Published: May 2009

“Unfavorable lipoprotein profiles and impaired glucose metabolism are linked to cognitive decline, and all three conditions may decrease lifespan. Associations between apolipoprotein C3 (*APOC3*) gene polymorphisms and impaired lipid and glucose metabolism are well-established, but potential connections between *APOC3* polymorphisms, cognitive decline and diabetes deserve further attention.

Cognitive function is associated with favorable lipid and glucose profiles, and these phenotypic traits often coexist in very long-lived individuals. For example, plasma high density lipoprotein cholesterol (HDL-C) is positively correlated and triglycerides are negatively correlated with cognitive ability in centenarians, and unimpaired cognitive function is linked to reduced risk of death in elderly individuals.

Triglycerides were reported to be significantly higher for those with diabetes. Diabetes also increases the risk of cognitive impairment which is likely to be mediated, at least in part, through dysregulation of lipid metabolism and impaired vascular integrity. However, with the exception of inconclusive reports evaluating relationships between *APOC3* and Alzheimer's disease, the extent to which APOC3 is associated with cognitive impairment is largely unexplored.

Altered lipid metabolism, like altered glucose metabolism, has been associated both with APOC3 concentration and also with altered cognitive ability, however no relationship between the three of them has been established before now.

Results: Apolipoprotein 3 (APOC3) modulates triglyceride metabolism through inhibition of lipoprotein lipase, and is regulated by insulin, thus representing a potential mechanism by which glucose metabolism may affect lipid metabolism.

THIS: Xunde Xian and Tingting Liu. Journal of Neuroscience 2009 “Lipoprotein lipase is also expressed in the brain, with highest levels in the hippocampus … involved in cognitive function. Findings in mice indicate that LPL plays an important role in learning and memory function, possibly by influencing presynaptic function”.

And then this: http://www.jlr.org/cgi/reprint/M400486-JLR200v1.pdf

Lipid homeostasis and apolipoprotein E in the development and progression of Alzheimer disease

Roger M. Lane, MD* and Martin R. Farlow, MD. Publ. in Journal of Lipid Metabolism 2005

“Genetic disorders of amyloid production and metabolism may produce early-onset forms of Alzheimer’s disease (AD), but the most common form of the disease is

sporadic and late onset. Dietary factors may be important in the etiology of AD, with poly- and mono-unsaturated fatty acids and n-3 double bonds (in ω-3 essential fatty acids [EFAs]) conferring protection, and an excess of saturated fats or n-6 double bonds (in ω-6 EFAs) increasing the risk.

*****In addition, it has been proposed (Henderson S. T. 2004 Med. Hypotheses) that the inhibition of lipid metabolism by high carbohydrate diets may be the most detrimental aspect of modern diets. AD may be similar to obesity, coronary artery disease (CAD) and type II diabetes mellitus in being a consequence of the conflict between our Paleolithic genetic constitution and our current Neolithic diet.*****

Diet may interact with apolipoprotein E (apoE) isoforms, such as apoE4 which may also suppress lipid metabolism, to determine the risk and rate of sustained lipid autoperoxidation within cellular membranes and the effectiveness of membrane repair.

Diet, insulin signaling, membrane lipid composition, apoE genotype and levels, amyloid processing and trafficking, Aβ oligomer damage to lipid membranes, oxidative stress and intracellular neurofibrillary tangle (NFT) formation are interrelated by many mechanisms. ApoE4 is associated with elevated peripheral lipid levels, decreased cerebral glucose metabolism, increased glial activation and excitotoxicity resulting in greater inflammation and oxidative stress, less effective sequestration of heavy metals, and increased Aβ deposition and NFT formation in the brain prior to the onset of symptoms of dementia.

The hypothesis presented in this section is that diets high in carbohydrate, particularly those with a high glycemic index, and low in EFAs, particularly ω-3 long chain PUFAs, increase the risk for developing AD. While these diets may also increase the risk of vascular disease, the AD risk may be mediated through effects on lipid metabolism and neuronal membrane lipid composition that induce changes in glucose transport, neurotransmission, antioxidant defenses, inflammatory responses, cerebral blood flow, and cognitive functioning. These effects may be modulated by apoE isoform, such as apoE4 that, like a high carbohydrate diet, decreases lipoprotein lipase activity and inhibits delivery of free fatty acid to glia and to neurons.

A well-defined risk factor for late onset AD is possession of one or more alleles of the ε-4 variant of the apolipoprotein E (APOE) gene. The APOE ε4 allele frequencies are low in populations with long historical exposure to agriculture, suggesting that consumption of a high carbohydrate diet may have selected against APOE ε4 carriers.

Populations with the lowest frequencies of APOE ε4 include long time agriculturalists, such as Greeks (6.8%), Turks (7.9%), Mayans (8.9%) and Arabs living in northern Israel(4%), while populations with the highest frequencies include long time hunter-gatherers, such as African Pygmies (40.7%), Papuans (36.8%) and Inuits (21.4%). [NB. In Europe: Italy 10%; France 12%; Holland 17%; Denmark 17.5%; Finland 19%; Sweden 22%. And in most populations at least 20% carry at least one copy of the E4 allele] .

