

# INTERNATIONAL HEALTH NEWS

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*This issue is mainly concerned with diabetes and cardiovascular disease. Both diabetes and pre-diabetes are becoming more prevalent each year and the associated increase in risk of microvascular and macrovascular disorders that come with the elevated blood sugar and elevated insulin levels is so great that it threatens both the public and private healthcare systems. The microvascular complications include problems with vision, kidney function, peripheral circulation and can result in kidney failure and the need for dialysis, loss of vision, and amputation due to poor peripheral circulation. Macrovascular problems cover the whole spectrum of cardiovascular diseases. This issue discusses glucose control and the impact of diet and weight loss on both cardiovascular risk,*

*diabetes and pre-diabetes.*

*In addition, a short update on statins is provided and as well, a new study on coenzyme Q-10 and heart failure is reviewed. Two studies on vitamin D and one on calcium scores round out the issue.*

*Finally, this issue includes a Research Review that discusses the diagnosis of both diabetes and pre-diabetes and what one can do to partially or totally reverse these conditions. The apparently rather unsatisfactory state of diabetes diagnosis guidelines may surprise some readers and is almost certainly not generally known. This review complements some of the topics covered in the main body of the issue.*

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*Wishing you all the best for a Happy Holiday Season and good health for the New Year,*

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

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## INTENSIVE DIABETIC GLUCOSE CONTROL. DOES IT PREVENT CVD EVENTS?

At the American Diabetes Association (ADA) Scientific Sessions meeting in June, 2008, the results of three trials (ACCORD, ADVANCE AND VADT) comparing intensive blood glucose lowering vs. standard therapy in Type 2 diabetics were reported, and simultaneously two of the studies were published in the *New England Journal of Medicine*.<sup>1,2</sup> These trials investigated the hypothesis that aggressive blood sugar lowering would positively impact the risk of adverse macrovascular

(e.g. cardiovascular) and microvascular (e.g. eye, kidney and nerve damage) events associated with diabetes. Subjects in general had established Type 2 diabetes of about 10 years duration and additional risk factors for cardiovascular disease (CVD) or documented CVD. These studies compared intensive intervention to standard treatment. One of the studies (ACCORD) had already gained notoriety by being halted in February, 17 months prior to the intended study end, because of increased mortality in the intensive intervention group. These studies all used aggressive drug treatment targeted at blood glucose levels, hypertension and dyslipidemia. Several blood glucose-lowering agents were used, sometimes simultaneously, and as well; control was assisted by insulin use when indicated. The blood glucose target employed glycated haemoglobin, HbA1c, which provides an average over several months and is widely used to monitor glucose control in diabetics. It is expressed as the percentage of haemoglobin glycosylated (i.e. reacted with glucose). These studies might be described as evaluating a prescription drug blitz!

None of the three trials showed any cardiovascular benefit associated with lowering HbA1c below 7%, the ADA recommended goal for standard therapy (other organizations recommend 6.5% or less). The mean baseline HbA1c levels were 8.1% (ACCORD), 7.2% (ADVANCE) AND 9.5% (VADT). ACCORD used the most aggressive intervention, achieved the lowest HbA1c levels (mean 6.4%), and as mentioned above, encountered excess mortality deemed unacceptable. Weight gain was not uncommon in these studies and some subjects experienced one or more episodes of dangerously low blood glucose (hypoglycemia). The overall results were greeted with disappointment and surprise by the cardiology and diabetology communities since there was prior evidence suggesting that the interventions might prove beneficial in reducing macrovascular events. Some suggested on the basis of these new results that glucose control to achieve near normal levels among patients with diabetes may not even be desirable. This represents a rather narrow view since there does not seem to be any debate regarding the merits of tight glucose control for reducing the risk of microvascular problems. ADVANCE achieved a mean HbA1c of 6.5% and VADT an average of 6.9%, respectively.

In spite of this overall failure, subgroup analysis revealed some macrovascular benefits. In each of the trials more than half of the subjects had no previous history of CVD events, i.e. the primary

prevention groups. ACCORD found for this subgroup a 25% reduction in non-fatal heart attack or stroke or a CVD related death in the intensive treatment group. ADVANCE found a 14% reduction in major macrovascular and microvascular events in the primary prevention group but this was mostly due to a reduction in kidney problems – a microvascular issue. Finally, VADT found that patients with less coronary calcification (presumably reflecting shorter duration and severity of atherosclerosis) whose glycemia was intensively treated had fewer CVD events than seen with those having the highest amounts of calcification.<sup>3</sup> The overall results suggest aggressive lowering of blood sugar for individuals with new or recently diagnosed diabetes or in patients with more established diabetes without advanced CVD may provide benefit, but this is regarded as speculative. However, there remains the problem found in ACCORD of enhanced mortality due to very aggressive intervention and the reason remains unknown. The other studies, which involved less aggressive therapy, did not see this effect.

In the October 27, 2008 issue of the *Archives of Internal Medicine* a meta-analysis of the cardiovascular outcomes of oral diabetes medications appeared which did not include the above studies.<sup>4</sup> Forty studies were included and there was a wide variation in baseline HbA1c levels. Only treatment with metformin was associated with benefit, and this was restricted to cardiovascular mortality where a risk reduction of 26% was found in comparison to a placebo or other diabetes medications. No significant benefit was found for cardiovascular morbidity and all-cause mortality for any drug. Also, only two of the studies included cardiovascular outcomes as defined endpoints. The authors comment that when it comes to choosing the safest oral agents, the quality of the data are problematic. As an editorialist pointed out, some exclusions used in the meta analysis including the use of insulin appeared arbitrary and the one positive result was heavily influenced by only one study.<sup>5</sup> Thus this meta-analysis does not seem to significantly change the picture presented by the three trials reviewed above.

In a commentary just published, Goodarzi and Psaty raise a critical point regarding the three most recent trials.<sup>6</sup> They point out that the focus was exclusively on glycemia without regard for insulin levels in spite of considerable evidence that insulin may play a direct role in vascular health. Some of the antidiabetic glucose lowering drugs used in these trials lowered and some raised insulin levels.

The authors point to a 1998 study (UKPDS) that found metformin treatment in overweight patients decreased heart attacks and strokes when the comparison was with conventional therapy. In addition, all-cause mortality, total diabetes endpoints and stroke were reduced when metformin was compared to insulin alone or sulfonylureas, another glucose lowering drug. But of these therapies, only metformin lowers insulin levels as well as glucose levels whereas the others increase insulin levels. They suggest that future studies should focus on aggressive control of insulin levels or insulin resistance rather than only on aggressive control of glucose levels. In the intensive glucose lowering studies reviewed above, no attention was paid to insulin levels and insulin was used as needed to assist in achieving the HbA1c targets.

A breath of fresh air was introduced into this matter by a commentary published shortly after the ACCORD study was terminated.<sup>7</sup> Westman and Vernon asked, "Has carbohydrate-restriction been forgotten as a treatment for diabetes mellitus?" They point out that before medications were available for the treatment of diabetes, experts recommended dietary carbohydrate restriction. In the 1923 edition of the famous textbook of medicine by Osler and McCrae the recommendation for diabetics was a distribution of energy intake corresponding to 75% fat, 17% protein, 6% alcohol and 2% carbohydrate. The recommended energy intake was about 1800 calories per day. In fact, historically, low carbohydrate diets have also been almost universally recommended for the treatment of obesity, starting well before 1900, and it was recognized very early that refined grains and sugar were contraindicated if weight loss was the goal. This remained the standard of practice until the advent of the "fat is bad" movement about 30 years ago.

