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In this issue we revisit a subject discussed several times in earlier newsletters. Involved is the use of coconut and medium-chain triglyceride oils for the treatment of cognitive decline and Alzheimer's disease. A new viewpoint has emerged with the hypothesis that Alzheimer's disease involves insulin-related dysfunction of cerebral glucose metabolism and is being called Type 3 diabetes. We will also review some of the information provided in Dr. Mary Newport's new book, "Alzheimer's Disease. What If There Was a Cure? The Story of Ketones". It was Dr. Newport's phenomenal success in reversing important aspects of her husband's Alzheimer's disease using first coconut oil and then a mixture of this oil and a medium-chain triglyceride oil, a treatment entirely consistent with the hypothesis that Alzheimer's disease involves hypometabolism and Type 3 diabetes.

Alzheimer's disease is probably the most serious disorder facing an aging population and a disease for which mainstream medicine offers no cure, no treatment to halt progression, and almost insignificant symptom control. When things get bad, the answer is to use drugs from the arsenal of powerful antidepressants and antipsychotics to address behavioral and control problems. Visit any nursing home to see first-hand how well this all works.

Thus what seems to be an approach that offers new hope deserves to be seriously considered. Since it involves specialized "food" obtained at a health or natural food store, readers will understand why it probably will never become an accepted treatment with completion of the required phase 1 through 3 clinical studies and then regulatory approval as a drug or more likely medicinal food. The active substances cannot be patented unless they are chemically modified. However, we are not talking about snake oil. These oils are metabolized in the liver to generate simple ketones which then provide a source of energy for brain cells suffering from hypometabolism of glucose, and this is exactly the same mechanism the body evolved eons ago to react defensively to starvation.

Also included in this issue is a the not unexpected news that more and more children are being treated with psychiatric drugs not approved for their indications, a critical discussion of new research suggesting that modest calcium supplementation increases the risk of heart attack, and news about a new study supporting the use of cranberry products to prevent urinary tract infections.

This issue also includes a Research Review which examines the foundations of evidence-based medicine and in particular, addresses the question, is the evidence reliable?

If you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

ALZHEIMER'S AND PARKINSON'S. A NEW DIRECTION AND A NEW HOPE

ALZHEIMER'S DISEASE

There has been growing interest in the hypothesis formalized in 2005 by Suzanne de la Monte that Alzheimer's disease (AD) and type 2 diabetes are strongly related disorders.[1] 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 be 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.[2] Abnormalities in metabolism have been linked to brain insulin and insulin-like growth factor resistance with disruption of signalling pathways that regulate neuronal survival, energy production, gene expression and brain plasticity.[3] This can contribute to or initiate the 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, and the mechanistic details are the subject of current research.[4]

Paralleling the interest in the theory of type 3 diabetes and reduced brain glucose metabolism was research which studied and attempted to intervene by feeding metabolic precursors of ketone bodies (three simple organic molecules of ketone structure—see Wikipedia). Metabolism occurs in the liver and then the ketones would pass the blood-brain barrier and act as replacement fuel for glucose. Of great interest were subjects with mild or moderate AD, and as will be discussed below, this intervention produced significant if not remarkable improvements in measures of cognitive performance and other manifestations of AD. In fact, the dietary induction of ketosis resulting in a significant level of ketone bodies in the circulation has a long history in the treatment of brain-related disorders since it has been used for epilepsy in both adults and children when all other approaches failed.

The developments described above have been ignored by most AD researchers who continue to be driven by the belief that beta-amyloid and tau protein present the most promising therapeutic avenues of research and targets for therapy. However, recently public awareness of the use of ketones or their metabolic precursors, which are medium chain triglycerides (MCTs) for the treatment of AD, has increased thanks to the power of the internet and social media. A turning point was in 2008 when Dr. Mary Newport, a medical doctor and founder and director of the neonatal intensive care unit at Spring Hill Regional Hospital in Florida, wrote an article titled "*What If There Was a Cure for Alzheimer's Disease and No One Knew?"* She described bringing her husband, who had moderately advanced AD, back from ongoing progression toward the full blown disease by the simple expedient of giving him an nutrient found in most health food stores.[5] The article was not published in a medical journal and her efforts to use it to promote awareness of the merits of this treatment among physicians involved in the treatment of AD failed. The article was reproduced on the internet, causing somewhat of a sensation in lay circles.

The nutrient first used was coconut oil which contains MCTs and later she switched to a mixture of this oil and pure MCT oil. The results were remarkable by any standard and have been mentioned in earlier issues of this newsletter. Dr. Newport has now authored a book titled *Alzheimer's Disease. What If There Was a Cure? The Story of Ketones,* which provides a journal of her husband's initial response and updates, her attempts at increasing awareness that the protocol really works, a large number of testimonials which are provided in detail, and in addition, the book contains a wealth of supporting information and evidence, mostly derived from the peer reviewed literature.[6] Dr. Newport uses the term "cure" but strictly speaking, this would involve the disappearance of the disease, not its control or induced regression.

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*."[7] There is considerable support for this view.[8-10] 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 dementia.[11]

In the US there are no drugs approved for dealing with behavioral and psychiatric problems which confront AD caregivers, either at home or in nursing homes. However, the whole arsenal of antidepressants, anxiolytics (for anxiety, disruptive behavior and resistance) and antipsychotics are widely used off-label (not approved for the indication). The problems and side effects associated with these drugs have been discussed at length in Research Reports of IHN (February and March, 2011 and also October 2011). These drugs simply alter symptoms and in some cases create zombies for whom care is easier. Many AD patients are on lifelong pharmacotherapy. Thus AD appears to represent an extreme example of over treatment and in many cases the offer of false hope. Once the disease has started to significantly impact the quality of life of both the patient and caregiver(s), the real nightmare begins and can last a long time.

One recent pharmaceutical approach involves monoclonal antibodies which target beta-amyloid in the brain, in keeping with the 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, the beta-amyloid hypothesis has dominated AD research for over 3 decades but success of this theory in informing therapy has been disappointing.[4] 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.[12,13] 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 hypometabolism, mitochondrial dysfunction and the need for an alternative fuel on a daily basis.

It is clear from the above that a very dismal picture emerges when one examines what mainstream medicine seems able to accomplish when challenged to treat someone with cognitive decline or AD. Small changes that seem to disappear over 6 months are hardly satisfactory. At present, AD is incurable and approved approaches to slowing the disease produce what seem to be trivial short-term benefits. This is a serious problem. According to the Alzheimer's Society, about 5.4 million Americans have AD, and most are over 65 years of age. In fact, 1 in 8 over 65 and 1 in 2 over 85 have symptomatic disease. The Society projects as many as 16 million cases by 2050.

In what follows, we will review briefly the alternative treatment using MCTs to address the problem of reduced glucose metabolism (hypometabolism) in the brain, the biological plausibility of this intervention, and recent developments.

In a recent review in the journal *Nutrition*, Cunnane *et al* present a three-phase view of the concept.[14] Phase 1 involves the development of brain glucose hypometabolism which leads to Phase 2 where it is postulated with supporting evidence that pathological changes occur in the microvascular system, reactions involving tau protein, brain shrinkage, beta-amyloid deposition, mitochondrial dysfunction and regional brain starvation. The end result is Phase 3 where clinical manifestations of AD finally appear. The Phase 2 neuropathology can also aggravate brain hypometabolism, creating a vicious cycle. The authors suggest that this cycle can be effectively broken by sustained improvement in brain metabolism, which can be achieved with ketones which act as replacement fuel for glucose. Perspective regarding the role of ketones in brain metabolism can be gained by considering that during starvation or very low carbohydrate intake, the liver turns to making ketones which then support cerebral metabolism. This defence mechanism evolved eons ago and was likely necessary for human survival.

