INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 215 **MARCH 2011** **20th YEAR**

This issue contains the second part of the review concerning psychiatric drugs and the alternatives. Research for this review turned up some interesting insights into a number of aspects of modern psychiatry. One concerns the DSM. This is an acronym for Diagnostic and Statistical Manual of Mental Disorders. The current edition (1994 with minor revisions in 2000) is the 4th and the new edition due out in 2013 is DSM-V. The functioning of the DSM effort (working group's draft posted in 2010, print copy due in 2013) calls to mind some aspects of the L'Académie Française, the "supreme court" of the French language in France. The DSM is the bible of modern psychiatry and claims to set out diagnostic guidelines for over 300 so-called mental disorders. The new edition is being prepared under what has been termed unnecessary and distorting secrecy with signed confidentiality agreements that limit the possibility of open and continuous exchange between the work groups and the profession in general. A draft of the new edition has been posted and has stirred up a lot of controversy. But this controversy also exposes the large division of opinion on all aspects of the challenge of describing and defining mental health problems. An opinion piece published in the Los Angeles Times in March 2010 helps create perspective. It was written by the chairman of the task force that created DSM-IV, Dr. Allen Frances, now Professor Emeritus, Department of Psychiatry, Duke University. Francis is viewed as a conservative in the context of his views of the DSM and the program to produce the revised 5th edition.

The opinion piece begins by a frank confession that the DSM-IV taskforce, while trying hard to be conservative, had inadvertently contributed to three false epidemics! These were attention deficit disorder, autism and childhood bipolar disorder. This remarkable statement underscores the potential for over-diagnosis and false positive diagnosis associated with the protocol inherent to the DSM where having a certain number of symptoms out of a long list qualifies the individual for being diagnosed with the disorder in question. There appears to be a large grey area where normal overlaps abnormal, and this generates a diagnostic system that appears highly imperfect—not an unexpected situation considering what is being attempted. If the end result was psychotherapy, then the concerns would be less than when long-term medication with potentially severe or disabling side effects is involved. An example: the removal of bereavement grief as an exclusion for major depressive disorder which would lead to this diagnosis in as little as two weeks for many individuals with bereavement grief. Thus the concern with the DSM-V, which expands the number of disorders considerably. The preparation of DSM-IV was almost totally dominated by the pharmaceutical industry, with conflicts of interest actually published in a critical peer reviewed paper. The cynical view is that the trend is such that almost everyone will be found with a mental disorder sometime during their lifetime and most will be medicated. We are almost there already. One out of four Americans 18 years of age and older suffer from a diagnosable mental disorder in a given year.

Insight is also available from the recent activity by mental health stakeholders regarding the development of new drugs. The discussions are premised on the fact that almost all the existing arsenal is based on drugs discovered over four decades ago by serendipity. Careful reading of proposals regarding what to do now reveal admissions that the model used in most areas of medicine, which begins with an understanding of molecular pathophysiology to generate novel targets for therapy, is absent in the development of psychiatric drugs, and that the continued development of medications following the current paradigm is unlikely to yield any new compounds with greater efficacy. These same discussions admit the serious limitations of the present arsenal of drugs and

call for the need look for and study molecular pathophysiology. Again, this can be interpreted as an admission that the critics are correct in saying that in most mental disorders, there is no as yet identified brain pathology or genetic predisposition present prior to the impact of psychopharmacotherapy on the brain.

The Prostate Monitor will return next month.

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

MAGNESIUM AND SUDDEN CARDIAC DEATH

A primary focal point for mainstream medicine involves the risk factors for coronary heart disease. Risk factors such as hypertension, smoking, family history and elevated cholesterol levels are routinely identified and treated. However, sudden death from cardiac causes (SCD) accounts for over >50% of all fatal cardiac-related events. Furthermore, most victims of SCD are not at high risk based on conventional risk factors and 55% of men and 68% of women have no clinically recognized heart disease prior to the SCD event. In addition, neither LDL levels nor total cholesterol levels are associated with the risk of SCD and incidentally, about half of all patients hospitalized for a heart attack have low or very low LDL cholesterol. Coronary arrhythmia appears to be fundamental to SCD and in fact a private joke among cardiologists is that two of the subspecialties involve being either an electrician or a plumber. A low long-chain omega-3 status as measured as a percentage of plasma fatty acids or the fatty acid content of red blood cell walls is a very significant risk factor for SCD which has yet to make it to mainstream although an assay has been developed and validated. Furthermore, elevating the levels of EPA and DHA measured in this fashion has been shown to have dramatic impact on the risk of SCD. A pharmaceutical company has tried to profit from this by marketing a prescription mixture of EPA and DHA at a huge mark-up compared to the equivalent pharmaceutical grade fish oil available in health food stores. Omega-3 fatty acids and SCD has been discussed on several occasions in this Newsletter and its associated Research Reviews (e.g. June 2008).

A number of studies suggest that magnesium also is associated with cardiovascular disease and SCD, the latter apparently related to its antiarrhythmic properties. These associations appear stronger with blood levels than dietary intake. As regards the association with SCD, prospective data is sparse with only one study reporting an inverse relationship. A recent study based on the Nurses' Health Study database provides considerable additional prospective data.[1] Over 88,000 women disease free in 1980 were followed for 26 years. Data were collected on magnesium intake along with a number of other dietary and lifestyle factors and the data updated every 2-4 years. A case-control analysis was carried out on 99 SCD cases and 291 matched controls. When the relative risk of SCD was determined by comparison between the highest and lowest quartiles of dietary intake of magnesium, there was a 37% decrease in risk whereas when plasma quartiles were used, the relative risk decrease was 77% with a significant and strong relationship between plasma level and risk. The estimates of dietary intake did not include

that from water, which may account for 20-30% of a person's daily intake.

As regards the dietary intake plus supplementation in this study, the lowest quartile had < 261 mg/day whereas the highest had > 345 mg/day, the latter with a median intake of 383 mg/day. These numbers refer to elemental magnesium, and one must be careful in reading labels to be sure the amount quoted is the elemental amount rather than the amount of the compound used. Magnesium citrate is a popular supplement but only contains about 14% elemental magnesium. Thus, a capsule containing 150 mg of Mg should weigh about 1000 mg. The supplements where the metal is associated with amino acids provide better absorption than, for example, the oxide. Foods rich in magnesium include wheat germ, almonds, wheat bran, peanuts, and walnuts, all of which contain over 100 mg of magnesium per 100 g serving. Only about 30-40% of dietary magnesium is actually absorbed. The authors point to evidence that most Americans do not meet even the recommended daily allowance even with the use of magnesium-containing supplements. It is not uncommon to read recommendations for optimum daily intake of magnesium from 600 to 800 mg. Excessive intake generally produces diarrhea.

BAD NEWS ABOUT SUGAR-SWEETENED BEVERAGES AND DIET SODA

Sugar-sweetened beverages (SSB) have become the primary source of added sugar in the U.S. diet. They contain sucrose (table sugar containing equal amounts of fructose and glucose), high-fructose corn syrup or fruit juice concentrates. All have essentially similar metabolic effects. Natural unsweetened fruit juice is not generally classed as a SSB.

A recent study based on meta-analyses examined the association between SSB intake and the risk of the metabolic syndrome and type 2 diabetes.[2] All the studies used had been adjusted for confounding by various dietary and lifestyle factors. In the metabolic syndrome study over 19,000 participants were involved yielding 5800 cases. For diabetes, about 310,000 participants yielded over 15,000 cases. When the lowest intake (none or < 1 serving/month) was compared to the highest (1-2 servings /day, SSB intake increased the risk of developing type 2 diabetes by 26% and the metabolic syndrome by 20%.

The authors make the following points regarding SSBs:

- They are considered to lead to weight gain since they have high sugar content, low satiety potential and lead to positive energy balance.
- The high level of rapidly absorbed carbohydrates lead through metabolic pathways to increased risk of diabetes and the metabolic syndrome.
- Other adverse effects associated with SSBs include a large and significant increase in the risk of coronary heart disease, glucose intolerance and insulin resistance, atherogenic dyslipidemia (high triglycerides, low HDL and small, dense LDL particles), visceral adiposity and increased risk of hypertension and gout.

It would seem that little more need be said about the merits of avoiding this type of beverage. Some find carbonated water almost as satisfying after getting over the sugar craving. A bit of lemon improves the beverage considerably.

Drinking diet soda may not be a good idea either. A study presented February 9 at the International Stroke Conference found evidence for an increase risk of stroke and heart attack associated with drinking diet soda every day vs. none at all. The study followed about 2500 adults over 40 for 10 years. Daily diet soda drinkers had a 48% higher risk of stroke or heart attack than those who abstained, a result that was corrected for confounding by smoking, diabetes, waistline size and other differences between the groups. A major weakness of this study is the absence of stratification by type of artificial sweetener and as well, it is not easy to correct for confounding due to lifestyle factors

common to diet soda consumers. While these results require confirmation and while there is no clear biological explanation, diet drinks sweetened with aspartame have for decades been the subject of considerable controversy starting with some questionable aspects associated with its approval. (Source, *New York Times* report from the conference)

DIAGNOSING DIABETES OR PREDIABETES—NOT THAT SIMPLE AFTER ALL

Glucose metabolism can be described as simply a continuum of functionality reflected in part by the time evolution of metabolic response to ingested carbohydrates, the fasting level of blood glucose, and the long-term average blood glucose level. In some respects, these are measures of convenience although there is great resistance to using the classical 2-hour glucose tolerance test due to the perceived inconvenience for all concerned. The absurdity of this view is emphasized by a comparison between the inconvenience a second blood draw and the inconvenience of diabetes.

Recently the American Diabetes Association, after decades of resistance, added the long-term blood glucose average to their set of criteria for prediabetes and diabetes. This long-term average is measured by an assay of glycated hemoglobin, also simply called HbA1c. What is involved is a reaction between glucose and hemoglobin with a time base introduced by the lifetime of red blood cells in the circulation. The current definitions are

	PREDIABETES	DIABETES
FPG mg/dL	100-125	≥126
HbA1c	5.7%-6.4%	≥6.5%
2-hr OGTT mg/dL	140-199	≥200

FPG = fasting blood glucose; HbA1C + glycated hemoglobin, OGTT = 2-hour oral glucose tolerance test.

Recently Lipska *et al*[3] examined the question of how well either the FPG or HbA1c identified individuals with prediabetes or diabetes. The researchers found significant discordance in identifying older (70-79 years of age) individuals with either of these two conditions. While either FPG or HbA1c identified similar number of cases, the two diagnosed populations only poorly overlapped. FPG missed about the same number as HbA1c. The possibility of false positives was not considered. The study thus suffered by not using as a standard the 2-hour glucose tolerance test, but this is in keeping with the philosophy that patients should not be inconvenienced and as well it may be difficult to recruit several thousand subjects who are willing to give up two hours starting from a fasting state.

In an accompanying editorial, Cohen *et al*[4] discuss some interesting aspects of the HbA1c test. First, the test has an error associated with the assay such that a laboratory report of 6.5% could be as low as 6% or as high as 7%. A patient with a laboratory result of 6.0% could be 5.6% or 6.4%, i.e. below the prediabetic cut-off or almost a diabetic. Furthermore, the editorialists present the view that the largest proportion of the individual variance in HbA1c values is determined by differences in biological determinants of the actual hemoglobin glycation process. Thus the measured marker is not really determining average serum glucose averaged with a dependable internal clock, the red blood cell life span. They point out that there is substantial variation in red blood cell life span in hematologically normal individuals, with and without diabetes and that this variation can alter HbA1c values by ± 15%. These two observations seem to render the above diagnostic guideline subject to serious false positives and false negatives. It seems important that some agreement be reached

regarding a gold standard for diabetes diagnosis and that it be used in all studies. The traditional standard was the 2-hour OGTT.

