

# INTERNATIONAL HEALTH NEWS

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*Today one of the most important health issues for those with a choice is what to eat, when to eat and how to eat. Advice from experts frequently does not reflect recent or even classical scientific knowledge, partly because there is a strong human tendency to uncritically hold on to well established and officially sanctioned notions. The trio of epidemics, obesity, the metabolic syndrome and diabetes, are not independent phenomena and good medical practice will screen for early signs, advise regarding prevention of progression and attempt to deal with established cases. But the subject is complex. Lean individuals can have the metabolic syndrome, just not accumulated visceral fat. Some obese persons are metabolically healthy. But these exceptions do not dilute the huge problem of millions who are prediabetics, diabetic or who have the metabolic syndrome, with or without being overweight or obese.*

*The epidemics cited arose in step with dramatic dietary changes in the developed world. Fat was demonized in the 1960s; carbohydrates became the first choice for a healthy food without much regard for the effects on blood sugar swings or long-term averages, or the associated abnormalities in insulin levels throughout the day. Sugar consumption skyrocketed. The traditional treatments for obesity and diabetes were abandoned because carbohydrate restriction conflicted with the new conventional wisdom that dietary fat was implicated in both heart disease and cancer. Governments and the official medical and nutritional organizations successfully waged war on fat. Population HDL levels declined, triglyceride levels dramatically increased, type 2 diabetes was no longer associated with older individuals, and the trio of disorders cited above achieved epidemic status with huge impact on chronic diseases. While this brief history lesson does not prove cause, it did suggest avenues of research that have proved extraordinarily enlightening. However, the results, being in conflict with the conventional wisdom, have not had much impact on the advice provided by official sources. Academic critics, especially those knowledgeable in endocrinology, in fact claim that the advice is in many cases the exact opposite of what is required.*

*Recently, more research has addressed the question of when to eat, particularly in reference to the importance of breakfast and its metabolic impact. In addition, it has been known for some time that there is a delay between eating and the brain signalling satiety and that slow eating and delaying second helpings are important, but unfortunately not in keeping with modern lifestyles. In this issue of IHN, some of these topics will be explored.*

*In addition, the subject of salvestrols will be updated with exciting news regarding progress detecting the enzyme CYP1B1, a specific cancer marker, in blood and also using the blood levels of salvestrols and their metabolites to detect and follow the progression or regression of cancer. News briefs include reversal of diabetes, statins and the risk of breasts cancer, and the remarkable benefit of hyperbaric oxygen therapy for stroke victims.*

*Finally, a commentary on atherosclerosis by Uffe Ravnskov and Kilmer McCully, the latter of homocysteine fame, is included. Dr. Ravnskov is the world's leading critic of the cholesterol hypothesis. This commentary just appeared on the website of the International*

Atherosclerosis Society, and Dr. Ravnskov has kindly allowed us to provide a copy for IHN subscribers.

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

Wishing you and your family good health,

**William R. Ware, PhD, Editor**

### Highlights

Salvestrols and cancer	p. 7
Reversal of type 2 diabetes	p. 9
Statin use and breast cancer risk	p. 9
Hyperbaric oxygen for stroke recovery	p. 10
COMMENTARY – <i>Infections may be Causal in the Pathogenesis of Atherosclerosis</i> , by Uffe Ravnskov and Kilmer S. McCully	p. 13

## INSIGHTS INTO OBESITY

### ADIPOSIITY 101

In 2007, Gary Taubes, winner of three Science in Society Journalism awards and other prestigious awards wrote a book titled *Good Calories, Bad Calories. Challenging the conventional wisdom on diet, weight control and disease.*<sup>1</sup> This scholarly work was followed in 2011 by *Why We Get Fat* which provides a shortened version. The earlier book provides extensive documentation. The endocrinology and metabolic science that is the basis of Taubes' views will provide a starting point for the following discussion of obesity.

Weight gain or obesity involves increase in fat cells. During any 24-hour period there is an ebb and flow of fat from fat cells. The fat cells also convert glucose into fat for storage. Insulin controls this ebb and flow as well as the flow of glucose into all cells. When glucose is high, insulin causes the fats cells to shut down the outflow of fat. Glucose and fat are the two major sources of energy generated metabolically and the body

burns glucose in preference to fat when there is sufficient glucose. Not only does the circulating level of glucose drive the secretion of insulin, but even thinking about eating can cause insulin secretion,

Dietary carbohydrates are metabolized and glucose produced which enters the circulation and triggers increased insulin production. Fat from a meal is then stored, glucose is burned for energy, and excess glucose is converted into fats and stored in fat cells. This partitioning for storage and energy production is under the control of insulin. Thus during the day glucose and insulin go up and down together mainly in response to eating and blood glucose levels, and when glucose and insulin are low, more fat flows from fat cells to provide energy. This can occur between meals and during the night. After the last meal of the day, once the glucose and insulin levels are back to the premeal level, the low insulin will signal fat release from fat cells throughout the night to provide energy required and for running the system (basal metabolism) without input of food. Balance requires that the fat gained during the fat storage phase (high glucose) is lost during the fat burning periods and insulin controls this cycle.