The central problem with AD is that during most of its natural history the only evidence of the status of an asymptomatic individual (aside from an autopsy) comes from PET scans and perhaps certain biomarkers,[15,16] since even mild cognitive impairment may not be evident, recognized or admitted until late in the development of the disease. Screening for early AD is certainly a subject of intense interest, but it may be decades before this becomes standard practice, and at present there is no approved intervention to deal with a positive screening result. However, the early signs of memory problems and mild cognitive impairment should trigger significant concern and prompt consideration of interventions based on alternative, even though such interventions are late in the natural history of the disease.

Starvation is obviously not a practical solution. Neither is a severely ketogenic diet, because adherence is a serious problem since 90% of energy must come from fat. Maintaining mild ketosis such that ketones appear in the urine is easier and many on low carbohydrate diets such the Atkins Diet and the South Beach Diet may achieve this at least part of the time, but no one knows if this is sufficient to deal with the challenges presented at the various stages of AD development. This brings us back to coconut oil, MCT oil which is a component of coconut oil, and commercial MCT preparations specifically designed for treatment of cognitive impairment and AD. However, it is important to realize that using an alternative fuel in the face of hypometabolism in the brain is not primary prevention. But including hypometabolism in the picture appears to be a major advance as is the hypothesis that AD is partly a diabetes-type disorder localized in the brain.[4]

One of the prominent researchers in the field of brain hypometabolism, Samuel Henderson, was instrumental in the development of a product to treat AD called AC-1202, which contained one MCT and could be taken as a dissolved powder. It was patented and tested in several trials and now recently in a large, multicenter randomized controlled trial which reported in 2009. The compound rapidly elevated serum ketone bodies in AD patients and resulted in significant improvement in cognitive scores when compared to the placebo.[17] These results were very positive, and to some would constitute convincing evidence concerning the validity of the hypometabolic hypothesis. This preparation, available only as a prescription “medicinal food” called Axona, contains only one ketone generating MCT, and is expensive compared to simply using a mixture of coconut oil and MCT oil. The latter also has the advantage of providing several ketones after liver metabolism with flexible dosing throughout the day.

Dr. Mary Newport first heard of the use of MCTs for AD in 2008 when she came across reference to Henderson’s patent, found AC-1202 contained a MCT and quickly ascertained that MCTs were present in coconut oil which was available at natural food and health food stores. She decided there was nothing to lose by trying coconut oil. This was a turning point in her husband’s life as well as hers, since she was the primary caregiver. Results were remarkably rapid, progression apparently stopped, and over the following 3-4 years many cognitive and behavioural deficits were significantly

reduced and what is even more interesting, many lost functions were recovered. In her words, she "got her husband back." In addition, sequential MRI studies revealed that the progression of brain atrophy had been totally halted. Conventional, approved treatments have never produced such a result, or in fact in a significantly sustained manner any of the above results, especially when the patient has fairly severe AD. Rather, the progression is relentless, going from mild cognitive impairment to finally the mental and physical helplessness of advanced AD. Today, most of the interest in this intervention is among lay persons who become aware of MCT and coconut oil while doing a Google search for AD treatments, or through the social media or by word-of-mouth.

In her book, Dr. Newport provides details and a summary of anecdotal reports (60 cases) she received after the do-it-yourself treatment became popular. Unfortunately, there is naturally uncertainty as to dose, source of MCTs, adherence, severity of the disease and the quality of reportage from caregivers concerning changes. Nevertheless, 90% of those who tried MCTs were improved, which translates into higher scores on tests, improved clock drawing, better cognition, more alertness, brighter outlook, improved awareness, less foggy or hazy behaviour, being able again to recognize people or places, being less distractible, and having a better sense of direction.

MCT oil yields higher serum ketone levels but the decline is more rapid than seen with coconut oil. Dr. Newport decided that coconut oil taken with MCT oil might help smooth out fluctuations with higher average levels and also have some other benefits not provided by the MCT oil since it contains other fatty acids. Thus she elected to use a mixture. This influenced their final protocol which involved using an approximately 1:1 mixture of coconut oil and MCT oil at a dose of 3 tablespoons with each meal and two at bedtime. To avoid diarrhea, the only know adverse side effect of MCTs, dose escalation (titration) is sometimes needed. It is important to note that while attention was paid to a healthy diet, the macronutrient intake of Dr. Newport's husband was not drastically altered with ketosis in mind. In fact, the use of MCTs has the advantage of not requiring significant diet changes and can even be used along with conventional but apparently mostly ineffective treatments. The advice to having medical supervision even with alternative or integrative therapy is of course wise, but implementing this in the face of sometimes fierce opposition from conventional practitioners can be a problem. *The use of MCT therapy is contraindicated for individuals with kidney disease.*

An interesting footnote to the Newport story was published in the September 2010 issue of *Heart, Health and Nutrition*, a popular newsletter by Dr. Stephen Sinatra, a cardiologist. In June he had reported on the success Dr. Newport had achieved treating her husband and suggested she add twice daily doses of Coenzyme Q-10 (200 mg), acetyl-L-carnitine (1 g), magnesium (200 mg) and ribose (5 g two to three times daily). This is the centerpiece of his approach to treating heart disease. She reported that on trying this, her husband's speech became more fluent with finding words easier, and he more consistently initiated conversations. All this occurred after a few days of the supplementation. Sinatra regards this as an impact on brain mitochondrial function where these supplements increase the efficiency of energy production, in this case mostly from ketones. Dr. Newport mentions these supplements in her book but does not indicate if she continued using them.

As mentioned above, dietary-induced ketosis has been used for decades to treat intractable epilepsy. Dietary ketosis also has been shown to enhance memory in mild cognitive impairment, and there is evidence of protection against neuronal insults, an increase in metabolic efficiency relative to glucose, and in general such diets appear to some extent to mitigate neurodegenerative mechanisms.[18,19] These observations further support the hypometabolism hypothesis and provide further justification for the ketone fuel replacement intervention.

Two other aspects of diet are relevant to the present discussion. Seneff *et al* have discussed the evidence suggesting that excess dietary carbohydrates, particularly fructose, coupled with a deficiency in dietary fat and cholesterol, may increase the risk of AD,[20] and Henderson has discussed the potential adverse effects of high carbohydrate diets in the context of AD.[21] But perhaps the most interesting observations concern the potential for the Mediterranean style diet to reduce progression of AD. In a paper published in the journal *Neurology*, Scarneas *et al* report on a study which found a very large and significant decrease in the risk of AD-associated mortality (77%)

associated with adherence to the classical Mediterranean diet.[22] This can be interpreted as a decrease in the rate of progression of the disease after it became symptomatic. Recently a meta-analysis of prospective studies found a significant association between a greater adherence to the Mediterranean diet and reduced risk of major chronic degenerative diseases including AD.[23,24] The mechanism is unclear and may not be related to the hypometabolic effects discussed here.

There are now at least two commercial sources of mixed coconut oil and MCI oil. One is Alpha Health Products, a Canadian firm which sells a salad oil with approximately the desired ratio of oils used by Dr. Newport. It includes omega-3 fatty acids as well. The other company is Fuel for Thought, which sells a competitive product. But both coconut oil and MCT oil are separately available from most natural and health food stores. The coconut oil is solid at room temperature. One simply melts the required amount of coconut oil to make up a mixture and then adds it to the MCT oil which is fluid at room temperature. The resultant mixture remains liquid at room temperature. When treating more severe disease where the desire is to achieve high doses, some ingenuity may be required regarding to mixing the oil with foods that make it easy to ingest and more palatable.

Apparently no one knows the dose of MCTs suitable for preventing the onset of mild cognitive impairment, if it indeed accomplishes this. In many older individuals, the silent disease is already advanced but there may be no clue as to benefit after starting on MCT therapy, although subtle, previously unnoticed symptoms may disappear and it is possible that benefit may become apparent. In treating symptomatic mild cognitive impairment or AD there are of course no dose studies either, and all one can do is increase the dose, observe the patient's changes, and stop at the point where success is achieved or the long-term tolerance level reached as determined by diarrhea.

