INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 212 **NOVEMBER 2010** **19th YEAR**

It is becoming more and more apparent that one of the challenges in the next decade or two, if not longer, will be for individuals to take a more active role in their own health issues. The driving force for this is already apparent. In the U.S., healthcare reform faces strong political opposition and the reforms in place fail to address the fundamental problems that will eventually bring down the system. It is predicted that by 2050, 30% of Americans could be diabetic and by 2020, 75% will be obese. By 2030, worldwide, one billion people will be sixty-five or older and, in some countries, the number over 65 years will outnumber those below 5-10 years of age. The political and social ramifications of this demographic shift are the subject of a constant stream of books such as H. S. Dent's "The Great Depression Ahead" and T. C. Fishman's "Shock of Gray". Prevalence of cardiovascular disease, cancer, diabetes, Alzheimer's disease, and Parkinson's disease, to name a few of the majors, increases dramatically with age and thus the vastly increased financial burden is inevitable. This is a burden placed on populations and governments that have their financial health measured partly by the magnitude of debt and the financial health is found to be highly precarious in many countries. It appears that draconian cuts in healthcare will be inevitable. The new austerity will probably put an end to drugs that offer insignificant or barely measurable benefits, frequently at very high cost, as well as drugs only marginally effective which, on balance, increase rather than decrease healthcare costs by virtue of their side effects and the resultant need for additional medication. Expensive procedures, which produce no more benefit than inexpensive ones, will no doubt decline in popularity. Drugs and procedures which produce negligible benefit compared to a placebo will probably no longer be in widespread use. Numbers needed to treat to produce benefit for one patient may become a more important consideration, as well as the numbers needed to treat to harm one patient. Standards for clinical significance in clinical trials might even increase and influence drug approval and nutritional recommendations. But the system has such a high inertia that change will only result from the strong forces associated with a profound crisis.

The growing but somewhat selective demand for strong "scientific" evidence of efficacy may actually work against achieving a better, cheaper system of healthcare by active exclusion of natural or unpatentable approaches that have not passed muster before regulatory tribunals. What seems certain is that there will be dramatic change. Responsibility for primary prevention will, out of necessity, partly if not significantly, shift to the individual who will turn to alternative medicine and natural approaches to health problems and probably to a healthier lifestyle. The prevalent philosophy of "a pill for everything" may not always be with us even though it currently appears to have almost as much support among the consumers as among the marketers. The era where the elderly typically take 10-20 prescription drugs daily may end, and this population may be better off as a result. Vitamin D supplementation in nursing homes may become standard. After all, nursing home residents receive about as much UV radiation as the Chilean miners trapped underground, who in fact were provided with vitamin D supplementation once contact had been established.

It will continue to be the goal of this Newsletter to provide readers with information concerning ways to reduce the risks of the diseases of aging and to encourage the integrative approach to treatment with emphases on efficacy, concern for side effects, and an appreciation of alternative approaches which may work as well or better than conventional therapy. Topics in this issue address some of these concerns. In addition, this issue includes a Research Review which attempts to address important issues associated with the obesity crisis.

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

METABOLIC MANAGEMENT OF BRAIN CANCER

The diagnosis of brain cancer at any age is bad news. Glioblastoma multiforme is the most common primary adult brain tumor. It develops rapidly with a short clinical history. Sometimes complete surgical removal of the tumor is possible without leaving any tumor tissue but in many cases tumor remains and the cancer progresses. Even when it is clear that complete removal is not possible, surgery is frequently required to relieve neurological symptoms. Aside from resection, the standard treatment involves radiation therapy frequently with chemotherapy with the intent to prevent recurrence, delay progression or provide palliation. These therapies may retard malignant glioma progression over the short term but they can facilitate recurrence and enhance growth over the longer term.[1,2] Only about 3% of patients with malignant gliomas survive 36 months. Furthermore, chemotherapy strongly impacts the quality of life and both chemotherapy and use of corticosteroids may even result in reduced survival in comparison to those not treated. Also, radiation therapy may lay the groundwork for accelerated tumor growth following treatment. Nevertheless, these represent the standard of care and are widely used in spite of obvious dismal efficacy. Aside from approaches that will take some time for approval if they work at all, research appears focused on variations and combination of the standard therapy protocol.[1]

An alternative approach exists which therefore should be of considerable interest, but for various reasons including its nutritional basis, it has been totally ignored by mainstream oncology for over 15 years. This is consistent with the general outlook of mainstream medicine which looks at nutritional approaches to cancer therapy with disdain. Yet the metabolic approach in question has been used for a long time in the successful treatment of epilepsy.[3]

Metabolic cancer therapy involves a calorie-restricted ketogenic diet which forces all cells in the brain to switch to a large extent from glucose to ketones for fuel. This is actually an adaptation related to food scarcity, long-term starvation or very low caloric intake. Fundamental to this therapy is a property of brain tumor cells that makes it difficult to switch from glucose to ketone fuel which in turn deprives these cells of needed energy and results in inhibition of angiogenesis (vascularization of the tumor) and promotes apoptosis (programmed cell death).[2]

Readers will recall that the aging brain suffers from a decline in the ability to metabolize glucose and this is related to neurodegeneration. As discussed in the last two Newsletters, by supplying the brain with alternate fuel in the form of ketone bodies generated by the metabolism of medium chain triglycerides (MCT oil or coconut oil), it appears possible to reverse Alzheimer's disease. The metabolic treatment of cancer is to some extent related in that the ketogenic diet provides ketones for brain metabolism but while the cells involved in neural competence are happy, the tumor cells are starved. Thus in contrast to cytotoxic therapy, one of the two pillars of oncology, this is a metabolically targeted therapy which only affects cancer cells without the side effects of systemic cytotoxic therapy which is only partially targeted on cancer cells.

It is perhaps not surprising, at least to those who are cynical, that the evidence base for this metabolic therapy is negligible by the standards of modern medicine. In fact all that appears to exist in the published literature are two pediatric case histories from 1995 and a just published case history which used a calorie-restricted ketogenic diet in combination with standard therapy.[4-6] In all three cases, the results indicated benefit well beyond what would have been expected from standard therapy. Experts tend to turn up their noses at case histories, and in this case the number is certainly limited. Yet this approach is biologically plausible, and is backed by a number of rodent and cell culture studies.[2]

Thomas Seyfried and colleagues at Boston College have for years been trying to generate interest in this approach to brain cancer. Their most detained attempt has just been published in *Biochemica et Biophysica Acta* and provides a comprehensive review of the entire subject.[2] In this review the authors argue that almost all brain cancer patients receive corticosteroids, which significantly elevate blood glucose levels. In view of what has been outlined above, this does not appear to be a good idea. They also take the position that it is incumbent on physicians treating brain cancer to inform patients of this alternative therapy. While the evidence for the latter is sparse to say the least, the evidence of the dismal performance of the conventional approach is overwhelming. Trying this alternative approach should be especially attractive to individuals who reject the conventional approach aside from surgery.

The just-published case history where a calorie-restricted ketogenic diet was used in conjunction with the standard therapy is of particular interest.[6] The patient was diagnosed with glioblastoma multiforme (GMB). She presented with progressive memory loss, and chronic headaches. Surgical resection was incomplete. During the immediate post-operative recovery period, the patient started a self-imposed water only fast, followed after two days by moderate food consumption and then resumed the fast. This was followed by 14 days of a calorie reduced ketogenic diet. All steroidal medication was stopped. The calorie reduced ketogenic diet consisted of a daily intake of 23 g of carbohydrate, 32g of protein and 42 g of fat which provided 600 calories. Part of the diet consisted of a commercial preparation called KetoCal which is formulated to provide a ketogenic diet for treating pediatric epilepsy. Then the standard radiation plus chemotherapy (temozolomide) was started on January 8, 2009. On February 24, an MRI found no evidence of either tumor or associated edema and on April 21 a PET scan found no evidence of recurrence and an MRI in July was also negative. After this MRI, the caloric intake of the protocol was not strictly followed, and an MRI in October revealed recurrence. This is as far as the published case history goes. The authors comment that to their knowledge there have never been reports of regression of GMB within 2.5 months of diagnosis in patients of any age using standard radiation and temozolomide therapy alone. They suggest that the combination of the metabolic and conventional approach greatly enhanced early cytotoxicity and apoptosis.

A second aspect of the metabolic requirements of glioblastoma cells is the need for glutamate dehydrogenase. When glucose metabolism is impaired, glutamine utilization remains, with a large increase in glutamate dehydrogenase activity. This parallel pathway limits the full potential of metabolic therapy. In fact, in cell culture studies, inhibiting glutamate dehydrogenase forces cells to turn to glucose.[7] It follows from this that the combination of impaired glucose and glutamate should have merit. Marsh *et al*[8] have shown that the glutamate inhibitor 2-deoxy-D-glucose (2-DG) along with a ketogenic diet is superior to either treatment alone in mice with implanted astrocytoma. There do not appear to be any clinical studies of either 2-DG alone or in combination with a ketogenic diet. The chemical 2-DG is available from chemical supply houses and thus of no interest to pharmaceutical companies.

The fact that this is all there is in the literature highlights the lack of interest in clinical trials of any sort associated with this metabolic therapy. The patient in the above case history elected to have conventional therapy, added metabolic therapy, and then relaxed the latter therapy with subsequent recurrence. This does not really answer the obvious questions such as what happens with just surgery and metabolic therapy, and what would have

happened if the metabolic therapy had been continued.

