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William R. Ware, PhD - Editor

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In this issue we review roughly where we stand at the end of 2014, especially in the context of chronic diseases associated with aging with emphasis on cancer, diabetes, cardiovascular disease and cognitive impairment and Alzheimer's disease. The only good news comes, not from the use of pharmaceuticals, but from alternative or integrative medicine including its important component, functional medicine. Functional medicine treats multiple causes and attempts to identify the complex interactions between the relevant components involved and recognizing a system with interconnections and multiple component causes. In the past few years, several important books have appeared that successfully apply functional medicine or multiple-cause and cause targeted medicine to major problems such as autism, multiple sclerosis and mental health problems. In addition, a recent study form UCLA discussed in this issue applies this same principle to successfully reversing mild cognitive impairment and early Alzheimer's disease. We now also have a therapy for slowing or partially reversing established Alzheimer's disease in coconut and MTC oil. The reversal of diabetes with diet discussed recently in IHN is an example of an intervention that dramatically changes a number of complex aspects of metabolism associated with the causes of diabetes and cures it. Presumably simultaneously, a number of chronic diseases such as cardiovascular disease, kidney disease, and various nerve disorders have been prevented, something that the standard glucose control medications have failed to achieve to any significant extent. Alternative therapies involving only a single intervention include the use of salvestrols for treating cancer. Aside from reversing diabetes, the only significant (large absolute risk reduction) approach to the prevention of cardiovascular disease involves simultaneously addressing four to seven critical risk factors, none of which are treated with drugs, and the key to success is to successfully address the whole set of risk factors.

Thus there has been considerable progress in the last few years, all unrelated to drug therapy. There is reason for optimism that new directions with merit are being recognized by respected medical researchers, but much justification also for deep concern. The interventions just described, aside from dealing with the risk factors of cardiovascular disease without drugs, will have a difficult road to acceptance much less regulatory approval. They are foreign to the way mainstream medicine functions today and the way medical students are taught to function tomorrow, a mindset based on narrow specialization, pharmacotherapy, and frequently the rapid process of diagnosis and then medication that address only symptoms or reduce biomarkers, many of which are not directly related to causation. Benefit is described in relative numbers, an inherently deceptive format, rather than absolute benefit which is rejected because the vast majority of therapies have very small absolute benefit and if this were emphasized, the practice of medicine would collapse. This is the current paradigm which controls how a significant part of modern medicine is practiced, and its influence powerful and all-encompassing with its dogma, its guidelines, its reliance on applying population results mindlessly to individuals, its career thought leaders from academia, the unwillingness of the regulatory agencies to rock the boat and the central driving power, the financial resources of Big Pharma. All of this does not bode well for a healthy old age, and the amazing statistics on the prevalence of chronic diseases in those over 65 discussed previously supports this grave concern.

Individuals who regard this state of affairs as not in their best interest are on their own. Fortunately, there are a growing number of recent books by practicing physicians that provide guidance in alternative approaches based on functional medicine that appear to hold great promise. They are listed at the end of this issue.

This issue also contains a review of the amazing therapeutic applications of curcumin. Presumably because of its powerful anti-inflammatory properties, it comes close to being a universal natural treatment encompassing a large number of disorders.

Wishing you and your family a HAPPY HOLIDAY SEASON and good health in the New Year,

William R. Ware, PhD, Editor

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YEAR-END 2014, WHERE DO WE STAND?

Over the years, IHN has attempted to keep readers up to date on advances in medicine that might impact their health and lives. The goal is stay healthy, have a good quality of life, age gracefully, and unless unrealistic expectations such as immortality exist, die quickly and peacefully. Simplistic? Perhaps. This is certainly not the story of most lives. The following provides a very brief summary of where we appear to stand in the context of this endeavour.

GENERAL APPROACH TO PREVENTION AND AVOIDING HARM

There should be little debate concerning the following. Eat a Mediterranean diet. Never drink or cook with tap water and preferably use only reverse osmosis water. For rural dwellers, use reverse osmosis on well water for drinking and cooking. Do not smoke at all or drink excessively. Exercise regularly. Detoxify with both supplements and a sauna (IHN Mar 2014). Use natural, toxin-free cleaning agents and personal care items. Attempt to maintain a toxin-free and chemical-free house by avoiding chemically treated furnishings. Avoid contact with commercial pesticides and herbicides. Supplement with a good multivitamin-mineral preparation. Pay attention to any move of fasting blood glucose above normal. Attempt to maintain weight as when a young and hopefully lean adult. Avoid all psychiatric drugs except in crisis situations and attempt to find solutions to mental health problems that do not involve pharmaceuticals. Attempt to minimize domestic and occupational psychological stress. Find a physician for primary care who practices integrative medicine if currently dissatisfied. Ideally, when asked at age 80 what drugs do you take, the answer should be none. Finally consider the remarkable incidence of cancer in pets. The dogs and cats are canaries in the mine. Another species of canary is represented by children. Consider the remarkable increase in a large number of cognitive and behavioral issues associated with childhood. The population percentage prevalences suggest something is terribly wrong.