A commonly used test of cognitive status regarded as highly informative is the clock test. The person is given a blank piece of paper and asked to draw a clock with all the hours around the circle and then place the two hands at a given time. It is surprising how many persons cannot do this or even draw a circle. People who cannot pass the clock test can still accurately read the time from a clock. One of the most fascinating aspects of Dr. Newport's husband's change was that initially he was totally unable to draw a clock, and a few weeks after starting coconut oil his clock, while not perfect, is impressive. This is illustrated in Dr. Newport's book and in the article on the internet.

The clinical trial results of AC-1202 and all the anecdotal evidence support the biological plausibility argument for ketones produced from MCTs as an alternative source of energy for individuals symptomatic for either mild cognitive impairment or AD. In fact, a remarkably consistent picture emerges. One fact stands out. There does not appear to be anything else that works as well. And the industry still seems to be lost somewhere along the highway named beta-amyloid.

If one examines the website of the Alzheimer's Association (Society) it is clear that they do little more than acknowledge the FDA approved AC-1202 prescription medicinal food, and they view coconut oil as a totally unproven folk remedy that does not merit attention even though it works the same by the same mechanism. It seems highly unlikely that placebo effects are present in Alzheimer's treatments and the remarkable changes that have been observed by countless individuals have never been produced by approved drugs. Thus the demands for randomized controlled trials (including a large one for AC-1202 to get drug status approval) are simply examples of how out of touch mainstream medicine is with reality. Why they do not demand placebo controlled trials for the use of anti-snake bite serum seems inconsistent with their "philosophy". The predictability and universality of the relentless decline in AD is really not that different than the after aftermath of a potentially fatal snake bite. Meanwhile, millions if not billions are spent on drugs for AD that are universally acknowledged as having minimal or no significant benefit.

Aside from MCTs, alternative treatments that have been studied also have not been found very effective, according to standards set by the Cochrane Collaboration group. These include Gingko biloba[25,26], vitamin E[27], and omega-3 fatty acids.[28] Increased consumption of vegetables but probably not fruit appears to have some merit in risk reduction.[29] Evidence for folic acid with or without vitamin B12 is inconclusive,[30] but evidence favouring vitamin D is encouraging, especially since vitamin D

deficiency is a widespread problem among the elderly, but more research is urgently needed regarding long-term high dose treatment.[31] However, the merits of these alternative approaches should not be entirely dismissed since the study quality is in general not very good.

PARKINSON'S DISEASE

Alzheimer's disease and Parkinson's disease (PD) are both thought to be associated in part with mitochondrial dysfunction. Furthermore, starvation diets decrease the tremors associated with PD and ketogenic diets are beneficial. PET scans also demonstrate that impaired glucose uptake in PD occurs in the expected areas of the brain.[32] This circumstantial evidence was strengthened by a very small clinical study which demonstrated that diet-induced high levels of serum ketones had a large impact on five PD patients. A standard diseases rating score was used and decreases in score indicting improvement ranged from 21 to 81% with a median of about 50%, over only 28 days.[33] Beyond this, evidence is almost non-existent. However, the success of MCT and coconut oil in AD is probably transferable to some extent to PD, and this could be highly significant for sufferers from this disease.

INCREASING NUMBERS OF CHILDREN USE PSYCHIATRIC DRUGS OFF-LABEL

A study just published in the *Archives of Psychiatry* examines the trends between 1993 and 2009 in the pediatric use of prescribed antipsychotic drugs.[34] These are powerful drugs used to treat bipolar disorder, schizophrenia and other serious mental problems as well as autism-related instability. This study found that only a small proportion of antipsychotic drug treatment in children (6%) and teenagers (13%) was for FDA-approved indications. During the period studied, prescription antipsychotic medication for children increased seven-fold and for teenagers five-fold. The majority of the prescriptions were ordered by doctors who are not psychiatrists. In the period 2005-2009, almost two-thirds of office visits resulting in antipsychotic drug therapy were for disruptive behavior for which there are currently no FDA-approved drug treatments. The lead author, Dr. Mark Olfson from Columbia University, commented that these drugs can deliver rapid improvement in children with severe conduct problems and aggressive behaviours, but it is not clear that they are helpful for the larger group of children with ADHD. In addition, he pointed out that their long-term effect on children's brain development has not been studied. Furthermore, non-drug therapy was largely ignored.

Readers of this Newsletter may recall the Research Review published in the February and March issues which devoted considerable space to the opinions of the high-profile psychiatrist Dr. Peter Breggin concerning psychopharmacology. In the online *MedlinePlus* (August 7, 2012) coverage of this paper, Dr. Breggin was quoted as saying "We have a national catastrophe. This is a situation where we have ruined the brains of millions of children." Breggin refers to these drugs as "lobotomizing" because they act on the frontal lobes of the brain. Breggin maintains that these drugs deliver their results by directly and in many cases permanently changing or damaging the brain and end up making the disorder worse in the long run as is evidenced by the common scenario of the need for a second and then a third drug, etc. and finally a person who has been mentally destroyed. The improvement is an illusion and the behavioral changes not due to solving the problem but disabling the brain. Of course, this view is not popular either among psychiatrists or the general practitioners and internists who prescribe these drugs, but they are probably unaware of the evidence which is provided an great detail in Breggin's medical monograph *Brain-Disabling Treatment in Psychiatry* published by Springer. In this very expensive book, Breggin thoroughly documents his thesis. Professionals who care for institutionalized children and teenagers should have no trouble relating what Breggin is proposing to what they see every day.

Additional critical comment from Dr. Simon Rego of the Albert Einstein College of Medicine in New York City is provided in the

MedlinePlus coverage. He highlights the uncertainty associated with the effects of antipsychotic drugs on cognitive, social and physical development of children and adolescents. He also emphasized that these drugs have serious side effects including weight gain, diabetes and heart problems.

The above is a description of mostly off-label use of drugs for unapproved indications. Court cases involving drug companies and criminal fines suggest that aggressive off-label promotion is common and fines represent the cost of doing business. Parents are solving a behavior problem with drugs that may forever alter the lives of their children and are being misled if told that these drugs have been proven in scientific studies to be safe even if taken over extended periods. If anything, a strong case can be made for just the opposite view.

Readers are referred to the October 2011 issue of the Newsletter for a discussion of the use of powerful psychiatric drugs in order to improve academic performance (Botox for the Brain). The same risk-taking is present in this new approach to education, getting good grades and being competitive. If all this is alarming to readers, just wait until the new diagnostic manual, DSM-V comes out with its huge expansion of mental diseases and increased need for pharmaceutical intervention.

CALCIUM AND HEART ATTACKS

A European prospective study just published in the journal *Heart*, a publication of the British Medical Association, deals with the impact of calcium supplementation on the risk of heart attack (MI), stroke and cardiovascular death.[35] This study received media attention since is suggested an 86% increased risk of MI if someone took a calcium supplement. Big number. Obviously something to avoid. Published in a high profile journal. Multicentre. Almost 24,000 participants. Who would want to argue with this. Dump your calcium supplement.

The authors do not provide numbers needed to harm (NNH) but these can be calculated from the data given, although two of the critical numbers were buried in the footnote to a table. Over 11 years, 1.6% of non-takers of anything had MIs, 2.73% of those who took only calcium had MIs and 1.87% of those who took calcium plus a supplement had MIs. By calculating absolute risk increases compared to non-users, these translate into numbers needed to harm over 11 years of one MI for 89 taking just calcium, and one MI for 340 taking calcium along with a supplement. The 86% increase in relative risk was for any calcium intake compared to non-use of any supplements with a NNH of 199 derived from an absolute in risk of MI of 2.1%. A much less impressive number.