Westman and Vernon cite a small study they and collaborators published in 2003 which illustrates the importance of the question they pose in the context of diabetic glucose control.<sup>8</sup> The subjects were diabetic (mean HbA1c, 10.0% which was very high and suggests poor control), overweight (mean weight, 270 lbs) and had the high triglyceride/HDL ratio characteristic of the dyslipidemia associated with the metabolic syndrome (mean 8.0). The dietary intervention was based on meat, chicken, turkey, other fowl, fish, shellfish, hard cheese, eggs, salads, and low-carbohydrate vegetables. Initially the carbohydrate allotment was 20 g per day with the goal of achieving ketosis. Once this was achieved, an additional 5 g of daily carbohydrate

was added each week until ketosis disappeared. This final carbohydrate intake level became the basis of the daily maintenance diet. Oral hypoglycemic drugs were discontinued at the start of the diet. Patients taking less than 10 units of insulin per day were taken off insulin and for those taking more, the dose was reduced at the start of the diet and used only as needed. The median follow-up was 8 months.

The results were highly satisfactory. HbA1c dropped 41% to a mean of 5.9% a value considered by many as close to normal. Recall the ADA target for diabetics is 7%. Body weight decreased by approximately 10%. Triglycerides dropped by over 50%, HDL increased by 8% and the triglyceride/HDL ratio changed by 55% to 3.6, a value reflecting the absence of metabolic dyslipidemia. Total and LDL cholesterol also decreased, but not significantly. In short, this dietary intervention, coupled with insulin if needed but no other medication, produced a reduction in glycemia lower than that obtained by the three intervention trials discussed above. Furthermore, a critical marker of dyslipidemia in the context of diabetes and insulin resistance was dramatically reduced. For example, in ADVANCE, triglycerides dropped only 9% and HDL was unchanged. LDL was their focus point. Westman and Vernon point out that their results were consistent with a study of a medical outpatient population, which included diabetics, treated for obesity with a low-carbohydrate diet. In fact, this type of diet has since 2003 been repeatedly demonstrated to reduce weight and normalize blood lipids, blood glucose and insulin. Incidentally, some of the dramatic drops in HbA1c were not accompanied by significant weight loss. While the study of Vernon *et al* was small and could not address CVD endpoints, it nevertheless demonstrates that diet alone (along with insulin in some cases if necessary) has the potential for achieving and in fact significantly exceeding the major blood glucose goals of the three intensive drug intervention studies discussed above.

In addition, Westman and Vernon<sup>7</sup> comment that from their perspective of familiarity with carbohydrate restriction and diabetes, the results of the ACCORD trial were not surprising. They tend to agree with one hypothesis regarding the increased mortality in the most intensive protocol as being related to hypoglycemia. High carbohydrate diets are common in diabetes management, especially because of the belief that the low-fat diet is the gateway to health, and standard practice is for

intensive medication to “cover the carbohydrate.” But they point out that in their experience, it is very difficult to achieve glycemic control without hypoglycemic reactions using this approach and when hypoglycemia is severe, it is associated with increased morbidity and mortality.

Finally, in April of this year, a group of researchers in the fields of diabetes, nutrition and blood lipids, including Westman and Vernon, published a paper suggesting it is time for a critical appraisal of dietary carbohydrate restriction for the treatment of Type 2 diabetes and the metabolic syndrome.<sup>9</sup> They make 5 points:

- Carbohydrate restriction improves the control of glycemia, the primary target of nutritional therapy, and reduces fluctuations in insulin.
- Carbohydrate-restricted diets are at least as effective as low-fat diets for weight loss.
- Substitution of fat for carbohydrate generally has a beneficial impact on markers for and incidence of CVD.
- Carbohydrate restriction improves the features of the metabolic syndrome
- Weight loss is not required for the benefits of carbohydrate restriction to be observed.

The authors point out that the current nutritional approach to treating Type 2 diabetes generally relies on dietary fat reduction which achieves only limited success and leads to the use of pharmacology. Carbohydrate restriction is both a

historical and intuitive approach to this problem and may provide a superior strategy.

This almost seems to be an understatement. If one can solve the problem of hyperglycemia and the associated hyperinsulinemia in diabetics purely by dietary measures, and if there is reason to believe that the associated insulin resistance may be partly or wholly reversible in Type 2 diabetics, then this would seem to be a very attractive approach which is based only on a natural therapy—food selection. The pain of carbohydrate deprivation is eased by the joy of eating a high fat and protein diet with no worry about its impact on the risk of heart disease, and while there may be problems such as constipation or even bad breath, the positive aspects are very appealing and the negative aspects pale in comparison to the inconvenience of foot amputation or a stroke.

The heavy use of glucose modifying drugs in the studies described above illustrates the modern approach to treatment. Not only does this simplify matters for the physician, but it also provides the ultimate in simplicity for the patient—just take the pills. It is unfortunate if this reflects reality in that lifestyle and behavioural modifications are difficult to implement and maintain and humans really like their “bad” carbohydrates. But for those who have what it takes to adopt the historical approach of exercise plus carbohydrate restriction and selection, the rewards seem very high indeed.

## WEIGHT LOSS AND REMISSION OF TYPE 2 DIABETES

In their most recent guideline on the management of diabetes, the American Diabetes Association (ADA) devotes the first section to lifestyle interventions and take what is perhaps a realistic position—it does not work for most and after an unsuccessful attempt generally characterized by the patient regaining some or all of the small amount of weight lost, drug intervention becomes the obvious next step. This is of course a complex issue since the reasons for the failure to achieve continuous weight loss and achieve a really beneficial target can have many explanations. Included are the use of the wrong diet, failure to adhere to a diet that might otherwise have produced results, or in some cases metabolic resistance to weight loss caused by interference by medications, thyroid dysfunction, total inactivity, etc. But it is now clear that a large and significant weight

loss can actually eliminate Type 2 diabetes. This is a difficult area to study since individuals with diabetes who are obese and are able to revert to a normal weight or simply being somewhat overweight are rare. One place to look for them is where a lot of bariatric surgery is done. This surgery is a predominantly restrictive procedure that reduces the stomach size but is not free of both morbidity and mortality, although these are relatively infrequent. A recent study from Australia examined the impact of this type of surgery on diabetics.<sup>10</sup>

Thirty recently diagnosed (< 2 years) diabetics with BMI between 30 and 40 who underwent laparoscopic adjustable gastric banding were compared with 30 diabetics who tried weight loss by lifestyle and diet changes. Of 60 patients enrolled,

55 completed the 2-year follow-up. In the surgical group 73% achieved remission as defined by fasting blood glucose of < 126 mg/dL (7.0 mmol/L) and a glycated haemoglobin of < 6.2% while taking no glycemic medications. In the lifestyle group, 13% achieved remission. In the surgical group the mean weight loss was 21.1 kg (46.4 lbs) whereas in the lifestyle group it was 1.5 kg (3.3 lbs). There were large and significant changes in waist circumference in the surgery group and as well, triglycerides dropped 71.7 mg/dL with a resultant value of 118.9 mg/dL which when taken together with the increase of 12.6 mg/dL in HDL, indicated the complete resolution of the dyslipidemia associated with the metabolic syndrome. The triglyceride and HDL changes in the lifestyle group were small and relatively insignificant. While surgery is of course only appropriate for a very limited group of patients, these results illustrate the impact of weight loss on diabetes and the metabolic syndrome.

The laparoscopic banding study is interesting in connection with the suggestion of Goodardi and Psaty regarding the potential role of hyperinsulinemia in the aggressive glucose control studies described at the start of this newsletter. For the surgery group, fasting insulin dropped from 19.7 to 9.8 micro units/mL whereas in the controls it increased from 18.7 to 24.1 micro units/mL. HbA1C dropped from 7.8% to 6% in the surgical group. These results suggest that significant weight loss, in this case induced by gastric banding provided both a decrease in fasting insulin and average glucose and diabetes remission. It would seem likely that these changes might be accompanied by a reduced risk of CVD, especially since there was a dramatic improvement in triglycerides, HDL and a standard measure of insulin resistance.