SPECIFICS. THE BIG FOUR CHRONIC DISEASES OF AGING

Prevention and treatment of the chronic diseases of aging represent one of the greatest challenges to modern medicine. It is not for a lack of trying, but truly effective approaches have eluded researchers. The use of relative risk reductions has been very important in preventing public anxiety and discontent. If it became widely known that almost all are not going to be significantly helped by the current offerings, an inescapable conclusion based on absolute benefits seen in randomized trials and cohort follow-up

studies, there would be widespread alarm. However, knowledge of this current state of affairs should prompt informed individuals to seek approaches outside mainstream medicine that offer a justified expectation of greater success.

The following appear to meet an acceptable standard with properly collected anecdotal evidence coupled with strong biological plausibility based on published research, or limited clinical or other studies that provide strong evidence of benefit, again coupled with strong biological plausibility. Naturally, mainstream medicine would dispute the value of this approach out of respect for the edifice of evidence-based medicine with its large randomized controlled trials and thousands of meta-analyses, but if one is desperate, something has to give. These appear to be the first-choice candidates, and what may be the best available alternatives.

- **Cancer**. Salvestrols offer remarkable and at this point in time unique potential for targeted, site independent prevention and therapy with no side effects. (IHN May 2014, July/Aug 2013) The use of salvestrols in prevention of both primary cancer and metastatic cancer is theoretically very attractive, but there is no evidence yet aside from the durability of remission when progression and metastasis would have been expected.
- **Diabetes or prediabetes.** The Newcastle Diet or its variations appear capable of total reversal of both. (IHN Oct and Sep 2014, Nov 2013). It would be surprising if the total reversal of diabetes does not also prevent diabetes-related chronic diseases such as cardiovascular disease, kidney disease and various neurological problems. Prevention should start with preventing or treating prediabetes. This dietary approach presumably works well since if it reverses diabetes, it surely reverses prediabetes and thus prevents diabetes.
- **Cardiovascular disease.** Prevention is the main issue. Mediterranean diet, exercise, smoking avoidance and moderate alcohol consumption together appear to be the answer. Selected from mainstream advice because of large absolute effects, typically around 80%, but only when combined.
- **Cognitive problems and Alzheimer's disease**. Coconut oil (medium chain triglycerides) (IHN Sep 2012). See below for an account of a new approach that appears to reverse mild cognitive impairment and early Alzheimer's disease, another example of a reversal if not a cure, which does not use drugs but a combination of up to twelve interventions, i.e. functional medicine. While both treatment and prevention are issues, an intervention that reverses mild cognitive impairment presumably prevents Alzheimer's disease since it is the precursor.

The above approaches to four major threats we all face appear to offer remarkable benefit, even cures, which standard therapies cannot accomplish, and as well as prevention. A few years ago, none of these interventions or actions would have appeared in the above list. There are many other beneficial actions related to general health one can take involving lifestyle, social interactions, diet, and supplementation. Many have been discussed in IHN, back issues of which are available in the archives. However, interventions that offer very large absolute benefit should be the first choice. The medical literature has tens of thousands of peer-reviewed papers describing interventions that reduce risk, biomarkers or symptoms. Always ask how much benefit is found, in absolute terms. In almost all cases, absolute benefit is small or negligible and the results merely hypothesis generating but very useful in drug marketing.

CURCUMIN IN TREATMENT OF VARIOUS DISEASES

Curcumin is component of the famous Asian spice turmeric, which has been used for centuries and is an important ingredient in many ethnic diets. Is has probably received more scientific attention than any other natural product. If one puts the words curcumin or turmeric in the search engine of the US National Library of Medicine, the Google equivalent for the medical literature called PubMed, over 8000 citations appear. Many of these comprise experimental studies such as those with cell cultures or animals, mostly rodents. Unfortunately, there are a very limited number of clinical (human) studies. The reason is both simple and disturbing. Curcumin and the other so-called curcuminoids extracted from the turmeric root cannot be patented and thus there are limited financial resources available to support clinical trials, independent of the compelling nature of the experimental data. Nevertheless, a paper titled *Therapeutic*

Rolls of Curcumin: Lessons Learned from Clinical Trials by Gupta *et al* cites 65 references to completed and published trials as of sometime in 2012.[1] There are other similar reviews as well. In their totality, the experimental and clinical studies embrace a remarkable ensemble of disorders, which in itself is an interesting phenomenon.