In the review of Seyfried *et al* [2], guidelines are suggested for implementing the dietary management of malignant brain cancer.

- Phase 1. Over a 10-14 day period a calorie-restricted ketogenic diet should be employed with targets of blood glucose of 3.0-3.5 mmol (55-65 mg/dL) and ketone levels between 4 and 7 nmol. Meters are available that allow home measurement of both blood glucose and blood ketones. The ketone strips are rather expensive. Blood ketone levels are considered more informative than urine levels. Monitoring is important since an excessive ketogenic diet can also raise glucose levels and defeat the purpose of the therapy. Water only fasting is also suggested periodically if necessary to keep glucose levels low and ketone levels high. Monitoring will allow flexibility in food choices.
- Phase 2. This involves surgical resection of as much of the tumor as possible. Ideally, there is a time window for Phase 1 prior to Phase 2.
- Phase 3. After surgery, the aim of the therapy is to keep metabolic pressure on surviving tumor cells. The authors suggest the possibility of using glutamate inhibitors such as 2-DG in conjunction with the calorie-restricted ketogenic diet but there does not appear to be recent human dose or safety studies. A human study in 1958 found serious side effects from high doses and there do not appear to be low-dose studies in humans in this context.

Finally, Seyfried *et al* comment that they are aware of several patients, both children and adults, who are presently using the calorie-restricted ketogenic diet approach and have had considerable success in retarding tumor growth. The many unanswered questions include whether or not a cure is possible with the metabolic approach where the tumor simply disappears forever. A related question is whether or not 2-DG is necessary along with the restricted ketogenic diet to accomplish the fatal starvation of all the tumor tissue. It is interesting in this context that one of the polyphenols in green tea, EGCG, was found in cell culture studies to decrease the same enzyme activity as is inhibited by 2-DG.[7] Green tea polyphenols are available in green tea extract, a popular supplement.

Readers are referred to earlier issues of the Newsletter where the use of Salvestrols are discussed and a case history presented for brain cancer (June 2008, October 2009) A study combining a restricted ketogenic diet and Salvestrol therapy would be very interesting.

SATURATED FAT AND CARDIOVASCULAR DISEASE

The absence of a link between dietary intake of saturated fat and cardiovascular disease (CVD) has been repeatedly examined in this Newsletter in both discussions of papers and in Research Reviews. Those who still believe in the saturated fat-heart hypothesis might object to the use of ketogenic diets for the treatment of brain cancer. They also object to low-carbohydrate diets and in particular the Atkins, South Beach and other diets and label them “fad diets.” Three recent papers in the *American Journal of Clinical Nutrition* all support the no-link position. One was reviewed in the July/August Newsletter.[9] Two others from the same issue of this journal are also of interest.

- A meta-analysis of 21 prospective cohort studies evaluating the association of saturated fat with CVD found no significant evidence for an association with coronary heart disease (CHD), stroke or CVD in general. Correcting for potential confounding by gender, age and study quality did not change the results. The group of studies in the analysis included 16 relating to CHD and 8 relating to stroke.[10]
- A large cohort study from Japan examined the association between saturated fat intake and mortality from both ischemic and bleeding strokes. The higher the intake of saturated fat, the *lower* the mortality.[11] In this study, the influence of

the replacement nutrient for saturated fat was investigated. Replacement of saturated fat with monounsaturated or polyunsaturated fat or carbohydrates was either significantly (polyunsaturated fat) or non-significantly associated with an increase in stroke mortality. This study also found no association between saturated fat intake and ischemic (occlusive) heart disease, heart attack, cardiac arrest or heart failure.

In a letter to the editor, Martijn Katan and Ingeborg Brouwer point out that when the intake of saturated fat decreases, it is replaced by something else. They criticize the meta-analysis because it failed to find what they consider an established effect, the benefit of substituting polyunsaturated fat for saturated fat.[12] The authors of the meta-analysis reply by pointing out that the main result of their study indicates the lack of an association of saturated fat and CVD as compared to carbohydrates which is the usual nutrient that replaces total and saturated fat, a result they point out is consistent with other studies.[13]

See also the July/August 2010 issue of the Newsletter where a paper directly addressing the saturated fat—carbohydrate matter is discussed.

It is clear from numerous papers in the recent literature that the notion that saturated fat is bad in the context of CVD and CHD is still alive and well, has a strong impact on physician opinion, guidelines and practice, and is a strong impediment to the use of low-carbohydrate diets for the control of diabetes, which incidentally was the traditional approach before pharmaceutical intervention became the norm. Readers are referred to the Research Review in the June 2009 Newsletter and especially to the section on saturated fat and cardiovascular disease. The lesson appears to be that dogma, if carefully nurtured and maintained by constant repetition from so-called experts, can be successfully kept alive, even among those with scientific training, long after there exists compelling evidence to the contrary. Instead, dogma evolves into mythology.

COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE IS INSULIN A MAJOR PLAYER?

A refreshing breeze has recently been blowing through the land of mental degenerative disease research. For several decades the beta-amyloid-tau protein hypothesis ruled supreme and dictated most of the academic and pharmaceutical research. Cynics called it the Holy Church of Amyloid. The repeated failure of drug interventions based on this hypothesis has encouraged researchers to think outside the box and also has brought to center stage research that takes a rather different approach. A discussion of one approach that used medium chain triglycerides for Alzheimer's disease appeared in the last two issues of the Newsletter. The biological plausibility of this approach depended on the age-related decreased in glucose metabolism in the impaired brain.

At the International Conference on Alzheimer's Disease held in Honolulu this past summer a study was reported which tested an intranasal insulin spray for 4 months. Just over 100 patients with Alzheimer's disease or mild cognitive impairment, a well known precursor of this disease, were treated. When compared to non-treated patients, those receiving the insulin via the nasal spray showed improvements in daily functioning. While most patients in the placebo group showed cognitive declines over this period, the insulin-treated patients did not. In addition, the researchers found lower levels of some abnormal proteins associated with Alzheimer's disease in the spinal fluid of the insulin-treated patients as compared to the placebo. The lower levels of these proteins in the spinal fluid correlated with improved memory and functional status scores (reported on WebMD, July 14, 2010).

The Chief Medical and Scientific Officer of the Alzheimer's Association provided WebMD with the standard conservative comments always voiced with unproven procedures, but intranasal insulin treatment for Alzheimer's disease and mild cognitive impairment is far from new and in fact has just been recently

reviewed.[14] The above report is consistent with studies examined in this review which support the hypothesis that brain insulin signalling essentially contributes to memory function in humans and that central nervous system insulin deficiency and resistance is a patho-physiologic feature of cognitive impairment such as seen in Alzheimer's disease. It is of interest that some researchers refer to this disease as "type 3 diabetes." The review concludes that intranasal insulin may be a useful option for the treatment and even prevention of this devastating disease.

LIFESTYLE INTERVENTION FOR TYPE 2 DIABETICS

When discussing the control of type 2 diabetes and preventing the deleterious effects of elevated blood glucose, it appears almost obligatory to mention or discuss lifestyle changes along with normal pharmaceutical approaches. A recent study (AHEAD) has investigated what can be accomplished by long-term lifestyle interventions on weight and cardiovascular disease (CVD) risk factors associated with diabetes.[15] Over 5000 diabetic individuals, mostly with the metabolic syndrome and elevated triglycerides were studied at a large number of centers for 4 years. The intensive lifestyle intervention (ILI) group was encouraged to increase physical activity and decrease energy intake to achieve and then maintain at least a 7% weight reduction. The dietary recommendations generally followed the low (lower) fat dogma. The results were compared with a group which received standard diabetes support education (DSE). The abstract conclusion section states the result that ILI can produce sustained weight loss and improvements in fitness, glycemic control, and CVD risk factors.

While these results were statistically significant, it can be argued that the study in fact failed to achieve meaningful results for the participants. Weight in the ILI group dropped from a mean of about 100 kg to 92 kg at one year and then when back up to a 4 year drop of only about 4 kg. While HbA1C, the glycated haemoglobin indicator of long term blood glucose control changed by over 6% at one year, at the end of the study the change was only 1.8%. Thus the mean HbA1c went from 7.3 to 7.17%. Most subjects continued to use glucose control medication throughout the study. At baseline, 47% of the ILI group had HbA1c ≤ 7% and at then end it was 57%. Although the indication of diabetes was mostly fasting blood glucose, the study is silent on its change even though blood samples were available. Thus the subjects in ILI remained obese at the end of the study, probably most still had the metabolic syndrome, and there was even an increase in the ILI group of those on medication. At baseline prior to randomization, 86% participants in this study, were on glucose lowering medication including insulin (15%) and at the end of the study, the numbers for the ILI group and the DSE group were 90.5% and 96% respectively. It can be argued that this is not a great success story. In fact, the study would appear to demonstrate that ILI as employed in this study produces only a temporary benefit, that it is driven primarily by weight loss, that at the end of 4 years the benefits were so small that their importance is debatable, and that this study further strengthens the belief that adhering to interventions that involve eating less and exercising more are not viewed by most individuals as worth the pain although they can be talked into trying it for an insignificant period of time compared to their estimated remaining lifetime.