No association was found for calcium supplementation and either stroke or CVD mortality. But people are probably now alarmed about the "danger" of calcium supplements. However, the authors are careful to use the word "may" to describe the risks their biostatisticians have uncovered. But they get high marks triggering media coverage that scares everyone and adds to the perception that supplements in general are to be avoided.

When the researchers looked for associations between dietary calcium intakes, which ranged from 500 to 1100 mg/day in 4 quartiles, no statistical associations were found. Supplementation was on average equivalent to being in the highest two quartiles of dietary intake, and thus presumably those who supplemented could have approximately doubled their total calcium intake.

When a study such as this stratifies by endpoint and tries up to four different statistical models and provides over 80 results, almost all of which are statistically insignificant, this makes one wonder about the two or three that turn out to show statistical significance. Also, when the result that made the news with its 86% relative risk increase is based on a very small number of MIs when calcium was supplemented, one also wonders if enough cases were observed to have any meaning. Out of 274 MIs observed while

following up on almost 24,000 individuals, only 20 MIs were observed in this subgroup. Thus when the abstract claims that taking calcium supplements *might* raise MI risk, it might have been better just to keep quiet until the question was settled. This study is also a nice example of the problems confronting anyone who wants a more complete picture of results than provided by relative risk increases. Full text is needed and then one digs and calculates.

A FOLK REMEDY FOR URINARY TRACT INFECTIONS—NOW BETTER EVIDENCE

Use of the American cranberry as a natural aid to retaining health goes back to colonial days. In the 20th century the health benefit most often attributed to the cranberry was its role in maintaining urinary-tract health. By 2000 there had been a number of observational and randomized studies which were inconsistent and many suffered from poor design.[36] A just published systematic review and meta-analysis by Wang *et* al of randomized controlled trials has provided an evidence base for this folk remedy.[37]

Urinary tract infections (UTIs) are a serious health problem. In the US it is one of the most commonly acquired bacterial infections in both the general population and those hospitalized. UTIs are estimated to cause about 7 million office visits per year, one million to the ER, and approximately 100,000 hospitalizations.[37] They are characterized by a significant recurrence rate and are most common among adult women. Mainstream medicine treats with antibiotics and mostly ignores what can be a serious adverse impact on gut bacteria.

In the analysis by Wang *et al*, 10 studies were identified that met their inclusion criteria of being randomized, controlled, reporting UTIs as an endpoint, and having results that could be expressed as an incidence rate. These studies involved 1494 subjects. It was found that using cranberries reduced the risk of UTIs by 38%. For women with recurrent UTIs, the reduction was 47%, for female populations 51%, and for children 67%. When the cranberries were from juice, the risk reduction was 53% whereas cranberry-containing products yielded a risk reduction of 62%. These results are consistent with a Cochrane review of 2008 where cranberry juice was found to prevent symptomatic UTIs with a risk reduction of 34% based on 4 trials, and for women with recurrent UTIs, the reduction was 39%.

Theories regarding the mechanism appear to favour a component of the berry inhibiting adherence of bacteria, and in particular *E. coli* to the bladder wall, but there are a large number of components of cranberries yet to be investigated.[37]

REFERENCES

(1) de la Monte SM, Wands JR. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. *J Alzheimers Dis* 2005 February;7(1):45-61.
(2) Hoyer S. Brain metabolism and the incidence of cerebral perfusion disorders in organic psychoses. *Dtsch Z Nervenheilkd* 1970;197(4):285-92.
(3) de la Monte SM. Metabolic derangements mediate cognitive impairment and Alzheimer's disease: role of peripheral insulin-resistance diseases. *Panminerva Med* 2012 September;54(3):171-8.
(4) de la Monte SM. Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. *Curr Alzheimer Res* 2012 January;9(1):35-66.
(5) Newport M. What if there was a cure for Alzheimer's disease and no one knew? *Accessed July* 2010;Available at: URL: http://www.coconutketones.com/whatifcure.pdf.
(6) Newport M. *Alzheimer's Disease. What If There Was A Cure?* Laguna Beach, CA: Basic Health Publications, Inc; 2011.
(7) Herrmann N, Chau SA, Kircanski I, Lanctot KL. Current and emerging drug treatment options for Alzheimer's disease: a systematic review. *Drugs* 2011 October 22;71(15):2031-65.
(8) Popp J, Arlt S. Pharmacological treatment of dementia and mild cognitive impairment due to Alzheimer's disease. *Curr Opin Psychiatry* 2011 November;24(6):556-61.

(9) Lanctot KL, Rajaram RD, Herrmann N. Therapy for Alzheimer's Disease: How Effective are Current Treatments? *Ther Adv Neurol Disord* 2009 May;2(3):163-80.
(10) Farrimond LE, Roberts E, McShane R. Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. *BMJ Open* 2012;2(3).
(11) McGuinness B, O'Hare J, Craig D, Bullock R, Malouf R, Passmore P. Cochrane review on 'Statins for the treatment of dementia'. *Int J Geriatr Psychiatry* 2012 April 2.
(12) Morris JK, Burns JM. Insulin: An Emerging Treatment for Alzheimer's Disease Dementia? *Curr Neurol Neurosci Rep* 2012 July 13.
(13) Shemesh E, Rudich A, Harman-Boehm I, Cukierman-Yaffe T. Effect of intranasal insulin on cognitive function: a systematic review. *J Clin Endocrinol Metab* 2012 February;97(2):366-76.
(14) Cunnane S, Nugent S, Roy M et al. Brain fuel metabolism, aging, and Alzheimer's disease. *Nutrition* 2011 January;27(1):3-20.
(15) Gustaw-Rothenberg K, Lerner A, Bonda DJ et al. Biomarkers in Alzheimer's disease: past, present and future. *Biomark Med* 2010 February;4(1):15-26.
(16) Mosconi L, De SS, Rusinek H, Convit A, De Leon MJ. Magnetic resonance and PET studies in the early diagnosis of Alzheimer's disease. *Expert Rev Neurother* 2004 September;4(5):831-49.
(17) Henderson ST, Vogel JL, Barr LJ, Garvin F, Jones JJ, Costantini LC. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. *Nutr Metab (Lond)* 2009;6:31.
(18) Krikorian R, Shidler MD, Dangelo K, Couch SC, Benoit SC, Clegg DJ. Dietary ketosis enhances memory in mild cognitive impairment. *Neurobiol Aging* 2012 February;33(2):425-7.
(19) Veech RL. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2004 March;70(3):309-19.
(20) Seneff S, Wainwright G, Mascitelli L. Nutrition and Alzheimer's disease: The detrimental role of a high carbohydrate diet. *European Journal of Internal Medicine* 2011 April;22(2):134-40.
(21) Henderson ST. High carbohydrate diets and Alzheimer's disease. *Med Hypotheses* 2004;62(5):689-700.
(22) Scarmeas N, Luchsinger JA, Mayeux R, Stern Y. Mediterranean diet and Alzheimer disease mortality. *Neurology* 2007 September 11;69(11):1084-93.
(23) Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Effectiveness of the Mediterranean diet: can it help delay or prevent Alzheimer's disease? *J Alzheimers Dis* 2010;20(3):795-801.
(24) Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. *BMJ* 2008;337:a1344.
(25) Birks J, Grimley EJ. Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev* 2009;(1):CD003120.
(26) Weinmann S, Roll S, Schwarzbach C, Vauth C, Willich SN. Effects of Ginkgo biloba in dementia: systematic review and meta-analysis. *BMC Geriatr* 2010;10:14.
(27) Isaac MG, Quinn R, Tabet N. Vitamin E for Alzheimer's disease and mild cognitive impairment. *Cochrane Database Syst Rev* 2008;(3):CD002854.
(28) Mazereeuw G, Lanctot KL, Chau SA, Swardfager W, Herrmann N. Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. *Neurobiol Aging* 2012 July;33(7):1482-29.
(29) Loef M, Walach H. Fruit, vegetables and prevention of cognitive decline or dementia: a systematic review of cohort studies. *J Nutr Health Aging* 2012;16(7):626-30.
(30) Malouf R, Grimley EJ. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. *Cochrane Database Syst Rev* 2008;(4):CD004514.
(31) Pogge E. Vitamin D and Alzheimer's disease: is there a link? *Consult Pharm* 2010 July;25(7):440-50.
(32) VanItallie TB, Nufert TH. Ketones: metabolism's ugly duckling. *Nutr Rev* 2003 October;61(10):327-41.
(33) VanItallie TB, Nonas C, Di RA, Boyar K, Hyams K, Heymsfield SB. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study. *Neurology* 2005 February 22;64(4):728-30.
(34) Olfson M, Blanco C, Liu SM, Wang S, Correll CU. National Trends in the Office-Based Treatment of Children, Adolescents, and Adults With Antipsychotics. *Arch Gen Psychiatry* 2012 August 6;1-10.
(35) Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). *Heart* 2012 June;98(12):920-5.
(36) Henig YS, Leahy MM. Cranberry juice and urinary-tract health: science supports folklore. *Nutrition* 2000 July;16(7-8):684-7.
(37) Wang CH, Fang CC, Chen NC et al. Cranberry-Containing Products for Prevention of Urinary Tract Infections in Susceptible Populations: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Arch Intern Med* 2012 July 9;172(13):988-96.