This discussion provides a good example of the danger in attaching too much significance to numerical thresholds which have diagnostic implications but have associated error limits, and even these limits may not be well defined. Perhaps it is time to return to the old-fashioned method of the 2-hr OGTT. The ideal 2-hour study of an individual's glucose metabolism involves measurements of fasting insulin and glucose followed by a drink containing 75 g of glucose. Blood glucose and insulin measurement are then made every half hour to map out the detailed response over 2 or more hours. This protocol is more informative than just the fasting and 2-hour glucose measurement. The data allows not only an evaluation of the hypothesis that the patient has diabetes or is prediabetic, but the addition of insulin measurements allows a better measure of insulin resistance. Definitions of diabetes must ultimately refer back to thresholds for risk of vascular damage associated with hyperglycemia. It appears that the relationship is non-linear and pinpointing a threshold is rather arbitrary, with some similarities with setting speed limits.

PROBLEMS WITH IDENTIFYING HYPERTENSION

When blood pressure is measured with a cuff and stethoscope, a precise measure is obtained by following some simple rules. These include having the patient rest prior to the measurement, not taking the readings while the individual is sitting with legs crossed, and slowly releasing the pressure to identify within a narrow range the appearance and disappearance of the sounds used to identify the systolic and diastolic values. Anyone who has taken their own BP using this classical method will understand that if the pressure is allowed to drop too fast, only an approximation to the precise numbers is obtained. Yet how many times have readers witnessed this in the office setting. Furthermore, the office setting is notorious for producing the "white coat effect" which results in potentially significant elevations in BP. Furthermore, variability is introduced by the time of day, medications and their timing, stress levels at the time of the office visit, etc. A recent study found intra-individual variations based on standard deviations of almost 9% at two office visits 6 weeks apart when the results for 163 patients were examined. If the true systolic pressure was 141 mmHg, i.e. just above the threshold for hypertension diagnosis, this means being one standard deviation either side would give 128 and 154 mm Hg! In this study, ambulatory and home measurements yielded variability of 5.5% and 4.2%.[5]

What appears to be a serious issue with office measurements is the impact of the duration on the resting period. A recent study of hypertensive patients found that over 16 minutes of rest, sitting in a chair, the systolic BP decreased by on average 11.6 mm Hg and it was necessary to wait approximately 10 minutes for 75% of this spontaneous fall to occur. Similar time changes were observed for the diastolic BP.[6] A rest of 10-15 minutes was required in routine clinical practice might be difficult to implement.

In view of these problems with the standard office BP measurement protocol, some hypertension specialists have suggested that BP data be collected either at home or with ambulatory 24-hr BP measurements. However, some of these problems appear to be eliminated by a protocol that includes automated office BP measurement. The patient relaxes alone (unobserved) in an examination room for 5-10 minutes while BP is measured periodically with an automated device similar to the home measuring monitors. This has been found to eliminate most of the white coat effect and as well, the automated instruments eliminate technical errors in the manual pressure release method with the common mercury or bourdon measuring device.[7] In one study of 50 patients attending the office of a hypertension specialist, the automated office measurements were compared with the initial manual measurement. The initial mean for two manual measurements was 162/85 mm Hg while the automated machine gave 163/86. The patient

was then left alone for 5 minutes and the mean of the 5 readings was 142/80. Then a final manual reading was taken and was still elevated at 157/88. Studies also suggest that 5 minutes is sufficient if the patient is left alone.[8]

A 24-hour average or mean awake value obtained by an ambulatory blood pressure monitor is generally being considered a superior approach to diagnosing hypertension, but this method is not easily adapted to general use and is expensive to implement. In addition, there is some discomfort, especially at night. In fact, it is generally recognized that ambulatory BP of 135/85 is roughly equivalent to a routine office value of 140/90 although differences of 9/3 appear closer to the truth. Differences between office and research quality measurements are larger and typically 10/5, leading to the suggestion that normal should be revised upward to 150/95. In two studies where the mean awake BP based on ambulatory measurements was compared with those obtained with the unobserved automated office method, the results were nearly identical whereas the correlation between the ambulatory BP and the routine manual office BP was poor.[8] The focus of these studies was on individuals with hypertension rather than identifying the disorder, but the problems with office measurements would appear also to apply to routine screening. The variations due to measurement technique, prior resting and the white coat effect are more than large enough to push a patient over the threshold from normal to meeting the definition of hypertensive.

There is growing interest in establishing the clinical credibility and utility of measurements using modern home monitoring devices. [9-11] These devices are for the most part accurate, provide reproducible results, are easy to use and permit measurement during the day and evening. Validation of the accuracy of the home device is generally necessary but hardly an obstacle to its use. However, there has been reluctance on the part of physicians to incorporate home measurements in the management of hypertension. Nevertheless, it is estimated that approximately 70% of hypertensive patients regularly assess the BP at home.[12] Data generated at home should be more reliable, allow better classification of the degree of hypertension, and allow the physician and patient to actively cooperate in the management and the achievement of targets. Dangerous fluctuations would also become apparent since measurements would be spaced out over the day and include the evening.

Thus far we have been concerned with variability and as well the consistent false elevation called the white-coat effect which can also lead to white-coat hypertension. However, there is also what is called masked hypertension where non-elevated office BP is accompanied by elevated out-of-office BP. Some consider both harmless but a recent study contradicts this view and demonstrates that both lead to greater long-term risk of developing sustained hypertension with concomitant increased risk in heart attack and stroke.[13] White-coat and masked hypertension were identified by combining office BP readings (once in the morning and once in the evening) with 24-hour ambulatory monitoring and home BP monitoring twice a day. A 10-year follow-up revealed that almost 50% of those with either white-coat or masked hypertension developed sustained hypertension compared with about 16% of the group who had normal BP by all measurements at the beginning of the study, and this result was independent of whether the definitions were based on office vs. ambulatory or office vs. home BP measurements. However, significant numbers of subjects regressed over the study period from white-coat or masked hypertension toward having normal BP, but identifying those prone to regress was not possible. In an accompanying editorial it was emphasized that both white-coat and masked hypertension, by themselves, convey an elevated risk of heart attack, stroke and death compared to those with normal BP.[14] Consistent with these results is a recent study from Finland where it was found that home-measured BP is prognostically superior to office BP in terms of establishing cardiovascular risk.[15]

Finally, the above measurement problems also impact clinical studies and further point to the inadequacies of not having BP data representative of when individuals are awake rather than having one value measured in an office, in many cases at a random time, but not in the evening. In a fascinating review just

published, Eoin O'Brien from University College Dublin points out that blood pressure measurement is one of the few areas in medical practice where nineteenth century methodology is still used in the twenty-first century, and this also extends to data collection in observational and clinical studies.[16] He makes a very strong case for the critical need to introduce 24-hour ambulatory measurements as the standard for drug assessment and provides a number of examples of how this generates critical information which allows the true evaluation and impact of a proposed intervention. Blood pressure is frequently used as a marker for the risk of cardiovascular morbidity and mortality in studies of the effectiveness of antihypertensive drugs. Incomplete information is provided by conventional BP measurement techniques. Of particular concern is the power of 24-hour ambulatory measurement to examine the impact of intervention on both nocturnal dipping and the morning surge, both of which are important in the context of cardiovascular endpoints.

One can only conclude that while elevated BP is universally recognized as a cardiovascular risk factor, its measurements, its thresholds, and decisions regarding treatment appear rather primitive. The reader is also referred to the November 2009 Newsletter where BP thresholds are discussed and as well, the radical suggestion that everyone should be on antihypertensive medication.

CRANBERRIES, VITAMIN D AND BLADDER INFECTIONS

Urinary tract infections, generally also termed bladder infections, are an important disease and are more frequent in women and after menopause. These bothersome infections can become increasingly difficult to treat and can require the use of very potent antibiotics. Furthermore, there is emerging resistance to antibiotics that are effective. While cranberry juice consumption is a popular preventive measure, a randomized controlled trial just published suggests little or no effect.[17] However, this result is inconsistent with an analysis of 10 placebo-controlled clinical trials where cranberry products significantly reduced the incidence of urinary tract infections by 35% over 12 months. There is evidence, although inconsistent[18] that high-dose vitamin C may be effective and this in fact may have confounded this latest cranberry juice study since the placebo (fake juice) also contained vitamin C. A recent study found that even 100 mg/day of ascorbic acid (combined with folic acid) reduced urinary track infections by 65% when compared with two other treatment groups that did not include this vitamin.[19]

A recent experimental study investigated the potential of vitamin D in this context.[20] The biological plausibility involves a natural human antimicrobial peptide cathelicidin (small protein) which is produced upon *E. coli infection* and has been found protective in both humans and mice. The study found that the metabolite 25-hydroxyvitamin D appeared to prepare human bladder wall cells to produce cathelicidin only when needed to protect the urinary tract from bacterial infection. Moderately high doses (2000 IU) did not produce increased blood levels of this peptide, again suggesting that the mechanism was one of local response to an infectious agent. The authors also raise the possibility of age dependent loss of vitamin D receptors leading to increase risk of urinary tract infections. Elevating levels of 25-hydroxyvitamin D could compensate for this.

In their discussion, the authors comment that there are no data available on vitamin D levels and urinary tract infections but there is an established link between vitamin D deficiency and tuberculosis as well as viral respiratory infections. They conclude that supplementation to restore "proper" vitamin D levels may help prepare the bladder interior surface cells to mount a stronger and faster immune response once bacteria enter the bladder. A trial that combined vitamin C, cranberry juice or extract, and achieving and maintaining optimum vitamin D status would be interesting.

STOMACH ACID SUPPRESSION AND PNEUMONIA

A recent study has examined the risk of pneumonia in hospitalized patients either taking or put on drugs that suppress stomach acid (proton pump inhibitors-PPI or histamine receptor antagonists).[21] The investigation consisted of a meta-analysis of a number of studies reported in the literature up to late 2009. In observational studies, PPIs increased the risk of pneumonia by 27% whereas the histamine receptor antagonists gave an enhanced risk of 22%. Randomized trials of the latter drug also found a 22% increase. This translates to about one case per 200 inpatients treated with acid-suppressive drugs. Perspective can be gained by the fact that 40-70% of patients admitted to hospital receive this type of drug treatment and in addition, a significant number are already taking one or the other at admission. There is thus good reason for concern regarding the morbidity and mortality associated with what may well be unnecessary medication. In fact, some attending physicians put all their patients on this type of drug. A study in 2000 examined this question and found that of hospitalized patients, 54% were receiving acid suppression and of these 65% were considered over-treated by a consensus review.[22] The generally recognized indication for the use of these drugs in hospital is to prevent stress ulcers. The problem is compounded by discharging patients with instructions to continue the medication.

The subject of the dangers of overuse of drugs that shut down stomach acid production was recently reviewed in this Newsletter (April 2010). As was discussed, there are many reasons why in general is not a good idea to mess around with a digestive system that has evolved over eons and serves normal humans very well indeed. Furthermore, there is growing evidence that acid reflux is only a very weak risk factor for cancer of the esophagus (see below). If this turns out to be correct, it dramatically decreases the rationale for eliminating stomach acid.

ANTIDEPRESSANTS FOR HOT FLASHES

It seems that the pharmaceutical industry is always looking for new uses for their drugs with the hope of eventually getting approval for what are off-label prescriptions. Sometimes, the proposed use seems rather bizarre. A recent randomized controlled trial has reported on the efficacy of an antidepressant (escitalopram, a selective serotonin reuptake inhibitor—SSRI) in treating hot flashes in healthy menopausal women.[23] While the sponsorship of this study was from U.S. government agencies, the authors had extensive conflicts of interest which included the manufacturer of the drug in question. It was reported that the use of this SSRI resulted in fewer and less severe hot flashes at 8 weeks follow-up as compared to a placebo. The same result was found in a study reporting in 2009 and supported by the manufacturer of the drug but published in a journal not requiring disclosure of author conflicts of interest.[24] To list the side effects of this drug would consume an excessive amount of space. The reader is referred to the internet where a number of sites provide lists. Included is the potential for suicidal thoughts. Furthermore, there are serious withdrawal issues with SSRIs. One can ask a simple question: is rewiring or disabling the brain (see Part I of the review on psychiatric drugs in the February 2011 issue) an intelligent approach to treating a phenomenon that cannot even be called a disease? This is not to deny the inconvenience and unpleasantness of serious hot flash episodes. Research on this use of antidepressants for hot flashes actually started with breast cancer survivors including those on anti-estrogen therapy and those for whom estrogen therapy for hot flashes was contraindicated. A review of non-hormonal therapies for hot flashes concluded that antidepressants “may be useful for highly symptomatic women who cannot take estrogen but are not optimal choices for most women.”[25] This appears to be an understatement.