The APOE ε4 encoded protein (apoE4) and a high carbohydrate diet may both suppress lipid metabolism in a similar manner (5). APOE ε4 by itself increases the risk for early-onset

coronary artery disease (CAD), and in combination with a high carbohydrate diet, the risk of CAD, and perhaps also of AD, is greatly increased.

High carbohydrate diets elevate insulin levels, increase insulin and insulin growth factor signaling, decrease lipoprotein lipase activities, inhibit the uptake of free fatty acids by cells and increase the serum 'residence' time of triglyceride (TG) rich lipoproteins, such as chylomicrons and very low density lipoproteins (VLDL).

The rate of clearance of TG rich lipoproteins and the uptake of free fatty acids depends mainly on the activity of lipoprotein lipases and is strongly influenced by insulin signaling.

Similar to a high carbohydrate diet, the apoE4 protein increases TG rich lipoprotein residence time by inhibiting lipolysis. It does this by binding to TG rich lipoprotein more avidly than apoE2 or apoE3, displacing apolipoprotein C-II (apoC-II), which is required for maximal rates of lipoprotein lipase catalysis, and resulting in decreased lipoprotein lipase activity.

In the brain decreased lipoprotein lipase activity inhibits delivery of free fatty acid to glia and to neurons. Inefficient delivery of EFAs to neurons leads to inhibited function of glucose transporters. The hippocampus is especially vulnerable to glucose insufficiency. As apoE4 and high carbohydrate diets both inhibit lipid metabolism, this may explain the selection against the APOE ε4 allele in populations with a long historical exposure to agriculture. CAD is likely to have been the selective force as it generally occurs earlier than AD.

Elevation of glucose and insulin levels resulting from high carbohydrate consumption induce lipogenesis and hypertriglyceridemia. The APOE ε4 allele may not be inherently damaging, only in combination with a high carbohydrate diet, which is damaging in itself and is likely to be a major contributor to the high risk of CAD, and possibly AD, in modern populations with or without the APOE ε4 allele.

A high carbohydrate diet, similar to apoE4, suppresses lipid metabolism and reduces delivery of EFA to cells in the brain. Disturbances in lipid metabolism within the brain compromise the integrity of cell membranes decreasing the function of membrane proteins. Mild chronic elevation of insulin/insulin-like growth factor (IGF) signalling accelerates damage to cortical neurons. Potential consequences of a high carbohydrate diet include both AD and insulin resistance, which is associated with cognitive impairment and functional decline".

High carbohydrate diets and Alzheimer's disease. Publ. in Med Hypotheses 2004

By **Henderson ST**. Publ. in Med Hypotheses 2004
Institute for Behavioral Genetics, University of Colorado

"Alzheimer's disease (AD) is a common, progressive, neurodegenerative disease that primarily afflicts the elderly. A well-defined risk factor for late onset AD is possession of one or more alleles of the epsilon-4 variant (E4) of the apolipoprotein E gene. Meta-analysis of allele frequencies has found that E4 is rare in populations with long historical exposure to agriculture, suggesting that consumption of a high carbohydrate (HC) diet may have selected against E4 carriers. The apoE4 protein alters lipid metabolism in a manner similar to a HC diet, suggesting a common mechanism for the etiology of AD.

Evolutionarily discordant HC diets are proposed to be the primary cause of AD by two general mechanisms. (1) Disturbances in lipid metabolism within the central nervous system inhibits the function of membrane proteins such as glucose transporters and the amyloid precursor protein. (2) Prolonged excessive insulin/IGF signaling accelerates cellular damage in cerebral neurons. These two factors ultimately lead to the clinical and pathological course of AD.

This hypothesis also suggests several preventative and treatment strategies. A change in diet emphasizing decreasing dietary carbohydrates and increasing essential fatty acids (EFA) may effectively prevent AD. Interventions that restore lipid homeostasis may treat the disease, including drugs that increase fatty acid metabolism, EFA repletion therapy, and ketone body treatment"

… … …

What these papers are suggesting is that many humans are literally intolerant of carbohydrates; that for a large, very large, number of people carbohydrates may have a serious, in fact catastrophic, effect on lipid metabolism, and that this impacts on both neurological and immune-system functioning.

This carbohydrate-lipid conection might also explain why a lot of people find the "Hay" diet useful, because it involves eating carbohydrates separately from proteins, if not from all fats. Not only does it almost automatically limit the number of times a day that a person eats carbohydrates, which would reduce the number of times that insulin must be produced and the stress this puts on the glucose homeostatic system, but it would also make more dietary fats available to the body than when they are eaten with carbohydrate and stored immediately because of insulin production.

I include a last paper on the subject of low to no carbohydrate diets and their protective effect on neurological functioning.