RESEARCH REVIEW

Evidence Based Medicine: Fact or Fantasy?

by William R. Ware, Ph.D.

INTRODUCTION

International Health News attempts to present results of medical research that are thought to be of interest to individuals who desire to retain their health or solve some medical problem. Thus the above is an important question. The books listed in the July-August IHN provide an excellent reading list and a source of documentation for some aspects of this topic.

Imagine a medical student inquiring in class: *Professor, how do we know that these vaccines like the one for mumps are really almost 100% effective?* Professor: *Because the companies that manufacture them are required to carry out extensive tests and submit results, in the US to the FDA, concerning the efficacy and safety questions. This process is an important aspect of evidence-based medicine.*

News Item, June 27, 2012 (Courthouse News Service): A primary care organization based in Alabama has filed a lawsuit against Merck after gaining access to a complaint filed in 2010 by two ex-Merck virologists who exposed what they alleged to be fraudulent testing designed to make the mumps vaccine appear to be 95% effective when it was far from that, and they claimed this had been going on for a decade with full knowledge of upper management. The implications with regard to both disease control and expenditures on less than satisfactory products (in fact allegedly fraudulent products) by both government and private health care systems, needs no further elaboration. Hundreds of millions of dollars are involved. Readers will recall that this was the company involved in the Vioxx scandal.

News Item, June 22, 2012 (*Wall Street Journal*). The two virologists also filed a whistleblowers lawsuit in U.S. district court for the Eastern district of Pennsylvania in 2010 which was ignored by the government but now has been unsealed and apparently will proceed. The lawsuit seeks an amount three times the damages incurred by the US plus the maximum amount allowed under federal whistleblower laws. The unsealing of this lawsuit prompted the above lawsuit in Alabama. Note these are simply allegations that have not been proven.

No reasonable, educated person would argue with the proposition that the practice of medicine should be based as much as possible on solid scientific evidence of efficacy, robust benefit to risk with both accurately defined and determined, while at the same time it should take into account the broad, individual characteristics of the patient that are considered and integrated into the physician-patient interaction and its outcome. At present, a significant fraction of all interventions and practices in modern medicine do not meet these evidence criteria simply because studies have never been or cannot be conducted or are deemed unnecessary. However, medicine is visualized as becoming more and more like a hard science and the phrase “scientifically demonstrated” or ”scientifically proven” is not uncommon in discussions of therapeutic issues.

While it has been around and evolving for decades, *Evidence Based Medicine* (EBM) is now the "in" thing, has its own journals, is central to medical education, and might be regarded by some as having achieved dogmatic or pseudo-religious overtones. Those devoted to promoting and enforcing EBM look with disdain on those who practice integrative or complementary medicine, reject most so-called natural therapies, look with great suspicion at any therapy based on case series or histories or other anecdotal evidence, exhibit attitudes that discourage "thinking outside the box," and hold the new era as obviously a huge advance over the days when the "art" and "clinical judgement" of medicine was based on years of personal experience combined with that of other practitioners and knowledge of published case histories. Historically this was an important aspect of the practice of medicine.

THE ISSUE OF EVIDENCE

Dr. Prathap Tharyan asks in the title of a recent paper, "Evidence based medicine: can the evidence be trusted?"[1] EBM by definition requires evidence. Evidence must be correct, not false or defective, must reflect reality, and as applied to the individual patient, be applicable and appropriate. The evidence component of EBM is obtained through research, laboratory and clinical studies, and product quality control, and the extent to which EBM can justify its current, exalted position in medicine depends on the level of both the scientific and ethical standards involved. All this is rather obvious. But there are serious problems with the evidence.[1] In fact, this is where the wheels come off the wagon, as will be discussed in this review. Interestingly, in discussions in the recent literature on the pros and cons of EBM, the validity, quality, and questions concerning fraud and dishonesty are rarely discussed or even viewed as issues. This is surprising. If one considers that one of the major activities in evidence based medicine in the end involve the writing of prescriptions, the administration of vaccines and the installation of devices, then the credibility and ethics of the companies involved are indeed an issue, and as the news items introduced above indicate, we can look more and more to the law courts and their public-domain documents to reveal some disturbing answers to this critical question. It should be unsettling to everyone from patients to those promoting dogmatic adherence to the precepts of EBM that companies supplying their main therapeutic agents are so frequently in the news in the context of congressional hearings concerning wrongdoing, and lawsuits, class action suits, and huge fines for criminal activity and huge civil case settlements.

GOOD STUDIES, BAD STUDIES

EBM arranges the various study types which constitute clinical evidence into hierarchies, of which there are a number of versions.[2] Generally, at the top sits the randomized controlled trial (RTC) and the meta-analyses of such trials. Near the bottom are so-called observational studies such as cohort follow-up studies, case-control studies and finally at the very bottom are case studies and expert opinion.[2] Studies involve observing events, measuring biomarkers or disease surrogates or other variables considered important, evaluating the success of a treatment by various measurement techniques, and observing adverse effects. However, it must be emphasized that a significant aspect of the science involved is the science of statistics, and in many instances, scientifically proven translates into statistically demonstrated as significant according to arbitrary but generally universally agreed upon standards. In fact, some would say that a heavy reliance on statistics distinguishes the soft from the hard sciences. This is not a criticism but recognition of the fundamental nature of studies involving variable human populations, or more generally, attempting to answer questions when large numbers of variables with wide ranges are involved, some of which can only be approximately measured. The science of EBM is more closely related to handicapping in horse racing than establishing the crystal structure of a protein, establishing the NMR spectrum of some organic molecule, or determining the properties on some new subatomic particle.

The rise of the RCT to be king of the mountain can in part be ascribed to the frequent phenomenon where negative RCTs contradict observational studies, in some cases observational studies which have had a large impact on clinical practice.[3] Thus the growing attitude that one cannot trust observational studies, even if they are large. Critics of observational studies can list a number of what they view as sensational failures, and hormone replacement therapy is one of the most commonly cited examples. In fact the real reasons for this disagreement and in fact other cases of disagreement are still being debated, and the criticism is an oversimplification. Furthermore, observational studies

are probably the best way to find adverse drug effects, the only way to study toxins which no one would willing be exposed to in a RCT, and the only practical approach to many question regarding health such as nutrition and lifestyle. But observational studies are merely hypothesis generating, they do not prove a causal relationship. Nevertheless, they can be part of a body of convincing circumstantial evidence regarding causality which in some cases cannot be easily dismissed. Observational studies thus have a place in EBM, but one that is controversial and debated.