Aside from antidepressants, other prescription drugs tried in this context include antihypertensive, anticonvulsants, and an

antispasmodic/sedative combination.[25] Inconsistent results, mostly fair to poor quality trials, and high levels of adverse side effects appear to characterize this approach. Natural isoflavone extracts from red clover or soy have also been tried. Trials failed to support the red clover extracts and soy isoflavones presented mixed results.[25] Folic acid has been tried for treating hot flashes. In a small controlled study a significant decrease in events was observed in the folic acid group as compared to the placebo group.[26] Only one dose was used, 5 mg/day, and in view of increasing evidence that taking high doses of the synthetic form of folate increases the risk of cancer, there are risk-benefit issues even with this semi-natural approach. Other supplemental forms such as 5-methyltetrahydrofolic acid that increase folate intake are available that avoid the high levels of unmetabolized synthetic folic acid. It is unfortunate that one of these was not tried.

NEWS BRIEFS

PESTICIDES AND EARLY CHILDHOOD NEURODEVELOPMENT

It appears that there has been a shift in residential pesticide use from organophosphorous compounds to pyrethroid insecticides. A recent study has examined the impact of exposure to these newer insecticides on childhood neurodevelopment during the first three years.[27] Exposure was determined from plasma levels from cord blood and from air samples taken during pregnancy. The cohort consisted of black and Dominican mothers and their newborns living in low-income neighbourhoods of New York City. It was found that exposure to piperonyl butoxide (PBO) was negatively associated with neurodevelopment, a result based on air samples. This association persisted after controlling for a number of confounding variables. Children who were in the highest quartile of exposure to PBO were three times as likely to be in the delayed development category as compared to those in the lowest quartile The authors comment that these changes as measured by a mental development index were comparable in magnitude to reports from studies of other prenatal neurotoxins known to affect young children. In addition, PBO is not in general considered particularly toxic.

ROASTING COFFEE BEANS ENHANCES ANTIOXIDANT CONTENT

In a paper due to be published in *Food Research International,* researchers at the University of British Columbia have examined the effect of roasting coffee beans on their antioxidant content and find the levels greatly enhanced as compared to the green beans. The benefits of consuming coffee have been extensively investigated and are frequently reported in this Newsletter. The researchers point specifically to aggressive prostate cancer, the risk of which was lowered by 60% in men who drank coffee as compared to those that abstained, and they suggest that the high antioxidant content of roasted coffee could provide part of the explanation.

GASTRIC REFLUX AND ESOPHAGEAL CANCER

Acid reflux (heartburn or GERD) has been discussed several times in this Newsletter including a Research Review. The thesis of the review was that it was not a very good idea to mess with the natural acidity of the stomach since the low pH was associated with both protective and digestive issues that even extended beyond the stomach. The strongest counter argument relates to the prevention of esophageal cancer (EC). A recent study found that the incidence of EC in men younger than 50 years who had GERD symptoms was in fact very low. (e.g. at age 35, it was only 10 per million. By comparison, risk of colorectal cancer (CRC) was almost 7-fold greater. For women, the risk associated with GERD was found to be extremely low independent of age. However, for older men, weekly GERD episodes did increase the risk, but the risk of CRC was still 3-fold greater. This study focused on the merits of screening for EC and concluded that its was not justified for men younger than 50 or women of any age.[28] For older men, apparently screening has not been established as accurate, safe or effective.

VITAMIN D AND MULTIPLE SCLEROSIS

As reported in the February Newsletter, the widely publicized official mainstream position is that most of us have adequate vitamin D status and that any connection between vitamin D and chronic disease (aside from bone problems) is unproven and should be ignored until proper studies are conducted—probably during the next two decades if at all. Thus a recent paper in the journal *Neurology* which examines sun exposure and vitamin D as independent risk factors for multiple sclerosis (MS) is of considerable interest. It was found that differences in leisure-time sun exposure, serum 25-hydroxyvitamin D levels and skin type additively accounted for a 32% increase in incidence of a first MS event (demyelinating events). Incidence also increased from low to high latitude regions in Australia (27º S to 43º S).[29] Viewed another way, the annual incidence was 4-fold greater at 43º S. This is another of many latitude studies that focus attention on vitamin D.

VITAMIN D AND RISK OF VIRAL CO-INFECTIONS IN WHEEZING CHILDREN

Epidemiologic studies have demonstrated that low vitamin D status is associated with increased risk of respiratory infections in young children. Also, low maternal intake of vitamin D during pregnancy and low umbilical cord blood levels of 25-hydroxyvitamin D have been associated with increased risk of childhood wheezing. Vitamin D supplementation also decreases respiratory tract infections in children. There is even a randomized placebo-controlled trial that demonstrated that a group of school-age children supplemented with 1200 IU/day of vitamin D had fewer influenza A viral infections. Now a recent study has shown that vitamin D has an antiviral action that might be important to wheezing children.[30] The researchers found that low serum 25-hydroxyvitamin D levels increased the risk of viral co-infection, specifically the risk of respiratory syncyhtial virus (RSV), rhinovirus or both. RSV is the dominant cause of bronchiolitis (swelling and mucus build-up in the smallest air passages in the lungs), whereas rhinovirus is the main trigger for wheezing necessitating hospitalization. This study was from Finland where most 2- to 3-year-olds do not take vitamin supplements. One third of the children had low vitamin D status.

REFERENCES

(1) Chiuve SE, Korngold EC, Januzzi JL, Gantzer ML, Albert CM. Plasma and dietary magnesium and risk of sudden cardiac death in women. *The American Journal of Clinical Nutrition* 2011 February 1;93(2):253-60.

(2) Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-Sweetened Beverages and Risk of Metabolic Syndrome and Type 2 Diabetes. *Diabetes Care* 2010 November 1;33(11):2477-83.

(3) Lipska KJ, de RN, Van Ness PH et al. Identifying dysglycemic states in older adults: implications of the emerging use of hemoglobin A1c. *J Clin Endocrinol Metab* 2010 December;95(12):5289-95.

(4) Cohen RM, Haggerty S, Herman WH. HbA1c for the diagnosis of diabetes and prediabetes: is it time for a mid-course correction? *J Clin Endocrinol Metab* 2010 December;95(12):5203-6.

(5) Warren RE, Marshall T, Padfield PL, Chrubasik S. Variability of office, 24-hour ambulatory, and self-monitored blood pressure measurements. *Br J Gen Pract* 2010 September;60(578):675-80.

(6) Sala C, Santin E, Rescaldani M, Magrini F. How long shall the patient rest before clinic blood pressure measurement? *Am J Hypertens* 2006 July;19(7):713-7.

(7) Myers MG. Why automated office blood pressure should now replace the mercury sphygmomanometer. *J Clin Hypertens (Greenwich)* 2010 July 1;12(7):478-80.

(8) Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. Measurement of Blood Pressure in the Office: Recognizing the Problem and Proposing the Solution. *Hypertension* 2010 February 1;55(2):195-200.

(9) Parati G, Omboni S, Bilo G. Why Is Out-of-Office Blood Pressure Measurement Needed? Home Blood Pressure Measurements Will Increasingly Replace Ambulatory Blood Pressure Monitoring in the Diagnosis and Management of Hypertension. *Hypertension* 2009 July 6;54:181-7.

(10) Agarwal R, Bills JE, Hecht TJ, Light RP. Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis. *Hypertension* 2011 January;57(1):29-38.

(11) Mancia G, Parati G. Home blood pressure monitoring: a tool for better hypertension control. *Hypertension* 2011 January;57(1):21-3.

(12) Parati G, Omboni S, Bilo G. Why Is Out-of-Office Blood Pressure Measurement Needed? Home Blood Pressure Measurements Will Increasingly Replace Ambulatory Blood Pressure Monitoring in the Diagnosis and Management of Hypertension. *Hypertension* 2009 July 6.

(13) Mancia G, Bombelli M, Facchetti R et al. Long-Term Risk of Sustained Hypertension in White-Coat or Masked Hypertension. *Hypertension* 2009 August 1;54(2):226-32.
(14) Messerli FH, Makani H. Relentless Progression Toward Sustained Hypertension. *Hypertension* 2009 August 1;54(2):217-8.
(15) Niiranen TJ, Hanninen MR, Johansson J, Reunanen A, Jula AM. Home-measured blood pressure is a stronger predictor of cardiovascular risk than office blood pressure: the Finn-Home study. *Hypertension* 2010 June;55(6):1346-51.
(16) O'Brien E. 24-hour ambulatory blood pressure measurement in clinical practice and research: a critical review of a technique in need of implementation. *J Intern Med* 2011;epublished Jan 21.
(17) Barbosa-Cesnik C, Brown MB, Buxton M, Zhang L, DeBusscher J, Foxman B. Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial. *Clin Infect Dis* 2011 January;52(1):23-30.
(18) Regal RE, Pham CQ, Bostwick TR. Urinary tract infections in extended care facilities: preventive management strategies. *Consult Pharm* 2006 May;21(5):400-9.
(19) Ochoa-Brust GJ, Fernandez AR, Villanueva-Ruiz GJ, Velasco R, Trujillo-Hernandez B, Vasquez C. Daily intake of 100 mg ascorbic acid as urinary tract infection prophylactic agent during pregnancy. *Acta Obstet Gynecol Scand* 2007;86(7):783-7.
(20) Hertting O, Holm A, Luthje P et al. Vitamin D induction of the human antimicrobial Peptide cathelicidin in the urinary bladder. *PLoS One* 2010;5(12):e15580.
(21) Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: systematic review and meta-analysis. *CMAJ* 2010 December 20;e published ahead of print.
(22) Nardino RJ, Vender RJ, Herbert PN. Overuse of acid-suppressive therapy in hospitalized patients. *Am J Gastroenterol* 2000 November;95(11):3118-22.
(23) Freeman EW, Guthrie KA, Caan B et al. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA* 2011 January 19;305(3):267-74.
(24) Defronzo DR, Menza M, Allen LA et al. Escitalopram reduces hot flashes in nondepressed menopausal women: A pilot study. *Ann Clin Psychiatry* 2009 April;21(2):70-6.
(25) Nelson HD, Vesco KK, Haney E et al. Nonhormonal Therapies for Menopausal Hot Flashes. *JAMA* 2006 May 3;295(17):2057-71.
(26) Gaweesh SS, bdel-Gawad MMM, Nagaty AM, Ewies AAA. Folic acid supplementation may cure hot flushes in postmenopausal women: a prospective cohort study. *Gynecol Endocrinol* 2010 March 16;26(9):658-62.
(27) Horton MK, Rundle A, Camann DE, Barr DB, Rauh VA, Whyatt RM. Impact of Prenatal Exposure to Piperonyl Butoxide and Permethrin on 36-Month Neurodevelopment. *Pediatrics* 2011 February 7;eds.
(28) Rubenstein JH, Scheiman JM, Sadeghi S, Whiteman D, Inadomi JM. Esophageal adenocarcinoma incidence in individuals with gastroesophageal reflux: synthesis and estimates from population studies. *Am J Gastroenterol* 2011 February;106(2):254-60.
(29) Lucas RM, Ponsonby AL, Dear K et al. Sun exposure and vitamin D are independent risk factors for CNS demyelination. *Neurology* 2011 February 8;76(6):540-8.
(30) Jartti T, Ruuskanen O, Mansbach JM, Vuorinen T, Camargo CA, Jr. Low serum 25-hydroxyvitamin D levels are associated with increased risk of viral coinfections in wheezing children. *J Allergy Clin Immunol* 2010 November;126(5):1074-6, 1076.