There are those who argue convincingly that ILI for type 2 diabetics can eliminate the need for medication, eliminate obesity and the metabolic syndrome and the patients appear clinically to no longer have the disease.[16] But the intensity of the required intervention is obviously vastly more than what was involved in this study. The essence of the problem is indicated in the failure of the ILI group to maintain weight loss and the almost trivial change in HbA1c. Calorie restriction combined with increased physical activity, if the energy intake deficit is constant, generally results in a rate of weight loss that gradually decreases until the subject reaches a new equilibrium point. In other words it is not linear nor should weight go up again if the calorie deficit and energy expenditure is maintained.[17] But if adherence is poor, then the results are

generally what one sees in this as well a numerous other studies, i.e. a sharp drop followed by a slow rise back to near baseline which translates into little meaningful benefit irregardless of statistical significance.

ASTHMA AND ACETAMINOPHEN USE

In the last decade there has been growing evidence of an association between asthma and the use of acetaminophen (paracetamol, Tylenol) both prenatal and by infants, young individuals and adults. The hypothesis was proposed 10 years ago when an inverse correlation was seen between the prevalence of childhood asthma in the US and the use of aspirin and a matching positive correlation with the use of acetaminophen. This prompted a number of studies which have recently been reviewed by Farquhar *et al*[18]. The evidence appears compelling.

- Prenatal use. Out of nine studies, the most recent just published[19,20], eight produced significant indication of risk with odds ratios ranging from 1.3 to 2.10 with most clustered about 1.70. Some of these studies had very large sample sizes, the largest being about 66,000 and 13,000. In almost all the studies, the outcome indication of an association was current wheezing.
- Childhood use. There have been four studies of this problem in the first year of life and four looking at children age 6-7. In all these studies significant odds ratios were obtained, and for the older children, high use vs. none resulted in three times the risk of wheezing or severe asthma symptoms. However, in children with a family history of allergic disease, a recent study failed to find an association between acetaminophen use and allergic disease.[21]
- Adult use. Three studies were available for the review. For frequent use (weekly or daily), the odds ratios were similar to those for children whose mothers has used acetaminophen as indicated above.
- Evidence-based on overall use. If one looks at prevalence and purchases per year of tablets and liquid acetaminophen between 1980 and 1986, prevalence of asthma cases went from 36 to 52 per 1000 people whereas purchases went from 580 million to 1.3 billion. This was matched by a similar decline in aspirin use.
- Mechanism. The review of Farquhar *et al* discusses a number of studies which provide a biologic plausibility for the causal relationship suggested but not proven by the above associations. The major suggested action is oxidant-induced inflammation and enhanced immune response (Th2). There is a weak protective effect of antioxidant diets in asthma.

Clearly, there is a need for definitive randomized controlled trials. A glance at the pain killer shelves at the drug store will reveal acetaminophen's popularity. However, this is an over-the-counter drug and such trials would be expensive and the probable results would not be favourable to those who make and market the chemical.

Readers are referred to the internet for a general discussion of side effects. One of the most serious involves the combination with heavy alcohol use which can easily be fatal.

THE AVANDIA SAGA

Safety of the glucose control drug rosiglitazone (Avandia) has been questioned for some time, especially after the meta-analysis published in 2007 by Nissen and Wolski from the Department of Cardiovascular Medicine, Cleveland Clinic. This analysis was updated in June of 2010.[22] Nissen and Wolski concluded that the totality of randomized clinical trials demonstrate increased risk of heart attack attributable to Avandia. In July, 2010 the FDA convened a joint session of the two relevant agency advisory panels to

consider the status of the drug. The combined panel was about 1/3 the size of the US Senate. Panel recommendations are apparently never binding. It was surprising that, given the pressure under which the FDA has been concerning a strong bias toward their *clients,* who pay the FDA large sums to have their drug applications considered, investigative reporters immediately dug up evidence of ties between panel members and the manufacturer of either Avandia or the drug most likely to benefit from a switch away from Avandia. Accusations of bias appeared in major newspapers. Just before this meeting, a study was published in the *JAMA* which compared Avandia and Actos with endpoints of heart attack, stroke, heart failure and mortality. It was found that compared with Actos, Avandia was associated with an increased risk of stroke, heart failure and all-cause mortality and an increased risk of a composite endpoint which added heart attack to this endpoint list.[23] The lead author is employed by the FDA and is a recognized critic of some of its practices.

The FDA gave the panel a rather large number of options upon which to vote. Only 12 out of 33 were in favour of withdrawing the drug from the market. The remaining votes were divided among several options for retaining the drug with varying degrees of warnings or restrictions. Finally a majority of the panel agreed that Avandia is not as safe as the similar drug pioglitazone (Actos, Glustin, Glizone, Pioz). To the uninitiated, this might seem inconsistent with the vote concerning withdrawal of the drug. The interested parties had to wait about two months before the FDA finally handed down its official decision which was to severely restrict but not withdraw the use of the drug. The European equivalent to the FDA simply suspended the drug. Nissen was quoted by *heartwire* (theheart.org) as saying that the FDA restrictions were essentially the same as suspending the drug. He pointed out that doctors will have to do so much paperwork to allow a patient to take Avandia that he considered this alone will keep 99% of prescriptions from being written. He regards the drug as "effectively gone." In the same commentary, he was quoted as follows: "And we have known for five years that this drug has been harming people….the company and the FDA both knew there was an increase in MI (heart attack) but failed to issue sufficient warnings or act to remove it, until now. There are still one million prescriptions a month being written for rosiglitazone. It just shows the power of marketing."

The restrictions placed on Avandia come under REMS, the acronym for risk evaluation and mitigation strategy. Under REMS, Avandia will be available to new patients only if they are unable to achieve glucose control on other medications or are unable to take Actos, the only other drug in the Avandia class. Current users who are benefiting from the drug will be able to continue if they choose to do so, but doctors will be required to attest to and document their patients' eligibility and patients are required to review statement describing the cardiovascular safety concerns associated with Avandia and acknowledge that they understand the risks. REMS is relatively new and it is not clear just how effective it really is. It is also being used in an attempt to control the widespread inappropriate use of prescription narcotics.

Avandia and Actos are used for what is termed intensive glucose control which generally translates to a lower HbA1c than normally obtained by the standard treatment of diabetes. It appears rather well established that diabetes increases by about two-fold the risk of vascular disease independent of other risk factors.[24] Two recent meta-analyses of the impact of intensive glucose control both found a significant reduction in non-fatal coronary events but no impact on stroke or mortality.[25,26] Most of the studies involved in these analyses did not employ Avandia. It is of interest that the reductions in HbA1c observed in intensive glucose control with pharmaceuticals can also be achieved through diet and exercise.[16] However, as discussed above, these lifestyle interventions must be aggressive. For example, in the first year of the intensive lifestyle study featured above, the mean HbA1c dropped 7.3% to 6.8% which is comparable to or better than found in the studies in the cited these meta-analyses. However, not only was this benefit not maintained, but also the 18 pound weight loss at year one almost completely disappeared over the next three years. Aggressive and substantial lifestyle management should be able to produce better outcomes.

MAMMOGRAPHY AND MORTALITY IN NORWAY

A new study has just reported that examined the reduction in breast cancer mortality attributable to mammography.[27] Women ages 50-69 were offered screening mammography every two years. Rates of breast cancer deaths were examined in four groups: two groups who from 1996 through 2005 lived in counties with screening (the screening group) or without screening (non-screening group). In addition, two historical comparison groups were used that from 1986 through 1995 mirrored the current groups. Data for over 40,000 women with breast cancer were available. The following death reduction rates were found per 100,000 person years: 7.2 in the screening group as compared to the historical non-screening group and 4.8 in the non-screening group compared to the historical non-screening group. The researchers calculate that the difference in reduction in breast cancer mortality between the current and historical groups that could be attributed to screening alone was 2.4 deaths per 100,000 person years.

In an editorial, H. Gilbert Welch attempts to put this in perspective.[28] He starts by assuming that mammography screening results in a 19% reduction in mortality from breast cancer. The 10 year risk of breast-cancer death for a 50-year-old woman is now about 4 per 1000 women. Assuming that this risk already incorporates the benefit of screening mammography, the risk estimate without mammography becomes 4.4 per 1000 women. Thus the number of women who will not die from breast cancer increases from 995.6 to 996.0 per 1000 women because of mammography. An alternative view is that the absolute benefit of 0.4 per 1000 is equivalent to the need to screen 2500 women over a 10 year period to avoid one death. That leaves 2499 screened with no breast cancer related mortality benefit. Out of this group, the editorialist estimates that 1000 would be expected to have at least one false positive result if the mammography was done in the US and between 5 and 15 women would be expected to have needless treatment with potential accompanying harm for a condition that was never going to harm them. He points out that the Norwegian study indicates that the decision regarding having mammography screening is a “close call.”