In the study discussed above by Vernon *et al*, subjects lost on average about 12 kg (27 lbs) and also experienced dramatic changes in markers for

diabetes and in the blood lipid picture, and this was of course without surgery—just rather severe carbohydrate restriction and very careful carbohydrate selection.

Thus it is possible with significant weight loss to reverse Type 2 diabetes and at the same time normalize what initially was a highly atherogenic blood lipid picture of high triglycerides and low HDL, a situation that is generally accompanied by a preponderance of small, dense LDL particles viewed by some as the only dangerous LDL. Also, the weight-loss approach has the potential of a permanent cure for diabetes whereas the drug treatment presumably does not. The problem is that study after study finds that the average individual cannot accomplish and then maintain a weight loss significant in the context of reversing or curing Type 2 diabetes. This is really good news for the pharmaceutical industry. However, there is no doubt considerable variation in the weight loss required in order that an overweight individual can move from the diabetic to the prediabetic state. The risk of microvascular damage due to hyperglycemia appears to become low when the HbA1c drops below 7% and the above studies suggest that this will occur with less weight loss than achieved in the studies described. The same can be said for fasting glucose where even a value of about 110 mg/dL (6.1 mmol/L) would be a very good result of a weight loss program for someone with diabetes. Realistic targets for HbA1c and fasting glucose may provide some with sufficient incentive to implement and adhere to carbohydrate and calorie restricted diets, exercise, and follow their progress with as glucose meter and periodic HbA1c assays rather than a scale. These two measures of glucose metabolism, while not providing a complete picture, nevertheless are more meaningful than pounds or kg lost. The Research Review which appears in this issue expands considerably on this and related subjects.

## **EATING FAST AND EATING UNTIL FULL—NOT ADVISABLE!**

Some would point out the French knew this all along. Now a study from Japan has provided numbers to back it up.<sup>11</sup> This was a so-called cross-sectional study which provides a snapshot of a current state of affairs. Approximately 1500 men and 2600 women were studied with measurements of weight, height and a determination of eating habits via a questionnaire. The self-reporting revealed that for men, 51% ate until full and 46%

ate rapidly. For the women, the comparable numbers were 58% and 36%. After correcting for confounding factors, eating until full increased the risk of being overweight by a factor of 2 for men and 1.53 for women. For eating quickly, men had an increased risk of being overweight of 1.84 whereas for women it was 2.09. If one ate until full and did it rapidly, the odds of being overweight were 3.13 for men and 3.21 for women. Interestingly, adjustment

for energy intake did not change these results, even though the speed of eating was correlated with total caloric intake. These results are of interest because it is well known that in the Western culture, both of these lifestyle habits are common, partly because meals are squeezed in between other activities regarded as more important such as work, recreation and dealing with issues related to child care and transportation. Also they are consistent

with the known time lag between starting to eat and the brain telling the individual that he or she has not had enough to eat. One needs to reflect on the traditional noon or evening meal in some European cultures where considerable thought goes into what is served and where the meal is savoured over an hour or more along with a bit of wine and a lot of friendly if not animated conversation. Unfortunately, there is evidence that this is changing.

## DIETARY PATTERNS AND HEART ATTACK RISK IN 52 COUNTRIES

This investigation<sup>12</sup> was part of the large INTERHEART case-control study conducted in 52 countries. The goal was to create a simple diet score that can indicate in a clinic, to a family doctor or to the individuals themselves, whether they are eating a 'heart healthy' diet. Food factor analysis, which has been used in other studies discussed periodically in this Newsletter and its Research Reviews, was used to identify three patterns which were called Oriental, Western and prudent. Oriental had a high loading of eggs, tofu and soy and other sauces and pickled food. The Western pattern was characterized by high intake of eggs, fried food, sugar, deserts, salty snacks, nuts and meat. The prudent pattern favored fruits, dairy products, nuts, raw vegetables, green leafy vegetables and deserts. After adjusting for known risk factors, it was found that those who consumed the prudent diet had a

30% lower risk of heart attack compared with people who ate little or no fruits and vegetables whereas those who ate a Western diet had a 35% greater risk of a heart attack compared to those who ate little meat or fried foods. The Oriental diet showed no relationship with heart attack risk. It was suggested that the protective aspects of the Oriental diet such as tofu were cancelled out by the unfavourable effects of the high salt content of soy sauces, creating a null result. One of the researchers was quoted by *theheart.org*, an online information service for the cardiology community (October 21), as saying, "when I think of my own training—which was fairly recent—there was very little information on nutrition or dietary advice. So you come out as a specialist who can treat a patient with a heart attack, but when it comes to prevention, there is not much training."<sup>13</sup>

## STATINS—THE GOOD NEWS

An interesting study was reported at the European Society of Cardiology Congress 2008. The study was called DECREASE III and the principal investigator was Dr. D. Poldermans of the Erasmus Medical Center, Rotterdam. The issue was the effect of high dose statin treatment on the fatal and non-fatal heart attacks and acute ischemia during or immediately after vascular surgery. While surgical procedures overall are associated with cardiovascular death of about 0.3%, vascular surgery carries a much larger mortality of around 2% and much of this is due to heart attacks during surgery. The researchers believe that at least half of these fatalities are due to coronary plaque rupture. They hypothesized that statins, being an anti-inflammatory, might stabilize coronary plaques and prevent these events. Patients who had never taken statins were enrolled and randomized to a statin or placebo for on average about a month prior to surgery and for 30 days after. Statistically significant

risk reductions of about 50% were found for ischemia (number needed to treat to prevent one event was 13) and cardiovascular death or non-fatal heart attack (the number needed to treat was 19). No adverse side effects were observed. The researchers believe that these very short-term beneficial results were due to non-cholesterol lowering effects of statins.

These results are interesting for two reasons. First, readers about to undergo vascular surgery should consider discussing this study with their surgeon. Second, these results emphasize what is becoming more obvious every day, i.e. statins have important physiological effects that have nothing to do with cholesterol lowering. In the above study, only the most diehard believer would ascribe the short-term results to lower cholesterol. Furthermore, there is no reason in general to believe that these so-called pleiotropic effects are only short-term. In fact, it

appears that nobody really knows how much of the benefit derived from statin therapy in secondary prevention is due to cholesterol lowering and how much is due to these pleiotropic effects. Just because a greater benefit is derived from a larger

dose, which produces a greater LDL lowering, does not prove that the greater LDL lowering was responsible, since the pleiotropic effects would also be expected to exhibit a dose dependence.

## STATINS—MIXED GOOD AND BAD NEWS

In the Research Review titled *Cholesterol, A Review* (Newsletter, February 2008) the SPARCL trial was discussed in the section on stroke. This was a secondary prevention trial of very high-risk patients who had experienced an ischemic or hemorrhagic stroke (bleeding stroke) or transient ischemic attack 1 to 6 months prior to enrolment and randomization to a high- dose statin or placebo. It was found that high-dose atorvastatin for over one year prevented 4.8 ischemic strokes but at the cost of 1.9 hemorrhagic strokes (strokes caused by bleeding rather than occlusion) per thousand treated. The investigators have just published a study of the hemorrhagic group designed to examine the risk factors present and the connection with LDL

levels.<sup>14</sup> It was found that hemorrhagic stroke was more frequent among those who had experienced a hemorrhagic stroke prior to enrolment. Elevated risk was associated with male gender and the risk increased with age. Those with serious hypertension at the last visit prior to the stroke were also at increased risk. There were no relationships between hemorrhage risk and LDL levels at entry or LDL levels during the study in treated patients and the risk of this type of stroke.

The bottom line appears to be that if one has had a hemorrhagic stroke, then the suggestion that statin therapy be employed to prevent a second stroke of either type should be viewed with great caution.

