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In recent issues of IHN a recurrent theme has been the failure of therapies to perform effectively as measured by the number needed to treat (NNT) to prevent one adverse event. Numbers ranging from 50 to well over 100 seem to be common as modern medicine attempts to prevent the adverse events associated with the chronic diseases of aging. Large relative risk reductions are balanced by dismal NNT. One is left to wonder if, rather than take a drug that will benefit only one out of fifty or one hundred, it is time to consider alternative approaches. In other words, there may be something better, but if it involves a natural product it cannot pass through the pearly gates of evidence-based medicine to achieve membership in the approved therapy set. Alternative or integrative approaches to treatment are of course not a new idea. In fact, all one has to do is read Dr. Mark Hyman's book "Ultraprevention" to realize that's there are parallel universes out there, one that involves personalized, integrative medicine which may fill the void created by the pharmacy full of pills and potions that merely deal with symptoms. All one has to do is think about the fact that there are shelves full of anti-hyperglycemic drugs and yet diabetics, even with well controlled markers, simply get worse and worse until the point is reached where one of the complications will probably take them down. However, individuals with a chronic disease such as diabetes or heart disease or mild cognitive impairment may not realize that there are alternatives, and that there are highly qualified medical doctors using the whole person system approach that can halt or reverse their downward spiral caused by health problems.

This issue features primary prevention of breast cancer. This is followed by a critique of a paper on red meat and atherosclerosis and the flip-flop on statins by the Cochrane Collaboration. Brief reports are provided for aspirin and melanoma, surprising results for blood pressure and the risk of coronary heart disease in diabetics, as well as dietary patterns for the prevention of Alzheimer's disease and the risk of diabetes associated with mercury exposure when young.

Suggestions for summer reading in the health-related subjects are also provided in this issue rather than as usual in the July-August issue. Included is a review of Mark Hyman's new book "The Blood Sugar Solution", which provides an excellent example of whole-person integrative medicine.

And finally, 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

BREAST CANCER. PRIMARY PREVENTION WITH DRUGS

The US Preventive Services Task Force recently published a draft of new recommendations concerning the use of estrogen blocking drugs in the primary prevention of breast cancer.[1] Tamoxifen and raloxifene have been recommended for a number of years for women who are at higher than average risk for breast cancer although tamoxifen is more commonly used in secondary prevention (recurrences) and raloxifene is most often recommended to prevent fractures in women with osteoporosis, although tamoxifen also decreases the fracture risk. An important issue is that in the context of primary prevention, very long-term use of these drugs is envisioned and therefore a risk/benefit analysis is important.

The USPSTF recommendations are based on 4 randomized placebo-controlled trials of tamoxifen and 2 for raloxifene. The tamoxifen studies in general involved an age range of 30-70 years and the presence of significant risk for breast cancer. The two raloxifene studies looked at post-menopausal women, one involving women with low breast cancer risk, the other a range of risk. For invasive breast cancer, tamoxifen was found to reduce the risk by 30%, raloxifene by 56%. For ER+ breast cancer, the numbers were 42% and 67% respectively. However, readers of IHN are by now familiar with how relative risk reductions distort the true benefit. The USPSTF also provides the events reduction over 5 years per 1000 women (n in the table below) which allows the calculation of numbers needed to treat to obtain one beneficial result, i.e. prevent the diagnosis of one cancer case. These numbers along with the range in which 95% of the numbers would be expected to fall are given in Table 1. Table 2 provides the same analysis for the three adverse side effects that achieved statistical significance in these studies.

Table 1. Absolute benefits associated with the prevention of breast cancer with either tamoxifen or raloxifene from placebo controlled studies

	Tamoxifen		Raloxifene	
Outcome	n	NNT (95% CI)	n	NNT (95% CI)
Invasive breast cancer	7	142 (83-250)	9	111 (71-250)
ER+ breast cancer	8	125 (77-333)	8	125 (83-250)

Table 2. Adverse side effects associated with treatment with tamoxifen or raloxifene

	Tamoxifen		Raloxifene	
Harmful outcome	n	NNH (95% CI)	n	NNH (95% CI)
Thrombolytic events	4	250 (111-500)	7	143 (66-500)
Pulmonary embolism	2	500 (167-10,000)		NS
Endometrial cancer	4	250 (100-1000)		NS

n = number of benefits (event reductions) compared to placebo per 1000 women over 5 years of treatment.
NNT = number needed to treat to produce one benefit with the 95% confidence interval over 5 years.
NNH = number needed to treat to produce one harmful event over 5 years.
NS = not statistically significant risk.