One conclusion easily reached is that there are vast numbers of cell culture and animal studies suggesting that curcumin is indeed a remarkable substance with beneficial biochemical actions associated with numerous diseases. These benefits are seen in markers of inflammation, markers of altered pathways and changes in a variety of other biomarkers. In addition, numerous actual beneficial effects on animals serving as models for a number of human diseases have been observed. Evidence of clinical efficacy, even though limited, calls for examination since there may already be sufficient justification for curcumin's use in certain situations, especially since the evidence is strong that over a large dose range, it is relatively harmless. This subject will now be explored.

Clinical studies using curcumin present a challenge due to significant problems with absorption from the digestive system into the circulation, i.e. so-called bioavailability. Curcumin is hydrophobic and after oral administration of a simple extract, very little appears in the circulation. Some studies used preparations with enhanced bioavailability, others did not, but the amount of curcuminoids, the active ingredients, absorbed in generally unknown. Thus, while the observation in clinical studies of benefit has some significance, negative studies cannot be used to demonstrate absence of benefit. It is also important to realize that some positive studies may seriously underestimate the actual benefit due to low doses. In what follows, the results of clinical trials for a number of common disorders will be briefly discussed. Many of the clinical studies looked only at biomarker changes without assessing clinical benefit, and some were mostly concerned with safety and tolerability. In general, patient clinical improvement was the criterion for inclusion in this discussion, although for some, improvement in biomarkers can be highly significant. We will focus mostly on clinical studies where curcumin was the sole intervention. In what follows, unless otherwise indicated, the documentation is in the above mentioned review which is available free on the internet.[1]

Inflammatory Bowel Disease and Irritable Bowel Syndrome (IBS)

Two major types are ulcerative colitis and Crohn disease. In one study of Crohn disease treatment, four patients completed the protocol of 360 mg curcumin three times a day for a month and then four times a day for 2 months. A significant improvement in symptoms was observed which was accompanied by reductions in sedimentation rates and C-reactive protein (CRP), consistent with a decrease in inflammation,

In a randomized controlled study of 89 individuals with ulcerative colitis it was found that two grams of curcumin a day when added to standard drug therapy reduced the relapse rate to 4.65% vs. 20.5% in the placebo control. A recent study used 500 mg/day along with prednisone in a woman with a 17-year history of ulcerative colitis. Standard medications had failed. After one year on this regime she was off steroids, having normal bowel function was in remission and there was no colonoscopy evidence of ulceration. In a study of 102 individuals, the prevalence of IBS was reduced by 53 to 60 % with one or two doses of a turmeric extract, along with marked decrease in IBS symptoms.

Arthritis

A study involving 50 patients based on standard pain evaluation methods as well as measures of mobility and inflammation found that after 3 months on 200 mg/d of high-bioavailable curcumin (Meriva) there was a reduction in the pain measure by 58%, walking distance went from 76 to 332 meters, and significantly decreased CRP levels indicating reduced inflammation. A long-term (8-month) study by this group found similar results. Remarkable decreases were also observed in the use of painkillers.

A recent randomized, double-blind, placebo controlled six-week study involving 53 patients examined the therapeutic effect of curcumin on knee osteoarthritis.[2] Standard scores and indexes were used to evaluate outcomes. It was found that for patients assigned 150 mg/day of curcuminoids in 3 divided doses there was significant improvement in pain and physical function but not stiffness when compared to

the placebo group. No significant adverse effects were observed. It was concluded that curcuminoids are an effective and safe alternative therapy for this disorder.

Chronic Bacterial Prostatitis

This disorder is difficult to treat with antibiotics due to poor penetration of the drug into the prostate. A study looked at the improvement of antibiotic treatment by adding two preparations, one containing Saw Palmetto and Urticadioica, two natural substances commonly found in prostate health formulations plus a mixture of 200 mg of curcumin and 100 mg of quercetin. The antibiotic was prulifloxacin. One month after therapy, 89% of on the combination therapy had no symptoms, whereas only 27% in the antibiotic alone group were this fortunate. Six month after treatment, no patients in the combination group had recurrence, whereas for those "cured" by the antibiotic treatment alone, 2 had recurrence. This study did not allow the evaluation of the effectiveness of curcumin alone. Nevertheless, this is a simple variation of a standard therapy.