## STATINS FOR CHILDREN

The recent recommendation of the American Academy of Pediatrics that statins be given to children at high risk of developing cardiovascular disease as adults was met with a storm of protest, but this almost entirely came from the media and thus only indirectly from the medical establishment. This apparently caught the pediatrics community by surprise. Perhaps it never occurred to them that the proposal to treat developing children as young as 8 years of age with an enzyme inhibitor that impacted multiple pathways and the synthesis of numerous chemicals would be strongly criticized on the grounds that there were absolutely no long-term studies of either safety or efficacy. In fact, the proposal was essentially justified on the basis of an extrapolation from adult studies which were almost entirely directed at the problem of secondary prevention (which is irrelevant in this context) with primary prevention grossly underrepresented, and for the limited adult primary prevention data that exists, yielded large numbers needed to treat to prevent one adverse cardiovascular event. The media had no trouble finding qualified medical experts who hammered away at these and other aspects of the proposal.

A perspective by Ferranti and Ludwig just appeared in the *New England Journal of Medicine* that relates to this important subject.<sup>15</sup> They reiterate the basic facts used by the critics. Cholesterol plays a key role in maintaining cell membrane fluidity, thereby influencing fundamental cellular functions including trans-membrane signaling. Also, about 25% of the total body stores of cholesterol are in the brain. Cholesterol is an essential building block for all steroid hormones including cortisol, aldosterone, estrogen and testosterone. Finally, a disorder that causes severe decline in cholesterol biosynthesis causes devastating multi-organ failure. Also, not only do statins inhibit cholesterol synthesis in the liver, some classes of statin inhibit cholesterol synthesis in other tissues, including the brain. They point out that at 8 years of age, a child's brain and other organ systems are in a stage of dynamic growth and development and this raises concerns regarding long-term pharmacotherapy initiated at this age which may adversely affect the central nervous system, immune function, hormones, energy metabolism and other systems in unanticipated ways. They also introduce a broader question concerning what is next for children, beta-blockers and diuretics for hypertension, aspirin for coagulopathy, insulin sensitizers for the metabolic

syndrome, and ultimately, insulin for Type 2 diabetes. To quote "once this door has been opened, the pharmaceutical industry will happily walk through it." Finally, these concerns should motivate alternate solutions which involve diet and lifestyle, and of course this would require definitive action on the part of adults who are responsible for what the authors aptly term "the world in which children live."

One of the authors of the perspective, Dr. David Ludwig, professor of pediatrics at Harvard and director of the Optimum Weight For Life program at Children's Hospital in Boston, has coauthored a book on the problems of diet and obesity in children. This book was reviewed in the July/August 2008 Newsletter.

## COENZYME Q-10 AND CHRONIC HEART FAILURE

Chronic heart failure (CHF) is on the rise. The connection between CHF, coenzyme Q-10 (CoQ-10) and statins is discussed frequently outside of mainstream medicine since statins inhibit the synthetic pathway for the endogenous synthesis of this enzyme. A study has just been reported in the *Journal of the American College of Cardiology* which investigated the relationship between CoQ-10 and survival in patients with CHF.<sup>16</sup> It was found that plasma CoQ-10 was an independent predictor of mortality in a group of 236 patients admitted to hospital with CHF. When a cut-point of 0.73 micromol/L was used, the group above this plasma level had approximately a 65% 5-year survival whereas for those below this level, it was 40%. The authors comment that there had been previously reported an independent inverse association between plasma cholesterol and total mortality and that the myocardium in patients with heart failure is deficient in CoQ-10. The authors cite 12 clinical studies which suggest benefits from CoQ-10

supplementation. In a meta-analysis of 8 studies, it was found that CoQ-10 supplementation significantly improved stroke volume, ejection fraction, cardiac output, and two other indices of cardiac function. Another meta-analysis found improvements in ejection fraction and cardiac output. Some of these studies may underestimate the benefits of CoQ-10 supplementation in that there are considerable differences in bioavailability among various formulations of this enzyme. The authors also comment that a multicenter intervention trial of CoQ-10 as an adjunctive treatment for CHF is underway which is randomized and double blind. However, examination of the description of the trial fails to reveal the nature of the enzyme preparation, only the dose which is 300 mg. Since bioavailability can vary by a factor of 2 or 3, this may be an issue when it comes to interpreting the results, i.e. was the dose high enough?

## CORONARY CALCIUM SCORE AND FRAMINGHAM CORONARY RISK

Another study has reported which found essentially no correlation between the extent of coronary artery calcification and the Framingham risk factor score.<sup>17</sup> The study group involved over 1600 asymptomatic Koreans age  $51 \pm 8$  years and 89% male. While the authors claim a statistically significant correlation, the coefficient was 0.26 which to anyone in the physical sciences means essentially no correlation at all. The authors courageously present a scatter plot where the calcium score is on a common log scale that actually compressed the scatter. Aside from a few outliers, it has the appearance of a shotgun pattern. The range of calcium score was zero to about 1000 and most of the subjects fell in the Framingham score range of 2 to 20% for the 10-

year absolute risk of coronary artery disease. When the correlation with individual risk factors was examined, the major contributors to the calcium score were age, systolic blood pressure, smoking, fasting glucose and HbA1c. LDL cholesterol had one of the lowest correlation coefficients observed. It was also observed that there was a strong positive relationship between age and the mismatch of Framingham and the calcium score. The authors conclude that calcium scoring may be clinically more useful in older individuals and/or individuals with the metabolic syndrome because of what they term a higher probability of obtaining additional information that the conventional Framingham score cannot provide.



## VITAMIN D AND RISK OF PREMENOPAUSAL BREAST CANCER

A German study just published in the *International Journal of Cancer* appears to be the first to use serum 25-hydroxyvitamin D (25-(OH)D) in a study of breast cancer risk in premenopausal women.<sup>18</sup> For premenopausal risk, earlier studies assessed dietary intake only, and food, even with a simple multivitamin, is a notoriously poor source of this essential vitamin. In this case-control study, the age range was 30 to 49 with the majority of subjects between 40 and 49 years. Extensive data was collected to allow adjustment for confounding by all the recognized risk factors. It was found that the risk of diagnosed breast cancer was reduced by 41% for women with plasma 25-(OH)D levels between 45 and 60 nmol/L and 55% when the level was  $\geq$  60 nmol/L. The reference was  $<$  30 nmol/L and while there was a 32% risk reduction between 30 and 45 nmol/L, this result did not achieve statistical significance. However, the trend over the entire 25-(OH)D range was highly significant. Some evidence

of a threshold was seen at 50 nmol/L. The association was stronger for women diagnosed with progesterone receptor negative tumors.

Considerable evidence suggests that 25-(OH)D levels  $>$  75 nmol/L are required for optimal health. In addition, vitamin D deficiency is widespread even at latitudes where there is sunlight-induced synthesis during the winter months. Thus appropriate supplement doses and safe upper limits of vitamin D3 constitute an important question. In a recent paper by Aloia *et al* in the *American Journal of Clinical Nutrition*,<sup>19</sup> it was concluded that a dose of 3800 IU/day was appropriate for individuals above a threshold serum level of 55 nmol/L and 5000 IU/day for those below that threshold. These intakes of supplemental D3 provided 25-(OH)D serum levels in the range of 75-220 nmol/L. The authors cite a number of studies which indicated that these are safe levels of intake and serum levels.