Thus while there is statistically significant benefit and large relative risk reduction, the numbers needed to treat are large with wide confidence limits. Even the NNT at the lower limit of the range is in all but one instance > 100. Treat > 100 women to prevent one cancer does not seem like an attractive proposition except for the drug vendors. Anyone not conditioned to the mindset of mainstream medicine will probably think that these numbers represent a drug therapy that does not work very well and some would consider that a gross understatement. In fact it is clear from the discussion in the USPSTF that some women reject the suggestion of preventive drug therapy for this very reason. They want something that works to provide significant protection if they are going to commit to years of taking a drug.[1]

The counter argument is that the number needed to treat to harm (NNH) is larger, suggesting a net benefit. However, the above are population numbers, and while most of the 6 study cohorts were at elevated risk of breast cancer, the risk/benefit analysis needs to take into account the risk of side effects and the benefits of drug treatment as a function of the projected risk of invasive breast cancer. This is not a simple task, but an analysis published in 2011 provides some guidance.[2] For invasive breast cancer treated with tamoxifen the cross-over from negative to positive benefit is between 3.5 and 4% for the 5-year projected risk of this cancer for the age range 50-59. For ages ≥ 60 years, benefit is still not seen at even 7% 5-year risk. On the other hand, for raloxifene, benefit was seen at any 5-year rate above 1.5%. These results are restricted to white non-Hispanic women with uterus. Different numbers apply to women who have had hysterectomies.

The USPSTF suggests a threshold for drug intervention for primary prevention of ≥ 3% 5-year risk of developing breast cancer, but some might argue that this is an oversimplification and women concerned with this issue need individualized expert advice and risk/benefit analysis in order to make an informed decision.

It is interesting to compare the above results with those recently reported for another class of drug also under study for primary prevention, the so-called aromatase inhibitors, which block conversion of peripheral androgens to estrogens. The enzyme aromatase also is found within breast tissue and causes local production of estrogens. Inhibitors have been used in treating metastatic breast cancer and preventing collateral breast cancer incidence.[3] Our interest here is in primary prevention.

A study recently reported involved a 3-year follow up of postmenopausal women (median age 63 years) with a median 5-year risk of breast cancer estimated at 2.3% on entry; 4560 women were assigned to either exemestane or a placebo.[4] For all invasive breast cancers the relative risk reduction was 65% and for ER+ cancers it was 73%. Enthusiasm for these large relative risk reductions is however tempered by the large numbers needed to treat over 3 years to prevent all invasive cancers or ER+ cancers. The numbers were 107 and 115 respectively, based on the absolute risk reductions reported. While data extended to 5 years, few women completed 5 years of therapy. There were no significant differences between the treatment and placebo groups in terms of the incidence of skeletal fractures, CVD events, other cancers or treatment-related deaths, and minimal quality-of-life differences were reported. While it is possible that a longer term study involving an adequate number of subjects completing therapy would yield a smaller number needed to treat to prevent one invasive breast cancer, no such study appears to have reported. Trial of another aromatase inhibitor, anastrozole, vs. a placebo does not appear to have reported.

What does one conclude? Drug therapies for primary prevention have impressive relative risk reductions, but the absolute risk reductions are very small and suggest the urgent need for drugs that "work" if is believed that needing to treat around 100 or more patients over 3-5 years to prevent one cancer is just not good enough. And for the estrogen blockers such as tamoxifen, as discussed above there appear to be recognized risk/benefit issues as well.

AMERICAN CANCER SOCIETY 2012 GUIDELINES ON NUTRITION AND PHYSICAL ACTIVITY FOR BREAST CANCER PREVENTION[5]

Nutrition and physical activity are the principal modifiable risk factors since genetic and reproductive factors are not modifiable. The guidelines emphasize the following as evidence based:

- Increased body weight and weight gain during adulthood are associated with increased risk of breast cancer among postmenopausal but not among premenopausal women. Calorie restriction is suggested.
- Alcohol intake is widely recognized as having an adverse impact on risk of breast cancer. Even low levels of alcohol intake (> one drink a day) are associated with elevated risk.
- Research suggests that physical activity in its own right is a factor for risk modification independent of the association with weight and hormone metabolism. Numerous studies have shown that moderate to vigorous physical activity is associated with decreased breast cancer risk both for pre- and postmenopausal women.
- In observational studies (follow-up), a dietary pattern rich in vegetables, fruits, poultry, fish and low-fat dairy products has been associated with reduced risk of breast cancer, but the effect is small except for ER- tumors.
- Fat intake does not appear to be an issue.
- High intake of certain carotenoids from red and yellow foods may be protective.
- Do not smoke.

These are relatively old recommendations but contain what is now generally recognized as essentially a healthy diet pattern and lifestyle which when comprehensively followed produces rather dramatic cancer risk reductions. If all these recommendations were followed according to the published details, the absolute risk reduction compared to non-adherence yields a number of 5 individuals needed to comprehensively adhere to the recommendations over 20 years to prevent one incident cancer.[6] This was discussed in the May 2013 IHN and can be compared to the numbers needed to treat in the range of 100 discussed above for drugs.

As has been featured in IHN several times, there is considerable evidence concerning the anti-cancer properties of certain fruit and vegetable constituents that are natural substrates of the enzyme P450 CYP1B1, This enzyme is expressed as a protein only in cancer cells, and when these substances are metabolized, a cell toxin in produced that kills only the cancer cells. This appears to work on both circulating cancer cells and localized cancer cells (tumors). A commercial preparation called Salvestrol (Platinum) is available where the extracts combined have been selected which are substrates for CYP1B1 and yield metabolites of high, specific cancer cell toxicity. They are extracted by special techniques from blackberries, blueberries, strawberries and tangerine peel. The highest potency is found when the fruits are older varieties and organically grown.[7] Thus this product or other fruit polyphenol extracts may actually provide better primary prevention than drugs. Only clinical trials will provide answers, but the published case histories with Salvestrol suggest that this natural approach may be more successful than needing to treat over 100 to get one

beneficial result.[7-10] Employing Salvestrol also satisfies the almost universal desire for a pill as compared lifestyle and diet changes. But then, why not combine both approaches?