BRAVE NEW WORLD OF THE PSYCHO-PHARMACY AND THE ALTERNATIVES

William R. Ware, Ph.D.

PART II
ALTERNATIVES

Try without antipsychotics. You can treat them better without medication. They become more interactive. They become themselves." Viljo Räkköläinen, Finish psychiatrist[1(p. 338)]

INTRODUCTION

The principal issues addressed in this review concern the risk-benefit of psychiatric drugs and if the decision is made to go against mainstream practice and reject suggestions or recommendations of this therapy, what are the alternatives. The dilemma is far from hypothetical. The prevalence and rate of increase of psychological disorders is large and sooner or later many readers of this review will be forced to confront this issue, either as regards their own problems or those of their children or parents.

Government statistics, ignoring illegal drug or substance abuse, confirm this. Sources include the Centers for Disease Control (CDC), the National Institute of Mental Health (NIMH) and the American Academy of Child and Adolescent Psychiatry.

- Approximately 1 in 20 of Americans aged 12 or older are diagnosed as depressed. Of these about 80% report symptoms that interfere with their ability to work and 35% report functioning is very or extremely difficult.
- It is estimated that 3% to 5% of school age children are diagnosed with attention deficient hyperactivity disorder (ADHD).
- About 2.6% of the U.S. population have bipolar disorder.
- About 1% to 4% of children are viewed as having conduct disorder and 1% to 6% are viewed as having so-called oppositional defiant disorder.
- Schizophrenia affects about 1% of Americans.
- Post-Traumatic Stress Disorder appears to affect about 5.2 million Americans.
- When major depressive disorders, mild depression and bipolar disorder are combined, the NIMH estimates prevalence at about 10% of the U.S. population over 18.
- The NIMH also estimates that almost 20% of Americans 18 and older meet the diagnostic criteria for anxiety disorders according to diagnostic criteria in current use.

This list does not include phobias, eating disorders, personality disorders, antisocial personality disorders or avoidant personality disorders. When the new diagnostic manual (DSM-V) comes out in 2013, both the number and prevalence of psychological disorders will considerably increase according to preliminary reports and commentary.[2,3]

There is no doubt that many of these diagnoses result in medication. The numbers for antidepressants, for example, put them at the top of the prescription frequency list in the U.S. in the period 2003-2004 for female patients of all ages and for both men and women between ages 18 and 44. They are in general the most prescribed drugs in the U.S. Almost all carry FDA black box warnings regarding suicide risk, and if one believes Breggin's view, discussed in Part I, they all disable the brain to a greater or lesser degree. Thus the belief that there is or should be considerable interest in avoiding drug therapy for psychological disorders and for any of a large number of behavior patterns that the conventional wisdom considers outside normal.

Some idea of the growth rate in prescriptions for antidepressants is available from the CDC. When the period 1995-1996 is compared with 2003-2004, based on visits to physicians offices or outpatient

clinics and using as a measure the number receiving one or more drug prescriptions per 100 visits over each two-year period, antidepressant growth was 92% in the age group 18-44 and 118% for all ages.

This looks rather like an epidemic. But there are some in the psychiatric community that point to significant overdiagnosis. In fact Dr. Allen Frances, a psychiatrist now emeritus professor and former chairman of the Department of Psychiatry at Duke University, who was the leader in the preparation of the fourth edition of the diagnostic manual (DSM-IV, 1994) currently used as a bible by the profession, made an amazing confession recently. In an editorial in the *Los Angeles Times* he stated that this manual was, in his opinion, unintentionally responsible for generating epidemics in AHDH, autism and childhood bipolar disorder. This resulted in unnecessary and potentially dangerous medication. In such journals as *Psychiatry Times* and *Psychology Today*, he has also repeatedly stated concerns regarding the new edition (DSM-V) currently available in draft form for comment. His message: "Beware of its unintended consequences." Francis believes that the proposals in the DSM-V draft could set off at least eight new false positive epidemics. He comments in the *British Journal of Medicine*: "The consequences are grave. For individuals, these include unnecessary treatment with drugs that have unproven benefit and known harm; stigma; difficulties in getting life insurance and disability insurance; and a reduced sense of personal responsibility and control."[2] It seems that we are well on the way where everyone sometime in life will have symptoms meeting the definition of mental illness and require treatment which at present is mostly in the form of pills.

GUIDANCE FROM POTENTIAL CAUSES FOR THE MENTAL HEALTH EPIDEMIC

One might wonder what has happened over the past few decades that caused over a quarter of Americans to be diagnosed with one or more of a several mental disorders, each classroom to have pupils with mild to serious problems attributed to diseased brains requiring drug therapy and toddlers now coming under close scrutiny by their doctors for treatable mental disorders. After all, the brain is noteworthy for its plasticity, its ability to compensate, its defence mechanisms such as the blood-brain barrier and its protective mechanisms against, for example, starvation or low blood sugar. The roundup of the usual suspects plus a few additions yields this short list.

- Neurotoxins from environmental sources including tap water, clothing, textiles, products for home use and personal care, pesticides and finally from food.
- Psychiatric drugs as well as a large number of other medications.
- Endocrine related disorders such as thyroid problems (hypo- or hyperthyroidism), diabetes and adrenal gland or pancreatic tumors.
- Polycystic ovary syndrome (risk elevation for depression about 4 times)[4]
- Autoimmune diseases such as lupus and Hashimoto's disease.
- Allergens mainly present in food, such as gluten.
- Frequent consumption of large amounts of refined sugars.
- Diets that are micronutrient poor. Candidates include diets made up of junk food, commercially prepared food, food from farmlands depleted over the years of many minerals and diets based on the avoidance of fruits, vegetables and fish.
- Dysfunction or deregulation of the circadian clock and some of the rhythms it controls.
- Chemicals used as preservatives or adjuvants in vaccines (substances that increase the immune response). According to the package inserts, in the U.S., childhood vaccines involve the injection of 56 distinct chemicals over the course of recommended vaccination schedules. No studies of adequate design or power and free of industry bias have ever investigated the long term impacts of this load of potential toxins, and this will in fact probably never happen.

Avoiding toxic substances is far from simple when they are produced yearly in mega-ton quantities and permeate our daily existence. Organophosphates which are, for example, implicated in ADHD are found in pesticides[5,6] and polyfluoroalkyl chemicals used in non-stick coatings, paper and textile coatings, and personal care products.[7] Psychiatric drugs appear to critics be eligible for classification as toxic. However, most of the items on this list suggest relatively simple interventions or diagnostic

issues. Thus how does one proceed in an organized and potentially successful fashion, initially considering the individual not on psychiatric drugs and wishing to avoid them?

In terms common to psychiatry, part of the diagnostic challenge is differentiating primary (psychiatric) from secondary (organic) psychosis, the latter being of interest in the context of this review.[8] First, there is the matter of thyroid disorders and diabetes. Depression frequently accompanies diabetes but as discussed below, how they interact is unclear. Thus, the diabetic suffering from depression is a rather special case since modern medicine does not generally cure diabetes but only attempts to control the progression of the adverse effects of this disease. The option of curing the diabetes and then seeing if depression persists is not practical. However, as discussed below, bringing blood sugar levels and fluctuations back to normal with diet has been used successfully in this context.

Thyroid disorders are somewhat different. The protocol for eliminating thyroid dysfunction is well established but the diagnosis of this dysfunction, especially if it is subclinical, presents problems that may require consultation with an endocrinologist. However, testing the hypothesis that the problem is hypothyroidism simply by providing hormone treatment can frequently clarify this issue over period of weeks.

In the differential diagnosis of possible causes of psychological symptoms, a number of other diseases, conditions and medications need to be considered as well as the possibility of substance abuse. This is actually a complex subject somewhat beyond the scope of this review, but the importance of ruling out secondary psychosis which can be treated and probably cured is obviously both important and challenging.[8] One wonders how often it is done properly and how often instead a psychiatric drug unrelated to the root cause is prescribed.

There remains the possibility that the root cause of the problem is multifactorial. On this basis it can be argued that a simple but multifaceted approach may offer the best hope of a rapid resolution of the problems once thyroid dysfunction and other medical problems have been definitively ruled out. This would mean addressing dietary factors through diet modification and supplementation with a combination of all the potential micronutrients that might be at low levels. Combining this with psychotherapy would represent a fairly comprehensive approach. Adding light and/or melatonin therapy would be a possibility if there were indications of problems with circadian rhythm. To try one intervention at a time, for example adding a micronutrient, eliminating a potential allergen, modifying a macronutrients in the diet (e.g. minimizing refined carbohydrates, especially sugar), trying to adjust circadian rhythms, or introduce psychotherapy may not be nearly as effective as simultaneously trying as many approaches as possible. The reason is simple. An unavoidable ignorance of root causes.

THE THYROID-BRAIN INTERACTION

The book *The Thyroid Solution* by Ridha Arem, M.D., an endocrinologist and clinical professor of medicine at Baylor College of Medicine, includes a lengthy discussion of the role of a dysfunctional thyroid in the mental problems being discussed in this review. Is a thyroid function assessment routine prior to prescribing antidepressants or antipsychotics, stimulants or tranquilizers? Doubtful indeed. Furthermore, subclinical but still important hypothyroidism would probably be ignored. Yet in some patients, the problems psychopharmacotherapy is trying to solve, apparently not very successfully, can be addressed with thyroid therapy. Such treatments generally involve a natural approach free of side effects and with other health benefits. However, the assessment of thyroid function is complex and the current guidelines or laboratory reference ranges prone to false negatives. In fact, the ideal response to a patient presenting with evidence of the need of psychopharmacy should probably be referral to an endocrinologist with experience in thyroid disorders. Given the widespread prevalence of psychological problems, if this became a standard of care it would overwhelm the endocrinology community!

The peer-reviewed literature on this subject is unclear due to issues with the definition and diagnosis of subclinical hypothyroidism and the approaches used to correct it if found or suspected. The reader is referred to Arem's book for a comprehensive discussion of the importance, diagnosis and treatment

of thyroid imbalance and its relation to mental problems. At the end of Chapter 5, which discusses the mind-thyroid connection, he makes the following points:

- The consequences of thyroid imbalance may include not only mental and emotional problems but even such serious conditions such as manic-depression. However, mild depression is the most common.
- For individuals prone to mood disorders and emotional problems, thyroid imbalance can magnify the symptoms.
- Hypothyroidism may be associated with borderline depression that presents as fatigue.
- It is now recognized that the thyroid hormones have a major biochemical function in the brain and significant impact on mood, emotions and behaviour.
- For anyone who is suffering form depression or has had depression in the recent past, the question of thyroid imbalance should be addressed, in particular if symptoms of thyroid imbalance are present.

DEPRESSION AND DIABETES

The association between depression and diabetes is well known but poorly understood. There is some evidence of a bidirectional nature, i.e. each is a causal factor for the other. However, two large studies only support the hypothesis that depression in diabetics results from the ongoing psychological stressors associated with a chronic medical condition.[9] A number of studies have been reported regarding treatments for depression in diabetes. These involve either antidepressants, psychotherapy or both. Mood improvement was reported in both, but in terms of diabetes, neither resulted in better medical outcomes. There is no evidence leading one to believe that the downside of psychopharmacy in this context is any different than described above. However, there is evidence of a strong and significant association between antidepressant use and diabetes risk that is not accounted for by confounders or mediators.[10]

In his book *Dr. Bernstein's Diabetes Solution,*[11(P.373)] the author describes a study done in the late 1970s at Rockefeller University in New York where the methods he promotes for blood glucose control were used on a group of depressed type 1 diabetics. The basis was simply severe carbohydrate restriction, the careful control of the nature of the carbohydrates, insulin when necessary and the use of home glucose monitoring to establish a protocol that works for each individual. The patients were initially tested to quantify the level of their depression, which was in the severely depressed range. The fascinating result was that once the patient's blood sugars came under control, the depression disappeared. By control, Bernstein means fasting, post meal and long-term (HbA1c) glucose levels that approximate that of non-diabetic individuals, something that mainstream diabetes control almost never achieves and in fact the conventional wisdom appears to regard as impractical. Bernstein is internationally recognized as able to achieve this result with many type 1 and type 2 diabetics. Patients simply have to learn to live with rather severe and selective carbohydrate restriction. There are of course several ways of interpreting the impact of this dietary intervention on depression in diabetics, but it is the result that matters, not only in terms of mental health but as regards the long-term neurological and vascular damage caused by chronic hyperglycemia.