## VITAMIN D AND DEPRESSION IN OVERWEIGHT AND OBESE INDIVIDUALS

In clinical studies, low serum levels of 25-hydroxyvitamin D (25-(OH)D), which is the storage form of vitamin D in the body, have been associated with reduced anxiety, depression and reduced cognitive function. Vitamin D has been implicated with what is called seasonal affective disorder, a condition characterized by depression-like symptoms during the winter months. In addition, there is an association between obesity and depression. A study has just been published that investigated the connection between vitamin D levels and depression in obese subjects.<sup>20</sup> The study group consisted of 159 males and 282 females with an age range of 20 to 70 years. At the start of the study, they were given a standard test to evaluate the extent of depression. They were then randomized into three groups - one received two capsules (20,000 IU each) of vitamin D3 per week, the second group one capsule of D3 and one of a placebo, and finally the third group received two placebos. Subjects with 25-(OH)D levels  $<$  40 nmol/L at baseline exhibited significantly higher levels of depression than those with levels  $\geq$  40 nmol/L. After one year, in the both vitamin D groups but not in the placebo group there was a significant improvement in depression scores. No

hypocalcaemia was observed. In the group receiving 40,000 IU/week, mean 25-(OH)D levels went from 55 to 112 nmol/L whereas for the group receiving 20,000 IU/week, the change was from 52 to 88 nmol/L. These large doses are not a misprint! The placebo group started at 52 and ended at 50 nmol/L.

These results are interesting for two reasons. The supplementation with vitamin D appeared to ameliorate symptoms of depression in this obese cohort suggesting a possible causal relationship. In addition, what might appear to be huge doses, when given once a week, are not out of line with those discussed above when converted to daily doses. In addition, this dose protocol produced serum levels of 25-(OH)D that are considered safe.

Finally, individuals who sit in front of a bright light for a short period each day during the winter to improve their mood and outlook might want to consider also taking sufficient vitamin D3 to bring their levels above 75 nmol/L. The lights employed for this purpose, while no doubt useful, are not UV sources and have no impact on vitamin D status.

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# REVIEW

## HOW DO YOU KNOW IF YOU HAVE DIABETES OR PRE-DIABETES?

William R. Ware, Ph.D.

### INTRODUCTION

The above is an important question given the current epidemic of adult-onset diabetes. The short answer is—ask your doctor who will order a test. However, as we shall see, it is far from that simple. Another short answer is that it simply a matter of a definition, and that there are more than one.

Diabetes is a metabolic disease characterized by abnormally elevated levels of blood glucose (hyperglycemia) resulting from defects in insulin secretion, insulin action or both. Chronic hyperglycaemia of diabetes is associated with the dysfunction, long-term damage and failure of various organs and systems, especially the kidneys, eyes, nerves, heart and blood vessels. These long-term complications include retinopathy with potential loss of vision, nephropathy leading to kidney failure, peripheral neuropathy with risk of foot ulcers, amputations, and neuropathy of the autonomic nervous system resulting in gastrointestinal, genitourinary and cardiovascular symptoms and sexual dysfunction. Thus diagnosing diabetes or pre-diabetes and then attempting to reverse the associated hyperglycemia or at least minimize the micro- and macrovascular damage is an important and significant challenge with profound public health implications.

The vast majority of cases of diabetics are so-called Type 2, which historically was termed adult-onset diabetes and is caused by a combination of resistance to the action of insulin and an inadequate compensatory insulin secretory response. Type 1 diabetes, on the other hand, is caused by an absolute deficiency of insulin secretion, frequently occurs at a young age and generally requires life-long insulin injections. In Type 2 diabetes the degree of hyperglycemia sufficient to cause pathologic and functional changes in target tissues may be present for long periods of time before diabetes is detected, although observable abnormalities in carbohydrate (glucose) metabolism are present. Thus in order to prevent vascular problems, it is very desirable to detect not only the presence of diabetes but to identify and treat the pre-diabetic state. This review is concerned with Type 2 diabetes.

It is estimated that 30% of individuals with diabetes are undiagnosed and of these, 25% already have microvascular complications at diagnosis, suggesting the disease had pre-existed for more than 5 years. One commonly used criterion for the presence of diabetes is elevated fasting glucose. However, it has been found that for the vast majority of patients, only a non-fasting glucose is measured—the so-called random or casual value. One study found only 3% of screening for diabetes was done with fasting plasma glucose.<sup>1</sup> This is surprising since measuring cholesterol requires fasting, and practically everyone seems to know their cholesterol status. The random glucose approach is a matter of convenience, but the result is strongly dependent on when the sample is drawn relative to the last meal and as well as what was eaten. There is no agreement on what random glucose value should lead to further investigation into the question of the presence or absence of diabetes or pre-diabetes, and the non-fasting glucose level used in the diagnostic guidelines is supported by very little evidence.

The progression to diabetes is characterized by a continuum of changing characteristics of glucose metabolism which are reflected in both fasting glucose and the magnitude and time evolution of the blood glucose response to food intake. Thus fasting glucose is just one of the indicators of the state of glucose metabolism. Another traditional tool for observing abnormalities in glucose metabolism is the oral glucose tolerance test (OGTT) which measures the blood glucose level over time after drinking a solution of glucose to end a fast. The blood glucose level at 2 hours is diagnostic for both diabetes and insulin resistance. For the diagnosis of diabetes, the approach has been to select glucose levels that reflect thresholds for microvascular-associated complications of hyperglycemia. Thresholds in this context are quite fuzzy and thus diabetes diagnostic criteria or evidence of impaired glucose metabolism are somewhat arbitrary. The tendency appears to be to err on the conservative

side given that undiagnosed diabetes presents serious health risks which may justify tolerating a certain level of false positive results.

## GUIDELINES FOR THE DIAGNOSIS OF TYPE 2 DIABETES

The most recent (2008) guidelines from the American Diabetes Association (ADA)<sup>2</sup> and the World Health Organization (WHO, 2003)<sup>3</sup> are almost identical. Traditionally, the OGTT was the “gold standard” for diagnosing diabetes. Now there is a choice, i.e. two “gold standards! In what follows the units for blood glucose used will be mg/dL and the alternative unit used in Europe and Canada, the mmol/L, will be given in parentheses. The conversion factor is 18 mg/dL per 1 mmol/L.

- Fasting plasma glucose (FPG)  $\geq 126$  mg/dL (7.0) OR
- A plasma glucose level of  $\geq 200$  mg/dL (11.1) at 2 hours after ending fasting with a 75-gram oral glucose challenge, the OGTT.

The guidelines differ only in that the ADA also includes a casual or random plasma glucose level of  $\geq 200$  mg/dL (11.1) and clinical symptoms of hyperglycemia (elevated blood sugar), which cannot be quantitatively specified. Problems with the random glucose test have been discussed above. The usual practice is to confirm a positive diagnosis with a repeat of the same measurement on another day. Thus the situation is simple. There is essentially a choice of two methods, both requiring fasting. Aside from the requirement of fasting, one option is convenient, the other viewed as inconvenient for the patient (sit and wait for 2 hours or return after 2 hours to the office or diagnostic laboratory) and can even induce nausea and vomiting. Because the OGTT is no longer required by the guidelines for positive diagnosis of diabetes, in many practices it has all but disappeared. But it can still be found included in very comprehensive physical exams and as well is used by specialists. But since these two high profile organizations offer an unqualified choice, one might assume that the two tests would essentially identify the same populations, diabetics and non-diabetics. The concern is undiagnosed diabetics, and this implies that either choice in diagnostic approach will reveal who they are. Surprisingly, the data indicate that this is not true.

The results of a large study illustrate the problem.<sup>4</sup> Data were collected from 13 populations in eight European countries and comprised over 17,000 men and 8300 women, age range 17-92. The relevant comparison in the context of this review is the agreement of classification of patients using the two above criteria in a cohort of individuals without a diagnosis for diabetes. In what follows, the term *WHO criterion* will refer to the diagnosis by an OGTT with a 2-hour post challenge plasma glucose  $\geq 200$  mg/dL since this was the earlier WHO required criterion, whereas the *ADA criterion* will refer to a FPG  $\geq 126$  mg/dL, the new gold standard. A total of 1517 individuals had diabetes according to either the ADA or WHO criteria. But among the 904 who had diabetes according to the WHO criterion, 473 (52%) had a fasting plasma glucose of  $< 126$  mg/dL mg and thus according to the ADA criterion did not have diabetes. When the same comparison was made for the 1044 who had diabetes according to ADA criterion, 59% failed to qualify for a diagnosis of diabetes according to the WHO OGTT criterion. Thus out of the total of 1517 individuals diagnosed by one or the other or both criteria, there was concordance between the two only for 413 individuals (27%). Individuals below the age of 65 were more likely to be diagnosed on the basis of the ADA criterion, whereas the WHO criterion was more likely to diagnose diabetes in lean individual and the ADA criterion more likely identify those middle-aged and obese.