Salvestrols are of course never mentioned by mainstream medicine (they do not meet the requirements of evidence based medicine) although there is a considerable peer-reviewed literature concerning the biologically plausible mechanism which Salvestrols exploit.[11] We may have to wait years for the mandatory randomized controlled trials with power to produce significant results in the context of primary prevention with population incidence rates of only 1-2%. This is the way the system works. But Salvestrols are sold as a dietary supplement so currently we have a free choice. The most enthusiastic proponents and users are in fact Germany.[12]

Attention is also directed to a recent paper by Schaefer in *The International Journal of Phytotherapy*, Vol. 1, Issue 2 (available in full text free online). The paper concerns the development of blood tests for early cancer detection which exploit the properties of CYP1B1, but the research also puts the biological plausibility of Salvestrols on a very firm footing.

RED MEAT AND ATHEROSCLEROSIS

A study just published by Koeth *et al* which was featured in the media identified a nutrient in red meat, L-carnitine, as a potential trigger for coronary atherosclerosis via a metabolite produced in the gut.[13] The first sentence in the paper cites two references justifying the statement that consumption of meat in the developed world is linked to cardiovascular risk. In the context of the research project, the title of the paper and conclusions presented, one can safely assume they mean red meat. In the first study cited which concerned women 30-55 years of age, multivariable adjusted risks for red meat, excluding processed meat, failed to find a statistically significant risk when consumption in the lowest quintile was compared to any of the higher quintiles (see Table 2 in paper).[14] A second study, which involved a meta-analysis of 20 studies with coronary heart disease, stroke and diabetes as endpoints, found that consumption of red meat was not associated with higher incidence of coronary heart disease, stroke or diabetes provided the meat was not processed. This result applied to both men and women over a wide range of ages.[15] Thus the focus on red meat risk shifts to processed meats, and the argument that red meat contains L-carnitine, that L-carnitine is atherogenic through a metabolite produced in the gut, and this therefore explains the cardiovascular risk of red meat is deceptive and misleading since unless the meat is processed (ham, sausage, bacon etc), *the risk the authors are addressing apparently does not exist*. It is clear from their paper that they are not just concerned with processed meats.

The case presented by Koeth *et al* can be summarized as follows:

- Intestinal microbes convert L-carnitine to trimethylamine-N-oxide (TMAO).
- TMAO accelerates atherosclerosis in mice.
- Omnivorous humans produce more TMAO than vegans or vegetarians, and these latter lifestyles are associated with lower CVD risk.
- Human studies on high-risk individuals (70% male, 69% smokers, 28% diabetics, 72 % hypertensive, 85% hyperlipidemic, 74% prior coronary artery disease, 80% prior cardiovascular disease, 29% obese) had the lowest 3 year survival when their plasma L-carnitine and TMAO were highest and the highest survival when the L-carnitine was either high or low and the TMAO low.

In their conclusions they suggest that their discovery of the connection between L-carnitine ingestion, gut bacteria production of TMAO and thus increased CVD risk has broad health-related implications and provides a linkage between red meat and arthrosclerosis

pathogenesis. Furthermore they suggest that the role of gut microbiota suggest new potential therapeutic targets for preventing CVD.

In connection with the above human studies described by Koeth *et al*, it is of interest to consider another recent study which examined the effect of L-carnitine on secondary prevention of CVD.[16] Given the above profile of the cohort in the human study of Koeth *et al*, the comparison appears relevant. This meta-analysis of placebo controlled secondary prevention trials found therapeutic use of L-carnitine resulted in a 25% reduction in all-cause mortality, 65% reduction in ventricular arrhythmias, and a 40% reduction in angina symptoms in patients who had experienced a heart attack. Thus we have conflicting results.

It is also significant that supplementation with L-carnitine is one of the pillars of the approach of Dr. Stephen Sinatra MD, a well-known cardiologist, used over many years to prevent and treat heart disease.[17-19]

Thus while the results reported by Koeth *et al* are suggestive of new avenues of research, it seems premature to use these results to condemn red meat, especial if it is not processed. After all, according the studies Koeth *et al* cite, unprocessed red meat does not even appear to present the risks with which they are concerned.

However, it should be pointed out that some (perhaps even most) unprocessed red meat contains highly undesirable contaminants such as antibiotics, pesticides, herbicides, residues from GMO feed, etc. Furthermore, the heme iron in red meat is highly absorbable and contributes to overall iron load, High iron loads present health problems including cardiovascular risks and it is not clear what the ideal level is in men or postmenopausal women. One thing is clear, premenopausal women have much lower iron stores than men of any age and also have much lower risks of CVD. For women, these risks increase significantly after menopause as does the iron load. These negatives associated with red meat seem to trump the unproven risk of L-carnitine. Moderation and consumption of red meat free of the above contaminants seems advisable although this is probably difficult if not impossible from some to implement. Blood donation strongly modifies iron stores without in general causing anemia.