Diabetes

A recent double blind placebo controlled study examined the effect of 1.5 g/d of curcuminoids on the progression in prediabetics to actual diabetes. After 9-month follow-up, 16.4% of the subjects in the placebo group were diagnosed with type 2 diabetes whereas in the treatment group there was none. Treatment resulted in deceased insulin resistance and improved functioning of the pancreatic beta-cells. Small decreases occurred in fasting blood glucose and the 3-month average HbA1c. Another study found 300 mg/day of curcumin reduced markers of oxidative stress and inflammation in type 2 diabetics.

Diabetic or Lupus-Related Kidney Disease

Animal studies suggest that curcumin exerts beneficial effects on type 2 diabetic nephropathy (kidney disease), an adverse effect of the disease with terrible consequences. A randomized, double blind, placebo controlled trial involving type 2 diabetics with uncontrolled hyperglycemia and a serious deterioration of kidney function were treated over 2 months with three daily doses of turmeric containing 22 mg of curcumin.[3] Changes in urine protein levels were dramatic, going from 4300 to 2400 mg/24 hr in the treated group, but unchanged from 4700 mg/24 hr in the placebo group. Values above 500mg/24 hr are considered the threshold for the indication of ongoing kidney damage. Also two inflammation markers directly associated with this side effect of diabetes were significantly decreased. Even more dramatic changes in urine protein levels were seen in a study that also used turmeric with the same 22 mg curcumin per dose using the same dosing schedule. Levels decreased from a baseline of 950 to 260 in 3 months in the trial group.[4]

Obviously one can wonder what would have been the benefit if a dose of curcumin normally used in clinical trials had been employed and for a longer duration.

Cancer

The review by Gupta *et al* lists 20 clinical trials addressing issues of cancer. However, there were no trials that looked at remission or related measures suggesting a significant impact on progression. However, for colorectal cancer curcumin therapy reduced the number and size of polyps. It also reduced PSA in prostate cancer patients and was found to be efficacious against multiple myeloma.

Major Depression

A study recently published compared an antidepressant, (fluoxetine) with curcumin, each alone or in combination. Outcome was judged by depression scales which attempt to quantify the magnitude of the disorder. It was found over 6 weeks that all three intervention groups experienced similar effectiveness. Thus curcumin was as effective as the antidepressant alone but did not enhance its effectiveness. Unfortunately there was no placebo group since in such studies as these, the placebo effect can be very strong and suggest no real benefit from interventions.[5]

Wound Healing

Topical application of curcumin has been found in a number of studies to have a powerful modulating effect on wound healing. This subject has recently been reviewed.[6] Beneficial action is found at all phases of the healing process, i.e. inflammation, cell proliferation and finally remodelling associated with

contraction and fibroblast proliferation. The result is faster healing. Bioavailability is an issue and preparations such as curcumin creams have been found to work well and are readily available online.

Ophthalmology
Curcumin has been demonstrated to be beneficial in treating diabetic retinopathy, glaucoma, age-related macular degeneration, and dry-eye syndrome as well as chronic anterior uveitis (inflammation of the iris).[7]

Reduction of C-Reactive Protein
C-reactive protein (CRP) is a standard biomarker of inflammation. It is not uncommon that elevated levels are transitory and reflect infections or problems that are temporary. Chronic elevated CRP is an indication of potential trouble due to the numerous serious disorders and diseases which are driven or aggravated by local or systemic inflammation. A recent meta-analysis of randomized placebo-controlled trials examined the CRP lowering effect of oral curcumin.[8] Six trials involving 179 subjects in the intervention group and 170 in the placebo group were eligible. Compared to the placebo, supplementation with curcumin reduced CRP by 6.4 mg/L, a large change. This effect was maintained in subgroups of trials that used bioavailability-improved preparations of curcuminoids and had supplementation periods of ≥ 4 weeks. Ideally, CRP levels below 1.0 mg/L are considered satisfactory, and apparently the lower the better. The famous Jupiter trial of statins in patients with elevated CRP had a threshold for eligibility of 2.5 mg/L. Patients with infections or inflammatory diseases, including diabetes, frequently present with levels well above 2.5 mg/L. Thus, the above mean decline with curcumin therapy in the study cited above was quite significant and since it presumably is related to an actual decrease in inflammation, may be associated with considerable clinical benefit.

Conclusion
Gupta *et al* [1] discuss numerous animal and other experimental studies of aspects of the action of curcumin which should lead to clinical studies. Its potential for phytotherapy directed at prevention and disease therapy appears immense and spans a remarkable range of diseases. Great progress appears to have been made in solving the problem of bioavailability and today highly bioavailable versions are readily available. Adverse effects appear to be minimal. The major obstacle is that curcumin is a natural product and clinical study funding must come from non-industry sources which are limited and in many cases these sources are anti-alternative medicine. With high bioavailability, it appears to be a wonder drug.