A smaller study published in 2003 reached essentially the same conclusion regarding the lack of concordance of the two criteria. Two hundred and twenty eight patients with a fasting glucose between 110 and 125 mg/dL, i.e. not diabetic according the ADA criterion, were given the OGTT. Using the WHO criterion, 33.6% had diabetes.<sup>5</sup> Other studies have found a similar disparity between using the OGTT as compared to FPG.<sup>6</sup>

Fasting glucose also varies from day to day by 12-15% and the laboratory variability is 4%. Using a variability of 15%, a value just below the diabetes diagnostic threshold of 125 could in fact be 144 or 109 mg/dL. There is another problem with the use of fasting plasma glucose as a single criterion for the diagnosis of diabetes. It turns out that the fasting glucose level varies systematically during the day. Individuals with an afternoon appointment who have been instructed to fast starting the night before will on average have a lower fasting glucose level than those with a morning appointment. One study found that the among those tested in the afternoon, difference was such that half of all cases of undiagnosed disease would be missed.<sup>7</sup>

It appears that while both the WHO and ADA criteria are equivalent in predicting microvascular diseases such as retinopathy, the OGTT is better at identifying those individuals with increased risk of cardiovascular disease associated with hyperglycemia.<sup>6</sup> However, it appears that both must be used to avoid missing a substantial number of individuals who should be tagged “diabetic.” Of course, if an OGTT were carried out, a FPG would normally be obtained just before the glucose challenge. Such an approach would considerably increase the number diagnosed, would require the unpopular 2-hour OGTT and presumably because of issues of “convenience” would not be acceptable today for screening except perhaps in the case of high-risk patients (or executives). Thus the failure to diagnose all diabetes cases seems to have been built into the system. An alternative approach which has been suggested involves a marker of blood glucose averaged over several months, glycated haemoglobin called HbA1c.

## GLYCATED HAEMOGLOBIN (HbA1c) AND THE DIAGNOSIS OF DIABETES

Another way of assessing hyperglycemia is to examine the long-time blood glucose average provided by what is called *glycated haemoglobin*, which is short for haemoglobin that has reacted with glucose. It is expressed as a percentage of total haemoglobin. Because the reaction of glucose with haemoglobin (glycation) occurs over the entire lifespan of the red blood cells (2-3 months), it provides a long-term measure of the average glucose level. An important feature of this haemoglobin fraction is that fasting is not required for a meaningful determination. Also, testing for HbA1c is already well established and routinely done in connection with monitoring glycemic control among diabetics. Given that HbA1c is in a sense a built-in glucose monitor that can be read with a blood test, it is not surprising that the level of this haemoglobin fraction can be used to identify individuals with diabetes or those at increased risk, and that there is growing interest in this application. What is surprising is that the latest American Diabetes Association (ADA) guidelines still recommend against using this marker.<sup>2</sup>

The evidence that HbA1c correlates with the average glucose level is quite strong. To examine the extent of the correlation, it is necessary to establish average blood glucose levels. During the day, the level varies due to post-meal elevations which then decline toward pre-meal values with rates that depend on the presence or absence of diabetes or pre-diabetes. During the night, the levels are typically low and for diabetics frequently increase in the early morning. Thus the ideal approach is interstitial continuous monitoring. In a recent study of a group of individuals which ranged from normal to diabetic, Nathan *et al*<sup>8</sup> used this continuous monitoring coupled with calibration from eight finger-stick measurements during the day and night. Glucose measurements were automatically made every 5 minutes for at least 2 days at baseline and this was repeated every 4 weeks during the next 12 weeks. In addition, finger stick measurements without the 3:00 A.M. measurement were used for at least 3 days per week when the continuous monitor was not being used. The average glucose level was calculated for each individual from approximately 2700 values collected over 3 months. A linear relationship was observed ( $AvPG = 28.7 \times A1c - 46.7$  mg/dL) with excellent correlation (a correlation coefficient of 0.84). An HbA1c value of 5% corresponded to an average glucose level of 97, 6% to 126, 7% to 154 and 8% to 183 mg/dL. Other studies also found linear relationships,<sup>9,10</sup> but the values found by Nathan *et al* are somewhat lower. The authors regard this as due to the use of continuous monitoring which provided more measurements during the night. These studies appear to quantitatively validate the belief that HbA1c is a reliable measure of average blood glucose levels over several months.

The next issue involves the ability of HbA1c to identify individuals with diabetes. From what was discussed above it is evident that there immediately arises the problem of a diagnostic reference or benchmark. There is no single gold standard for the diagnosis of diabetes. Thus some studies use the traditional WHO OGTT threshold and some use the fasting plasma glucose (FPG) cut-off of  $\geq 126$  mg/dL. Involved are issues of screening, and thus the *sensitivity* and *specificity*. Sensitivity is the percentage of tested individuals at or above a cut-off point who have diabetes. Specificity is the percentage of tested individuals below the cut-off point who do not have diabetes.

Since the latest guidelines essentially make fasting plasma glucose (FPG)  $\geq 126$  mg/dL the criterion for a diagnosis of diabetes, it is of interest to examine head-to-head comparisons of FPG and HbA1c where the old gold standard, the OGTT, is used as a reference. In a paper published in 2007, Bennett *et al*<sup>11</sup> reviewed a number of studies in order to examine this question. HbA1c and FPG were similar in their ability to identify diabetics. They found that an optimum cut-off point for HbA1c was  $> 6.1\%$  which gave a sensitivity of 78-81%, i.e. the percentage of individuals with diabetes who were correctly identified based on the OGTT standard. It

should be recalled that when FPG was compared to OGTT in the studies described above, FPG failed to identify approximately 50% of those diagnosed using the OGTT as a reference. The authors also point out that HbA1c exhibits less intra-individual variations and better predicts both micro- and macrovascular complications.

Recent studies have used the FPG cut-off as a reference and examined the predictive power of HbA1c. Ginde *et al*<sup>12</sup> examined 6700 individuals undiagnosed for diabetes and representative of the U.S. population for whom HbA1c and FPG were known. FPG  $\geq$  126 mg/dL was taken as diagnostic for diabetes. If a positive diagnostic threshold for HbA1c of  $\geq$  6.1% was selected, they found that 68% of those with diabetes (sensitivity) and 98% of those without the disease (specificity) were correctly identified. Thus they take the position that this threshold is not a satisfactory stand-alone criterion for a definitive diagnosis of diabetes but rather identifies those requiring confirmatory testing. However, using a cut-off point of  $\leq$  5.4%, gave the false negative rate of  $<$  1% and identified patients who could be reliably excluded from the diagnosis of diabetes and additional tests. The range of 5.5% to 6.0% represented a grey area where it was found that HbA1c may exclude diabetics in moderate but not high-risk groups. Risk was determined by age, gender, race, hypertension, waist circumference, triglycerides and HDL cholesterol, i.e. components of the metabolic syndrome. Ginde *et al* point out that their cut-off of 6.1% was consistent with results from other studies.