COCHRANE COLLABORATION CHANGES ITS VIEW OF STATIN BENEFITS IN PRIMARY PREVENTION

The issue here is the prevention of adverse cardiovascular events in individuals who have not had an acute event, even though they may be at high risk. In 2011, The Cochrane Collaboration, an independent international group that engages in systematic reviews and meta-analyses, concluded that "…only limited evidence showed that primary prevention with statins may be cost effective and improve patient quality of life. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk." However, they added "There was evidence of selective reporting of outcomes, failure to report adverse events and inclusion of people with cardiovascular disease." A threshold of ≤ 10% secondary prevention was used in study selection, so there is, as with most other meta-analyses of statins in primary prevention, some contamination with secondary prevention.

In recent new analysis of 2013 they concluded "Reductions in all-cause mortality, majors vascular events and revascularizations were found with no excess of adverse events among people without evidence of CVD treated with statins."[20] This new spin was the result of adding 4 new trials to the 14 used in the 2011 analysis. JUPITER was included which may have been confounded by the huge effect of Crestor on serum 25-hydroxyvitamin D levels, since vitamin D status is very important in cardiovascular risk.[21]

It is of interest to examine the absolute event rates in the various categories of acute events and to estimate an approximate number needed to treat to prevent one event (NNT) for the data in the new Cochrane analysis. The NNT is only approximate due to the variable number of years of treatment and differences in study populations. A typical period was 4 years. An alternative way of looking at the results is to calculate the chance of not having an event. For example, if in the control group 5.1% died whereas in the treatment group it was only 4.4%, then the chance of being alive after a few years without treatment is 94.4% but with treatment it is 95.6%. The equivalent NNT is 1/(0.051 – 0.044) or 143. Anyone who believes that there are no adverse statin side effects is ignoring the well-known under reporting and a considerable literature.[22,23]

The table below summarizes the results of this latest meta-analysis. When an excess of 100 individuals must be treated to achieve one beneficial result over, for example, 4 years some would say it is time to find a better intervention.

STATINS FOR PRIMARY PREVENTION
2013 COCHRANE COLLABORATI0N REVIEW

EVENTS	PLACEBO %	STATIN %	NNT*
ALL-CAUSE MORTALITY	5.1	4.4	143
FATAL CHD	1.3	1.1	500
NON-FATAL CHD	2.8	1.9	111
FATAL CVD	2.1	1.7	250
NON-FATAL CVD	4.0	3.0	100
FATAL STROKE	-	-	∞
NON-FATAL STROKE	2.0	1.3	142

** Approximate (over 4-5 years) due to variable study durations and baseline risk*

When a composite endpoint was used which comprised everything from death to revascularization (bypass surgery or angioplasty) and in some studies even severe angina, the NNT was 71 based on absolute rates of 3.8 and 2.4%. However, this includes so-called soft endpoints which can be strongly influenced by physician attitudes, both medical and otherwise, and there was considerable variation in the placebo event rate, which renders the NNT uncertain.

Relative risk reductions were typically around 25%, which sounds like an attractive benefit until one examines the NNT in the above table. However, the relative reduction in all-cause mortality was 14%, which can be compared with the NNT of 143. Furthermore, the reviewers point out that among the 18 trials, only JUPITER showed a strong evidence of reduction in total mortality. Prior meta-analyses of pure primary prevention with statins have always come up with no effect for this endpoint. As mentioned above, the somewhat impressive results of JUPITER may have been due to vitamin D. Furthermore, one can question the inclusion of this study in the meta-analysis due to the special nature of the cohort, i.e. selected for an elevated level of an inflammation marker, C-reactive protein, and the large number of diabetics included in the study.

NEWS BRIEFS

ASPIRIN LOWERS RISK OF MELANOMA

Researchers extracted data for postmenopausal women 50-79 years of age from the Woman's Health Initiative to examine the question of the preventive value of aspirin in the skin cancer melanoma.[24] It was found that compared to non-aspirin users, those taking aspirin had a 21% (fully adjusted for confounders) lower risk of melanoma and the risk reduction increased when the data was stratified by years of use. Overall, in the 12 year study, the 21% relative risk reduction corresponds to an absolute risk reduction of 0.21% (similarity of the numbers accidental) with this result independent of the use of crude incidence or incidence per 100,000 person years. The bottom line is that the number needed to treat over the study period is approximately 480 for 12 years to prevent one incident melanoma. Thus the 21% relative risk reduction, while impressive, is totally misleading and the risk reduction in absolutes terms would appear to lack clinical significance in spite of statistical significance, and given the potential for side effects, the use of aspirin for this objective does not appear justified.