WHAT CAUSES ALZHEIMER'S DISEASE AND WHAT CAN BE DONE ABOUT IT?

Look up websites such as that of the Mayo Clinic or the Alzheimer's Association and all one finds in the sections on causes is reference to plaques, tangles, family history or genetics. One gets the impression that the hope for the future is in the genetics. The plaques are made up of a protein called amyloid-β and while there is no disputing the fact that it is closely associated with Alzheimer's disease (AD), what is debated is whether it is a marker or a causative factor. The so-called amyloid hypothesis has dominated AD research and thinking for the past two decades with more than 18,000 articles concerning this associate ion. However, clinical trials of drugs that decreased the brain load of amyloid-β failed in a spectacular fashion, causing no doubt many sleepless nights for those whose careers have been intimately associated with this hypothesis. There is growing evidence that in fact amyloid is a downstream marker, not a cause, and growing interest, albeit long delayed by the distraction of the amyloid hypothesis and the 18,000 papers, in finding the actual causes.[9] However, there is considerable evidence suggesting vascular causes.

There are no therapies for AD that are more than marginally effective or durable, and these mostly address symptoms or undesirable behavior. However, the need is urgent with the aging population, families ill equipped to act as caregivers and cash-starved healthcare systems. It is easy to imagine a financial disaster in the making with the epidemics of diabetes and age-related cognitive impairment and AD, which are together capable of bankrupting many modern societies.

Mainstream medicine treats early to moderate stages of AD with cholinesterase inhibitors (Aricept, Exelon, Razadyne and rarely Cognex). For moderate to severe stages, memantine, a drug that regulates the activity of glutamate, a chemical involved in learning and memory, is frequently employed. According to Herrmann *et al* in a recent journal article, "*Currently available treatments for AD are symptomatic and do not decelerate or prevent the progression of the disease*."[10] There is considerable support for this view.[11-13] Statins, which seem to have been tried for almost every sickness of mankind, are described in a recent Cochrane review as having insufficient evidence to recommend their use in the treatment of AD.[14]

One recent pharmaceutical approach involves monoclonal antibodies which target beta-amyloid in the brain, in keeping with the above discussed, long-held but frequently debated view concerning the role of this peptide in the pathophysiology of AD. The drug companies Pfizer and Janssen announced in early August that they were halting the development of the anti-amyloid drug bapineuzumab after a series of negative clinical trial results. Other anti-amyloid strategies have also yielded disappointing results in patients with AD (MedPage Today, August 6, 2012). One example is semagacestat, a drug expected to decrease beta-amyloid build-up. Compared to a placebo, it actually appeared to worsen the disease and increase the risk of skin cancer. The clinical study of this drug was halted in the fall of 2010. In fact, it now seems generally agreed that while the beta-amyloid hypothesis has dominated AD research for over 3 decades, success of this theory in informing therapy has been profoundly disappointing.

Another new approach, which recognizes that insulin problems may play a role, involves intranasal introduction of insulin into the brain. This new approach has shown short term benefits in cognition.[15,16] What is interesting is the focus in this research on the connection between insulin and signalling pathways and also beta-amyloid-insulin competition rather than what may really be important, hypometabolism, mitochondrial dysfunction and the need for a replacement for glucose as a fuel on a daily basis. Thus, an attractive alternative to the amyloid view is what has been called the type-3 diabetes hypothesis. While discussed earlier in IHN in a different context, it seems appropriate to reopen this subject since it points directly to a promising, inexpensive and natural therapeutic approach, not only to AD but to the precursor cognitive impairment and even Parkinson's disease.

The hypothesis was formalized in 2005 by Suzanne de la Monte that AD and type 2 diabetes are related disorders.[17] It was suggested that the dysfunction of glucose metabolism and insulin action in the brain, which in part leads to mitochondrial dysfunction and decreased energy production, could be significantly responsible for the changes and damage that are observed as AD develops. This led to the suggestion that AD being called type 3 diabetes. However, the notion that there is a connection between AD and decreased glucose metabolism (hypometabolism) in the brain goes back to at least 1970.[18] Abnormalities in metabolism have been linked to brain insulin resistance and insulin-like growth factor resistance with disruption of signalling pathways that regulate neuronal survival, energy production, gene expression and brain plasticity.[19] This can contribute to or initiate the observed neuropathology of AD. In this context, the use of PET scans with a metabolic tracer have provided significant and extensive evidence supporting the presence of hypometabolism, and supporting the notion of type 3 diabetes. The mechanistic details are the subject of current research.[20]

The main features of the hypothesis are nicely summarized by de la Monte in a recent review.[21] This is paraphrased below.