Buell *et al*<sup>13</sup> also used the FPG  $\geq$  126 mg/dL as the standard for diagnosis of diabetes. They suggest that if used alone, an HbA1c of  $\leq$  6% could be considered normal, 6.1% to 6.9% pre-diabetic, and  $\geq$  7% diabetic. As an alternative, a value of  $\geq$  5.8% should trigger measuring FPG or conducting an OGTT. They note, as have others that diabetic complications did not develop or progress in most Type 1 or Type 2 diabetics when the HbA1c was  $<$  7%.

Recently Saudek *et al*, a group of six independent experts from the U.S., provided an up-to-date examination of the issues associated with using HbA1C for screening and diagnosis of diabetes. They point out that HbA1c does not require fasting, better reflects longer term glycemia than does plasma glucose, can be assayed with well standardized and reliable laboratory methods, and that non-glycemic factors that might interfere are rare. Based on an examination of the literature, they suggest that a HbA1C level  $>$  6.0% should prompt further testing and follow-up, that a level of 6.5% to 6.9% or greater, confirmed by a fasting glucose or OGTT test, should establish the diagnosis of diabetes, and that a level  $>$  7% if confirmed by just a second HbA1c test should also establish the diagnosis.<sup>14</sup> It is interesting in connection with the 7% cut-off that data from Peters *et al*<sup>15</sup> indicated that HbA1c  $\geq$ 7% identified 99.6 % of patients with diabetes according to the OGTT standard.

It can be argued that the cut-off of 6% for the boundary between normal and abnormal or for having cause for concern may be somewhat high since apparently only a cut-off closer to 5.4% indicates a very low probability of having diabetes.

Saudek *et al*<sup>14</sup> also examine the ability of HbA1c to predict the future development of diabetes. Studies that address this issue all suffer from the fact that there are two different "gold standards" for classifying individuals as having diabetes and the agreement is modest. Nevertheless, Saudek *et al* cite studies that found (a) baseline HbA1c and body mass index were the only significant predictors of new onset diabetes with HbA1c the stronger; (b) FPG-defined future diabetes risk increased exponentially with baseline HbA1c; and (c) in a Japanese cohort, a baseline HbA1c  $\geq$  5.8, regardless of the FPG, carried a 10-fold increase in the risk of diagnosed diabetes over 7 years. This last result also underscores the likelihood that a cut-off for concern, additional testing and intervention in the region of 5.5% or at least somewhat less than 6% might be a good choice.

What appears to emerge from the above studies is that the three tests in question are all far from perfect and that the ability of diagnosing diabetes is improved by using a second but different test to avoid missing cases or to provide confirmation. The old approach used the OGTT a single gold standard and it was indicated if FPG suggested the risk of diabetes. Since HbA1c is a much more convenient option than the OGTT, the combination of FPG and HbA1c appears to be attractive, especially with HbA1c as the initial screening test using the protocol suggested by Saudek *et al*. But for HbA1c levels above 7%, Saudek *et al* return to the single test, if confirmed, as an adequate diagnostic for diabetes. Accepting the proposal of Saudek *et al*, however, goes against the current guidelines, although requests from a patient to include HbA1c in routine blood work should not be met with much resistance, given that the test is very commonly used to monitor glycemic control in diabetics.

It is worth reiterating that a weakness in all of these studies is having two diagnostic “gold standards” for diabetes and they not only identify somewhat different groups within a population but also even differ in which aspect of diabetic pathology they monitor. It is also clear that the current guidelines, when they yield a diagnosis of diabetes based on only one test, even if confirmed by the same test, are merely indicating that a certain definition of the disease has been satisfied, with a not insignificant probability that a different test based on a different definition might be negative. But then, given the continuous progression from normal to abnormal glucose metabolism reflected in either impaired fasting glucose or impaired glucose tolerance or both (see below), picking a point in this progression where a label of diabetes is attached is somewhat arbitrary anyway. However, the single test approach may be harmful in that it implies a definite yes or no diagnosis exists, and when it is “no” the presence of dysfunctional glucose metabolism that is almost as dangerous as diabetes may be ignored and the opportunity for highly beneficial interventions missed. However, while the above discussion suggests that there are inconsistencies and an arbitrariness in the diagnostic protocols, the other side of the coin is that criteria based on either FPG, OGTT or HbA1c, when diabetes is indicated, are with a high degree of certainty indicating an enhanced risk of microvascular associated disease which must be addressed. What is worrisome is that even in the absence of a diagnosis of diabetes, insulin resistance should be a key concern, and the only definitive way to establish its presence is with the “inconvenient” OGTT. Those reluctant to order such a test should realize that the pathological results of insulin resistance are also “inconvenient.” This leads us to a discussion of pre-diabetes; the state one passes through on the way to diabetes.

## DIAGNOSIS OF PRE-DIABETES

According to the Centers For Disease Control, at least 25% of U.S. adults are known to have pre-diabetes but only 4% of these are actually currently diagnosed.<sup>16</sup> These numbers do not bode well for the future health of this population. Impaired fasting glucose and impaired glucose tolerance are the hallmarks of the pre-diabetic state. Either is sufficient to indicate pre-diabetes. The present guidelines define these two conditions as follows<sup>2,3</sup>

- Impaired Fasting Glucose (IFG). WHO: FPG 110 to 125 mg/dL (6.1-6.9). ADA: FPG 100 to 125 mg/dL (5.6-6.9). WHO adds 2-hr PG < 140 mg/dL (7.8) if the OGTT is done.
- Impaired glucose Tolerance (IGT). WHO and ADA: OGTT 2-hr plasma glucose  $\geq$  140 and < 200 mg/dL (7.8-11.1). WHO adds FPG < 126 mg/dL (7.0) as an additional condition.

The only significant difference between the WHO and the ADA is the lower limit for impaired fasting glucose. The ADA now defines normal fasting plasma glucose as < 100 mg/dL. However, WHO adds an upper limit to the 2-hour OGTT result to exclude IGT and thus identify *isolated* IFG. Identifying IGT requires an OGTT since IGT is related to the body's response to increased blood glucose, the normal source of which is food-derived carbohydrate. The WHO adds a FPG condition of < 126 mg/dL to their IGT criteria since exceeding this cut-off “diagnoses” diabetes which would imply IGT.

The 2008 ADA guidelines<sup>2</sup> treat IFG and IGT as equals in the context of pre-diabetes and do not take a position as to when an OGTT is desirable. But this position ignores the fact that the physiological basis of IFG and IGT are different. The normal control of fasting glucose depends on the ability to maintain adequate basal insulin secretion and appropriate levels of insulin sensitivity in the liver to control glucose output. The OGTT measures the response to absorption of a glucose load which involves both suppressing liver glucose output and enhancing glucose uptake in the muscles and liver. This requires a prompt increase in insulin secretion and adequate liver and muscle sensitivity to insulin. IGT is associated mostly with peripheral muscle insulin resistance, i.e. lack of insulin sensitivity.

If either 110 or 100 mg/dL for FPG is regarded as normal and >126 mg/dL is considered diagnostic for diabetes, then there is an intermediate state in between which is called IFG and which is viewed as a pre-diabetic state. However, as discussed above, this of necessity presents only a partial picture of an individual's glucose metabolism since it is based exclusively on the fasting state. An equally important if not more important problem in the context of pre-diabetes is how the body handles ingested glucose, mostly in the form of carbohydrate, and whether the resultant swings in post meal blood glucose are normal or abnormal. Independent of whether or not an individual falls in the IFG category, it would seem highly desirable to investigate the possibility of IGT, and the standard approach is and always has been the OGTT, as illustrated in the above guidelines. To determine how well a patient handles food-derived blood glucose, the only way outside of a research setting to obtain an

answer is to provide the patient in a fasting state with a glucose challenge and see what happens. The point is that some who have IFG will also have IGT, others will not, and some who have IGT will have IFG, others will not. Thus there is also the problem of identifying those with isolated IGT and if a normal FPG terminates any further investigation of glucose metabolism, isolated IGT will be missed. Given that IGT is a marker for the pre-diabetic state and that in the context of diabetes prevention, knowledge of its presence is important, it seems that avoiding the "inconvenient" OGTT if the FPG is normal is counter productive.