Clinical trial results are of great financial significance to the companies involved and most trials are sponsored, executed and interpreted by companies. Thus there is a real potential for conflict of interest, bias, the temptation to rig studies, cheat, lie, conceal data adverse to the company interests, alter results to obtain an indication of benefit, play games with the statistics, and manipulate the regulators. These practices indeed occur and have generated a considerable popular and academic literature partly based on hard evidence from the public records of numerous court proceedings, leading to convictions and billions in criminal fines and civil settlements.

Suspicions are also raised when studies supported by industry and those with private or government support which address the same issue are compared. Industry supported studies almost always achieve positive results, but when the sponsor has no financial interest, the percentage of positive studies drops dramatically. Since the vast majority of clinical trials are sponsored by the industry, this gives one pause to reflect on the integrity of the main pillar holding up EBM.

Clinical studies are frequently farmed out to commercial study providers who then run them, in some instances with little oversight from the sponsor and in countries with few regulations concerning the ethical conduct of medical research. If one ignores ghost writing, academic involvement in clinical trials has dropped dramatically in recent years. In some studies recruited participants are hired guinea pigs drawn from a narrow social stratum not representative of the population visualized as end users of the drug or treatment.[4] Companies are able to control the data collection so the individual investigators may never see the whole body of results. This is a problem with the multicenter studies that EBM likes so much. The hiring of ghost writers for important clinical papers presenting results in major journals is common practice. The ghost writer of course works for the sponsors. Academics not directly involved with the design or conduct of the study put their names on the journal articles presenting the results to provide credibility.

Documents obtained under court order and entered into the public domain have become a gold mine for individuals interested in documenting the inner workings of the pharmaceutical industry in the context of both clinical studies and marketing. It is amazing that these researchers can get their results published in major journals. Any student of this subject will soon conclude that the answer to the question posed by Professor Tharyan is no! *The evidence cannot be implicitly trusted, even though many studies are undoubtedly honest and unbiased.* It is not clear that the present system can overcome these problems, although there is considerable effort being expended to curb some of the practices which seriously undermine the credibility of EBM.

SPIN THE RESULTS

Another issue concerns the standards for acceptable efficacy. RCTs frequently count events in the treated and control groups. From this can be calculated the absolute benefit or harm. If 3% in the treated group and 4% in the control group experienced an endpoint event (such as a gastric bleed, stroke, heart attack etc. depending on what was being studied), then the absolute risk reduction was 1% and the number need to treat (NNT) over the period of the trial to prevent one event was 100, and 99 were treated with no benefit and in some cases at considerable cost and perhaps harm. But the relative risk reduction was one percentage point starting from 4% and going to 3%, or 25%, a much more impressive result!

Studies also compute odds ratios or hazard ratios which also yield relative risk reduction results. An odds ratio of 0.75 represents a risk reduction of 25%. But these odds or hazard ratios can be subjected to extensive statistical manipulation to correct for confounding and even more sophisticated analysis can be done to correct for other aspects of the trial. For these measures of trial results, focus

shifts to the so-called confidence interval (CI) as a measure of statistical significance. The universally used CI gives the range for the ratio that has a 95% chance of not occurring by chance, and for the result in question to be statistically significant, the CI must not contain 1.00, the result if there is no effect. However, one sees studies, which call attention to what is viewed as an important result when the odds ratio is 1.01, a 1% *relative* risk, and presented as significant because the confidence interval is 1.0005 to 1.015. This is charitably called a small or modest size effect, but in fact is probably meaningless and merely reflects low standards of both the journal involved and the referees used. Conservative clinicians like very large so-called size effects, e.g. odds ratios of 0.2 or smaller or 2.0 or even greater before they show much interest. This reflects concern that for ratios near 1.00, the probability of unrecognized confounding is high, even if the result is statistically significant. Furthermore, statistical significance does not automatically mean clinical significance, a point that seems to have been forgotten by some journal editors, referees and the media.

Trial results look best when presented in relative terms and this is the almost universal practice. A 40% risk reduction is much more impressive than needing to treat 100 patients to produce one beneficial result. The patient is impressed with 40%, has no way of knowing what is really going on and cannot calculate the absolute change from the relative change without more data. Relative benefits are emphasized in most guidelines. The NNT may be downplayed or never mentioned to the patient or even unknown to the physician. But these are population studies, and the NNT represents how many in the population studied are needed to be treated to prevent one adverse event or result in a beneficial event. The question then of course arises, what is an acceptable number? There is no consensus. It is a judgement call and in fact arbitrary, especially when the harms are poorly identified, if at all. How much important should be assigned to probabilities derived from large trial populations when the issue is whether or not to treat an individual patient. Population based studies in fact involve a wide range of patient characteristics and in some cases a rigged population.[1]

Critics claim that harmful events are downplayed, studies are too short to reveal them, may be rigged to produce low numbers of such events, post-approval reporting after marketing is underway is negligible, and thus the risk/benefit analysis is complex or frequently impossible. Many published studies make it difficult if not impossible even to derive NNT or NNH from the tabulated data.

RCTs involve groups of participants that may not be representative of the populations needing treatment for a disorder. After all, in some cases participants are recruited by paying physicians rather large sums per subject to get them into a study. In other cases, the subjects are recruited via tabloid class newspaper advertising and paid to participate (the guinea pigs). Studies that are farmed out to commercial firms take over everything including recruiting and frequently operate in small countries with minimal supervision and strong incentives to please the sponsoring company. One can also question for many studies the required table in the published report comparing all the characteristics of the placebo and treated groups. Some study designs have a pre-trial period where subjects deemed unsatisfactory in terms of the desired outcome are disqualified, an obvious source of potential bias impacting the application of the results to the intended end-user population of the drug or procedure in question.

Modern statistical software allows those doing the statistical analysis to effortlessly try a large number of approaches, variations and assumptions and view the end results that will appear in the final publication. Most readers of the results will be unable to judge if the most appropriate statistical approach was used or if there was bias in statistical manipulation.

THE META-ANALYSIS—A PLATINUM STANDARD?

If the RCT is the gold standard strived for in EBM, then the meta-analysis (adjusted or weighted pooling or grouping of study results) of RCTs has been called the *Platinum Standard*.[5] Meta-analyses are held in high regard and have a profound impact on guidelines and views of the merits of a therapy. But the meta-analysis is not a simple exercise. The results have utility only if the studies selected are of quite similar populations, i.e. homogeneous. Prior to amalgamating the data, the reviewers must select and then assign weights to the studies according to a set of guidelines. These weights can, for some analyses, determine whether the results favour treatment or placebo, or

treatment A vs. treatment B. There is an unsettling and disturbing objectivity problem in this process. This was recently demonstrated when a high level of variability was found when a group of raters from the same department were given 165 trials and asked to rate according to the Cochrane Collaboration guidelines for bias assessment.[6] Not only was the inter-rater agreement poor, the assignments significantly impacted the results of the subsequent meta-analysis.

In addition, reviewers cannot arbitrarily exclude studies. If studies with a negative outcome that have been suppressed or concealed so it is impossible to consider them, this invalidates the whole analysis. This was the case with meta-analyses on the efficacy of antidepressants. When they were repeated after the FDA revealed and provided negative study results that qualified for inclusion but were suppressed, the beneficial effect disappeared completely except for very severe depression, a result that caused quite a stir in the halls of psychiatry.[7,8] The point is that meta-analyses are not simply a statistical tool for improving or achieving acceptable significance by combining studies, they represent an exercise that offers its own opportunity for bias and lack of objectivity, which undermines the credibility of their position as the platinum standard of EBM. Anyone can do the calculations by simply purchasing one of a number of commercial computer programs, but then the challenge begins. The above considerations become more critical when a large number of studies of variable size, most of which fail to be statistically significant, yield through meta-analysis a small effect size (e.g. an odds ratio of say 0.9 for a protective benefit). Is it clinically significant?