MAGNESIUM AND SUDDEN CARDIAC DEATH

Sudden cardiac death (SCD) occurs in about half of all mortality associated with cardiovascular disease. Readers of this Newsletter will probably be aware that one of the most important preventive measures is a high omega-3 status as measured by the omega-3 fatty acid composition of the red blood cell walls. Those with high levels dramatically reduce their risk. A recent study has now implicated magnesium as another important player. The major risk factors for SCD include diabetes, hypertension, smoking, family history of heart attack, and obesity, but the majority of SCD occurs in those with no prior history of cardiovascular disease. The risk found in several studies has been shown independent of cholesterol levels. A recent study has examined the risk of SCD according to the blood levels of magnesium. When those in the highest quartile (quarter) of serum levels of magnesium were compared with those in the lowest, it was fond that high magnesium provided an almost 40% risk reduction in a model fully adjusted for a large number of confounders. A curious aspect of the results was the lack of association with dietary magnesium intake. The authors discuss this paradox and cite other relevant studies. The impact of dietary magnesium on blood pressure is inconsistent as is its impact on CVD risk. There do not appear to be informative studies regarding supplementation. Magnesium is generally regarded as an important micronutrient in the context of heart health. Sinatra recommends 400-800 mg daily over and above that obtained from food.[29]

REFERENCES

(1) Seyfried TN, Shelton LM, Mukherjee P. Does the existing standard of care increase glioblastoma energy metabolism? *The Lancet Oncology* 2010 September;11(9):811-3.
(2) Seyfried TN, Kiebish MA, Marsh J, Shelton LM, Huysentruyt LC, Mukherjee P. Metabolic management of brain cancer. *Biochim Biophys Acta* 2010 September 8.
(3) Kim dY, Rho JM. The ketogenic diet and epilepsy. *Curr Opin Clin Nutr Metab Care* 2008 March;11(2):113-20.
(4) Nebeling LC, Miraldi F, Shurin SB, Lerner E. Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports. *J Am Coll Nutr* 1995 April;14(2):202-8.
(5) Nebeling LC, Lerner E. Implementing a ketogenic diet based on medium-chain triglyceride oil in pediatric patients with cancer. *J Am Diet Assoc* 1995 June;95(6):693-7.
(6) Zuccoli G, Marcello N, Pisanello A et al. Metabolic management of glioblastoma multiforme using standard therapy together with a restricted ketogenic diet: Case Report. *Nutr Metab (Lond)* 2010;7:33.
(7) Yang C, Sudderth J, Dang T, Bachoo RG, McDonald JG, DeBerardinis RJ. Glioblastoma Cells Require Glutamate Dehydrogenase to Survive Impairments of Glucose Metabolism or Akt Signaling. *Cancer Res* 2009 October 15;69(20):7986-93.
(8) Marsh J, Mukherjee P, Seyfried T. Drug/diet synergy for managing malignant astrocytoma in mice: 2-deoxy-D-glucose and the restricted ketogenic diet. *Nutrition & Metabolism* 2008;5(1):33.
(9) Jakobsen MU, Dethlefsen C, Joensen AM et al. Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. *Am J Clin Nutr* 2010 June 1;91(6):1764-8.
(10) Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* 2010 March 1;91(3):535-46.
(11) Yamagishi K, Iso H, Yatsuya H et al. Dietary intake of saturated fatty acids and mortality from cardiovascular disease in Japanese: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) Study. *Am J Clin Nutr* 2010 October 1;92(4):759-65.
(12) Katan MB, Brouwer IA, Clarke R, Geleijnse JM, Mensink RP. Saturated fat and heart disease. *Am J Clin Nutr* 2010 August 1;92(2):459-a.
(13) Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Reply to MB Katan et al. *Am J Clin Nutr* 2010 August 1;92(2):460-1.
(14) Benedict C, Frey WH, Schioth HB, Schultes B, Born J, Hallschmid M. Intranasal insulin as a therapeutic option in the treatment of cognitive impairments. *Exp Gerontol* 2010 September 14.
(15) Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med* 2010 September 27;170(17):1566-75.
(16) Bernstein RK. *Dr Bernstein's Diabetes Solution*. Revised Edition ed. Little, Brown and Company; 2003.
(17) Hall KD, Jordan PN. Modeling weight-loss maintenance to help prevent body weight regain. *Am J Clin Nutr* 2008 December;88(6):1495-503.
(18) Farquhar H, Stewart A, Mitchell E et al. The role of paracetamol in the pathogenesis of asthma. *Clin Exp Allergy* 2010 January;40(1):32-41.
(19) Perzanowski MS, Miller RL, Tang D et al. Prenatal acetaminophen exposure and risk of wheeze at age 5 years in an urban low-income cohort. *Thorax* 2010 February;65(2):118-23.
(20) Shaheen SO, Newson RB, Smith GD, Henderson AJ. Prenatal paracetamol exposure and asthma: further evidence against confounding. *Int J Epidemiol* 2010 June;39(3):790-4.
(21) Lowe AJ, Carlin JB, Bennett CM et al. Paracetamol use in early life and asthma: prospective birth cohort study. *BMJ* 2010;341:c4616.
(22) Nissen SE, Wolski K. Rosiglitazone Revisited: An Updated Meta-analysis of Risk for Myocardial Infarction and Cardiovascular Mortality. *Arch Intern Med* 2010 June 28.
(23) Graham DJ, Ouellet-Hellstrom R, MaCurdy TE et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 2010 July 28;304(4):411-8.
(24) Sarwar N, Gao P, Seshasai SR et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010 June 26;375(9733):2215-22.
(25) Marso SP, Kennedy KF, House JA, McGuire DK. The effect of intensive glucose control on all-cause and cardiovascular mortality, myocardial infarction and stroke in persons with type 2 diabetes mellitus: a systematic review and meta-analysis. *Diab Vasc Dis Res* 2010 April;7(2):119-30.
(26) Ray KK, Seshasai SR, Wijesuriya S et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009 May 23;373(9677):1765-72.

(27) Kalager M, Zelen M, Langmark F, Adami HO. Effect of screening mammography on breast-cancer mortality in Norway. *N Engl J Med* 2010 September 23;363(13):1203-10.
(28) Welch HG. Screening mammography--a long run for a short slide? *N Engl J Med* 2010 September 23;363(13):1276-8.
(29) Sinatra S, Roberts JC. *Reverse Heart Disease Now*. New Jersey: John Wiley & Sons; 2007.

RESEARCH REVIEW

OBESITY, AN OLD PROBLEM, A MODERN CRISIS

William R. Ware, Ph.D.

INTRODUCTION

By now, practically everyone in the developed world is aware that there is an obesity problem if not a crisis. It has no socioeconomic boundaries since it is common to the rich and poor, inhabitants of developed and underdeveloped countries, and even seen in aboriginal populations. Obesity is generally regarded as the gateway to chronic and degenerative diseases, and those who worry about healthcare economics and the funding of public and private systems wring their hands in despair at the simple projections of future financial disaster common to most models.

The history of obesity, especially in prehistoric times, is unclear. There is evidence from so-called Venus figurines, the earliest apparently 35,000 years old, which showed clearly obese women. Figurines dated 12,000 years old also confirm the observation, but it is not known if these represented a stylised notion or how a significant fraction of women looked at the time. This was still the hunter-gatherer era and well before the advent of agriculture and the cultivation and grinding of grain. In fact, there are carvings going back beyond 100,000 years that also suggest obesity was present. In addition, there are both wall paintings and mummified remains dating to 1500 BC indicating that an Egyptian queen was clearly obese. A thousand years later Hippocrates described obesity and by the early 1800s, William Wadd, the Surgeon Extraordinary to the King of England had published a book on obesity. He also described the post-mortem examination of an obese person and found extensive fat deposits that are also seen today. Later in that century, a gentlemen named Banting (no relation to the discoverer of insulin) became famous for his pamphlet on a low-calorie low-carbohydrate diet he had found successful after consultation with the famous physician William Harvey.[1]

Much more recently, the rapid increase in prevalence of obesity has become of general concern. One piece of evidence comes from comparing National Health and Nutrition Examination Surveys (NHANES) which attempted to capture a vast number of health-related characteristic of the general U.S. population. By comparing the 1970 and 2000 surveys, it is found that women 20-29 years of age in the early 70s had a mean body mass index (BMI) of 23 which is mid normal. In the period of 1999-2002 the survey found that women 50-59, the age then of the earlier cohort, had a mean BMI of 29 (at the threshold of obesity), representing a weight gain of approximately 35 pounds in an average of 28 years.[2] According to models discussed below, the energy intake would have to be about 370

calories more at the older age to maintain the new BMI as an equilibrium weight. This can occur gradually with small increases in energy intake over that required to maintain a stable weight at the younger age.[2,3] Since control of such a small increment is impossible to implement on a daily basis, the only alternative would be to cut back on energy intake and/or increase activity by addressing weight increases when they becomes apparent. That this was not and is not being done is indicated by the above data and the prediction by the *Organization for Economic Cooperation and Development* that by 2020 three-fourths of Americans will be obese or overweight.

There is no lack of theories as to the cause of obesity, and certainly no shortage of schools of thought regarding the best diet to combat it. Book stores have shelf after shelf of diet books based on an amazing variety of philosophies. Gary Taubes has published his *magnum opus* titled *Good Calories, Bad Calories,* which goes on for 600 pages and has a level of sophistication equal to any good academic work. Furthermore, the academic nutritional literature is overloaded with studies on diets from many viewpoints and there is no shortage of what appears to be junk science. If one puts "obesity" as a title item in PubMed, this marvellous medical literature search engine brings up over 3000 papers in the past 12 months. The diet books keep coming out, dozens of studies report each month, the media eagerly cover new events in the nutritional world, generally without the proper perspective, and individuals of all ages just get fatter and fatter. At one extreme, there are some who no longer fit in the standard airplane seat, and some who can only be taken from home to the hospital by cutting a hole in a wall and using a crane and then a truck. Of course there is the other extreme described by the term anorexic, accompanied by anthromorphic features which fashion models currently exhibit in a somewhat mild form and some adolescents in an extreme form. But that is a different topic. There are, however, also large numbers of individuals who are of normal weight, but for some if not many of these, weight is probably creeping up and fat starting to accumulate around the waistline.