"Neuroprotective and disease-modifying effects of the ketogenic, (no carbohydrate, high fat) diet"

By Gasior M, **Rogawski MA**, **Hartman AL**.
Epilepsy Research Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda

Publ. Behavioural Pharmacology 2006

The ketogenic diet has been in clinical use for over 80 years, primarily for the symptomatic treatment of epilepsy. A recent clinical study has raised the possibility that exposure to the ketogenic diet may confer long-lasting therapeutic benefits for patients with epilepsy. Moreover, there is evidence from uncontrolled clinical trials and studies in animal models that the ketogenic diet can provide symptomatic and disease-modifying activity in a broad range of neurodegenerative disorders including Alzheimer's disease and Parkinson's disease, and may also be protective in traumatic brain injury and stroke. These observations are supported by studies in animal models and isolated cells that show that ketone bodies, especially beta-hydroxybutyrate, confer neuroprotection against diverse types of cellular injury. This review summarizes the experimental, epidemiological and clinical evidence indicating that the

ketogenic diet could have beneficial effects in a broad range of brain disorders characterized by the death of neurons.

Interestingly, foods which are high in essential fatty acids are also high in zinc and Vitamin D; meat fat, egg yolk, and oily fish, like wild salmon and sardines. And they are definitely not carbohydrates so are allowed on the ketogenic diet.

Questions from audience (about the last section) … … and questions from me:

Who here has been diagnosed diabetic, or told that they are pre-diabetic?
Who knows that they suffer from hypo or hyperglycemia, that is to say wildly fluctuating blood sugar levels?
Who thinks that they may have a problem with sugar/carbohydrates?
Who here needs frequent and regular access to carbohydrates, esp. simple sugars?
Who starts the day with carbohydrate?
Who here needs frequent, regular, or even constant access to fluids, whether coffee and tea, juices, or just water?

… … …

CONCLUSION:

This presentation is just a taste of the myriad, complex, inter-connected ways in which diet can affect mental, and physical, health. I had intended to include more in my presentation; about gastrointestinal bacteria, systemic candida, the effects of soya and the cabbage family on the thyroid, aswell as vitamin and mineral deficiencies, (especially zinc, vitamin D, and vitamin B6) but I have the feeling that the information about food intolerance, (including the widespread one to carbohydrates), is not only almost more than enough to take in/process in one morning, but that it is the most important.

As Dr. Charlton said, “The most striking aspect of the malaise theory of depression is that it is about the body and not the brain”, and the man from Cornell 70 years ago, “Surely the time has come to put away the notion that psychiatry deals just with mind disease … only in Wonderland can we find the grin without the cat”.

That’s one of the things that I find most fascinating, even exciting, about all this; that what we perceive, our experience of the world, may be, as Dickens says in “The Christmas Carol”, “ … an undigested bit of beef, a blot of mustard, a crumb of cheese, a fragment of an underdone potato”.

I was told, by a member of the programme committee, that this subject, diet and mental health, was very “on topic”, relevant to this year’s theme of “Effective Living”. And yet I realised that for many people it could seem the opposite of that, because if diet has an effect on your mental health aren’t you even less in control of your life than you thought?

What on the face of it would seem to be a very simple statement; “Food has an effect on me, on my mental health, and so I need to choose carefully what I eat” is actually a surprisingly powerful paradox. Food has an effect on me, so I will choose the foods whose effects I prefer, or desire, but who, or what, is desiring, and choosing, if food has an effect on your perception, mood, understanding, etc?

Following an exclusion diet has been a bit like I imagine yoga being, except that instead of focussing on the experience of breathing, I have concentrated on the process of eating. I have become aware of the effect that food has on my experience of life, my choices and perceptions of things. And struggled with the question; where do "I" stop and where does my environment begin?

For a long time, years, I didn't even realise that this was what I was struggling with; I thought I was just having trouble keeping to my exclusion diet. I thought that the reason I felt so utterly crushed when the diet didn't seem to be working was because I hadn't been excluding the right things. I thought that if I got it right the diet would free me, make me independent of environmental influence and pressure, that I would find "me".

I was struggling with the sense of myself, my relationship with the world, and it has been an immense relief to understand and accept that "I" am not just "permeable", (as in "leaky gut" syndrome implies, with the drive to make oneself "less permeable" which frequently follows from that perspective), but fundamentally without boundaries, inseparably part of the universe, that its influences go through me, are me, all the time, just like food.

To conclude, ;) the best approach is simple; cut carbohydrates down or completely out, and eat more fish, (especially oily fish), eggs, and meat. Green vegetables; parsley, lettuce, green-beans, etc are probably a good idea too.

Niesche, from "Zarathustra":

"On the Despisers of the Body"

"The awakened and knowing say ; body am I entirely, and nothing else.

And soul is only a word for something about the body.

The body is a great reason, a plurality with one sense, a war and a peace, a herd with a shepherd.

An instrument of your body is also your "little" reason, which you call spirit, or mind, a little instrument, and a toy of your great reason.

Behind your thoughts and feelings there stands a mighty ruler, an unknown sage. In your body he dwells; he IS your body.

There is more reason in your body than in your best wisdom."

Good luck! ☺ ☺ ☺