When this system is in balance, weight is maintained and there is a fat reserve for periods of low food intake but a stable weight. Imbalance results in net weight loss or fat storage and weight gain which can be slow but insidious and yield over a number of years the overweight and obese states. Releasing fat from fat tissue and then burning it for energy requires the negative stimulus of low insulin.

If insulin levels do not drop sufficiently or are abnormally elevated, the fat release and burning is reduced or inhibited and fat is accumulated in fat tissue. Anything that causes the secretion of abnormal amounts of insulin or keeps insulin levels elevated for an abnormal period will lengthen the fat storage periods and shorten the fat burning periods during the 24 hour period of eating, working and sleeping. This bias toward fat storage then over an extended period can result in excessive fat accumulation and obesity.

Abnormally elevated insulin levels not only prevent stored fat from becoming fuel when needed, but elevated insulin levels lock up carbohydrate stored in liver and muscle tissue. Cells start signalling hunger and this leads to overeating to rectify the problem. As fat accumulates, muscle is added to support the fat, and total energy demand and appetite increases—an appetite for carbohydrates which is the only nutrient cells mainly burn for fuel when insulin is elevated. This is a vicious cycle and illustrates that humans can be driven to crave precisely the carbohydrate-rich foods that contribute to becoming fat.

The overriding principle appears to be that carbohydrates determine insulin secretion and insulin drives the accumulation of body fat. Furthermore, it is well known that carbohydrates differ significantly in their blood glucose elevation ability (as measured by the glycemic index). Thus, in Taubes' view, carbohydrate selection and consumption are keys to the problem of weight control. In Chapter 16 of *Why We Get Fat* he provides an interesting review of the history of the mainstream view of carbohydrates in obesity. He traces the belief that carbohydrate consumption and its restriction were keys to the development and avoidance of obesity from 1755 to the 1960s. Carbohydrate restriction was widely advocated and practiced for weight control. Furthermore, lists of foods to avoid prepared by prestigious medical institutions are identical to what we find today in the non-mainstream literature. Avoid bread and everything else made with flour, cereals, potatoes and all white root vegetables, foods containing sugar and all sweets. What happened to change all of this to he points where carbohydrates became major component of the recommended core diet for everyone?

The answer is the advent of the fat is bad hypotheses in the 1960s which of necessity caused a switch to much heavier consumption of carbohydrates and eventually also high carbohydrate junk food. The fact that this hypothesis is in most of its essential features totally false has been discussed repeatedly in IHN. An unproven idea became the driving force for a new dark age in medicine and even as calls for evidence based medicine grew, the overwhelming evidence against the fat is bad notion was aggressively ignored.

The above discussion ignores some important aspects of the obesity problem. A recent book by Robert H. Lustig, MD, an internationally renowned pediatric endocrinologist at the University of California, San Francisco, has provided a detailed account of other factors driving obesity and what can be done about it.<sup>2</sup>

### **LEPTIN RESISTANCE**

Basic to the thinking of Dr. Lustig and others is the belief that obesity is partly a leptin resistance disorder. Leptin is a hormone that is produced by fat cells in proportion to their triglyceride content and once in the circulation, gets past the blood brain barrier and links changes in body fat stores to adaptive responses generated in the hypothalamus. Its function is to control energy balance by signalling for changes in food intake and involuntary energy expenditure, including basal metabolism. From the point of view of evolution, the principal physiologic role of leptin is viewed as a response to and defence against reductions in body fat that might impair survival and reproductive fitness. Elevated levels of leptin are normally found in obese subjects in proportion to their adipose mass. However, while administration of leptin to obese humans reduces food intake, this is only effective among those at the lower end of the obese BMI and who have low leptin levels. The more obese the individual and the higher the leptin levels, the less effective becomes the treatment with leptin, and in the limiting case, it is totally ineffective.<sup>3</sup> This is the basis of the notion of leptin resistance, analogous to insulin resistance in type 2 diabetics. Thus obese persons are viewed as having

an impaired feedback system which otherwise would prevent them from overeating by adjusting appetite and energy expenditure.

In leptin deficient animals due to genetic defect, obesity is the norm and injections of leptin reduced food intake and increased activity back to normal. This also has been tested on the few children identified with this problem.<sup>4</sup> In humans without this genetic defect, those who are obese have plenty of leptin so that they are not deficient but resistant.

In children with a surgically or cancer treatment damaged hypothalamus who can't receive and act on leptin signals, this is interpreted as starvation and there is an increase in insulin production over and above that triggered by glucose. In these children, a drug that reduces insulin production causes them to lose weight and feel better.<sup>5</sup> As discussed below insulin is involved in leptin resistance.

### **RELATION TO INSULIN RESISTANCE**

There is also growing evidence that insulin inhibits leptin signalling and thus there is leptin resistance associated with elevated insulin levels which is the hallmark of insulin resistance and obesity.<sup>6,7</sup> Thus insulin resistance and leptin resistance are a deadly combination. When insulin levels in the hypothalamus are chronically high, leptin cannot signal the hypothalamus or the hypothalamus will not respond to high circulating leptin levels.