What we eat and how much we eat and then what happens is a highly complex subject containing a grand mixture of psychology, physiology, biochemistry, genetics, lifestyle, the nutritional environment and culture within the home and to some extent the neighbourhood and country of residence, and the human response to highly sophisticated food marketing. All this makes for a difficult subject to research and probably an impossible subject to cover adequately in medical school. The most relevant studies require carefully controlled human subjects studied over long periods, studies which in general are too expensive and offer difficulties in recruiting. Judging by the hundreds of published diet studies, it appears difficult if not impossible to impose an intervention for longer than about six months, many studies have shorter interventions, and the net result is a final weight loss that represents a small and perhaps insignificant percentage of the total weight the subjects should want to lose. Even the best studies are complicated by considerable human variability.

In the 21st century it is quite impossible to conduct studies lasting a year or two on large numbers of subjects typical of the general overweight or obese population who are confined to an institution, fed nothing but experimental diets prepared in-house, and for which physical exercise data is available. Out in the real world, people enrolled in diet studies tend to cheat, adherence is poor, the drop-out rate notoriously high, and it is not uncommon for target diet macronutrient distributions to be missed. Studies are plagued by inaccurate recall and a host of other biases and confounders. There is no general agreement regarding the macronutrient distributions in diets described by terms such as *low-carbohydrate* or *low-fat.* Health effects of diets have traditionally been judged partly by changes induced in blood lipid levels, and even small and probably clinically irrelevant elevations of LDL were viewed with alarm. Diet studies that focus on one issue or item such as fat, protein, or some micronutrient are of questionable relevance since the components of a diet are eaten together and to are some extent synergistic.

The complexity of the problem of potential causes of obesity is illustrated by an incomplete list of suggested factors, either in general or associated with its prevalence or the rate of increase.[4]

- Genetic factors
- Thyroid dysfunction

- Gut bacteria problems
- Energy dense foods
- Urban environment influencing exercise
- Increased portion sizes
- Inexpensive energy dense food sources
- Increased use of high fructose corn syrup
- Junk food vending machines
- Decreased physical education (PE) in schools
- Mother's age at individuals birth
- Selective mating of individuals genetically predisposed to obesity
- Decline in hours of sleep
- Environmental chemicals that are endocrine disrupters
- Pharmaceuticals
- Ambient temperature
- Intrauterine effects
- Sedentary lifestyle, TV video games, heavy computer use
- Psychological influences on eating behaviour
- Excessive sugar consumption
- Excessive refined carbohydrate consumption
- Aggressive marketing of energy dense junk food
- Metabolic dysfunction influencing basal metabolic rate and thermogenesis
- Natural defences against starvation or chronic food shortages
- Positive energy imbalance

Most of these could be lumped under the major categories of excessive energy intake, conversion of the total energy contained in food into the fraction that is actually utilized (more or less the fraction assimilated), metabolic energy expenditure and exercise energy expenditure.

There is considerable overlap of items in this list. Some represent potential modifiable factors. Many lack an evidence base of much significance. The problem with this list is that quantitative translation and weighting to produce meaningful guidance that is tailored to any given individual is difficult. Thus there is the need to zero in on the items of the greatest importance.

Those who prefer a simple picture merely state that all that matters is the balance of calories in and calories out and that obesity arises from the inability to control intake which is frequently attributed to weak willpower or a character defect, and the sedentary nature of modern life. Unfortunately, this leaves a lot unexplained and is a serious oversimplification of human nutritional biochemistry and the underlying physiology and control mechanisms. A major aspect ignored by this simple picture is the ability of the body to compensate and produce the changes in metabolism and energy usage precipitated by weight loss which work against the dieter. There is also a significant limit as to what most will tolerate in terms of caloric deficit, especially if the intervention is long-term. Exercise is also not an option with some. Therefore there are significant barriers to applying the approach based on energy balance. However, there is probably no sensible and viable alternative.

An argument for excess food consumption being a root cause of obesity is found in a recent study which was able to account for the increase in population weight in the U.S. over 30 years based on an analysis of national food consumption. Swinburn *et al* estimate that the food energy intake in the 1970s was 2398 calories/day whereas in the 2000s it was 2895 cal/day. According to their mathematical models of energy balance and weight gain, this is more than enough to account for the obesity epidemic.[5] Hall *et al* have used a similar model to examine the same question and find that government food consumption data from which they calculate the change in population energy intake appears to be in excess of that required to explain the epidemic. They suggest that the official figures underestimate food waste.[6] The model used by Hall and coworkers will be discussed below. It is important to note that weight loss or gain is not linear and metabolic adjustments related to weight loss or gain impact energy utilization and intervene to alter rates of weight change.

In this review we will and see what we can find that is convincing and useful. The two major issues are preventing obesity and losing weight after becoming overweight or obese.

ENERGY (CALORIC) BALANCE

The fundamental principle here is the conservation of energy, also called the First Law of Thermodynamics. But the application is not simple. Food has a basic caloric content which can be measured by complete combustion to water, carbon dioxide and the end products from the nitrogen and sulphur content. This is done in a calorimeter, usually termed a bomb calorimeter because the reaction occurs at high oxygen pressure in a heavy steel container about the size of a large yogurt container. But this is not what happens to ingested food. The fat, protein and carbohydrate are not completely converted into molecules used by cells to generate energy. The conventional rules of thumb which takes into account the various inefficiencies comes up with protein and carbohydrate contributing 4 calories per gram and fat contributing 9 calories per gram (actually kilocalories, but we will use the nutritional simplification of terminology). Refined calculations identify poorly metabolized food components and use lower numbers. The point is that these are only average values and they are universally applied to estimate the energy intake of diets.

The energy from food intake is used for a large number of functions and processes. Basic to the argument of the conservation of energy school is that if there is energy left over it is stored as mass, generally fat, and increases weight. If there is a deficit, then one has a decline in weight. But the energy utilization processes are complex and subject to large individual variation.

The total daily energy expenditure while at rest is called the basal metabolic rate (BMR). This is the energy at rest used to keep the system functioning. The BMR actually accounts for more than 50% of the daily energy expenditure. Some consider it an attractive target for pharmaceutical intervention.

Finally, there is a rule of thumb used in nutritional analysis that an energy intake deficit of 500 cal per day is equivalent to one pound weight loss per week. This is of course a rough generalization, but is amazing how often one can use this number to rather accurately predict the initial weight loss in a study given the calorie deficit and the duration. This translates into 500 calories per day yielding 52 lbs per year. But a 500 calories deficit out of say 2200 is far from starvation, and yet it predicts 156 pounds in three years. In other words, this rule of thumb implies that the fixed calorie restriction will produce a constant rate of decrease in weight over long periods. This is not true since metabolic adjustments intervene due to the loss of both fat mass and fat-free mass and this energy deficit no longer produces the indicated weight loss. Studies suggest that the adjustments start within a few months.

The bottom line appears to be that if one can account for the utilizable energy that gets into the system and all the energy expenditure processes, then one is bound to find that energy is conserved. The problem is with the details.

LOW-FAT VS. LOW-CARBOHYDRATE DIETS

With the advent of the Atkins diet and the subsequent explosion of related low-carbohydrate diets (LCD), interest gradually developed in conducting controlled studies to evaluate this diet and its officially sanctioned and promoted competitor, the low-fat diet (LFD). There have now been an amazing number of studies and space does not permit a detailed review. But a general consensus seems to be developing.[7] It is consistently observed that LCDs result in more initial weight loss than LFDs. Many explanations have been advanced, but the only one that does not appear to be refuted is that the LCD reduces spontaneous energy intake frequently without the dieter being aware this is happening. When comparison studies carefully equalize energy intake and take into account physical activity, the weight loss differences become small or negligible, but this is very difficult to do in studies with free-living populations who are monitored by interviews. Studies of this question are also confused by LCDs that are not really low-carbohydrate. But the evidence at present shifts the emphasis back to calories rather than the distribution of macronutrients as the main concern in weight loss. But when one is considering weight gain, there is still the viscous circle of high intake of high

glycemic carbohydrates stimulating insulin secretion and fat storage and ultimately increasing insulin resistance which makes matters worse.

The LCD appears to result in an improved lipid profile, especially with regard to triglycerides (dramatic decrease) and HDL (significant increase), and an improvement in indicators of healthy glucose metabolism. The very low carbohydrate diet has been the traditional (old fashion) approach to dietary control of blood sugar levels in diabetics and prediabetics, both short-term and long-term (HbA1c), although this is not recognized or promoted in modern times by professional organizations, probably because of the belief that the increased fat content is dangerous and the low carbohydrate aspect is viewed as unacceptable to many patients. Pills are the modern answer with insulin injections used to "cover" high carbohydrate intake.

It has become increasingly more difficult to justify opposition to the elevated fat content of the LCD. As Mozzaffarian and Ludwig point out in a recent commentary, the proportion of total energy from fat appears largely unrelated to the risk of cancer, cardiovascular disease, diabetes or obesity and saturated fat, targeted by nearly all governmental agencies and professional organizations, has little relation to heart disease provided one is dealing with most prevailing dietary patterns.[8] A meta-analysis just published confirms this view.[9] No significant evidence was found for the view that dietary saturated fat is associated with increased risk of coronary heart disease or cardiovascular disease and a study from Japan has recently demonstrated saturated fat *was inversely* associated with both hemorrhage and ischemic stroke subtypes.[10] Many in mainstream medicine or nutritional science still do not agree with this view and the food industry is still capitalizing big-time on the notion that fat is bad.