- Insulin and insulin growth factor (IGF) deficiency drives AD that is postulated to be a metabolic disease of the brain. The abnormalities seen in the spectrum of systemic insulin resistance diseases correspond to that seen in AD.
- The result of brain insulin/IGF resistance is the initiation of a cascade driven by increased oxidative stress, neuron inflammation, impaired cell survival, mitochondrial dysfunction, and endoplasmic reticulum (an organelle or cellular subunit) stress. This compromises the function of brain cells, disturbs neurotransmission, impacts amyloid-β functions and causes the tangles and plaques to accumulate, the hallmarks of AD.
- The progression of AD is attributed to a feedback loop in the above processes that worsens the effect of insulin resistance and as well, increases the formation of reactive oxygen species and nitrogen

species which form undesirable adducts to lipids, proteins, and DNA and permanently damage cellular and molecular functions.

- It is also proposed that chronic low-level exposure to nitrosamines through diet, smoking and agriculture exposure, plus excessive intake of fats and simple sugars, is partly responsible for the insulin resistance epidemic.

In the cited review as well as in another review also by de la Monte[22], the detailed evidence and documentation for this hypothesis is presented. The hypothesis concerning the cause of AD suggests opportunities for prevention.

Closely related to the above hypothesis is what might be called "The Starving Brain Hypothesis." or the "Hypometabolism Hypothesis." Because of insulin resistance, the brain is unable to metabolize adequate glucose for its needs, which in fact are very large. This hypothesis relates more to the day-to-day dysfunction than to the causes and progression. It focuses on brain cells that are not permanently damaged but simply not functioning optimally due to impaired glucose metabolism. Correcting this might address some of the impairments associated with the overall effects of the type 3 diabetes, improve the quality of life and even turn the clock back or arrest progression of AD.

In the September 2012 issue of IHN, the featured topic was an apparent solution to the starving brain problem. The approach is simple. Provide the brain with a fuel that does not require insulin for metabolism, in this case what are called ketones or more correctly ketone bodies, a source of which is coconut oil or a refined oil called medium chain triglycerides also simply known as MCT Oil. The reader is referred to this issue in the archives for the details, and in particular for the contribution of Dr. Mary Newport in publicizing this therapy, which worked so well for her husband. Her book which is in its second edition is highly recommended.[23] In fact Dr. Newport received so many positive anecdotal reports that she was able to convince a university research group to undertake a clinical trial of coconut oil/MCT oil in AD patients which is now ongoing.

There is also a preparation available by prescription called Axona, which contains a patented MCT that has undergone a successful clinical trial.[24] However, MCT oil or coconut oil or mixtures thereof are readily available from health food stores. One can even argue that the elderly might benefit from taking moderate doses for prevention of cognitive impairment. The risks have not been systematically investigated, but there do not appear to be any adverse effects associated with taking this alternate brain fuel.

Does type 2 diabetes increase the risk of cognitive impairment and AD? This question has been examined recently in a review by Hiroyuki Umegak.[25] Type 2 diabetes was observed in 4 studies to increase the risk of both dementia and AD, with increases ranging from 50% to 230%. In a discussion of possible mechanisms, the presence of type 2 diabetes was associated with blood brain barrier dysfunction, cerebral impaired neurogenesis, inflammation, hyperglycemia, insulin resistance and vascular dysfunction. These, alone or in combination were postulated with supporting evidence indicating that type 2 diabetes contributes to acceleration of AD pathology, impaired circulation and ischemia (blood clots in this case leading to vascular dementia).

The real challenge is reversing type 3 diabetes, which is a different problem than providing alternate brain fuel that does not need insulin for metabolism. The principal feature of the type 3 diabetes hypothesis for AD involves brain cell insulin resistance, and the summary of the hypothesis given above suggests a number of external and modifiable causative factors. As recently discussed in IHN, in the case of type 2 diabetes or prediabetes, dietary interventions can normalize insulin sensitivity and eliminate hyperglycaemia. Animal studies suggest that there may be an opportunity for benefit in such interventions in humans in the context of AD or mild cognitive impairment.[21,22] The benefit of alternate brain fuel in the form of ketone bodies as a way to reverse cognitive impairment and AD appears unknown, and the large improvements seen in some cases treated with coconut/MTC oil do not represent a cure and benefit may be limited by the presence of permanent damage. Early treatment of mild cognitive impairment with this therapy thus appears to be an interesting area.