When leptin resistance is present, appetite is uncontrolled and inactivity becomes the norm. As the obese individual eats, the brain is sending signals that indicate persistent hunger even when the fat cells are generating high levels of leptin which should be generating a signal of being satiated. High levels of insulin being produced during eating simply aggravate the problem, especially in the presence of insulin resistance where increased amounts of insulin are needed to respond adequately to increased dietary glucose. High insulin levels mean more energy stored as fat. More fat means more leptin. But leptin no longer is functioning as it should to curb appetite.

### **WHICH DIETARY COMPONENTS ARE IMPLICATED?**

Studies have revealed components that are positively associated with leptin resistance and obesity yielded interesting and potentially useful results.<sup>8</sup> Animal studies were used and found the following:

- Dietary fructose contributed to obesity through palatability, over eating and impaired leptin responsiveness that exacerbated the palatable diet/over nutrition induced weight gain. Two different pathways were identified and fructose-driven leptin resistance was reversible.
- Consuming a 30% sucrose solution causes rapid onset of insulin resistance and the activation of a pathway that can also induce leptin resistance. A standard procedure for diet induced obesity in rats is to use a high-fat/high sucrose diet. Such a diet can induce leptin resistance such that the animals were resistant to injected leptin after only 17 days.

The sucrose molecule contains one molecule of glucose and one of fructose joined together. High fructose corn syrup (HFCS), a very common substitute for sucrose, is in fact almost equivalent with approximately equal content of glucose and fructose as free molecules. Modern Western diets are replete with fructose from high fructose corn syrup and sucrose which are widely used in processed foods.

The fact that fructose is a bad nutrient is evident from the following. Fructose does not stimulate insulin and thus leptin does not rise to put a break on eating. Fructose consumption generates liver insulin resistance and causes chronic elevated insulin levels, the dangers of which are discussed above both for the impact on leptin and on the fat storage process in general. High levels of the glucose component of HFCS lead to insulin resistance and fat storage. The visceral fat storage is particularly dangerous.

The typical American sugar consumption depends on who does the calculation. The US Department of Agriculture corrects for waste and comes up with about 77 lbs/year. This is 0.2 lbs/day, or 91 g, is roughly 4 tablespoons and contains almost 400 calories or 20% of a 2000 cal/day diet. However, this is a population average, and obviously for a significant population, the consumption is much higher. Other recent estimates have been higher, typically around 100-120 lbs/year. Sugar is one of the most important biologically plausible drivers of obesity quite apart from the calorie content because of its fructose and glucose content, and if the ideal sugar consumption is near zero, then the magnitude of the obesity problem becomes clear as does a potentially hopeless aspect.

### **INDICATED ACTION**

What has been described above is a mechanism for out-of-control eating driven by the failure of food intake to impact appetite and uncontrolled eating of particular foods, some of which trigger the failure of the appetite control mechanism related to leptin. At the same time, the addictive foods which induce leptin resistance increase insulin and can lead to insulin resistance and enhanced fat storage, which exacerbates the problem.

If one views obesity as partly a hormonal problem, then according to Dr. Lustig, one should take four actions.<sup>2</sup>

- Reduce insulin levels and improve leptin sensitivity and lower appetite. Since glucose drives the pancreas to produce insulin, this requires cutting back on refined carbohydrates as well as completely eliminating fructose and therefore sucrose and high fructose corn syrup. Improve liver insulin sensitivity by limiting liver fat which means limiting fat and carbohydrates together. Consumption of fiber will also lower insulin, and improving muscle insulin sensitivity by exercise is important. The obese frequently have insulin resistance and high insulin levels are common with type 2 diabetics since they have insulin resistance. It is well known that type 2 diabetics can improve their insulin sensitivity by severely restricting carbohydrates, especially sugar and foods containing refined starch.
- Eat breakfast, get adequate sleep and stop night-time binging. This recommendation is justified by breakfast reducing the hunger hormone ghrelin. Resisting the hunger after dinner which is caused by severe insulin resistance, and avoid the adverse effects on stress due to poor sleep patterns. Eating before bed reduces the fat burning that occurs during the night.
- Eat slowly allowing the biochemistry time to act and signal adequate food and reduce appetite. It takes about 20 minutes before the signal of fullness is generated in the brain.
- Keep cortisol levels low by reducing stress which will also reduce the deposition of energy into visceral fat. After exercise cortisol declines and the lower level persists for a considerable time.

The above picture leads to a description of obesity. Due to leptin resistance the brain thinks there is low leptin which indicates starvation. The nervous system goes into the conservation mode incorrectly sensing starvation, driving down energy expenditure including basal metabolism, physical activity and quality of life. The nervous system also drives up appetites. High food consumption drives up insulin levels and energy storage. Weight continues to increase even if food intake is reduced, and the incorrect signals from the brain render action very difficult. To summarize Lustig's view, hunger, and reward conspire to undo attempts at weight loss. Gluttony and sloth are real, but are the result of changes in brain biochemistry.