LIPID-LOWERING DRUGS AND PSYCHIATRIC ADVERSE REACTIONS

A recent review summarizes the reported adverse reactions associated with lipid-lowering drugs.[12] It is well known that the reporting system is highly imperfect and misses almost all cases. Nevertheless, there are reports of the whole spectrum of mood disorders, cognitive disorders, sleep disorders, perception disorders as well as a variety of fatigue related symptoms. A small fraction of the incidents reported were severe, and all showed improvement on discontinuation of the lipid-lowering treatment. Some reports included positive rechallenge experiences. The adverse reactions were seen with both statins and fibrates, which suggest that in some cases it is the lipid lowering rather than the HMG-CoA reductase inhibition that is involved. Thus part of a careful differential diagnosis in this field must include questions about lipid-lowering drug use. Many of the psychiatric disorders ascribed to taking these drugs come under the guidelines as indications for psychopharmaceutical therapy, which

obviously fails to get at the root cause. Given the minute percentage of adverse effects that are reported and recorded, this may be a significant and not fully appreciated problem.

There is emerging mechanistic evidence involving statin induced impairment of the function and dynamics of a serotonin receptor.[13] It is noteworthy that statins use appears to be associated with transient global amnesia.[14] The above indications of potential harm do not agree with those presented in a recent review based on gathering data from statin studies where the impact on mood was part of the side effect assessment rather than from an adverse effect reporting center. However, the studies included were industry supported and the review published in a journal not requiring declaration of conflict of interest.[15] Industry studies tend to downplay adverse effects. Accumulated evidence also suggests that there is a connection between low and especially very low cholesterol levels, mood symptoms and the risk of suicide but such results are difficult to correct for confounding.[16-18]

DIET, SUPPLEMENTS AND MENTAL DISORDERS. THE MICRONUTRIENT DEFICIENCY MODEL

First, the evidence from dietary patterns. Patterns are important because obviously humans generally eat a mixture of foods at each meal. A number of recent studies have looked for dietary patterns that reduce the risk of depression,[19,20] the outcome of schizophrenia[21] and mental health of adolescents such as avoiding depression/withdrawal and delinquent or aggressive behavior.[22] Typically, these studies find the optimum diet in this context to emphasize fruits, vegetables and fish, a diet many individuals do not fancy. One recently published study of Australian women compared a traditional diet rich in vegetables, fruit, meat, fish and whole grains with the Western diet of meat pies, fried foods, pizza, chips, hamburgers, white bread, sugar, flavoured milk drinks and beer.[23] They found the traditional diet provided the lowest risk (adjusted for confounders) of developing depression or anxiety disorders. Consistent with these results, studies find an association between adherence to the Mediterranean diet pattern and the a low incidence of depression and a high degree of mental health.[24-27] This pattern is characterized by high consumption of vegetables, fruit, nuts, cereal, legumes and fish, a high mono to saturated fatty acid ratio, and moderate alcohol consumption. A large, 12 year follow-up study in Spain found high intake of *trans*-fatty acids increased the risk of depression whereas monounsaturated and polyunsaturated fatty acids and olive oil were protective. These results are important since the consumption of *trans*-fatty acids is six times greater in North America as compared to Spain.[28] The beneficial nature of certain diet patterns relates to some of the suspected factors listed above since they tend to be micronutrient rich but not calorie dense and are low in sugars and food additives. However, the mechanisms for various pattern associations are not clear. Inflammatory processes, antioxidant content, and the ability to influence protective factors in the brain have been evoked.[23]

The question of which micronutrients, i.e. vitamins, minerals, classes of fatty acid, or individual amino acids, might be most important in connection with mental health has interested nutritionists for a long time. The classic example is vitamin B1 deficiency causing pellagra which in terms of neurological symptoms is indistinguishable from schizophrenia. It is cured by vitamin B1 supplementation. In a recent review of micronutrients implicated in mental health, Kaplan *et al*[29] list folate--folic acid, vitamins B1, B6, B12, lecithin, calcium, chromium, magnesium and selenium. They cite 15 studies with endpoints related to mood and depression, 8 of which are randomized controlled trials. All found benefit with regard to single micronutrient interventions. Other micronutrients with known brain functions are vitamin E, choline, iron and zinc. While single micronutrient studies satisfy the purist who insists that only one variable can be changed at a time, the fact remains that the human diet contains a grand mixture with highly variable amounts of these substances. It can be argued that it is therefore more realistic to study interventions using mixtures of micronutrients. This in fact has produced some very interesting and significant results, which is not surprising since the synthesis, uptake and breakdown of neurotransmitters require enzymes, and every enzyme reaction or action involves one or more cofactors, many of which are vitamins and minerals. Therefore, multiple deficiencies become very important.

Kaplan *et al*[29] list 13 studies involving supplement mixtures of which 6 were randomized controlled trials (RCTs). The mixtures varied considerably with some using only folate and B12 or mixtures of a few vitamins. However, they also discuss five case-series studies that used a proprietary 36-

ingredient formula of vitamins, minerals and amino acids (EMP+), and two RCTs that used either 26- or 23-ingredient formulas of vitamins, minerals, and essential fatty acids. These studies revealed very significant benefits for individuals with mood, temper, rage and anxiety disorders and children and adults with bipolar disorder. One of the RCTs involved young adult prisoners with a history of antisocial and violent behaviour. There was a significant decrease in these behavioral problems between the 26-ingredient intervention group and the placebo group. Another RTC involved schoolchildren disciplined for violating school rules. A 23-ingredient supplement resulted in a significant decrease in rule infractions as compared to the placebo group. Since the publication of the review by Kaplan *et al*, seven additional studies using the 36-component mixture have been published.[30-36] Beneficial results were found for bipolar disorders in children and adolescents, the management of autism, ADHD and obsessive compulsive disorder (OCD). The mixtures containing a large number of components should have considerable appeal since it is difficult to identify and characterize deficiency, especially on the scale of 36 items, and also there are few useful guidelines for what constitutes a deficiency, given that there is great human variability in the amounts of some micronutrients required for optimum health, mental or otherwise.

A landmark study by Bruce Ames and colleagues, then at the University of California at Berkeley, examined a number of minerals and vitamins for their role as cofactors (coenzymes) in enzyme mediated processes or in genetic expression.[37] Genetic variations alone accounted for a large variation in levels of cofactors necessary for normal biological function, and both minerals and vitamins were implicated as cofactors in a wide assortment of processes. One single micronutrient may be involved in dozens of processes. Cofactors are non-protein chemical compounds that bind to proteins and are required for their biological activity. These proteins are frequently enzymes critically involved in innumerable biochemical processes.[38] Some enzymes require several cofactors and zinc for example, is an essential cofactor for more than 100 enzymes. We obviously evolved to acquire from diet the required cofactors in the required amounts in order for our biochemistry to function properly. However, there are large variations in the levels of cofactors required for any given biochemical step, and some are caused by mutations. The levels required relate to the strength of binding of the cofactor to the target protein. When it is low, greatly enhanced concentrations of a given cofactor may be required to achieve normal function. This can translate into a large dose of a vitamin or mineral. A number of these enzymes are critical in the brain biochemistry.[37,38]

While the above is an oversimplification, it indicates why it is not particularly informative to study just single micronutrients in the context of a dysfunctional state and why studies using a large number of micronutrients make more sense. In the field of the nutritional aspects of mental disorders, the principle of one variable at a time offers a huge if not insurmountable barrier to progress. Furthermore, failures of studies that change only one micronutrient provide live ammunition for the anti-supplement community which further retards progress. Fortunately, there are a number of medical scientists who recognize this and have contributed greatly to progress in this field.

The micronutrient deficiency model is also particularly relevant to children, especially considering the prevalence of nutrient-poor diets. The study of Ames and colleagues underscores the serious nature of the decline in the nutrient value of foods over time. Furthermore, for various reasons, parents may make poorer and poorer choices for their own food and that of their children. There are generational aspects to food choice. Children reject parents' old-fashioned ideas about fruits, vegetables and variety. There emerges a new generation of parents and with it the potential for changed attitudes that impact this new generation's children. Also, as children are allowed wider scope in eating, junk food approaches the norm at noon in many school environments or when a fast meal is required. Nutrient poor but high-energy foods have become common, are very successfully marketed to children and are major sources of calories. It is not only obesity that results, but also a deficiency in micronutrients. Children can become successful in influencing what they eat at home. The net result may be a slow, progressive development of deficiencies in micronutrients that are critical cofactors for numerous biochemical reactions and critical for brain function. These deficiencies start to impact brain function resulting in behavior problems which increase child's ability to oppose nutritional suggestions of parents. A feedback loop develops. The worst cases are the institutionalized. Micronutrient deficiency obviously occurs in adults as well.

THE MOST STUDIED SUPPLEMENT MIXTURE

The supplement mixture that has received the most clinical attention is *EMPowerplus* (EMP+). As mentioned above, twelve studies have all found beneficial effects. These were all case or database analysis studies. The mixture contains most of the vitamins and minerals that are found in popular multivitamin preparations and in addition, undisclosed amounts of phenylalanine, citrus bioflavonoids, the amino acids L-glutamine and L-methionine, grape seed extract, ginkgo biloba, germanium sesquioxide, and nickel. If one compares the vitamin-mineral content of the typical daily dose from 15 capsules of EMP+ with, for example, the Life Extension One-A-Day supplement, the only significant differences (ignoring calcium and magnesium) are as follows. According to data on the manufacturer's website (Truehope), EMP+ contains about three times as much folic acid, vitamin B12, biotin and chromium, five times the manganese, and 10 times the potassium. Life Extension multivitamin contains 4 times as much thiamine, five times the pantothenic acid and three times the riboflavin, but no amino acids, grape seed extract, ginkgo, germanium or nickel. Thus EMP+ can not be regarded as providing mega doses. If one ignores some of the more esoteric non-vitamin and mineral components the two could be made roughly equivalent simply by adding a low-dose B complex supplement and a bit of chromium and manganese.

How important the other differences are is of course unknown, but several of the items are readily available and taken by millions of people every day (grape seed extract, ginkgo, and citrus bioflavonoid). The packaging of EMP+ allows the administration to be spread out over the day. How important this is appears unknown. EMP+ also contains considerably more calcium and 600 vs 100 mg of magnesium. The one-a-day multivitamins in general tend to have very little of these two micronutrients since the amounts generally regarded as optimum would make the pills or capsules too large. Anyone wishing to attempt to duplicate the results of studies that used EMP+ can easily make up a roughly equivalent supplement. The three amino acids are also readily available but the company does not disclose the dose levels.

If one takes a large sample of individuals with, for example, major depression or bipolar disorder, and finds that EMP+ significantly relieves their symptoms or puts them in remission, this result could be due to just one or two of the components of the mixture or to a synergism between a numbers of the ingredients. In addition, which ingredient or ingredients are most active will probably vary from person to person. Thus, mixtures obviously address the problem of unavoidable ignorance as to specific deficiencies. But this has for ages been the basic philosophy of taking a multivitamin, something that is now recommended even by mainstream medicine.[39]

If one compares the EMP+ protocol with that used in the prison inmate study described above, what is striking is that good results were obtained in the prison study with much lower doses of vitamins and minerals (similar to government daily requirements). To the vitamin mineral mix was added essential fatty acids and all but the omega-6 linoleic acid were also at low doses, and the jail study did not use the other non-vitamin-mineral supplements found in EMP+. Similar observations apply to the unruly student study. This suggests that micronutrient deficiencies correctable by small levels of supplementation may be of much greater significance in mental health than generally appreciated.