THE KETOGENIC DIET

The extreme form of the low-carbohydrate diet is the ketogenic diet. Through a very low intake of carbohydrates, and a high intake of fat, the metabolism shifts to using fat as the principal energy source. The true ketogenic diet is generally associated with the treatment of epilepsy and was developed in the 1920s for pediatric application. The induction and low-carbohydrate phases of the Atkins diet resemble a ketogenic diet, but there is no limitation on energy intake aside from that inadvertently instituted by the patient. Atkins describes the indication phase in terms of lipolysis, the burning of fat and this process is naturally accompanied by the production of ketones, thus ketosis. This is not to be confused with diabetic ketoacidosis which occurs in insulin-deficient individuals with out of control blood sugar levels. In view of the studies that find similar weight loss from either low-carbohydrate or low-fat diets if there is identical energy intake and physical exercise, there would appear to be no need to push carbohydrates down to the point where ketosis can be observed, for example, through the presence of ketones in the urine. In the Atkins diet, the induction phase carbohydrate intake is about 20 grams, which can produce mild ketosis in some. By comparison, a low-carbohydrate diet with 20% or 30% of energy derived from carbohydrates would, for an energy reduced diet of say 1500 calories, involve 75 to 112 g per day which would not be a ketogenic diet and exceeds the carbohydrate intake during most of the Atkins protocol. Aside from bad breath and constipation, Atkins found no evidence of side effects that merited concern, and there have been a number of controlled studies of this diet which also do not report serious side effects.

Therapeutic ketogenic diets should only be undertaken under the supervision of a physician experienced in this approach. There are potentially serious side effects, the most common of which can be identified by various blood and urine tests.[11]

THE HALL-JORDAN MODEL

If it is indeed true that the two limiting types of diet, low carbohydrate and low fat, produce approximately the same weight loss and problems with sustaining the loss, and that differences are probably due to absence of equivalence in energy intake, compliance or physical activity, then the focus shifts simply to the caloric intake, body composition and its relation to metabolism, and energy expenditures through metabolism, exercise and daily physical activity. It is important to recognise that what happens during calorie restriction and/or increased exercise is not a steady weight loss but weight changes which steadily diminish, and if the calorie deficit is maintained, a new constant weight

will be reached which represents a metabolic adjustment, mostly due to the decrease in fat mass. The failure of most studies to achieve this new equilibrium appears to be a manifestation of the short term of the intervention relative to the follow-up followed by an inadequate or flawed protocol for weight maintenance. In the model to be discussed, the final new steady weight is the principal issue, not how long it takes to get there.

A model recently published by Hall and Jordan in the *American Journal of Clinical Nutrition* addresses these issues in what appears to be a highly rigorous fashion and the end result is a set of online calculators which enable patients and/or their physicians to estimate the caloric deficit required to reach a new but sustainable weight.[3,12] The input concepts and parameters are simple enough, but the mathematics which we will not to worry about is a bit complicated.[3] This model is much more complex than the 500 calories a day equals a pound a week or the tables easily found on the internet giving the miles one must walk or run to for a given caloric expenditure.

The Hall-Jordan model takes into account the initial weight, the energy input from food, the thermic effect associated with the energy input, the fat mass and fat-free mass as variables during the weight loss, and the influence of physical activity, its dependence on body weight and its changes introduced by the weight loss protocol. The various weighting factors are derived from a number of relevant studies and the final model was validated by comparison with controlled diet studies where the required information was available. The agreement seems impressive. For the correlation of measured vs. predicted steady-state weight after intervention the coefficient was 0.83. It was 0.91 for the measured vs. the predicted change in energy intake required to achieve the observed change in body weight to achieve the new steady state. For studies on humans, these are remarkably good correlations. The authors provide a table as an example. Full text of this paper is in the public domain at the journal website.[13]

The online calculators based on the Hall-Jordan model are also of interest. Of the four with links on the cited web page,[12] the one easiest to use is the one that only requires input of gender, age, height, initial weight and the change in energy intake contemplated (a negative sign before the number is required). This particular calculator also requires input changes in physical activity. This last factor is introduced with a parameter called PAL and the input form has a box providing guidance for this number according to the level of activity running from sedentary to very active. A number of results are then calculated, the most interesting of course being the new steady-state weight expected. Note that these calculators use the proper unit kcal whereas in this discussion we have used the term calorie as equivalent, in keeping with lay nutritional parlance.

The Hall-Jordan model appears to represent considerable progress with a very serious problem which is that if one looks at the hundreds of diet studies in an attempt to gain insight and guidance as to what to do to lose weight in general, the only result will be confusion. There is a grand mixture of junk science, studies with unrealistic protocols (total daily energy intake of only 500 calories, i.e. a deficit of 1000 to 2500 calories per day), macronutrient distributions that are all over the map and frequently identified with vague terms, etc. A real zoo indeed. In contrast, the Hall-Jordan model relies on only “gold standard” studies of energy expenditure, detailed input from a number of studies of the physiology of nutrition, and the model takes into account the metabolic changes that accompany the loss of fat mass and the relationship between weight at any time during the diet and physical activity energy expenditure. The integration of all these concepts into a plan for weight loss requires a mathematical model which in would be very difficult to apply without the aid of a computer. Readers familiar with mathematics can view the equations in the cited paper.

Consider the following example based on this model. An obese man (BMI = 35) weighs 230 pounds (105 kg) and wishes to have a BMI indicating not overweight. To achieve a BMI of 24 requires the loss of 72 pounds or 33 kg. According the model, this will require a decrease in energy intake of about 600 calories per day in order to eventually reach the new equilibrium weight of 158 pounds. It is assumed that there is no change in physical activity. This model does not predict the time required. By increasing the calorie deficit the weight loss should be more rapid and then as the target is approach, the calorie deficit can be reduced and allowed to approach the new equilibrium value of

600, but the implication of the model is that one is stuck with this new energy intake if it is desired to maintain the new BMI.

Hall and coworkers have also examined the predicted time course of weight loss based on extensions of their steady-state model discussed above. For example, if a 100-kg individual were to be subjected to approximately a 500 cal energy deficit, two different models both predicted the approach to the new steady weight would be about 50% in one year, 85% in two years and 92% in 3 years. The new equilibrium weight was about 74 kg. A discussion of the details of the models is beyond the scope of this review.[14,15] The researchers point out that the slow approach to a new steady state for humans has been found in a number of studies. In the example cited, extrapolation of the initial drop over the first few months yields a one-year weight that approaches the 24 kg that the 500 calories = 1 pound rule of thumb would predict at one year, but there is continuous compensation and it takes three years rather than one to reach a weight loss of about 24 kg or 53 pounds. These numbers are all approximate and are taken from graphs. As pointed out above, diet studies rarely keep the initial protocol beyond 6 months.

Hall and Jordan comment that since reaching a new desired weight that requires a substantial weight loss may require several years, consideration of an accelerated weight loss phase followed by a weight maintenance phase may be appropriate. In their model they provides guidance as to the dietary and activity changes necessary for weight maintenance, something for which no other clinical tool is currently available.[3] This allows the estimate of the extent to which a caloric deficit in use exceeds that required to maintain the weight at any stage in the decline.

There are a number of online calculators that determine the energy burned by exercise. For example, one calculator found that if one weighed 230 lbs, walking 45 min at a moderate rate of 3 miles per hour yields 272 calories burned or about 1900 calories per week. Using 3500 calories burned as the equivalent of one pound, then this activity provides about an additional half pound compared to no exercise. While this may not seem like much, if one is on a diet with a reduced energy intake of 500 calories, then the initial rate of weight loss will be about one pound without exercise, but 1.5 pounds with exercise. It becomes significant. Results from these online calculators should be considered only approximate since the weight loss associated with exercise varies with weight.

The cited paper for the Hall-Jordan model does not discuss potential reasons for failure. The studies used to obtain weighting factors and other parameters presumably did not include individuals where there were unusual difficulties in achieving weight loss. The factors that might cause failure merit a brief discussion.

MODIFIABLE IMPEDIMENTS TO WEIGHT LOSS

In his classic book *Dr. Atkins' New Diet Revolution,* a chapter is devoted to what he terms metabolic resistance. Over the years in his practice, Atkins treated a large number of patients who had great difficulty losing significant weight independent of the program they used, including his. He lists the major factors that can cause metabolic resistance.

- Excessive insulin resistance (low insulin sensitivity)
- Use of certain prescription drugs or hormones
- Hypothyroidism which may not be evident from blood tests

Atkins' suggestions are in the context of the failure of his low carbohydrate diet with a very low carbohydrate induction period followed by a gradual increase in carbohydrates, but still kept low. This diet should improve insulin sensitivity, but for some it may not be enough. To further increase insulin sensitivity, he suggests L-carnitine, starting with 500 mg three times a day and then increasing to as high as ten times this. In addition, coenzyme Q-10 (300 mg daily) with larger doses if this does not help. The reader is referred to the Research Report in the Dec 09/Jan 10 issue of the Newsletter for guidance regarding insulin resistance. See the section on the diagnosis of pre-diabetes.