The fundamentals as outlined by Taubes and augmented by Lustig provide a guide to dealing the obesity problem. It is noteworthy that both agree on the importance of severe restriction and selection of carbohydrates. No sugar, no starches, no bread, no pasta or rice. Lustig points out that these restrictions are part of all successful diets. We appear on the way to

coming full circle and in a decade or so may actually find the protocols popular from the 1700s to the 1960s coming back in fashion in mainstream medicine and nutrition.

### **IMPORTANCE OF BREAKFAST**

Readers may remember that grandma believed in the importance of always having a good breakfast. Some lifestyles do not allow this and breakfast may be skipped altogether or might consist of a doughnut and coffee grabbed on the run. There are at least three issues, i.e. skipping, calorie content and specific food or macronutrient content. Concerns center on weight and the risk of the metabolic syndrome, type 2 diabetes and cardiovascular disease.

A study just published examined for female breakfast eaters with the metabolic syndrome the question of the impact of how the daily caloric intake was divided between the three major meals.<sup>9</sup> Obese women were divided into two groups, a so-called breakfast group (BF) which consumed 700 calories at breakfasts, 500 calories at lunch and 200 calories at dinner. The dinner group (D) consumed the same number of calories but breakfast, lunch in dinner contained 200, 500 and 700 calories respectively. The trial lasted 12 weeks and the results are fascinating. Compared to the baseline values, at week 12, the BF and D groups had weight loss of 11 and 4%, fasting blood glucose of decreases of 11.5 and 4.2%, fasting insulin decreases of 51 and 29%, and the decreases (beneficial) in the insulin resistance measure of 57% and 32.5%. There was also a greater decrease in waist circumference in the BF group compared to the D group. Graphs of weight loss showed for the BF group a steady decline whereas for the D group, the very common U shaped curve where the weight loss trend reverses. Results for the oral glucose tolerance test were significant better in terms of the 2 hours glucose and insulin values for the BF group compared to the D group. Fluctuations throughout the day in blood glucose and insulin were much more favourable for the BF group compared to the D group. In the BF group, triglycerides decreased whereas HDL increased, a reversal of the pattern of dyslipidemia in the metabolic syndrome, and for the D group despite weight loss, an increase in triglycerides was observed. Greater satiety was also observed in the BF group. This was consistent with an earlier study from the same group where it was found that a high carbohydrate and protein breakfast may prevent weight regain by reducing diet induced compensatory changes in hunger and craving.<sup>10</sup>

The authors comment that previous studies have shown that insulin sensitivity and glucose tolerance decreases progressively throughout the day and this may partly explain why evening or night eating is often associated with weight gain. In addition, both groups had the same caloric intake at lunch, serum glucose and insulin responses were significantly lower in the BF group. This suggests the BF breakfast provided a protective effect against post lunch hyperinsulinemic response after the following meal. The results also suggest that the caloric distribution used in the BF group may provide reduced risk for the development of type 2 diabetes and that the BF protocol was significantly beneficial for individuals with the metabolic syndrome.

Omission of breakfast or irregular breakfast habits has received considerable recent attention. It has been found that

- In the large Health professional Follow-up Study it was found that breakfast omission was associated with an increased risk of type 2 diabetes in men even after adjusting for BMI.<sup>11</sup>
- Omitting breakfast was found to adversely impact insulin sensitivity and fasting blood lipids in lean, healthy women and the practice could lead to weight gain if there was a subsequent high energy intake.<sup>12</sup>
- In the Nurses' Health Study, irregular breakfast consumption was associated with higher type 2 diabetes incidence.<sup>13</sup>
- Relative to infrequent breakfast consumption, daily breakfast was strongly associated with reduced risk of a spectrum of adverse metabolic conditions such as obesity, metabolic syndrome and type 2 diabetes.<sup>14</sup>

- In a group of regular breakfast eaters, missing breakfast causes metabolic and hormonal differences in responses to food consumed later in the morning as well as differences in appetite and compensatory increase in energy intake which would explain the association between regular breakfast eating and maintenance of a healthy body weight.<sup>15</sup>
- Eating breakfast has been found associated with a significantly lower risk of coronary heart disease in men.<sup>16</sup>

Finally, a study compared a breakfast containing two eggs (energy % Carb/fat/protein 22:55:23) to a high carbohydrate breakfast (72:12:16) and found the egg breakfast more effectively promoted satiety and reduced subsequent energy intake during the day. This was consistent with reduced insulin, glucose and ghrelin response, the latter a marker for hunger, throughout the day. The authors pointed out that the results support the role of insulin as a key participant in appetite regulation independent of ghrelin.<sup>17</sup>

## **BIOLOGICAL PLAUSIBILITY OF SALVESTROLS AND RELATED BLOOD TESTS FOR CANCER**

In the spring 2013 issue of *The International Journal of Phytotherapy*, Dr. Brian Schaefer has presented the current status of knowledge of how salvestrols work and describes how salvestrols can be incorporated in a blood test for early cancer.<sup>18</sup> He has also written a highly recommended book on salvestrols.<sup>19</sup>