OMEGA-3 DEFICIENCY AND THERAPY

The role in mental health of the omega-3 polyunsaturated fatty acids, and in particular the two long-chain acids EPA and DHA, is controversial due to inconsistent results. However, many studies were of low quality or used intervention doses that appear inadequate. In the case of patients with depression, a recent meta-analysis indicated that lower levels of EPA, DHA and total omega-3 fatty acids were associated with depression. However, intervention studies suggest that only high omega-3 doses and only DHA are relevant in this context.[40] Consistent with this, long-term fish intake is also associated with less severe depressive symptoms among both elderly men and women.[41]

In the case of schizophrenia, as Malcolm Peet discusses in a recent review, most observational studies have shown reduced levels of DHA, and there is evidence from randomized placebo controlled trials that omega-3 fatty acids might prevent the conversion to a first-episode psychosis and reduce the drug requirement for treating first-episode patients.[42] However, Peet points to the dangers of single nutrient therapy and comments that in his own practice attention is given to the

reduction of harmful nutrients and increasing nutrients that are important for mental health. From the description of his intervention, it appears that it is similar to the use of the multivitamin-mineral mixture described above plus DHA and EPA.

In the context of ADHD, a recent study examined the association between omega-3 levels and various mental problems in schoolchildren. Some associations were found with omega-3 levels and high levels were associated with decreased inattention, hyperactivity and behavior, emotional and conduct difficulties as well as increased prosocial activity. These observation were based on teacher and parental reports.[43]

ROLE OF VITAMIN D IN MENTAL HEALTH

The multiple roles of vitamin D in health become more and more apparent each month as new studies appear. In fact, it was hard to believe that the Institute of Medicine in the U.S. very recently took a highly publicized and ultraconservative position advising Americans that most of them had adequate levels and that the evidence was weak for higher levels being generally beneficial. The IOM panel was focused on bone health, had no vitamin D experts, and yet the consensus was put to the media as a general condemnation of anything but near trivial supplementation. In the context of mental health, vitamin D has increasingly been implicated in the pathology of mental illness including depression, bipolar disorder and schizophrenia.

With regard to depression, there appears to be only one randomized clinical trial vs. a placebo. The intervention involved 20,000 to 40,000 IU per week for a year. Vitamin D supplementation was found to ameliorate depressive symptoms on the basis of changes in assessment scores.[44] Another recent intervention study confirmed these results.[45] A recent study found that vitamin D deficiency (25-hydroxyvitamin D ≤10 ng/mL) was associated with late-life depression and deficiency was also associated with living in northern latitudes.[46] However, taken as a whole, cross-sectional studies (snapshot studies) have provided a mixed picture. One recent review recommends greater supplementation in older adults,[47] whereas another takes a more conservative position which gave greater weight to the inconsistent cross sectional studies.[48]

There do not appear to be any randomized clinical trials concerning the use of vitamin D supplementation to treat schizophrenia. However, there is considerable evidence that vitamin D status is important in the etiology of this disorder, both early in life and in general.[49-53] For example, a Finnish birth-cohort study found that supplementation during the first year of life reduced the risk of diagnosis of schizophrenia over the next 31 years. The risk reductions were very large (75% to over 90%). But the risk reduction was restricted to males.[52] The accumulation of positive data has led to a call for a clinical trials of vitamin D supplementation for both prevention and therapy.[54]

GLUTEN SENSITIVITY AND FOOD ALLERGY

Gluten sensitivity involves heightened immune response to ingested gluten. Glutens are the main storage proteins of wheat, but there are a large number of members of this class of protein. The most common medical problem associated with gluten sensitivity is celiac disease. Early studies found that untreated patients presented evidence of psychological disturbances, especially depression. In one study, 35% of patients with celiac disease reported a history of psychiatric disorders including depression, personality changes and psychosis.[55] In these early studies, gluten-free diets seemed to provide benefit. However, depression in celiac disease may simply be associated with difficulties in adjusting to this chronic disorder rather than to the disease itself.[56] It is noteworthy that in patients where the hallmark intestinal problems associated with celiac disease resolved, this did not prevent the development of neurological problems.

There is a more convincing association between gluten sensitivity and schizophrenia. A recent review documented a drastic reduction if not full remission of schizophrenic symptoms after an intervention involving gluten elimination.[57] However, this only occurs in a subset of patients. For them, gluten elimination is obviously highly beneficial if not essential. An antibody study of recent-onset and multi-episode schizophrenia found that while patients may share some immunological features with celiac disease, their immune response to one of the principal glutens was different from those with this

disease. In addition, individuals with recent onset of psychosis or multi-episode schizophrenia do not in general have clinical manifestations of celiac disease nor laboratory parameters diagnostic of this disorder. However, they may share some of the pathobiologic features of celiac disease.[58]

It is interesting in this context that one of the cornerstones of the alternative treatment of schizophrenia championed for decades by the Canadian psychiatrist Abram Hoffer was that patients avoid any foods to which they were allergic. This of course included glutens. He suggested that while elimination diets were recommended, a simple food allergy history may reveal the presence and identity of allergens.[59] The remainder of Hoffer's approach involved supplements of B vitamins including B3 (niacin), B6, and as well vitamin C, zinc, and manganese. In addition, no sugar at all was allowed. Patients also underwent psychotherapy.

MELATONIN, LIGHT THERAPY AND SLEEP DEPRIVATION

The amazing complexity of humans and other living species is illustrated by the presence of an internal master clock influenced by the time of day through an interaction with light and the day-night fluctuation. A number of biological processes have so-called circadian rhythms which repeat over each 24 hour interval and are driven by this clock. Blind individuals, for example are unable to synchronize to the day/night cycle or do so at abnormal times. For individuals with normal sight, it is possible to adjust circadian rhythms either with the hormone melatonin, bright light or sleep deprivation. Melatonin is secreted by the pineal gland in response to the onset of darkness and its level builds and then declines during sleep. Its secretion can be inhibited by exposure to bright light during the night.

Disturbance of sleep or secondary insomnia is frequently associated with psychiatric disorders and circadian rhythm abnormalities have been observed as a comorbidity of depression and other psychiatric problems. The night time peak in melatonin secretion is blunted in drug-free schizophrenic subjects and this pattern is not improved after antipsychotic drug therapy. The stimulants used to treat ADHD frequently are associated with insomnia, which interacts unfavourably with the disorder. The traditional response to sleeping problems involves the class of drug termed hypnotics. These have two very undesirable aspects. One involves dysfunctional carry-over to the next day. The other is addiction, now also called dependence, which is common in long-term use and is also associated with withdrawal symptoms. Because hypnotics, while commonly used, are not indicated nor regarded desirable for long-term treatment of insomnia, some physicians have turned to antidepressants. Part of the rationale is that some believe (erroneously) that all or most insomnia is a symptom of depression, and thus antidepressant therapy is the treatment of choice.[60] The reasons why this is not a good idea have been outlined in Part I of this review. In addition, one side effect of antidepressants is insomnia (!), which occurs in a few percent to over a quarter of those taking this class of drug.[61] In addition, there is a carry-over to the next day involving drowsiness.

Insomnia also accompanies jet lag and reflects a mal-adjusted internal circadian clock in need of resetting. Thus supplementation with melatonin, a commonly used treatment for jet lag insomnia and resetting the circadian clock, is of interest in mental health since it involves merely enhancing an endogenous hormone level timed to generate peak melatonin at the optimum period during the night, and accomplishing this without side effects such as next-day mental and functional problems. The connection between sleep patterns and melatonin has prompted the industry to develop patentable drugs guided by the physiology of melatonin and to tinker with melatonin receptors through targeted drugs. This is motivated mostly by the desire for patent protection. Thus the important issues include the efficacy of melatonin in the context of bringing about normal sleep patterns and the impact of this on mood and functionality in individuals with psychiatric problems.

Another way to reset the circadian clock is with bright light used at a certain time. This is a well known treatment for seasonal affective disorder (SAD), also known as winter depression. Individuals suffering from SAD sit in front of a bright light in the early morning and may experience considerable if not total relief from seasonal depression.

Light therapy turns out to be a complicated subject since the color of the light (wavelength) is important as well as the intensity and timing relative to the rise and fall of melatonin during darkness. In addition, the use of melatonin must be timed properly and care must be taken with exposure to light during the melatonin secretion period. Proper use of these two tools also requires establishing the strength, length and timing of secretion relative to the day/night cycle. This can be accomplished by urine tests for a metabolite. A detailed discussion of the use of melatonin is beyond the scope of this review, which will only include a discussion of some clinical trials that relate to the treatment of disorders under consideration in this review. The following clinical trials with melatonin supplementation appear of interest.

- Melatonin was used to treat individuals with what is called delayed sleep phase syndrome (DSPS), which is characterized by the inability to fall asleep and to awake at conventional times (e.g. awake well past midnight and wake-up past noon).[62] The study was randomized, double blind, cross-over and placebo controlled. For analysis, the subjects were divided into two groups, depressed and not depressed. It was found that melatonin significantly reduced depression scores in the depressed group. Sleep continuity improved in both groups compared to the placebo. In the depressed group, melatonin supplementation altered favourably the internal melatonin cycle. In fact, one of the principal differences between DSPS patients with or without depressive symptoms was their temporal melatonin excretion patterns. The authors comment that it is likely that the melatonin treatment phase advances the delayed circadian rhythms in DSPS patients and this may mediate the amelioration of depressive symptoms. A steady internal and external phase relationship appears to be crucial for stable and normal mood state (i.e. the timing between core body temperature and cortisol as well as the timing of sleep with respect to the day/night cycle. Incidentally, the patients in this study were not taking psychiatric drugs.
- The impact of melatonin therapy was examined in a randomized double blind placebo controlled study of schizophrenic patients with insomnia.[63] It was observed that relative to the placebo, melatonin significantly improved the quality and depth of night time sleep and increased its duration with no morning hangover. The intervention also significantly reduced sleep onset latency, heightened freshness on awaking, improved mood and improved daytime functioning. All the patients were taking an antipsychotic drug.
- A recent review of randomized and observational studies from 2003 to 2007 involving ADHD patients with insomnia found that melatonin appears safe and well tolerated in most children with this problem. Clinically relevant advances in sleep onset and total sleep time were found. The only RTC with a long-term follow-up found melatonin therapy also improved behaviour and mood as reported by parents. In this study the patients were 100% stimulant free.[64,65]

These studies reinforce the notion of a connection between mood and sleep patterns and the value of melatonin therapy.

Light therapy and sleep deprivation have passed the experimental development phase and are now considered powerful clinical interventions for everyday treatment of depression with response and relapse rates similar to those obtained with antidepressant drugs. Good results are even obtained in difficult–to-treat conditions such as bipolar depression. This subject has recently been reviewed by Benedetti *et al.* [66]

While light therapy, sleep deprivation and supplemental melatonin therapy can easily be accomplished at home without professional assistance, the therapies are of sufficient inherent complexity that this is not recommended. Rather, consultation with a sleep clinic or an expert in this area is strongly advised. However, this therapeutic modality should not be ignored since it appears almost totally free of adverse side effects or withdrawal problems and furthermore can presumably be combined with other alternative approaches described in this review. A major advantage is the rapid onset of benefit.

ST. JOHN'S WORT

This plant extract became popular in the late 1980s, mostly in Europe and especially in Germany. A recent meta-analysis by the Cochrane Collaboration of studies that compared St. John's wort and

either a placebo or various antidepressants found the extracts superior to a placebo in patients with major depression and of similar effectiveness as standard antidepressants but with fewer side effects.[67] There may be issues with product variability, with the interaction with other medications and with the absence of long-term studies focused on adverse effects. The mechanism of action is not clear, but it is suspected that it acts like psychiatric medications. Its use would depart from the general philosophy of the alternatives discussed in this review in that its use does not represent an adjustment in macro- or micronutrients that form part of the normal human diet, hormone levels or aspects of lifestyle. "Nature's medicines" are not *a priori* harmless.