BMJ EXPOSES HUGE PROBLEMS IN CLINICAL STUDIES

Last year the *British Medical Journal* put out a call for papers concerning extent, causes and consequences of unpublished evidence from clinical trials (not infrequently with negative or null results or showing too many adverse side effects). On January 3 and 4 of this year the results were published online. Lehman and Loder in their editorial[9] review the highlights of this cluster of papers, prefacing their remarks by the comment that it may come as a shock to clinicians that the evidence from clinical trials they depend on for guidance is not necessarily relevant, reliable or properly disseminated. In fact, a large proportion of evidence from human trials is unreported and much of what is reported is done so inadequately. One study incorporated unpublished data into existing meta-analyses of nine drugs approved by the FDA between 2001 and 2002. This reanalysis produced identical results of efficacy in only 7% of studies and the remainder were equally split between showing greater or lesser benefit.[10] Lehman and Loder comment that most of the interventions currently in use and recommended in guidelines are based on trials carried out before mandatory pre-trial registration, and they describe the reported difficulties investigators have in acquiring a complete set of data, where searching for and obtaining data from unpublished trials can take several years.

One paper examined the impact of the requirement that, as of 2005 prior trial registration became a condition of later publication in many journals, and the additional requirement for publicly funded studies in the US, a summary report must be published within 30 months of study completion. Ross *et al*[11] found that, for publically funded studies between 2005 and 2008, more than half of completed trials failed to report within the required time. Another study found compliance with a regulation of 2007 that changed the time to 12 months for a summary of completed studies was a dismal 22%.[12]

The editorialists also comment on the interesting phenomenon that using the search item "randomized controlled trial" misses a large number of papers indexed by Medline (PubMed) which adds to the difficulties of searching for trials when doing systematic reviews and meta-analyses. Their overall conclusion:

"What is clear from the linked studies (this BMJ set) is that past failures to ensure proper regulation and registration of clinical trials, and a current culture of haphazard publication and incomplete data disclosure, make proper analysis of the harms and benefits of common interventions almost impossible for systematic reviewers. Our patients will have to live with the consequences of these failures for many years to come….The evidence we publish shows that the current situation is a disservice to research participants, patients, health systems, and the whole endeavour of clinical medicine."

Not a good report card but consistent with a considerable body of earlier critical literature and highly relevant to the issue of the trust one can place in the evidence used in EBM.

TWO CONCRETE EXAMPLES

Two examples should make everyone think twice about the evidence aspect of EBM. One is the Vioxx saga involving Merck and the other the infamous Study 329 from GlaxoSmithKline concerning the pediatric application of the drug Paxil. Both have involved lawsuits and both in retrospect put patients given these drugs at increased risk of serious side effects that were, on the basis of court records and other evidence, suppressed by the manufacturers. Interestingly enough, the media played an important role in bring these scandals to the attention of not only the public but congress and various state attorneys general. Eric Topol's book[13] contains a first-hand description of the Vioxx story and David Healy's book[14] deals with the Paxil matter, and as well a critical analysis of the Paxil case has appeared in the medical literature.[15] The Paxil story provides a good example of ghost writing. Its key study report published in a high-impact journal was in fact written by a ghost writer employed by a private company engaged in preparing articles for publication.[14]

In *Pharmagedon* (Chapter 4) David Healy discusses a serious issue that was involved in both of these scandals, the practice of restricting access to trial data even for individuals involved in the study and authoring reports.[14] His discussion includes the impact of commercial research organizations and off-shore studies and multicenter studies, all of which also provide the opportunity to restrict knowledge of the full data set for a study such that aspects unfavourable to the sponsor are buried within the veil of company secrecy. He also describe the practice of coding as non-compliant those subjects that in fact suffered serious side effects that should have been reported as such, thus providing a rich source for bias.

THE BENEFIT TO RISK ISSUE

The proper implementation of EBM must obviously consider both beneficial results and harmful events. Otherwise, it is a farce. History teaches that adverse events are suppressed, underestimated, studies rigged to give low adverse event rates, and there are even statistical problems with the analysis of the probability of adverse events that are different than beneficial results. Vioxx has become the textbook example of marketing with the full but suppressed knowledge of serious side effects. This practice has resulted in a number of pharmaceutical companies becoming heavily fined felons and settling for huge amounts in civil suits. There is also the fundamental problem that clinical studies of efficacy are too short and too small to uncover what in the long-run can be side effects serious enough to highly discourage the use of an intervention, but this is unknown at the time of regulatory approval and the immediate intense marketing including expensive TV ads at prime time, especially on the major networks.

GUIDELINES

An essential aspect of EBM involves the official guidelines from professional societies and governments. They provide a perceived solution to the many problems associated with critical appraisal, keeping up with the literature, and knowing what the "experts" in a field think. Adherence to guidelines are being used to judge physician performance in group settings or hospital staff settings and then used to pressure adherence to EBM and discourage the use of old fashioned judgement and intuition and treatment based on experience. Some physicians no doubt find this highly offensive. It is also an issue in reimbursement or insurance coverage of treatments. In the limiting case scenario, accountants and MBAs will take over the control of how medicine is practiced. Insurance companies already play a significant role in exercising treatment control and in part this is based on guidelines, expert opinion and the dictates of EBM.

Electronic records allow the matching of patient presentation and test results with treatment received and allow easy analysis of medical staff performance, even providing a list of nonconformists. Hospital discharge prescriptions can be easily compared with guidelines with the same result. This whole approach is based on the results of studies, some of which, considering past experience, are certain to be wrong, and on guidelines, some of which are strongly influenced if not more or less written by the pharmaceutical industry, and some of which do not even represent the unanimous

views of the writing panels but reflect medicine by democratic vote. This is also the way regulatory drug approval decisions are made, if one takes a charitable view. One can imagine the endpoint where a patient sits at a computer terminal and answers a series of question concerning the reason for an office visit, and a nurse or secretary inputs such data as blood pressure, weight, and lab results. The computer then examines the patient data base and decides on the most probably diagnosis and the printer spits the out the analysis and a prescription. The physician on duty, like the supervisor of a set of trading desks on a bank's bond trading floor, checks this over and may be satisfied without a classical office visit. This is not that far removed from what goes on in the 10 minute office visit if guidelines rule the practice. It also illustrates the concern of many physicians that the full enforcement of the EBM culture will destroy personal medicine as they know and practice it.

Success in treating to targets is easy to monitor from electronic records. But to make this a physician or clinic performance parameter ignores the controversial aspect of some high-profile targets. For example, a recent editorial which appeared in a major journal was directed at the developers of new cholesterol treatment guidelines (ATP—IV) and provided three reasons to abandon LDL targets.[16]

- There is no scientific basis to support treating to LDL targets.
- The safety of treating to LDL targets never been proven.
- Tailored treatment is a simpler, safer, more effective and a more evidence-based approach.

The goal of this challenge was to encourage change that would ensure a reduction of under- and overtreatment and as well promote appropriate treatment with statins. Blood pressure targets provide another example.[17,18] and along with LDL, represent common targets in wide clinical use today. Raging controversy regarding screening for breast and prostate cancer has been in the headlines for over a year.

Guidelines, viewed as a centerpiece in EBM, are in reality only partly based on RCTs and associated meta-analyses. Other evidence of necessity is given weight. The writing groups must also rely on their own expert clinical experience and may be influenced by their clinical background and a variety of biases. Disagreement may be resolved by a process which results in guidelines becoming in part a democratic exercise. The end results then appear in journals of the highest impact and become like a catechism with profound influence and held up as how to practiced EBM.

Thus standards of practice have their limitations, not only because they can be very controversial yet accepted, but because they include a one-size-fits-all approach. This approach works very well when you take your BMW in to the dealer with a problem. Guidelines and protocol will probably be followed rigorously. Highly trained technicians analyse the problem by plugging the car into a computer. The problem is identified, will probably correspond to the "patient's" symptoms and presentation, and will be fixed and the car then tested. But cars are simple compared to humans.