BLOOD PRESSURE AND RISK OF CORONARY HEART DISEASE IN DIABETICS

If one is diagnosed as having type 2 diabetes, it is quite likely that glucose lowering medication, statins and antihypertensive medication will be recommended, either to initiate or continue. The aggressive control of hypertension for diabetics and the belief that "lower is better" was based on randomized controlled trials in the 1990s. However, this has now been questioned since contrary evidence has been forthcoming. The most recent is a follow-up study of 12,600 white and 17,500 African American diabetics 30-94 years of age who were studied for 6 years.[25] Blood pressure data was collected on average 14.6 times during follow-up. Heart disease was defined as a heart attack or unstable angina. It was found that the minimum risk occurred for the blood pressure range 130-39/80-89 mm Hg. Risk *increased* below this range, and for 140-159/90-99 and ≥ 160, the only statistical significant result was an increased risk seen in those under 50 years of age. Plots arising from continuous modeling suggest the risk increases in general in the two higher ranges, but the data analyzed in terms of hazard ratios with confidence intervals do not support this and suggest only non-significant results, for both white and African Americans if the age is ≥ 50. For the oldest group, the continuous model actually indicated an *inverse* association between heart disease risk and blood pressure.

The authors comment that their results are consistent with the ACCORD study where intensive blood pressure lowering below 120 mm Hg in diabetics did not produce a beneficial effect, and the INVEST study where tight control (<130 mm Hg) was not associated with improved outcome compared a control group with systolic blood pressure at 130-139 mm Hg in patients with diabetes. They also point to a recent UK study which found a U-shaped association with either systolic or diastolic blood pressure and all-cause mortality among type 2 diabetics and other studies have found an inverse association between blood pressure levels and all-cause mortality among elderly diabetic patients.

The authors suggest that there is currently no robust evidence favouring a target of a systolic of< 139 mm Hg. It is interesting that in December, 2012, the American Diabetes Association issued new clinical guidelines that included a systolic target of < 140 rather than < 130 mm Hg.

The reader is referred to the April IHN for a comparison of this primary prevention study, which involved patients free of symptomatic heart disease, and the impact of blood pressure lowering in secondary prevention.

DIET AND RISK OF ALZHEIMER'S DISEASE

One approach to seeking guidance in the association between diet and disease is to use a hypothesis driven or *a priori* approach. This involves searching for a dietary pattern that, for example, minimizes risk. Such an approach allows for synergistic interactions between foods and is thought to offer advantages over studies focused on one type of food such as fruit or fat. A diet pattern study concerning the risk of developing Alzheimer's disease (AD) has just reported.[26] A cohort of 2148 subjects was followed for 3.9 years during which 253 subjects developed AD.

A diet pattern was identified where there was a statistically significant 38% relative risk reduction on comparison of the highest to the lowest tertile of adherence. This dietary pattern was characterized by higher intakes of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits and dark and green leafy vegetables and a lower intake of high-fat dairy products, red meat, organ meat and butter. In terms of macro and micro nutrients, the protective diet pattern was rich in omega-3 and omega-6 fatty acids, vitamin E and folate, but poor in saturated fat and vitamin B12. From the number of cases in the lowest and highest tertiles of adherence, one can calculate the absolute risk reduction which was 0.083, giving an impressive number needed to adhere to the diet over four years to prevent one case of incident AD of 12. A similar number can be derived from the plots of AD free survival probability with time.

Saturated fat was one of the hypothesized factors and the authors provide citations concerning the positive association with risk. However, examination of the three cited studies,[27-29] revealed no statistically significant association between the risk of either AD or vascular associated AD and saturated fat. Thus the foods containing saturated fat rather than saturated fat per se come under suspicion.

Readers will no doubt recognize that the dietary pattern found to minimize the risk of developing AD- is similar to the Mediterranean diet and the authors comment that adherence to this dietary pattern has also been found to be related to lower risk of AD.

MERCURY EXPOSURE IN YOUNG ADULTS AND FUTURE DIABETES

An interesting study has just reported where the mercury load status (via toenail analysis) in young adults 20-32 was determined and the incidence of diabetes and pancreatic β-cell function examined over a subsequent period of 18 years. When the highest vs. the lowest quintiles of initial mercury load were compared, those in the highest had a 65% increase of incident diabetes. A decrease in β-cell function also correlated with increasing mercury load.[30] This association was only evident after adjustment for demographic, major lifestyle and dietary factors, particularly weight and intake of long-chain omega-3 fatty acids and magnesium, both of which are protective.

The authors comment that these results are consistent with a number of experimental studies with both cell cultures and animals, but that human data is sparse and contradictory and there is no relevant human data available from Western countries. However, several studies from Taiwan, Turkey and Mexico found positive associations that supported results found in this study.

It is also well established that in general there is an association between heavy metal loads and both pancreatic islet function and the development of diabetes. A recent review discussed, arsenic, cadmium, mercury and nickel, although the latter lacked human studies.[31]

We live in a world where we have no idea regarding our intake of heavy metals and unless the issue is pursued, no knowledge of body loads. Symptoms for many problems caused by toxic metals are initially silent and when they start appearing, are easily confused with other causes. Tests to control the importation of contaminated foods are insignificant compared to the magnitude of the problem and food grown in countries with highly polluted waters has

been found in some cases highly contaminated and still reached our supermarket shelves. Arsenic and lead in rice are a good example (see BBC News, April 10, 2013).