Salvestrols were introduced to IHN readers in the June 2008 issue and updated in October, 2009 and July/August 2012 with emphasis on case histories. The basic facts are as follows. Cancer cells from all types of cancer studied express an enzyme called CYP1B1 which will act on certain substances that migrate into the cell and become so-called substrates. The enzyme then catalyzes the conversion of the substrate to a metabolite, a new chemical which is or may be cytotoxic and thus result in cell death. The cytotoxin generating substrates, which are called salvestrols, vary considerably in the cytotoxicity of the metabolites produced and this has been extensively and quantitatively studied using cultured cancer cells from various cancer types. CYP1B1 expressed at levels of biological significance appears to be unique to cancer cells and thus the salvestrol represents the much sought after magic bullet which kills cancer cells but has no effect on normal cells. This magic bullet or targeted therapy concept is currently all the rage in cancer research with mechanisms mostly involving immune retractions. The fact that salvestrols represent one example of a targeted therapy has been largely ignored since the substrates proven to be powerful anti-cancer agents are fruit extracts and thus of no interest to the pharmaceutical industry. The required clinical trials needed for regulatory approval are of course very expensive. Nevertheless, a large number of case histories reporting in most instances complete regression now exist which give cause for optimism and strongly suggest that salvestrol therapy should not be ignored.<sup>20-23</sup>

In the paper cited above, Schaefer reports on the results of several unpublished studies which address two aspects of the unique biological activity of CYP1B1. One involves developing a highly sensitive test for the enzyme in blood plasma and determining the very low background levels in individuals free of cancer as a point of reference. The presence of the enzyme above a threshold would then indicate cancer but not pinpoint the site. The second area of interest involves using the CYP1B1 catalyzed metabolic process in cancer cells as an indicator of the presence of the disease. This involved developing a sensitive blood test for both the substrate (salvestrol) and the cytotoxic metabolite. Failure to find the metabolite upon administering the salvestrol suggested no cancer. Finding the metabolite indicates the presence of cancer cells, given the evidence of the action of the enzyme to produce the metabolite. Established cancer cells would consume some of the salvestrol and produce metabolite, and the extent to which this happens is measured and provides an

indication of the severity of the cancer. In the limiting case, most if not all of the substrate is used. In the absence of cancer, none is.

The quantitative analysis for CYP1B1 proved challenging. The research group developed an antibody specific for human CYP1B1 and perfected sample preparation and the detection method based using a sample of blood plasma to what they believe is the required sensitivity and specificity. They were then able to detect CYP1B1 in healthy volunteers but at minute levels which they interpreted as probably due to cancerous or precancerous cells that are being naturally killed off on a daily basis. Vastly larger amounts were detected in cancer patients. For example, levels of CYP1B1 were 92 to 6291 times higher in blood from lung cancer patients than in healthy individuals. Based on an estimate that about a billion cancer cells were necessary before the disease becomes clinically evident, the sensitivity of the blood test to detect the enzyme required 1000 times fewer cancer cells. They estimated that in general, this provided the potential for detection of cancer almost 6 years prior to clinical presentation. Work continues to perfect this so-called proteomic approach. But even at the stage of development when the paper was written, if CYP1B1 could be detected at levels above the background, then the verdict is clear, the patient has cancer, and there are no false positives. These results are of course consistent with the observations from many laboratories over more than a decade indicating that CYP1B1 was unique to cancer cells.

The second approach involved finding a salvestrol which would abundantly produce metabolite through the action of CYP1B1. It was required that the metabolite not be present in food. Both blood and urine tests employing a standard analytical technique (high performance liquid chromatography) were then used to examine first what happened with healthy volunteers. When given a gram of salvestrol, they were able to reliably detect and measure the salvestrol in both blood and urine. The peak occurred 3 hours after ingestion. There was no metabolite detectable. When trials were done on cancer patients, the metabolites were detectable and the salvestrol level dropped. Patients with advanced disease used up all the salvestrol yielding only metabolite. Blood and urine tests were consistent. Tests with patients with a fairly broad array of common cancers such as breast, stomach, kidney, prostate etc all gave the same results—the metabolite was found for all, confirming that the metabolite was a universal cancer marker.

The results of both the proteomic and metabolic approaches not only confirm that the mechanism advanced for the action of salvestrols is correct, but that these blood and urine tests provide not only a very sensitive tool for detecting cancer, but also allow for determining the success of therapy. While the location of the cancer is not indicated by these tests, salvestrol therapy also is independent of the site. In addition, the proteomic test allows much earlier detection and treatment than is possible today.

In earlier issues of IHN case histories were presented which provided evidence that the cytotoxic metabolites were indeed effective in eliminating established cancer. They therefore are almost certain to play a role in primary prevention as well or in effectively dealing with very early cancer. It is of interest in this context that tissue associated with the enlarged prostate exhibits CYP1B1 expressed as the enzyme and suggests that salvestrols may have a role in controlling benign prostatic hyperplasia (BPH).<sup>24</sup> This surprising result suggests that hyperplastic tissue in the prostate is in fact cancerous or that precancerous tissue expresses CYP1B1.