PHYSICAL EXERCISE

There is considerable evidence that physical exercise is beneficial for depression, including major depression and anxiety. However, most of the studies addressing this issue have methodological problems and thus the evidence base is somewhat weak.[68] The use of exercise as a treatment for depression has been tried for individuals of all ages, for postpartum depressive symptoms, and as an addition to drug treatment. In general, beneficial results have been obtained either for all groups, judged alone or in comparison with no exercise. It is significant that when compared with psychotherapy or drugs, exercise was found to be about as effective, and exercise enhances to some extent the effects of drug therapy. Various forms of exercise have been studied including walking, walking briskly, jogging and gym workouts.[69,70] There is some evidence that duration of exercise sessions is more important than frequency.[70] Evidence generated by controlled studies for benefit in ADHD appears very limited since there seems to be very little interest in the question. However, a recent book by John J. Ratey, M.D. titled *Spark. The Revolutionary New Science of Exercise and the Brain,* deals with this subject at length with many case histories drawn from the author's clinical experience. Included is his experience with exercise and ADHD and its beneficial effect.

Exercise is obviously an important therapeutic intervention, which should be free of side effects, unless there are medical contraindications, and obviously has many non-psychological benefits as well. If one can treat depression as successfully or even better with an exercise program than with drug therapy, given what has been discussed above about the latter, the choice seem obvious. Adding exercise to other alternative approaches appears straightforward.

WITHDRAWAL OF MEDICATION

A significant problem in this field is the individual on medication who is not doing well or getting worse. While drug withdrawal is not really an alternative therapy, withdrawal, either alone or accompanied by alternative therapy is an option. Withdrawal from medication is associated with considerable risk and must be done under the supervision of someone trained in the field. Typically, the substitute therapy would be some form of psychotherapy, but the other alternatives described above might be appropriate as well. When confronted with patients under psychiatric polytherapy and doing poorly, mainstream medicine does not appear to have medication withdrawal on their radar screen.

In Chapter 16 of his book *Anatomy of an Epidemic* Robert Whitaker describes his visit to Seneca Center in California, which may be the last residential facility where severely troubled children under county or state control are treated without psychiatric drugs.[1] The Center's therapeutic philosophy is nicely summarized by the approach which asks not what is wrong with this child but what has happened to the child. When the children come to the center, they are lethargic, they are just a "blank" and there is only minimal engagement possible. The staff can simply not "get through to them." Withdrawal can take a month or two and can be difficult for all concerned. Behavior modification therapy is used. The staff describes what happens once the kids are off medication with the descriptive phrase "they come alive." One can engage them and get a sense of who they are, their personality, their sense of humor, and what kinds of things they like to do. They begin to think of themselves in a new way and the find that they can control their own behavior. The behavior modification program is accompanied by house rules but the focus is on reinforcing positive behavior and the children are given increasing responsibilities. Whitaker does not mention any other alternative therapy. It is quite possible that the diet provided by the center corrected some of the micronutrient deficiencies likely present at this stage in the evolution of the mental problems of these young people.

One is left to wonder if there was anything fundamentally wrong with these kids before a drug treatment program which in the end involved failed polypharmacy and ultimately what amounted to commitment to an institution.

Withdrawal of medication is the antithesis of the "absolute devotion to the paradigm" approach of ever-increasing doses and changing medications while the patient simply appears to get worse and worse. Thus, it appears to be an integral part of the alternative approach once someone has been unsuccessfully medicated, and it lends itself nicely to many other alternative therapies.

PSYCHOTHERAPY

Classical psychotherapy has evolved to include changes in the traditional focus common a half-century ago and as well as a number of distinct variations including behaviour modification and cognitive remediation therapy. Individuals saying no to psychopharmaceutical interventions clearly should consider this alternative, either alone or in combination with other alternative approaches. Both clinical psychologists (mostly Ph.D.s), psychiatrists and other highly trained and licensed practitioners are involved in this area and it is not uncommon in studies that include a psychotherapy arm that the results are comparable to drug interventions. It is also easy to argue that psychotherapy has a stronger evidence base than the psychopharmaceutical approach, given the profound weakness in the evidence base for the latter. A detailed discussion of this subject is beyond the scope of this review.

CONCLUSIONS

If we accept Peter Breggin's assertion, supported by hundreds of peer-reviewed studies and his clinical experience as well as that of other critics in the psychiatry community, many drugs directed at real and not-so-real psychological problems actually work by disabling the brain. We must also accept the net result which is a deficit in many of the mental attributes we normally view as part of our humanness. It is no wonder that the drop-out rate in clinical studies is so high. It has frequently been observed that depression is an essential aspect, perhaps necessary, of the human experience. Huxley in the *Brave New World* predicted that everybody can be cured from depression once the right pharmaceutical-biological intervention is found. But this aspect of utopia is equivalent to changing the very nature of the human condition.[71] This is not to deny the partial benefits, although sometimes temporary, in some acute disorders, but there appears to be little doubt that this is a speciality in trouble with no mainstream way out. Breggin is far from alone crying in the wilderness—he just has a high and well deserved profile.

The original belief in chemical imbalances in the brain as the causal factor in mental disorders appears to have led researchers and clinicians down the wrong road and to a dead end. We appear to be witnessing unacknowledged desperation implied by individuals treated with higher and higher doses and more and more drugs. It is not uncommon to see lists in the baseline data tables of a study where many subjects were on three to four psychiatric drugs. What is not listed is how many are zombies or near zombies. Promotion of the conventional wisdom has been so successful that turning back now would represent a huge admission of error. The natural history of well-established therapies that work poorly if at all is that they endure long after the cat is out of the bag.

The approaches described in Part II of this review can be divided into two categories. The first involves looking for medical conditions or medication that could account for the symptoms and dealing with this possibility first. This includes ruling out street drug use. It is hard to think of any other term than malpractice when someone with a medical disorder such as subclinical hypothyroidism presents with depression and is given a psychiatric drug as the first line of treatment. The second category includes the interventions discussed above. Many can be tried simultaneously. Professionals' assistance in some cases is important; good examples being therapy directed at circadian rhythm problems and of course psychotherapy. High on the list should be addressing the possibility of micronutrient deficiencies with a multi-component supplement and as well, embracing a Mediterranean-type diet or a diet rich in fruits, vegetables and fish. Obtaining a 25-hydroxyvitamin D assay and acting on the results appears to be important. The importance of exercise is hard to overemphasize. Finally, a very strong argument can be made for starting psychotherapy, either with a

psychiatrist, a psychologist, or someone with specialized training and certification in this field. The strong placebo effects seen in studies of psychiatric drugs are interesting because they point to the self-correcting ability of the human mind-brain system. Non-drug interventions such as psychotherapy and its variations presumably augment this natural tendency to self-correct, whereas drug interventions appear to have the potential to hinder it.

It is not possible to predict *a priori* which approach will successful, or if several will work together to produce favourable results. But the most important point is that by electing the alternative approach one is avoiding the side effects, the spellbinding, the potential for a downward spiral and polypharmacy, and the withdrawal problems associated with psychiatric drugs. There appears to be no way ahead of time of ascertaining whether or not one is going to be lucky with psychiatric drugs and not have serious problems, but the large numbers who do experience problems, single drug failure, multiple drug failure and even disability appears far from insignificant and should provide a powerful incentive for seeking alternatives unless the condition in question is severe or represents a true crisis.

Of necessity, alternative approaches will for at least the foreseeable future, suffer from inadequate studies or the absence of evidence that satisfies mainstream purists, simply because adequate studies are so expensive that the industry becomes the principal potential source of financing, and the industry views alternatives to drugs with fear and quite correctly as incapable of producing profits regarded as significant. Reflect on 36 large, randomized, placebo controlled trials to satisfy purists regarding the efficacy of each individual component in the EMP+ supplement. These would be preceded by phase I and phase II studies to establish safety and dose guidelines. Government bodies can and have provided support for studies of alternative approaches, but it traditionally and historically has been only token support. Thus, anyone wishing to solve a personal mental problem without pharmaceutical intervention must be satisfied with a level of evidence that is, with the exception of psychotherapy, generally unacceptable to mainstream medicine, and they should expect opposition from mainstream caregivers. But critics maintain that the evidence for the benefits of the pharmaceutical approach is fatally flawed and corrupted by the suppression of negative clinical study results, biased selection of study subjects, the downplaying, at least in public, of serious if not devastating side effects, the inflation of benefits and the avoidance of long-term studies and marketing practices that end up triggering legal proceedings.[72-74] This industry behaviour pattern does not inspire confidence or respect, but it is accepted as generating what the profession widely promotes as evidence-based medicine.

Preparing this review was accompanied by a unique revelation. It appears that literally huge, perhaps unprecedented numbers of individuals are being treated with drugs that not only do not work very well if at all but do harm, in some cases permanent, to their most precious possession, the brain. This is even tacitly acknowledged, at least to some extent, by mainstream psychiatry which is now seeking a new direction, a new paradigm and is witnessing major drug companies abandoning the field. Ignoring medical disorders which are root causes of psychological problems and which are readily amenable to curative therapy outside the realm of psychiatry dooms the patient at best to long-term therapeutic failure. Nevertheless, the remarkably extensive use of psychiatric drugs, not only by psychiatrists but by internists and family doctors, makes it clear that this so-called standard of care is the norm, supported by professional organizations, guidelines, government regulators, standard approved textbooks and prestigious institutes. An eye opener, indeed.

Finally, the reader is advised that it is not the intention of this review to downplay the serious nature of some mental disorders, their connection with disability, nor the value or necessity of pharmaceutical intervention in some situations. Please read the disclaimer at the end of this document.

DISCLAIMER

The information presented in this review is not intended to be medical advice nor should it be regarded as such. The reader is also advised that stopping taking psychiatric drugs is associated with significant risk and that withdrawal can be very dangerous and should be carried out only under the close supervision of a medical professional. Please consult your healthcare provider if you are interested in following up on the information presented in this review.

REFERENCES

(1) Whitaker R. *Anatomy of an Epidemic*. New York: Crown Publixhers; 2010.
(2) Frances A. The first draft of DSM-V. *BMJ* 2010;340:492.
(3) Frances A. DSM in Philosophyland: Curiouser and Curiouser. *Bulletin of the Association for the Advancement of Philosophy and Psychiatry* 2010;17(2):3.
(4) Dokras A, Clifton S, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Obstet Gynecol* 2011 January;117(1):145-52.
(5) Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG. Attention-Deficit/Hyperactivity Disorder and Urinary Metabolites of Organophosphate Pesticides. *Pediatrics* 2010 June 1;125(6):e1270-e1277.
(6) Eskenazi B, Huen K, Marks A et al. PON1 and Neurodevelopment in Children from the CHAMACOS Study Exposed to Organophosphate Pesticides *in Utero*. *Environ Health Perspect* 2010 August 19;118(12).
(7) Hoffman K, Webster TF, Weisskopf MG, Weinberg J, Vieira VM. Exposure to polyfluoroalkyl chemicals and attention deficit/hyperactivity disorder in U.S. children 12-15 years of age. *Environ Health Perspect* 2010 December;118(12):1762-7.
(8) Freudenreich O. Differential diagnosis of psychotic symptoms: "Medical "Mimics". *Psychiatric Times* 2010;27(12):56-61.
(9) Egede LE, Ellis C. Diabetes and depression: Global perspectives. *Diabetes Research and Clinical Practice* 2010 March;87(3):302-12.
(10) Rubin RR, Ma Y, Marrero DG et al. Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program. *Diabetes Care* 2008 March;31(3):420-6.
(11) Bernstein RK. *Dr Bernstein's Diabetes Solution*. Revised Edition ed. Little, Brown and Company; 2003.
(12) Tatley M, Savage R. Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. *Drug Saf* 2007;30(3):195-201.
(13) Shrivastava S, Pucadyil TJ, Paila YD, Ganguly S, Chattopadhyay A. Chronic Cholesterol Depletion Using Statin Impairs the Function and Dynamics of Human Serotonin 1A Receptors. *Biochemistry* 2010 June 3;49(26):5426-35.
(14) *The statin damage crisis*. Duane Graveline, M.D., MPH.; 2009.
(15) While A, Keen L. The effects of statins on mood: A review of the literature. *Eur J Cardiovasc Nurs* 2010 September 25.
(16) Papakostas GI, Íng³r D, Iosifescu DV, Mischoulon D, Fava M. Cholesterol in mood and anxiety disorders: review of the literature and new hypotheses. *European Neuropsychopharmacology* 2004 March;14(2):135-42.
(17) Beasley CL, Honer WG, von Bergmann K, Falkai P, Lutjohann D, Bayer TA. Reductions in cholesterol and synaptic markers in association cortex in mood disorders. *Bipolar Disorders* 2005;7(5):449-55.
(18) Troisi A. Low cholesterol is a risk factor for attentional impulsivity in patients with mood symptoms. *Psychiatry Research* In Press, Corrected Proof.
(19) Samieri C, Jutand MA, Feart C, Capuron L, Letenneur L, Barberger-Gateau P. Dietary patterns derived by hybrid clustering method in older people: association with cognition, mood, and self-rated health. *J Am Diet Assoc* 2008 September;108(9):1461-71.
(20) Akbaraly TN, Brunner EJ, Ferrie JE, Marmot MG, Kivimaki M, Singh-Manoux A. Dietary pattern and depressive symptoms in middle age. *Br J Psychiatry* 2009 November;195(5):408-13.
(21) Peet M. International variations in the outcome of schizophrenia and the prevalence of depression in relation to national dietary practices: an ecological analysis. *Br J Psychiatry* 2004 May;184:404-8.