Inexpensive metal load tests are available with the required samples mailed to a laboratory after the test is ordered by a physician. Such data seems obviously of growing importance and there are a number of substances commonly available in health food stores that are capable of binding and eliminating (chelating) heavy metals. Examples include green tea extract, N-acetyl cysteine combined with R-lipoic acid and selenium, curcumin, quercetin, and silymarin. The only concern appears to be the concomitant elimination of essential non-toxic minerals. This appears easily addressed with a good multivitamin-mineral supplement although ideally a detoxification program should be carried out under professional supervision with serial tests of metal loads. Anecdotal reports suggest that dramatic improvements in a number of health issues are possible. Prescription chelators are available and commonly used, even in pediatric detoxification, and heavy metal urine tests involving before and after analysis with a prescription chelator challenge are also available. However, detecting and treating toxic metal overload appears well off the radar of mainstream medicine but is well within the domain of alternative and naturopathic medicine.

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BOOK REVIEWS

SUGGESTIONS FOR SUMMER READING RELATED TO HEALTH AND WELLNESS

The Body & The Brain Diet. A simple diet and exercise plan to obtain and maintain a healthy body and mind. **Brian Sturgeon, MD. CreateSpace Independent Publishing Platform, 2013 (available at amazon.com)**

This is a fascinating real-life story of a surgeon who was physically going downhill very fast. He was overweight, had very low HDL, very high triglycerides, probably had experienced a severe angina attack, and had just been diagnosed with type 2 diabetes. He had pain problems in his feet and hands, problems with combined high level of thirst and constant

urination, psoriasis, and a high erythrocyte sedimentation rate (inflammation). He was put on anti-glycemic drugs, offered statins, told to exercise and visit a nutritionist/dietician. Her amazing advice was to maintain his weight, eat 8 slices of bread a day but no bananas, and consume low-fat cottage cheese. The drugs caused hypoglycaemia, a serious matter for a surgeon. Eight slices of bread a day would have certainly have made matters worse.

Dr. Sturgeon (a pseudonym) dismissed the dietary advice after observing that a flu induced several-day fast had a remarkable effect on his fasting blood glucose, even in the absence of metformin. He embarked on a self-designed no-medication program with a highly restricted carbohydrate diet (including no bread or sugar) low in saturated fat and meat, and started a progressive exercise program. The exercise program evolved to include 35 minutes a day on a treadmill and 5-10 minutes doing resistance exercises. Over about 3 months his weight went from 220 to 185 lbs, fasting blood glucose from 300 to 82-95 mg/dL, and HbA1c from 8.5% to 5.5%, blood pressure from 130/85 to 100/65. Blood lipids normalized, the psoriasis resolved as did the peripheral pain. This a compelling case history of the rapid and successful reversal of diabetes markers to normal and the resolution of peripheral vascular problems without using medication.

Sturgeon's book contains chapters concerning important dietary details and the exercise program. It is strongly recommended that diabetics and prediabetics read this book since there appears to be both skepticism and resistance to the approach he successfully employed to deal with a serious but very common health problem. Case histories are held in low regard by evidence-based medicine. However the dietary approach he used is backed by an extensive body of evidence and sound biological plausibility, and exercise is well known to increase insulin sensitivity. The trouble is, type 2 diabetics want pills, not diet and exercise, and love their carbohydrates. Mainstream medicine is only too willing to oblige. Dr. Sturgeon avoided being conned into believing that by lowering his fasting blood glucose and HbA1c with existing drugs he would avoid the disastrous complications of his disorder. However, your editor would take issue with the inclusion of diet drinks if they contain aspartame due to the aspartame to methanol to formaldehyde process.

This book provides straight forward and easy to follow guidance which should enable many diabetics to make real progress toward getting off medication and increasing their chances of reversing or avoiding the complications of diabetes, which is of course the only reason why people take anti-glycemic drugs in the first place. The book may also help diabetics to avoid some of the mainstream recommendations which emphasize high carbohydrate intake. The author's message is clear. I did it and you should be able to do it.

Tarnished Gold. ***The sickness of evidence-based medicine. Steve Hickey, PhD and Hilary Roberts, PhD.*** **CreateSpace Independent Publishing Platform, 2011 (available at amazon.com)**

Opinions vary as to the birthday of evidence-based medicine (EBM) but it is clear that its rapid rise to its present exalted position started about 20 years ago. The concept involves the integration of the best research evidence with clinical expertise and patient values. Today EBM has become similar to an established religion, has its own thought leaders, its own journals, and is an integral part of medical school curriculum.

At the heart of EBM, and perhaps the most controversial, is the hierarchy of evidence. In the order of significance, importance, "scientific" value, and eligibility to influence public health policy, insurance eligibility, treatment guidelines and the care of individual patients the hierarchy is as follows:

- Systematic reviews of randomized controlled trials and meta-analysis.

- Randomized controlled trials (RCTs). Subjects are placed in two groups at random and one group serves as the control, placebo or otherwise (such as another drug).
- Cohort studies follow-up such as the famous Nurses' Health Study.
- Case-control studies where cases are assembled and then controls are found in numbers that frequently exceed the cases.
- Case series, for example a study based on 100 consecutive patients attending a clinic for some indication.
- Case reports or histories.
- Expert opinion.

Noteworthy items absent from this list are studies of the mechanism of any given disease, and animal and laboratory studies. Furthermore, if there is an "alternative" treatment for some disorder backed by overwhelming mechanistic justification and experimental evidence that meets the highest scientific standards followed by impressive anecdotal evidence, e.g. case histories of an extraordinary level of therapeutic effectiveness, it will still not pass muster with EBM. In addition, to satisfy the requirements of EBM in this example is generally financially impossible unless the approach is patentable, which is almost always not the case with alternative therapeutic agents.