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## NEWS BRIEFS

### REVERSAL OF TYPE 2 DIABETES

The reversal of type 2 diabetes must *a priori* involve normalizing pancreatic beta cell function and reversing insulin resistance. An interesting study was published in 2011 describing the impact of an 8 week severe calorie restriction protocol (600 cal per day) tested on 11 obese individuals.<sup>25</sup> Pancreatic beta cell function was measured along with liver insulin sensitivity, insulin response, liver glucose output, and fasting blood glucose. In addition, MRI was used to determine both liver and pancreatic fat levels. These latter two measurements relate the impact of fat deposition on liver insulin sensitivity and pancreatic beta cell function.

After only 7 days, fasting blood glucose and liver insulin sensitivity normalized and liver fat decreased by 30%. Over 8 weeks, beta cell function increased toward normal and pancreatic fats decreased. Following the intervention, the participants gained back some of the weight lost over 12 weeks, but the HbA1C remained steady and the fat content of both the pancreas and liver did not increase.

The authors interpret these results as indicating that type 2 diabetes has a single common cause, excess fat accumulation in the liver and pancreas. They also emphasize that this study demonstrated for the first time the early time course during which liver fat stores and glucose production fall in response to a dietary restriction in type 2 diabetics. These results also emphasize the general picture provided earlier in this newsletter that diabetes is strongly related to fat storage driven by insulin. However, the long-term durability of this intervention remains in question and must depend on the post study diet. Thus the general principles outlined in the discussion of obesity should apply.

It is important to emphasize that current drug interventions for type 2 diabetes do not reverse diabetes and mostly appear to be totally ineffective if the concern is complications. As pharmacists who follow their clients long term are known to comment, diabetics just get worse while taking their pills but they are lowering their blood sugar.

### STATIN USE AND BREAST CANCER RISK AMONG WOMEN AGE 55-74

A recent case-population-based case-control study conducted in the area around Seattle, Washington examined the relationship between statin use and both invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) of the breast and included subjects with statin use exceeding 10 years.<sup>26</sup> Ever use for  $\geq 10$  years was associated with a 1.78 fold increase in IDC and a 1.82 fold increase in ILC. Both were statistically significant and absolute risk increase gave a number needed to treat to harm one person (NNH) of 50 over a period of  $\geq 10$  years. For current use the figures were 1.83, 1.97 and also a NNH of 50. For subjects with a history of high cholesterol, ever use for  $\geq 10$  years doubled the risk of IDC and increased the risk of ILC by 2.43 fold. NNH were 14-16. For current use or ever use, both for  $< 10$  years, there was no statistically significant increase in risk. The authors suggest that these results imply the long-term disruption of the pathway inhibited by statins (mevalonate

pathway) or the long-term lowering of serum cholesterol may contribute to breast carcinogenesis.

Breast cancer risk vs. cardiovascular risk reduction with statins is an important issue in interpreting this type of study. In primary prevention, at least six studies have found that cholesterol levels, unless they are low, present no risk for cardiovascular events in either elderly men (generally > 65 years of age) or women.<sup>27-32</sup> Studies that focused on women came to the same conclusion.<sup>33-35</sup> JUPITER found benefit, but only in women with elevated C-reactive protein and 42% in the study has the metabolic syndrome and most were overweight and some obese. The study may have been seriously confounded by the drug increasing dramatically the vitamin D levels. Half the participants had no heart disease.<sup>36</sup> Also, the validity of JUPITER has been challenged.<sup>37</sup> A study just published involving almost 120,000 subjects found in a population free of heart disease and diabetes that high total cholesterol or LDL in both males and females over 50 did not present a risk and in fact in general was protective as was HDL when mortality was the issue.<sup>38</sup>

For secondary prevention of cardiovascular events with statins, a meta-analysis which included studies involving older women found that for all-cause mortality, CVD mortality, any heart attack or any stroke, significant benefits were found over 4-5 years which would appear to outweigh the risks of breast cancer.<sup>39</sup>

The increased risk of breast cancer was found only for the use of statins over more than 10 years, but the current practice appears to favour prescription of statins for life. However, the statin intervention studies cited mostly involved shorter studies, typically over 4-5 years, although it is unlikely that this would change the conclusion involving primary cardiovascular disease prevention vs. breast cancer risk.