Prescription drugs most likely to interfere with weight loss include estrogens such as in hormone replacement therapy and birth control pills, antidepressants and antipsychotics, insulin and insulin stimulating drugs, steroids, diuretics and beta-blockers, antihistamines, and protease inhibitors (HIV and hepatitis medications).[4]

An under-active thyroid, generally called hypothyroidism, may be responsible for more obesity and resistance to weight loss programs than is generally recognized. In simple terms, an under-active thyroid slows metabolism and makes one more resistant to weight loss. Anecdotal reports suggest that even diets restricted to less than 1000 calories a day combined with walking several miles a day can fail to reverse weight gain when one has an under-active thyroid. For hypothyroidism, the first challenge is diagnosis since the standard blood tests, according to Atkins, do not catch all cases. Dr. David Brownstein, author of *Overcoming Thyroid Disorders,* strongly agrees and regards hypothyroidism as seriously under diagnosed. The conventional approach involves the thyroid stimulating hormone assay (TSH). An elevated level is an indication that the pituitary gland is sensing a low thyroid hormone levels. The standard reference range used is that TSH under 4.5 mIU/L is normal. But as Brownstein points out, there are many physicians and organizations that believe this upper limit is too high. He proposes a threshold for suspecting hypothyroidism at 2.0 mIU/L but other suggest 3.0 mIU/L. In Brownstein's practice, he finds the range of TSH of 0.3 to 2.0 mIU/L as indicating optimal thyroid function. In diagnosing hypothyroidism, he uses thyroid status blood tests, medical history, basal body temperature and a general physical exam. The blood test looks for elevated TSH and low levels of the thyroid hormone T3. Individuals can have normal TSH and T4 (the other thyroid hormone) and yet be have an under active thyroid because of poor conversion of T4 to T3. His protocol for measuring basal body temperature involves an armpit temperature measurement upon awakening but before getting out of bed. The measurement should last 10 min and be repeated for 5 consecutive days. For premenopausal women the temperature study should be started on the second day of menstruation. For everyone else, when to start makes no difference. A temperature below 98.2ºF (36.8ºC) may indicate hypothyroidism. The lower it is, the stronger the indication and degree of hypothyroidism.

Brownstein lists a number of factors that can inhibit T4 to T3 conversion. It is interesting that medications mentioned above that are associated with weight gain such as beta blockers, birth control pills, estrogen, and steroids appear in this list. He also mentions obesity which suggests a positive feedback component to the thyroid-obesity connection.

Clearly, individuals having trouble with the diet/exercise approach to weight loss need to worry about hypothyroidism and also about false reassurances provided by the normal laboratory ranges from blood tests and the conventional wisdom. Readers are referred to Dr. David Brownstein's book for a complete discussion of the diagnosis and treatment of hypothyroidism. Based on his clinical experience, the favored approach for treatment involves using dried (desiccated) glandular thyroid products which he prefers over the commonly used T4 derivatives. In his book, Atkins describes experimenting with escalating doses of the thyroid product to test the hypothesis that hypothyroidism is a cause of difficulty in weight loss.

NATURAL NON-DIET APPROACHES

The widespread difficulty many overweight and obese individuals have losing weight has made finding a prescription drug a high priority in the pharmaceutical industry. The drug discovery philosophy follows the standard paradigm of targeting some process involved in some aspect of the problem and designing an inhibitor or enhancer. Pharmaceuticals appear to have side-effect problems. Approaches using natural products employ the same paradigm. The most high-profile ones are as follows:

- White kidney bean extract (Phaseolus vulgaris). This extract contains an inhibitor of alpha-amylase, a digestive enzyme responsible for the breakdown of complex carbohydrates such as starches into simple sugars which can then be absorbed in the small intestine. It is marketed as a dietary supplement Blockal and the trade term of the enzyme inhibitor is *Phase 2* or *Phaseloamin 2250*. There appear to be only two randomized studies. In one, treated subjects lost on average

6.5 pounds whereas the placebo group lost 1.45 pounds over 30 days.[16] In the second study, a white bean extract prepared for the investigators or a placebo was given for 30 days to a group involved in a multicomponent weight-loss program. The treatment enhanced the weight loss from 4.7lbs to 6 lbs.[17] Toxicity studies of Blockal involving high doses in rats suggest this extract is safe to use (on rats).

- Glucomannan. This is a gel producing, viscous water-soluble polysaccharide that comes from a plant root (konjac root). Glucomannan appears to reduce appetite because of its powerful bulk forming properties in the stomach. It decreases the rate of absorption of nutrients and thus decreases the glucose and insulin response to meals. There is also some evidence that it acts through promoting satiety and fecal energy loss.[18] The reduction in the increase in blood glucose after eating can be considerable, e.g. by one-half.[19] These hydrophilic polysaccharides are of great interest to the pharmaceutical industry with hundreds of papers published each year. Glucomannan, which can not be patented, is widely used in Asian countries and in the US for food thickening, improving bread texture, as a dietary fiber, etc. Toxicity studies are limited but it is a traditional food additive in China and Japan.[20] Keithley and Swanson review twelve clinical trials. At doses of 2-4 g/day glucomannan was well tolerated and resulted in significant weight loss in both obese and overweight individuals.[18] Glucomannan has also been observed to benefit constipated adults.[21]

- The seed extract from the West African plant *Irvingia gabonensis*. This extract from the seeds of a mango-like fruit also goes by the identifier IGOB131. It is thought to inhibit fat cell formation and to increase adiponectin levels and decrease leptin levels. The former is secreted from fat cells. Its increase may help induce weight loss. Leptin helps control food intake and energy expenditure.[22] Egras *et al*[23] recently reviewed studies of this extract for inducing weight loss. Two randomized controlled studies were identified. In one, after 12 weeks of treatment there was a 12% decrease in body weight and a 10% decrease in body fat compared to the placebo group. In a one-month study there was a 5.3% weight decrease compared to a 1.32% decrease in the placebo group.

- Green tea extracts. It has recently been demonstrated that green tea extracts taken orally can increase the resting energy expenditure and thermogenesis (production of body heat linked to the oxidation of body fat). This has led to studies of its potential for weight loss.[24] The active ingredients are thought to be catechins including the extensively studied epigallocatechin-3-O-gallate (EGCG). A recent study by Di Pierro *et al*[24] is of particular interest. One hundred individuals on a low-calorie diet were divided into two groups, one receiving a coated tablet containing highly bioavailable green tea extract, the other serving as a control. After 3 months, the treatment group lost 30 lbs. vs. 11 lbs. for the controls. Significant benefits in the treatment group compared to the controls were also seen in waistline, BMI, and cortisol levels. HDL increased by over 21% in the treatment group compared to 10% in the controls. Leptin, which was not measured in the control group, was dramatically decreased in the treatment group. These results were achieved with a green tea preparation (*GreenSelect Phytosome*) with greatly enhanced bioavailability. No adverse side effects were observed to be associated with this product, which Di Pierro *et al* claim is consistent with unpublished animal toxicity data. The importance of bioavailability is clear from a very recent systematic review and meta-analysis of green tea catechins and weight loss where only modest effects were found.[25] Either green tea itself or poorly absorbed extracts were used in all the studies in the analysis. Thus there appears to be only one study indicating strong benefit simply because there is only one study that achieved high enough absorbed levels of EGCC and other catechins.

A weight-loss formulation of all the above agents is available commercially (Life Extension Foundation) with the only variation being a hydrophobic fiber product claimed superior to glucomannan. The green tea component is the highly absorbable product. There do not appear to be any safety studies related to this mixture as compared to the individual ingredients although as indicated above, there do not appear to be any concerns about the individual components, although for some, the evidence is weak.

This approach attempts to replace or enhance energy intake restrictions with a somewhat artificial intervention, and if the protocol is terminated, then to maintain the new and perhaps more easily achieved weight it is necessary to find the new equilibrium energy intake for a given level of physical activity. It can be argued that it is not a good idea to directly interfere with digestive or metabolic processes by consuming chemicals, which while natural, are not necessarily present in our natural diets, at least not at the concentrations required for promoting weight loss, and it does not appear to make sense to do this as a life-long approach to weight control.

MEDICAL APPROACHES

The pharmaceutical industry is well aware of the problems associated with loosing weight through diet and exercise. The solution is dictated by the present drug development paradigm discussed several times in the Newsletter, i.e. use chemicals to block or inhibit, the same way the natural extracts work. This approach has been nothing but a disaster. Most recently, sibutramine (Meridas, originally used as an antidepressant) has been withdrawn due to unacceptable side effects. Among other things, it increases blood pressure and heart rate and also increases serious cardiovascular events. Most readers will remember the withdrawal of fen-phen in the 1990s. Recently full clinical trials of rimonabant, briefly marketed in Europe but not in the U.S. were discontinued. Another new drug as well as a combination of two drugs were turned down by the FDA because of concerns over a number of side effects. Those involved in "treating" the obese despair over a nearly empty toolbox. One can argue that the experience with diet drugs is just one more example of the flawed paradigm that requires meddling with biochemical pathways and processes using synthetic chemicals foreign to humans, meddling that clearly yields unintended results frequently unrelated to the target disorder and far removed for the site of the problem. Over the years there have been countless examples.