Clearly, an issue deserving clinical study involves the impact of the total reversal of type 2 diabetes, such as accomplished by the Newcastle Diet or its variations, on cognitive impairment and AD. A related question concerns the impact of bariatric surgery on the same brain pathology, since for many individuals this intervention cures type 2 diabetes. It is thus very interesting that bariatric surgery has been found to lead to what may be lasting improvements in impaired cognition.[26,27] This strongly implies some degree of reversibility is possible, strengthens the postulated connection with type 2 diabetes and highlights the great importance of the work of Taylor's group in reversing diabetes.

Thus the answer to the question of what causes AD is far from clear. There is clearly a need for a paradigm change concerning therapy development. The recent results of new approaches are encouraging. One is discussed below.

A NOVEL APPROACH TO REVERSING COGNITIVE DECLINE FROM UCLA

The current approach to the treatment of mild cognitive impairment and early or advanced Alzheimer's disease is based on the common drug discovery paradigm, one target, one drug. Neurodegenerative disease therapeutics are regarded as one of the greatest failures in biomedical drug development. For Alzheimer's disease at any stage, there is not a single therapeutic that exerts anything beyond a marginal, unsustainable effect on one or more symptoms. The failure of hundreds of clinical trials has led some to question the merits of the current drug development approach.[28,29]

The need for effective therapy could not be more urgent. Alzheimer's disease related cognitive decline affects 5.4 million in the US and 30 million globally. If no effective therapy is found, by 2050 the numbers are 13 and 160 million. Anyone acquainted with individuals with cognitive decline will know just how big a disaster this is for the patients, the caregivers, family and healthcare systems. Thus the following report of the reversal of cognitive decline represents a big step forward.

In two recent publications from the University of California, Los Angeles, Dale Bredesen has suggested that AD probably involves a number of dysfunctional processes which impact the entire cerebral network and even involve deleterious positive feedback mechanisms.[28,29] He postulates that AD results from an imbalance in an extensive plasticity network in the brain. Therefore, it is understandable that mono-therapeutic interventions have failed. It follows that system therapeutics and system biological approaches are needed. This implies that a combination of a number of interventions is required at levels, which exceed the threshold for rectifying a sufficient number of the system problems to produce an effective therapy. In the most recent paper, he lists 25 areas of therapeutic intervention that can be justified on the basis of experimental literature.[29] This paper as well as the earlier one cited above are available free. Go to PubMed and put the following PMID numbers one at a time into the search box, 23703924 and 25324467, and use the button in the upper right hand corner of each abstract to get the pdfs.

The latest paper also contains the results of a preliminary study on a group of patients with memory problems and mild cognitive impairment (MCI) with or without early AD, and as well, two more advanced cases of AD. Three case histories are included in the paper which involved 12 of the 25 areas of intervention suspected as important by Bredesen. In the table, the interventions used in these case histories are summarized. Patient 2 also took vitamin C, 1g/d, vitamin D, 400 IU/day, Zinc picolinate, 50 mg/d and alpha-lipoic acid, 100 mg/d.

The results of this program with eleven patients followed found that 6 who had been unable to work because of the disability associated with MCI or early AD, were able to go back to work. Another patient who benefited had not been forced to quit work. One patient with AD improved, the other declined. Both had a history of 4 years of memory decline. The author points out that an improvement large enough to allow resumption of work, i.e. a job, is an important outcome for any successful therapeutic intervention.

Aside from citicoline, this program of diet, exercise and supplementation contains nothing at all unusual. Citicoline, incidentally is a supplement that supports brain cell structure and function by promoting phospholipid production. Bredesen suggests that studies would find each intervention, if used alone, to

produce modest if any measureable benefit. Thus the power of functional medicine. One might argue that this does not apply to coconut oil.

While these results are both anecdotal and very preliminary, they appear to offer great hope for individuals with MCI or MCI/early AD. They also provide a splendid example of the dividends paid when the one target-one drug paradigm is abandoned in favor of a total system approach. This so-called functional medicine works for autism and MS (see the book list at the end of this issue), and is seen when all or most modifiable risk factors in, for example, cardiovascular disease, are simultaneously addressed. As Bredesen points out, system approaches present great challenges in connection with regulatory approval of a treatment and this impediment will probably persist until there is a major change in the way treatments are approved. There is of course also the problem that the therapeutic program he is perfecting does not involve patented drugs and thus funding for large clinical studies may be difficult to obtain, and the whole approach probably opposed by advocates of evidence based medicine until their requirements are met.