## **HYPERBARIC OXYGEN FOR STROKE RECOVERY. EVIDENCE OF LATE NEUROPLASTICITY**

Post-stroke treatment involves intensive functional therapy and other rehabilitation programs. The results are variable but generally only partially successful and many victims are left with serious incapacitation and quality of life issues. One of the therapies that has been tried is hypobaric oxygen therapy (HBOT) but five controlled clinical trials were either inconclusive or contradictory. However, these trials all involved intervention early after the event. A recent study has just reported which tested the hypothesis that HBOT had its greatest potential for benefit if carried out after the damage phase is over.<sup>40</sup>

In this randomized, controlled trial, those who had suffered a stroke 6 to 36 months earlier were randomized into two groups. One was given 40 treatments whereas the other group served as a control and then also received the same treatment. In the controlled phase, no improvements were observed in the control group but significant neurological improvements were found, even in those in late, chronic stages. When the control group was then treated, similar beneficial results were obtained. Imaging studies (two types of scan) were found to correlate well with clinical improvements and elevated brain activity was detected mostly in regions of live cells with low activity. Three case histories were given with accompanying scan pictures. The recovery of significant functionality and quality of life should impress anyone who reads these histories. For the initially treated group and the subsequently treated control group, highly significant changes were observed in the National Institutes Stroke Score Scale and scores in daily living and quality of life. The scatter plot provided suggests that everyone benefited. There was no overlap.

This study supports the hypothesis that HBOT should be given during the regeneration phase of stroke recovery rather than during the degeneration phase, and that benefits result that most stroke patients and their families would welcome. Furthermore, the authors comment that in their experience, more than 40 treatments may provide additional benefit.

The protocol involved 5 daily treatments a week for 8 weeks, 90 minutes each, 100% oxygen at 2 times normal atmospheric pressure. HBOT requires a hyperbaric chamber and they are not that common. If the results of this study became common knowledge among stroke patients and their families, the demand would probably skyrocket and face opposition from sceptics and those devoted to upholding evidence based medicine who might demand much larger trials and long post treatment follow-up, and ignore the sensational case histories presented. Such is the nature of medicine today. This would be unfortunate since HBOT is far cheaper than prolonged physical therapy and appears to work much better than existing therapies in the time frame at issue. The report is available free (Google PMID2335971).

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## COMMENTARY

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### Infections May Be Causal in the Pathogenesis of Atherosclerosis

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According to the current view, atherosclerosis is an inflammatory disease initiated by endothelial dysfunction caused by hypercholesterolemia, hyperhomocysteinemia, or other toxic factors. Endothelial dysfunction is said to allow LDL-cholesterol and monocytes to enter the arterial wall, where LDL-cholesterol becomes oxidized and taken up by macrophages. However, there is no association between the concentration of cholesterol in the blood and the degree of endothelial dysfunction, and neither autopsy nor angiographic studies nor electron beam tomography have found an association between degree of atherosclerosis and total or LDL cholesterol [1]. Furthermore, high cholesterol is not a risk factor for women and old people; in fact, more than twenty studies have shown that old people with high cholesterol live the longest [1]. Several authors have pointed out that the inflammation does not start in the intima, but in the adventitia, and they have suggested that the crucial factor is a narrowing or total obstruction of vasa vasorum causing hypoxia of the arterial wall [1-8]. If so, the question is, what causes obstruction of the vasa vasorum?

### Arguments for an Infectious Etiology

More than one hundred reviews have pointed to an association between infections and cardiovascular disease (CVD), and remnants of more than 50 bacterial species and several viruses have been identified in atherosclerotic arteries, but none in normal arteries. Most authors consider it as a secondary phenomenon, but many observations suggest that the infections may indeed be causal [1,2].

Cardiovascular mortality increases during influenza epidemics and a third of patients with acute myocardial infarction or stroke have had an infectious disease immediately before onset [1]. Periodontal infections are associated with an increased risk of CVD, and their treatment improves endothelial function and reduces the intima-media thickening of the arteries [2]. Serological markers of infection are often elevated in patients with CVD and are

also risk factors for such diseases. The coronary arteries of children who die from an infectious disease are narrowed, and their walls are thickened in those who survive [2]. A strong argument is also that early signs of atherosclerosis have been produced by experimental infections in chickens, mice, and mini-pigs [2].

The classical study of early atherosclerosis in young American soldiers killed in Korea is frequently cited as proof that atherosclerosis starts in early adulthood. In that study, 77.3% had gross evidence of coronary disease and 15% had more than 50% luminal narrowing. However, such severe changes have never been observed in autopsy studies of young people who have died from other causes. The explanation may be that many of these soldiers had severe, infected wounds before they died. As the author stated, "thrombosis occurred especially in cases in which extensive trauma and shock exerted their influence."

In a post-mortem study of several thousand victims in the concentration camp in Dachau, extensive atherosclerosis was seen in individuals younger than 35 years. Many had severe infections, and the degree of arteriosclerosis was related to the duration of internment in the camp. Other than severe stress, there was no dietary cholesterol or saturated fat, no smoking, no lack of exercise, no obesity or other risk factors for arteriosclerosis [2].

### **Lipoproteins Are Anti-Infectious**

To understand why the microorganisms are localized to the arterial wall and why their presence leads to atherosclerosis, it is necessary to consider the importance of the innate lipoprotein immune system. Although documented for decades by more than a dozen research groups, it is little known that the lipoproteins partake in the immune system by binding and inactivating all kinds of microorganisms and their toxic products. In animals HDL is the predominant actor; in man it is LDL. Human LDL inactivates up to 90% of *Staphylococcus aureus* alpha-toxin, and it inactivates an even larger fraction of bacterial lipopolysaccharide (LPS). The importance of this system has been documented in laboratory studies, animal experiments, and observations in patients with CVD [1,2,9].