If diet drugs are required to realistically address the fact that most overweight and obese individuals can not accomplish and maintain significant weight loss by exercise and diet, then the pharmaceutical therapy presumably would be for life. Otherwise it would be a component in a yo-yo scheme. But long-term safety can not be tested in humans prior to regulatory approval, so there are unknown and potentially terrible risks with this approach. Some feel that the obesity crisis is such a serious public health threat that diet drugs should be allowed on the market for formal post-release safety trials which they point out may offer the only hope for discovering serious side effects. Industry support of such studies would be a risky business, given the history of forced drug withdrawal or restriction due to side effects that turned up even in lax and informal post-approval surveillance. Lifelong use is the dream of the industry but may be a nightmare for the patient.

Then there is the brute-force approach, bariatric surgery, which limits the stomach capacity.[26] This definitely leads to highly significant weight loss and favorable changes in a number of risk markers, but most would consider it as a last resort. Once one has reached a desired weight and has the procedure reversed (if possible), then the energy intake to maintain the new weight becomes a big issue. The type of bariatric surgery called laparoscopic Roux-en-Y gastric bypass has proved quite successful in producing dramatic weight loss with almost all patients achieving greater than 45% excess weight loss with mean changes typically of 40-50 kg (88-110 lbs).

Finally, it is being seriously suggested that a technique used successfully in Parkinson's disease called deep brain stimulation has potential in treating obesity.[27] Appetite and satiety centers in the brain have now been well documented and offer the possibility of electrical manipulation. Electrodes are inserted into the appropriate spots in the brain and connected to an implanted device that is remotely controlled. While there is considerable experience with this technique for treating Parkinson's, there are no studies regarding efficacy for obesity.

CONCLUSIONS

The general conclusion seems to be that energy intake and energy expenditure, either internal or external, are the controlling factors on which weight control and the reduction in obesity must rely. For weight loss, the calorie restricted low-carbohydrate diet has merit over the calorie restricted low-fat diet for reasons associated with triglycerides, HDL cholesterol and insulin resistance, to which should be added enhanced satiety which makes calorie reduction easier. Physical activity must be factored

in but dietary calorie intake has the potential for a much grater impact simply because exercise equivalent to a 500 or 1000 calorie daily deficit is not possible for many individuals.

The apparent equivalence of low-carbohydrate and low-fat diets does not invalidate the view that diets high in high-glycemic foods can have a deleterious effect on weight control through the impact on insulin levels and ultimately insulin sensitivity and thus insulin resistance. This involves the weight gain aspect of this subject directly, but insulin resistance can impact the success of weight loss interventions.

The guidelines developed by Hall and Jordan apply to the average individual and will require modification for some individuals. As with most chronic disorders, obesity is best prevented, not treated, and when the BMI enters into the overweight range of ≥ 25, this is the time to take action. Thus an important component of remaining healthy at all ages is to make weekly or monthly use of a scale and to act when weight creeps up by reducing energy intake and/or increasing physical activity until the increase is halted and the BMI returns to "baseline," which should be the lifelong target. Individuals for whom this does not work, or those who can not lose weight no matter what protocol they follow, then it is urgent to investigate other solutions. Hypothyroidism should be high on the list of suspects.

The emphasis on calories should not distract the dieter from concerns over what constitutes a healthy diet and it would appear important to include at least a typical multivitamin in the protocol. But there is considerable evidence that men and postmenopausal women should avoid iron containing multivitamins unless they are anemic, and natural folate is much to be preferred to folic acid. Attention also needs to be paid to the long-chain omega-3 content of the diet and supplement regime, as well as the vitamin C, magnesium, coenzyme Q-10 and vitamin D intake since desirable amounts are not generally provided by the typical multivitamin. Healthy diets and healthy diet patterns have been discussed repeatedly in this Newsletter.

Finally, the underlying assumption in this review is that obesity is bad. This ignores the well known paradox of the so-called healthy obese. They have high BMI but normal blood lipids, normal blood glucose metabolism which translates into normal fasting bloods glucose and insulin levels and a low HbA1c, and normal blood pressure. While they are lucky, there remain the majority who are no so fortunate. The evidence that obesity increases the risk of chronic degenerative and cardiovascular diseases is overwhelming. Obesity is associated with diabetes, and diabetes in turn is associated with not only elevated cardiovascular risks but vascular problems in general. The end result can have a much larger impact on the quality of life than a non-fatal heart attack as is illustrated by the prevalence of diabetic vascular problems which lead to visual problems as well as circulation problems ultimately requiring the amputation of toes, feet and even legs.

REFERENCES

(1) Haslam D, Rigby N. A long look at obesity. *Lancet* 2010 July 10;376(9735):85-6.
(2) Katan MB, Ludwig DS. Extra calories cause weight gain--but how much? *JAMA* 2010 January 6;303(1):65-6.
(3) Hall KD, Jordan PN. Modeling weight-loss maintenance to help prevent body weight regain. *Am J Clin Nutr* 2008 December;88(6):1495-503.
(4) McAllister EJ, Dhurandhar NV, Keith SW et al. Ten putative contributors to the obesity epidemic. *Crit Rev Food Sci Nutr* 2009 November;49(10):868-913.
(5) Swinburn B, Sacks G, Ravussin E. Increased food energy supply is more than sufficient to explain the US epidemic of obesity. *Am J Clin Nutr* 2009 December 1;90(6):1453-6.
(6) Hall KD, Guo J, Dore M, Chow CC. The progressive increase of food waste in America and its environmental impact. *PLoS One* 2009;4(11):e7940.
(7) Foreyt JP, Salas-Salvado J, Caballero B et al. Weight-reducing diets: are there any differences? *Nutr Rev* 2009 May;67 Suppl 1:S99-101.
(8) Mozaffarian D, Ludwig DS. Dietary guidelines in the 21st century--a time for food. *JAMA* 2010 August 11;304(6):681-2.

(9) Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* 2010 March 1;91(3):535-46.
(10) Yamagishi K, Iso H, Yatsuya H et al. Dietary intake of saturated fatty acids and mortality from cardiovascular disease in Japanese: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC) Study. *Am J Clin Nutr* 2010 October 1;92(4):759-65.
(11) Hartman AL, Vining EP. Clinical aspects of the ketogenic diet. *Epilepsia* 2007 January;48(1):31-42.
(12) Hall-Jordan Calculator. *http://www2 niddk nih gov/NIDDKLabs/LBM/HallAJCN2008 htm* 2010.
(13) Hall-Jordan Model Full Text. *http://www ajcn org/cgi/reprint/88/6/1495* 2010.
(14) Chow CC, Hall KD. The dynamics of human body weight change. *PLoS Comput Biol* 2008 March;4(3):e1000045.
(15) Hall KD. Predicting metabolic adaptation, body weight change, and energy intake in humans. *Am J Physiol Endocrinol Metab* 2010 March 1;298(3):E449-E466.
(16) Celleno L, Tolaini MV, D'Amore A, Perricone NV, Preuss HG. A Dietary supplement containing standardized Phaseolus vulgaris extract influences body composition of overweight men and women. *Int J Med Sci* 2007;4(1):45-52.
(17) Udani J, Singh BB. Blocking carbohydrate absorption and weight loss: a clinical trial using a proprietary fractionated white bean extract. *Altern Ther Health Med* 2007 July;13(4):32-7.
(18) Keithley J, Swanson B. Glucomannan and obesity: a critical review. *Altern Ther Health Med* 2005 November;11(6):30-4.
(19) Kraemer WJ, Vingren JL, Silvestre R et al. Effect of adding exercise to a diet containing glucomannan. *Metabolism* 2007 August;56(8):1149-58.
(20) Alonso-Sande M, Teijeiro-Osorio D, Remunan-Lopez C, Alonso MJ. Glucomannan, a promising polysaccharide for biopharmaceutical purposes. *Eur J Pharm Biopharm* 2009 June;72(2):453-62.
(21) Chen HL, Cheng HC, Wu WT, Liu YJ, Liu SY. Supplementation of konjac glucomannan into a low-fiber Chinese diet promoted bowel movement and improved colonic ecology in constipated adults: a placebo-controlled, diet-controlled trial. *J Am Coll Nutr* 2008 February;27(1):102-8.
(22) Oben JE, Ngondi JL, Blum K. Inhibition of Irvingia gabonensis seed extract (OB131) on adipogenesis as mediated via down regulation of the PPARgamma and leptin genes and up-regulation of the adiponectin gene. *Lipids Health Dis* 2008;7:44.
(23) Egras AM, Hamilton WR, Lenz TL, Monaghan MS. An evidence-based review of fat modifying supplemental weight loss products. *J Obes* 2011;2011.
(24) Di PF, Menghi AB, Barreca A, Lucarelli M, Calandrelli A. Greenselect Phytosome as an adjunct to a low-calorie diet for treatment of obesity: a clinical trial. *Altern Med Rev* 2009 June;14(2):154-60.
(25) Phung OJ, Baker WL, Matthews LJ, Lanosa M, Thorne A, Coleman CI. Effect of green tea catechins with or without caffeine on anthropometric measures: a systematic review and meta-analysis. *Am J Clin Nutr* 2010 January 1;91(1):73-81.
(26) Buchwald H, Avidor Y, Braunwald E et al. Bariatric Surgery: A Systematic Review and Meta-analysis. *JAMA* 2004 October 13;292(14):1724-37.
(27) Halpern CH, Wolf JA, Bale TL et al. Deep brain stimulation in the treatment of obesity. *J Neurosurg* 2008 October;109(4):625-34.

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