(22) Oddy WH, Robinson M, Ambrosini GL et al. The association between dietary patterns and mental health in early adolescence. *Preventive Medicine* 2009 July;49(1):39-44.
(23) Jacka FN, Pasco JA, Mykletun A et al. Association of Western and Traditional Diets With Depression and Anxiety in Women. *Am J Psychiatry* 2010 March 1;167(3):305-11.
(24) Sanchez-Villegas A, gado-Rodriguez M, Alonso A et al. Association of the Mediterranean Dietary Pattern With the Incidence of Depression: The Seguimiento Universidad de Navarra/University of Navarra Follow-up (SUN) Cohort. *Arch Gen Psychiatry* 2009 October 1;66(10):1090-8.
(25) Sanchez-Villegas A, Henriquez P, Bes-Rastrollo M, Doreste J. Mediterranean diet and depression. *Public Health Nutr* 2006 December;9(8A):1104-9.
(26) Munoz MA, Fito M, Marrugat J, Covas MI, Schroder H. Adherence to the Mediterranean diet is associated with better mental and physical health. *Br J Nutr* 2009 June;101(12):1821-7.
(27) Sanchez-Villegas A, Henriquez P, Bes-Rastrollo M, Doreste J. Mediterranean diet and depression. *Public Health Nutr* 2006 December;9(8A):1104-9.
(28) Sanchez-Villegas A, Verberne L, De Irala J et al. Dietary Fat Intake and the Risk of Depression: The SUN Project. *PLoS One* 2011 January 26;6(1):e16268.
(29) Kaplan BJ, Crawford SG, Field CJ, Simpson JS. Vitamins, minerals, and mood. *Psychol Bull* 2007 September;133(5):747-60.
(30) Rucklidge JJ. Successful treatment of OCD with a micronutrient formula following partial response to Cognitive Behavioral Therapy (CBT): a case study. *J Anxiety Disord* 2009 August;23(6):836-40.
(31) Rucklidge JJ, Gately D, Kaplan BJ. Database analysis of children and adolescents with bipolar disorder consuming a micronutrient formula. *BMC Psychiatry* 2010;10:74.
(32) Mehl-Madrona L, Leung B, Kennedy C, Paul S, Kaplan BJ. Micronutrients versus standard medication management in autism: a naturalistic case-control study. *J Child Adolesc Psychopharmacol* 2010 April;20(2):95-103.
(33) Rucklidge JJ, Harrison R. Successful treatment of bipolar disorder II and ADHD with a micronutrient formula: a case study. *CNS Spectr* 2010 May;15(5):289-95.
(34) Frazier EA, Fristad MA, Arnold LE. Multinutrient supplement as treatment: literature review and case report of a 12-year-old boy with bipolar disorder. *J Child Adolesc Psychopharmacol* 2009 August;19(4):453-60.
(35) Rucklidge J, Taylor M, Whitehead K. Effect of Micronutrients on Behavior and Mood in Adults With ADHD: Evidence From an 8-Week Open Label Trial With Natural Extension. *Journal of Attention Disorders*.
(36) Gately D, Kaplan BJ. Database analysis of adults with bipolar disorder consuming a micronutrient formula. *Clinical Medicine:Psychiatry* 2009;2:3-16.
(37) Ames BN, Elson-Schwab I, Silver EA. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K(m)): relevance to genetic disease and polymorphisms. *Am J Clin Nutr* 2002 April;75(4):616-58.
(38) Ames BN. A role for supplements in optimizing health: the metabolic tune-up. *Arch Biochem Biophys* 2004 March 1;423(1):227-34.
(39) Willett WC. *Eat, drink and be healthy, The Harvard Medical School guide to healthy eating.* Simon & Schuster; 2001.
(40) Milte CM, Sinn N, Howe PR. Polyunsaturated fatty acid status in attention deficit hyperactivity disorder, depression, and Alzheimer's disease: towards an omega-3 index for mental health? *Nutr Rev* 2009 October;67(10):573-90.
(41) Bountziouka V, Polychronopoulos E, Zeimbekis A et al. Long-term fish intake is associated with less severe depressive symptoms among elderly men and women: the MEDIS (MEDiterranean ISlands Elderly) epidemiological study. *J Aging Health* 2009 September;21(6):864-80.
(42) Peet M. Omega-3 polyunsaturated fatty acids in the treatment of schizophrenia. *Isr J Psychiatry Relat Sci* 2008;45(1):19-25.
(43) Kirby A, Woodward A, Jackson S, Wang Y, Crawford MA. Childrens' learning and behaviour and the association with cheek cell polyunsaturated fatty acid levels. *Research in Developmental Disabilities* 2005 May;31(3):731-42.
(44) Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med* 2008 December;264(6):599-609.
(45) Shipowick CD, Moore CB, Corbett C, Bindler R. Vitamin D and depressive symptoms in women during the winter: a pilot study. *Appl Nurs Res* 2009 August;22(3):221-5.
(46) Stewart R, Hirani V. Relationship between vitamin D levels and depressive symptoms in older residents from a national survey population. *Psychosom Med* 2010 September;72(7):608-12.
(47) Cherniack EP, Troen BR, Florez HJ, Roos BA, Levis S. Some new food for thought: the role of vitamin D in the mental health of older adults. *Curr Psychiatry Rep* 2009 February;11(1):12-9.

(48) Bertone-Johnson ER. Vitamin D and the occurrence of depression: causal association or circumstantial evidence? *Nutr Rev* 2009 August;67(8):481-92.
(49) McGrath J, Brown A, St Clair D. Prevention And Schizophrenia:The Role of Dietary Factors. *Schizophrenia Bulletin* 2010.
(50) McGrath JJ, Burne TH, Feron F, kay-Sim A, Eyles DW. Developmental Vitamin D Deficiency and Risk of Schizophrenia: A 10-Year Update. *Schizophrenia Bulletin* 2010 November 1;36(6):1073-8.
(51) Humble MB, Gustafsson S, Bejerot S. Low serum levels of 25-hydroxyvitamin D (25-OHD) among psychiatric out-patients in Sweden: Relations with season, age, ethnic origin and psychiatric diagnosis. *The Journal of Steroid Biochemistry and Molecular Biology* 2010 July;121(1-2):467-70.
(52) McGrath J, Saari K, Hakko H et al. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. *Schizophrenia Research* 2004 April 1;67(2-3):237-45.
(53) Hedelin M, Lof M, Olsson M et al. Dietary intake of fish, omega-3, omega-6 polyunsaturated fatty acids and vitamin D and the prevalence of psychotic-like symptoms in a cohort of 33,000 women from the general population. *BMC Psychiatry* 2010;10:38.
(54) McGrath J. Is it time to trial vitamin D supplements for the prevention of schizophrenia? *Acta Psychiatr Scand* 2010 May;121(5):321-4.
(55) Burk K, Farecki ML, Lamprecht G et al. Neurological symptoms in patients with biopsy proven celiac disease. *Mov Disord* 2009;24(16):2358-62.
(56) Collin P, Kaukinen K, Mattila AK, Joukamaa M. Psychoneurotic symptoms and alexithymia in coeliac disease. *Scand J Gastroenterol* 2008;43(11):1329-33.
(57) Kalaydjian AE, Eaton W, Cascella N, Fasano A. The gluten connection: the association between schizophrenia and celiac disease. *Acta Psychiatr Scand* 2006 February;113(2):82-90.
(58) Dickerson F, Stallings C, Origoni A et al. Markers of Gluten Sensitivity and Celiac Disease in Recent-Onset Psychosis and Multi-Episode Schizophrenia. *Biological Psychiatry* 2010 July 1;68(1):100-4.
(59) Hoffer A. Chronic schizophrenic patients treated ten years or more. *Journal of Orthomolecular Medicine* 1994;9:7-37.
(60) Wiegand MH. Antidepressants for the treatment of insomnia : a suitable approach? *Drugs* 2008;68(17):2411-7.
(61) Becker PM, Sattar M. Treatment of sleep dysfunction and psychiatric disorders. *Curr Treat Options Neurol* 2009 September;11(5):349-57.
(62) Rahman SA, Kayumov L, Shapiro CM. Antidepressant action of melatonin in the treatment of Delayed Sleep Phase Syndrome. *Sleep Med* 2010 February;11(2):131-6.
(63) Suresh Kumar PN, Andrade C, Bhakta SG, Singh NM. Melatonin in schizophrenic outpatients with insomnia: a double-blind, placebo-controlled study. *J Clin Psychiatry* 2007 February;68(2):237-41.
(64) Bendz LM, Scates AC. Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder. *Ann Pharmacother* 2010 January;44(1):185-91.
(65) Hoebert M, van der Heijden KB, van G, I, Smits MG. Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. *J Pineal Res* 2009 August;47(1):1-7.
(66) Benedetti F, Barbini B, Colombo C, Smeraldi E. Chronotherapeutics in a psychiatric ward. *Sleep Med Rev* 2007 December;11(6):509-22.
(67) Linde K, Berner MM, Kriston L. St John's wort for major depression. *Cochrane Database Syst Rev* 2008;(4):CD000448.
(68) Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA. Exercise for depression. *Cochrane Database Syst Rev* 2009;(3):CD004366.
(69) Greer TL, Trivedi MH. Exercise in the treatment of depression. *Curr Psychiatry Rep* 2009 December;11(6):466-72.
(70) Strohle A. Physical activity, exercise, depression and anxiety disorders. *Journal of Neural Transmission* 2009 June 1;116(6):777-84.
(71) Cutcliffe JR, Lakeman R. Challenging normative orthodoxies in depression: Huxley's Utopia or Dante's Inferno? *Arch Psychiatr Nurs* 2010 April;24(2):114-24.
(72) Fava GA. The intellectual crisis of psychiatric research. *Psychother Psychosom* 2006;75(4):202-8.
(73) Whitley R. Is psychiatry a religion? *J R Soc Med* 2008 December;101(12):579-82.
(74) Healy D. Irrational healers? *Psychother Psychosom* 2008;77(4):198-200.

Editor: William R. Ware, PhD

INTERNATIONAL HEALTH NEWS is published 10 times a year by
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
E-mail: editor@yourhealthbase.com World Wide Web: http://www.yourhealthbase.com

ISSN 1203-1933