The EBM hierarchy is intended to allow proper weight to be given to acceptable, reliable evidence when examining the literature, writing guidelines or deciding how to treat a patient. The meta-analyses of RCTs have become the gold standard for regulatory approval and are central to the framing of practice guidelines. Medical students were expected to become knowledgeable in reading reports of clinical studies based on the RCT model and published in peer-reviewed high-profile journals, and to use this knowledge for a lifetime of practice, remaining current by reading papers and guidelines.

The purists are thus inclined to pay attention mostly to RCTs as the basis of EBM. To be told that what one is doing is not evidence based is a serious accusation although this describes a substantial faction of modern medical practice. The RCT, according to this view, is the only valid, reliable source information relating to causality. The RCT achieved this stellar status because of the belief that it provided evidence free of bias and confounding and that the results could be stated in a scientific manner using agreed upon statistical methods and standards for uncertainty. Thus EBM is viewed as more or less equated with scientific methods and scientific proofs. However, there are degrees of being scientific. It is of interest that in sciences such as physics or chemistry, notions of a hierarchy of evidence would seem bizarre, and odds ratios and confidence intervals rarely needed.

Questioning the conventional wisdom that EBM is the supreme guiding light for the practice of medicine is akin to heresy, although one does not need to look very hard to find highly detailed and well thought-out criticisms of some of its major tenets. For example, an entire issue of *Perspectives in Biology and Medicine* (Volume 52, #2) was devoted to articles that included severely critical discussions. A recently published book collects and documents this criticism.

Tarnished Gold, a scholarly criticism of EBM, was published in 2011 and the points raised and discussed are valid today. Both authors are well qualified to deal with the subject and in this book they discuss in depth every aspect described above and expose hundreds of scientific and logical flaws in the philosophy and basic assumptions. One is left with an understanding of the danger posed by EBM that must be considered along with its benefits. The authors demonstrate with countless examples how EBM, rather than being the enlightened way of the future, exposes patients to risks that cannot be ignored.

The turn down what appears to be the wrong road had the best of intentions, and not all aspects of EBM of course are bad, but the problems inherent in this philosophical construct are serious, fundamental, systemic, and to the critics, it is indeed the wrong road that modern

medicine is proceeding down with grim determination and what to some appears to be a closed mind.

The Blood Sugar Solution. ***The ultra healthy program for losing weight, preventing disease and feeling great now.*** **Mark Hyman, MD. Little, Brown and Company, 2012**

Mark Hyman was co-medical director of Canyon Ranch for 10 years and is the founder of the Ultra Wellness Center which he directs. Dr. Hyman is a well-known advocate of integrative medicine, preventive medicine, and the approach to wellness and illness through viewing the individual as a whole system and acting accordingly. This is obviously not the approach of modern medicine with the 10-minute office visit, generally focussed on one complaint. He has written numerous books including *Ultraprevention* a guide to staying healthy for life.

In *The Blood Sugar Solution* he presents a comprehensive plan for preventing diabetes, treating and reversing prediabetes and full-blown diabetes. He terms the modern epidemic we are witnessing as *Diabesity*. The book starts with a discussion of diabesity and its causes and then exposes seven myths about obesity and diabetes that "keep us sick." These are

- Diabetes is genetic.
- Diabetes is not reversible.
- Pre-diabetes isn't a problem until it turns into full-blown diabetes.
- Once you start on insulin, there is no going back.
- Lowering blood sugar with medications prevents death and heart attacks in diabetics.
- Heart surgery and angioplasty are good treatments for diabetics with heart disease.
- Weight loss is necessary for the reversal of diabetes.

After several short chapters on his general philosophy and approach to diabesity, he presents seven steps to treating it. These involve boosting yours nutrition, regulating your hormones, reducing inflammation, improving digestion, maximizing detoxification, enhancing energy metabolism and dealing with toxic psychological problems. This illustrates the system approach. Compare this with the common reaction to an elevated fasting blood sugar or HbA1c, i.e. a prescription for metformin, the suggestion to exercise more and a referral to a nutrition expert who will probably do more harm than good by following conventional guidelines.

The remainder of the book presents a handbook and guidebook to aid the individual in implementing the seven-step program and when to seek expert medical assistance, for example, he provides a program for self-administered detoxification which includes food and supplements, but provides a quiz for determining when to seek medical care for severe toxin overload. This is followed by chapters on illustrative menus, a seven day meal plan, advice on supplements and additional helpful advice.

Throughout the book there are quizzes aimed at assisting the reader in self-evaluation in the context of both diabesity and general health.