It would appear that this is the first time pre- or early-Alzheimer's has been reversed to the extent observed. This is big news. Medical researchers have for quite some time been saying, we need early diagnosis so we can treat this disease. No one apparently asked them the details of the planned protocol. Is it just symptom attenuation that they are suggesting? In fact, the answer would of necessity been, we are still waiting for one. It would appear that until the UCLA work, treatment to significantly reverse these conditions was a fantasy, but the UCLA work will probably not be accepted as evidence based. That is the way the rules of the game are written. It remains to be seen if medium chain triglycerides/coconut oil will accomplish the same result for this stage of the disease. This letter intervention was included in the UCLA trial, but for only one case history was it among the supplements or lifestyle modifications tried.

INTERVENTIONS USED IN CASE HISTORIES			
DETAILS FOR THREE PATIENTS	P1	P2	P3
Eliminate simple carbs, eat more fruits & vegetables	Y	Y	Y
Stress reduction. Yoga, meditation	Y		Y
Take oral melatonin for better sleep	Y	Y	Y
Daily vitamin B12 as methylcobalamin 1 mg/day	Y	Y	Y
Vitamin D3 daily 2000-5000 IU/day	Y	Y	Y
Fish oil or EPA/DHA daily 180/320 to 500/700 mg/d	Y	Y	Y
Coenzyme Q-10 daily 200 mg/day	Y	Y	Y
Improve oral hygiene	Y		
Fast dinner to bedtime and 12 hrs dinner to breakfast	Y	Y	Y
Exercise	Y	Y	Y
Probiotics		Y	
Coconut oil		Y	
Citicoline 500 mg twice a day		y	Y

FUNCTIONAL MEDICINE READING LIST

- ***The Disease Delusion. Conquering the causes of chronic illness for a healthier, longer and happier life***. Jeffrey Bland, PhD. HarperCollins, New York, 2014.
  *www.*amazon.com/exec/obidos/ASIN/0062290738/internationaheal

  This book provides an up to date introduction to functional medicine, a coming revolution in medicine. It will change the way you look at medicine. Dr. Bland is called the godfather of functional medicine. In this book he elegantly explains the essential tools needed to attempt to overcome chronic ailments of modern society.

- ***The Autism Revolution. Whole-body strategies for making life all it can be***. Martha Herbert MD with Karen Weintraub. Harvard Health Publications, Harvard Medical School. Ballantine Books, New York, 2014.
  *www.*amazon.com/exec/obidos/ASIN/0345527208/internationaheal

  This is a "must read" for anyone with an autistic child. A Harvard assistant professor of neurology and a pediatric neurologist at Masochists General Hospital describes her journey from looking at and treating autism according to the conventional wisdom to a whole body, web-like network view that appears to be the only really successful approach. This book calls for a revolution in autism therapy. As Dr. Herbert comments, "it is terrifying to imagine our future without this revolution." The book is authoritative, compelling in its case histories, and sensational in the accomplishment described.

- ***The Wahls Protocol. How I beat progressive MS using Paleo principles and functional medicine.*** Terry Wahls, MD with Eve Adamson. Avery, 2014.
  *www.*amazon.com/exec/obidos/ASIN/1583335218/internationaheal

  A remarkable personal history of an academic physician stricken with multiple sclerosis and declining rapidly into disability. It describes how through functional medicine, a whole body approach, she reversed the course of this disease, something almost unheard of if the individual was already in a wheelchair, and today she can again do rounds in the hospital and no longer even needs a cane. A wonderful example of what can be accomplished by thinking outside the box and the merits of the approach inherent in functional medicine.

- ***Gut and Psychology Syndrome*. *Natural treatment for dyspraxia, autism, ADD, ADHD,* dyslexia, depression, schizophrenia**. Natasha Campbell-McBride, MD. Medinform Publishing, Revised Edition. Cambridge 2010.
  *www.*amazon.com/exec/obidos/ASIN/0954852028/internationaheal

  A classic in functional medicine applied to mental health problems, especially in children. The revised 2010 edition is still highly relevant today.

- ***Ultra-prevention***. Mark Hyman, MD and Mark Liponis, MD. Scribner, New York, 2005.
  *www.*amazon.com/exec/obidos/ASIN/0743448839/internationaheal

  Another classic in this field. Already in 2005 the basic principles and philosophy of functional medicine were set out in language the layman could understand and with a narrative to which sick individuals could relate. One of the authors, Mark Hyman, wrote the preface to Jeffry Bland's book described above. That preface puts the whole subject in marvellous perspective.

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