The presence of foam cells in the arterial wall is said to be due to uptake of oxidized LDL (OxLDL) by macrophages, but test tube experiments have shown that lipopolysaccharides from various microorganisms are able to convert macrophages to foam cells in the presence of human LDL, indicating that oxLDL may be created as a side effect during the oxidation of the microorganisms inside the macrophages.

The protective role of the lipoproteins has been documented in many ways. For instance, hypocholesterolemic rats injected with LPS have a markedly increased mortality compared with normal rats, but they survive if injected by purified human LDL; and hypercholesterolemic mice challenged with LPS or live bacteria have an eight-fold increase of LD50, compared with normal mice. In agreement with these experiments, low cholesterol in man is a risk factor for mortality due to infectious diseases [1].

### **Why Vasa Vasorum Becomes Obstructed**

Microorganisms form complexes with lipoproteins, producing aggregates that contain microbial remnants and lipoproteins. The size of such aggregates may impede their passage through capillary networks, in particular the vasa vasorum of the artery walls because of the high extra-capillary pressure. The size of the complexes may increase in the presence of hyperhomocysteinemia because homocysteine reacts with LDL to form homocysteinylated LDL aggregates. Autoantibodies against homocysteinylated or oxLDL may also enhance the aggregation. Furthermore, the lumens of vasa vasorum are narrowed by hyperhomocysteinemia, which causes endothelial dysfunction [1,2,9].

## **Creation of the Vulnerable Plaque**

Obstruction of the vasa vasorum by aggregated lipoprotein complexes containing microbial remnants may lead to cell death because of localized ischemia of the vascular wall. Vasa vasorum may rupture, causing hemorrhage and a release of the microbes and their toxic products. With a healthy immune system, the microorganisms may be eliminated, new capillaries will enter the lesion, and reparative processes will convert the dead tissue into a stable, fibrous plaque. But in case of an insufficient clearing of the microorganisms and the ensuing inflammatory response, cell death may accelerate creating a vulnerable plaque, the preferential site for rupture and occluding thrombosis [1,2].

## **Clinical and Pathological Observations**

Thus, in our view LDL-cholesterol does not enter the artery through the endothelium, but via the capillary web of the vasa vasorum. Oxidation of LDL does not take place before LDL has entered the macrophage but occurs after phagocytosis, as part of the process of inactivating microorganisms by oxidation with reactive oxygen species. A reason for considering the vulnerable plaque to be a type of micro-abscess, as originally suggested by William Osler 100 years ago, is that its temperature is higher than that of the surrounding tissue. Whereas neutrophils, the hallmark of pyogenic infections, are rare in stable plaques, they are always found in and around the core of vulnerable plaques, and there are just as many neutrophils in the intact as in the ruptured plaques, contradicting the assumption that their presence is secondary to rupture [1].

Our interpretation explains the clinical and laboratory similarities between myocardial infarction and myocarditis. It also explains the frequent occurrence of bacteremia and sepsis in myocardial infarction complicated with cardiogenic shock. It explains why fever, diaphoresis, leukocytosis, and elevation of inflammatory markers in the blood, including CRP, the classical symptoms of an infectious disease, are common findings in myocardial infarctions. Our interpretation agrees with the almost constant finding of neutrophils in the myocardium 24 hours after an acute myocardial infarction, as well as in infarctions of other organs caused by thrombosis secondary to rupture of vulnerable plaques.

Fatty streaks are not necessarily the precursors of atherosclerotic plaques because they are present in the fetus and are more frequently found in early than late childhood, presumably reflecting a normal and reversible response to infections. Hydrodynamic pressure is usually cited as the reason that atherosclerosis is localized only within systemic arteries. This explanation is probably correct, not because the arterial pressure damages the endothelium, but because the lipoprotein complexes are trapped more easily in vasa vasorum of the systemic arteries where the tissue pressure is much higher than around the veins and the pulmonary arteries. The focal occurrence of atherosclerotic lesions is also in better accordance with a microbial genesis. If elevated LDL cholesterol were the most important cause, atherosclerosis should be a more generalized disease. That inflammation should be the cause of atherosclerosis is also unlikely, because all trials with anti-inflammatory drugs have increased CVD mortality. This fact is in accord with an infectious origin of atherosclerosis, however, because inflammation is a necessary step for healing of infections.

## **Final Comments**

Our interpretation is in accord with several of the classical risk factors for CVD. For instance, infections are more prevalent in smokers and diabetics. Hyperhomocysteinemia is found in B vitamin deficiency, smoking, hypertension, hypothyroidism, renal failure, mental stress and aging, all classical risk factors for CVD. Mental stress also stimulates the production of cortisol, and an excess of cortisol promotes infections. The suggestion that excess iron is a risk factor for vascular disease is also in accordance, because bacterial growth is stimulated

by the presence of free iron.

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