Saving Normal. ***An insider's revolt against out-of-control psychiatric diagnosis, DSM-5, big Pharma, and the medicalization of ordinary life.*** **Allen Frances, MD. Harper Collins (William Morrow), New York, 2013**

This book has appeared almost simultaneously with the publication of the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders--Fifth Edition* (DSM-5), published by the American Psychiatric Association (APA). Dr. Allen Frances is professor emeritus and former chair of the Department of Psychiatry and Behavioral Science at Duke University School of Medicine. He was chairman of the DSM-IV Task Force and part of the leadership

group for DSM-III and its revision, DSM-IIIR. Thus he is eminently qualified to write on the title subject of this book. He has been a very high-profile critic of the process of writing DSM-5 and the final result, and in fact his latest negative commentary was just published in *Annals of Internal Medicine* (May 17). In this paper he points out that the APA refused a petition for an independent scientific review of DSM-5 that had the endorsement of more than 50 mental health associations. He also takes the following position:

"My advice to physicians is to use the DSM-5 cautiously, *if at all (emphasis added)*. It is not an official manual; no one is compelled to use it unless they work in an institutional setting that requires it."

Frances' involvement with the previous addition caused him considerable disappointment subsequent to its publication. The intention of DSM-IV was to only make additions that were supported by strong evidence and to try to hold the line regarding diagnostic inflation. Only 2 new disorders were added. This caution did not prevent the unexpected occurrence of three market-driven (drug company driven) diagnostic fads. In the past 20 years, the rate of ADHD tripled, the rate of bipolar disorder doubled, and the rate of autism increased by 20-fold.

However, what is at issue here goes well beyond DSM-5, impacts everyone and is the subject of Dr. Frances' new book. The title suggest the main theme, *Saving Normal*, and this translates into the central question, what is normal in the context of human beings, their behavior, their problems, their aches and pains etc. If one sets the bar too high, individuals with real and serious problems will go undiagnosed and treated. If it is set too low, overdiagnosis and overtreatment will occur. The boundary between normal and abnormal is fuzzy, potentially if not inherently arbitrary, and yet where it is set has a profound influence on the practice, not only of psychiatry but of medicine, and as well the view taken by individuals of others.

Saving Normal is divided into three parts, normality under siege, psychiatric fads can be bad for your health, and getting back to normal. In Part I, after a discussion of the problems inherent to defining normal, there is a historical section "From Sharman to Shrink" which provides interesting historical insight into how illness, both mental and otherwise, was viewed from early times to present. This part is concluded with a discussion of diagnostic inflation, a subject that should concern everyone. Part II discusses overdiagnosis and overtreatment in the context of psychiatry, i.e. psychiatric fads. The fads of the future are of particular interest because the discussion involves the predicted damage from DSM-5. The fads of the future include:

- Turning tantrums into a psychiatric disorder
- Making a disease out of forgetfulness associated with aging
- Gluttony becomes a mental illness
- Adult ADHD could become the new diagnosis *du jour*
- Mourning is confused with melancholia
- Turning passions into addictions
- Mixed anxiety/depression—turning everyone into a patient
- Behavior addictions (e.g. internet, shopping, working, sex, golf, jogging) become an addiction disorder
- Mislabelling medical illness as a mental disorder
- Hepephelia and hypersexuality.

Frances suggest that this is not just diagnostic inflation, but hyperinflation, and the consequences associated with labelling both the young and adults and the opportunity to over-medicalize should be of great concern. If these disorders are treated, the probability is high that drugs will be used since psychotherapy has become uncommon, poorly reimbursed, and lacking in trained practitioners. In fact, throughout the book the author emphasizes the

importance of recognizing that many of the drugs in widespread use have side effects, some very serious, offer the potential for addiction, and some carry explicit warnings concerning the enhanced risk of suicide. Furthermore, most of the prescriptions for psychiatric drugs are currently written by physicians outside the specialty, frequently with cursory evaluation of the patient.

The remainder of the book is devoted to possible solutions. For example, one section is titled "We are fighting the wrong war on drugs." Central to any discussion of solutions is the role of the pharmaceutical companies in promoting psychiatric drugs, both to the profession and directly to the public. He provides table listing the civil and criminal fines paid by large pharmaceutical companies between 2004 and 2012. The numbers are staggering until one realizes that they represent merely a small fraction on the cost of doing business, even though the unit is millions and the totals in billions of dollars. The book concludes with fascinating case histories.

Maybe it is a good idea to read the case histories first (Chapter 9). These descriptions of failed therapy are important for the understanding of the depth of the crisis in which psychiatry finds itself and the potential danger it poses for the general public. However, Frances puts the case histories in perspective by adding successful ones, although there is more psychotherapy in the success stories which confuses the issue.

One good reason for reading this book is to gain full perspective on what is going on around us, and what is happening to our children, friends, and associates. One does not have to look far to find someone already on psychiatric drugs or to imagine the impact of the "future fads" which potentially label half the people who live down the street as mentally ill. Frances points out the serious consequences being labelled as mentally ill can have in the context of insurance or employment eligibility, self-esteem, stigma, sense of abnormality, success of a marriage proposal, or the inability to adopt a child or pilot a plane.

The importance of being "normal" should be clear. The potential disaster associated with being mislabelled abnormal, and especially mentally ill, should also be clear. This book clarifies the predicted role of DSM-5 in increasing dramatically the probability of this happening.

Readers interested in a more detailed history of DSM-5 and the controversy surrounding its preparation are directed to a just–published work *The Book Of Woe. The DSM and the unmaking of psychiatry,* by Gary Greenberg, a practicing psychotherapist. It provides many insights into modern psychiatry and its current "thought leaders."

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