IMPLICATIONS

Thus as the designers and followers of EBM set forth to view and use the evidence, they are confronted with studies that may be flawed, rigged, biased, present an incomplete picture of the totality of the data or poorly designed and then consider with great respect meta-analysis of multiple studies which also have the potential for significant if not fatal flaws. Many of those who believe they must rely on the evidence of EBM are not even skilled or familiar with biostatistics and studies have suggested that many are unable to knowledgably analyze tables of results in the papers that contain the evidence, even if they overcome the subscription firewall to full-text. Such are the problems when dealing with the complex problems of human illness in an atmosphere of severe financial conflicts of interest and huge and mind boggling amounts of money at play, while providers grapple with continuing to financially support health care in the face of a huge demographic problem and a culture that pays only lip service to true, effective prevention.

The concept of EBM is an oversimplification of complex therapeutic or screening problems, is only scientific in the context of statistics, and as Eric Topol points out in his book *The Creative Destruction of Medicine*, EBM must evolve to become personalized medicine, not population medicine.[13] But

EBM permeates and distorts guidelines which are key tools in everyday practice. The scientific basis is mostly the science of statistical evaluation of data gathered in population studies, and all that results are sets of probabilities. Thus the above analogy to handicapping horse races. Viewed critically, EBM, although undeniably a significant step in the right direction, appears to be a fantasy and at best simply work in progress with a lot remaining to be accomplished. Yet it provides a pedestal on which critics of alternative and integrative medicine can stand and forcefully present their condemnation in the name of "science."

Some features of the problem of why studies cannot be trusted are:

- Dose selected is too small.
- If a natural product is involved, doses in the treated arm not significantly greater than the intake in the placebo group.
- Placebo easily detected.
- Pre-trial exclusions rig the study in favour of the treatment.
- Selection of the study population prior to randomization biases the study in favour of benefit.
- The population studied does not correspond to the intended or expected users of the treatment or drug.
- The drug or treatment works only on a single phenotype, but the non-responders dilute the results to insignificance. A potentially important benefit missed.
- The study population is too small.
- Errors occur in accessing compliance.
- Drop-out rate too high.
- The placebo group is contaminated by individuals taking the treatment or drug or undergoing a screening procedure.
- The endpoint is a surrogate and thus cannot be rigorously extrapolated to clinical benefit which was not measured.
- Critical parameters are omitted from the data used to show the treatment and control groups are essentially equivalent.
- Multicenter studies differ center by center on critical aspects of one or more of the aspects of the study.
- Study data selectively included in the statistical analysis, especially when multicenter studies are involved and each center sees only its own data.
- Statistical analysis may be done repeatedly using a variety of different approaches and assumptions until the desired result is obtained.
- Several studies are conducted, but only the one with a favourable result is revealed, with the negative studies suppressed.

J.P. Ioannidis presented four reasons why most published research findings are false.[19]

- The smaller the studies, the less likely the findings are true.
- The smaller the effect, the less likely the findings are true.
- The greater the financial and other interests involved, the less likely the findings are true.
- The hotter the scientific area, the less likely the research results are true.

Finally, while it is widely accepted that the gold standard for EBM is the RCT, this in itself has the potential to limit and retard successful therapies, perhaps even for decades or forever. Bradford Hill, the architect of the RCT, remarked on the dangers of giving excessive prominence to this type of trial

"*Any belief that the controlled trial is the only way would mean not that the pendulum has swung too far but that it had come right off the hook."*[20]

There are many critical questions in medicine that cannot be answered by RCTs. The approach is either impossible to implement or unethical or too expensive. The RCTs needed for drug approval cost mind boggling amounts of money and drive the industry to farm out such studies to third world

countries and use human guinea pigs. All of this provides a severe impediment to progress and reaching a goal of having a truly reliable knowledge base. Critics of alternative medicine should consider the danger of rejecting treatments with clear benefit unattainable by conventional approaches simply because of the absence of RCTs. It will be clear that EBM has "gone over the cliff" when RCTs are required for hospitals to continue using anti-venom to treat snake bite.

While EBM discourages or even penalizes thinking "outside the box." EBM encourages development and testing of patentable drugs which were suggested by the beneficial action of some natural product and then slightly modified to make them eligible for patent protection when the natural products might work better—something that would never be determined. In general, only private or government funds are available to finance RCTs of natural products, and both funds and interest appears severely limited. Most nutritional supplements will never undergo RCTs, and may even be outlawed because of the absence of "scientific evidence," an outcome that is more probable than most realize. In the US, companies cannot even simply list citations to studies in the peer-reviewed literature from top universities suggesting benefit of their product without triggering FDA disapproval which can even take the form of a swat team raid with crushing confiscation of property and records. Demonstrating with a RCT that a substance or intervention is harmful is in generally impossible to implement and unethical. Thus it seems clear that rather than deify EBM, a rationalization of evidence standards and medical and regulatory practice is needed in order to prevent the unintended consequences. Post-approval and marketing surveillance has been demonstrated to have fundamental problems which may never be solved, although efforts are being made.

Advocates of EBM can shrug off criticism by simply pointing that no system is perfect and this is the best we have. This is obviously debatable since the alternative is a mixture of evidence taken with a grain of salt and old fashioned clinical experience, intuition and judgement, and the recognition that the patient is a single individual not necessarily sufficiently like the average study participant to make study results and guidelines necessarily relevant.

The bottom line: how can an "operating system' with its rules and protocols such as EBM prove satisfactory when it is based on "scientific" data from studies where a significant number will later be demonstrated as false, dishonest and side effects understated, perhaps intentionally.[8,19]

REFERENCES

(1) Tharyan P. Evidence-based medicine: can the evidence be trusted? *Indian J Med Ethics* 2011 October;8(4):201-7.
(2) Rawlins M. De Testimonio: on the evidence for decisions about the use of therapeutic interventions. *Clin Med* 2008 December;8(6):579-88.
(3) Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005 July 13;294(2):218-28.
(4) Elliott C. *White coat black hat. Adventures on the dark side of medicine*. Boston: Beacon Press; 2010.
(5) Stegenga J. Is meta-analysis the platinum standard of evidence? *Stud Hist Philos Biol Biomed Sci* 2011 December;42(4):497-507.
(6) Hartling L, Ospina M, Liang Y et al. Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. *BMJ* 2009;339:b4012.
(7) Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med* 2008 February;5(2):e45.
(8) Ioannidis JP. Effectiveness of antidepressants: an evidence myth constructed from a thousand randomized trials? *Philos Ethics Humanit Med* 2008;3:14.
(9) Lehman R, Loder E. Missing clinical trial data. *BMJ* 2012 January 3;344.
(10) Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *BMJ* 2012 January 3;344.
(11) Ross J, Tse T, Zarin D, Xu H, Zhou L. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *BMJ* 2012 January 3;344.
(12) Prayle A, Hurley M, Smyth A. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 2012 January 3;344.

(13) Topol E. *The creative destruction of medicine. How the digital revolution will create better health care*. New York: Basic Books (Perseus); 2012.
(14) Healey D. *Pharmagedon*. Berkeley and Los Angeles: University of California Press; 2012.
(15) Jureidini J, McHenry L, Mansfield P. Clinical trials and drug promotion: Selective reporting of study 329. *International Journal of Risk & Safety in Medicine* 2008;20:73-81.
(16) Hayward RA, Krumholz HM. Three Reasons to Abandon Low-Density Lipoprotein Targets. *Circ Cardiovasc Qual Outcomes* 2012 January 1;5(1):2-5.
(17) Arguedas JA, Perez MI, Wright JM. Treatment blood pressure targets for hypertension. *Cochrane Database Syst Rev* 2009;(3):CD004349.
(18) Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;338:b1665.
(19) Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005 August;2(8):e124.
(20) Hill AB. Reflections on controlled trial. *Ann Rheum Dis* 1966 March;25(2):107-13.

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