What is really at issue here is the question of the presence of insulin resistance and this is much more difficult to establish than IFG. Gerald Reaven, who some would call the father of the metabolic syndrome, has recently pointed out that "it is not clear that the use of IFG provides a particularly effective way to identify either the presence of insulin resistance or to predict CVD risk."<sup>17</sup> Reaven and coworkers studied a group of 490 men and women free of any disease and not taking any drug that influenced carbohydrate metabolism. All were subjected to an insulin resistance evaluation based on measuring insulin-mediated glucose disposal, a complex procedure suited only to the research setting. This allowed the classification of the group into tertiles, the lowest third representing insulin sensitive and the highest those classified as being strongly insulin resistant. Then the ADA criteria given above were applied to classify the individuals with regard to having normal glucose tolerance (NGT). Out of 404 classified as having NGT, 104 were in the insulin resistant tertile. Thus 26% of those who were the most insulin resistant were missed by the fasting glucose criterion and would not have been considered pre-diabetic even though their insulin resistance was high and carried an unfavourable prognosis.<sup>18</sup>

Another example is provided by a recent study.<sup>5</sup> Two hundred and twenty patients with a FPG between 110 and 125 mg/dL, i.e. IFG were evaluated by an OGTT. It was found that 32.8% had IGT, 33.6% also had Diabetes and only 33.6% had normal glucose tolerance. The missed diabetics in this study have been discussed above. The measurement of fasting glucose provided an incomplete picture of the glucose metabolism in this cohort.

Thus it is interesting to examine what role HbA1c might play in this context. This was investigated by Geverhiwot *et al*<sup>19</sup>. A group of 225 patients with FPG  $\leq$  108 mg/dL (6.0), which by earlier guidelines was normal, underwent an OGTT and an HbA1c measurement. Of these, 45 had IGT (20%) and 7 had diabetes (3%) by the WHO criteria. Subjects with abnormal glucose tolerance had higher HbA1C levels and a cut-off of 5.6% gave optimal sensitivity and specificity to predict a 2-hour glucose of  $>$  140 mg/dL (7.8), i.e. IGT. Note that a low FPG did not rule out IGT. While this was a small study, the result that 20% of those with a FPG  $<$  108 mg/dL had IGT suggests that if one really wants to know about the status of their carbohydrate and glucose metabolism, then even when the FPG is at the high end of normal (or just above it by the new ADA guidelines), obtaining a HbA1C value can provide additional valuable information and could justify an OGTT to get a definitive answer. Also, it calls into question the use of an HbA1c cut-off of 6.0 or 6.1% below which one need not have any concerns. Being concerned about pre-diabetes is just as important as being concerned about diabetes.

The diagnosis of the condition called the metabolic syndrome should also be a wake-up call even if the fasting glucose is below the cut-off ( $<$  100 mg/dL used as a factor in the diagnosis of this disorder). Other factors in the metabolic syndrome definition are strongly correlated with insulin resistance, which is in fact considered to be at the root of the adverse outcomes associated with this syndrome.<sup>20</sup>

## **HbA1c AND RISK OF CARDIOVASCULAR DISEASE AND OTHER COMPLICATIONS OF HYPERGLYCEMIA**

Epidemiologic studies have consistently demonstrated a positive association between HbA1c levels and cardiovascular disease in patients both with and without diabetes.<sup>21-26</sup> In fact, HbA1c levels appear to be an independent risk factor for CHD and CVD and also account for the failure of conventional risk factors to explain all of the enhanced risk associated with diabetes.<sup>22</sup> There are several proposed mechanisms which link hyperglycemia with adverse cardiovascular outcomes. These include inflammatory cytokines, endothelial dysfunction and hypercoagulability in the setting of platelet activation which initiates a cascade of events accelerated by hyperglycemia.<sup>22</sup>

In one of the largest prospective follow-up studies (the Epic-Norfolk study) 4662 men and 5570 women between the ages of 45 and 79 were assessed from 1995 to 1997 and followed until 2003. Most were non-diabetics. Persons with HbA1c  $<$  5% had the lowest rates of CVD and mortality. An increase of 1 percentage point was



associated with an increase in risk of death from any cause of 24% in men and 28% in women. These risk elevations were independent of age, body mass index, waist-to-hip ratio, systolic blood pressure, cholesterol levels, smoking and a history of CVD.<sup>25</sup> The Epic-Norfolk study also examined HbA1c levels and mortality in diabetics. It was found that glycated haemoglobin levels explained most of the excess mortality risk associated with diabetes in men and was a continuous, positive risk factor.<sup>27</sup>

The strong and consistent association between CVD and HbA1c levels indicates that concern over levels above around 5% and especially  $\geq 6\%$  should be motivated by the recognition that hyperglycemia is not only a risk factor for diabetes and its multiple microvascular complications, but also for CVD in general. This would seem to provide a strong argument for its routine measurement during physical examinations, even in the absence of risk factors for diabetes.

Hyperglycemia also appears to impact the risk and progression of several common cancers. In fact, the notion that “cancer loves sugar” is part of long-standing folklore. Positive associations have been found between FPG and liver cancer risk, and the incidence of non-Hodgkin’s lymphoma, colorectal cancer, bladder cancer, thyroid cancer, multiple myeloma and breast cancer after age 65.<sup>28</sup> Elevated HbA1C ( $>7.5\%$ ) has been identified as an independent predictor of clinically aggressive colorectal cancer in patients with Type 2 diabetes.<sup>29</sup>

## **DEALING WITH DEFECTIVE GLUCOSE METABOLISM**

Knowing that one has impaired fasting glucose, impaired glucose tolerance or an elevated HbA1c is of little use unless there are interventions that will normalize hyperglycemia. This is a problem that faces not only pre-diabetics but also diabetics. Type 1 diabetics attempt to control glucose levels with diet and insulin injections. Many Type 2 diabetics do not require insulin and are advised to exercise, lose weight, perhaps change certain dietary practices and even take prescription medicine designed to aid in glucose control. Pre-diabetics may be offered similar dietary and exercise advice or the problem may be simply be ignored by a medical culture that concentrates on “real diseases” which it treats mostly with pharmaceuticals. In fact, in a 2007 statement on IFG and IGT which carried the subtitle “Implications for care,” the ADA fails to mention dietary details or modifications at all and simply recommends exercise, weight loss or drugs (e.g. metformin), thereby ignoring considerable research regarding the dietary aspect of hyperglycemia.<sup>30</sup>

Dietary and lifestyle changes that may prove beneficial when glucose metabolism is defective have been discussed in a recent research review in this Newsletter (Part II, July-August, 2008). While that review was concerned with the reduction of the risk of coronary heart disease, the same principles and actions are applicable to the problems discussed in this review. The use of diet and exercise for the prevention of coronary heart disease applies equally well to the prevention of diabetes and insulin resistance and in fact, the review on coronary heart disease risk and its reduction deals at length reducing the risk of diabetes and the metabolic syndrome. The risk reductions of 80-90% in the incidence of diabetes obtained in the prospective studies cited, which were through diet and exercise, provide confirmation that the selection of carbohydrates and the dietary glycemic load are indeed critical factors. The success of dietary and lifestyle interventions in the context of IGF and IGT can be judged by periodic HbA1c determinations. In fact, this may be the best way to assess intervention progress. It is important to recognize that IFG and IGT are intermediate states along the path to diabetes and preventing diabetes *a priori* means arresting the progression of IGT and IFG ideally reversing these metabolic abnormalities.

There appear to be only three randomized trials of changes in lifestyle and diet that addressed individuals with IGT.<sup>31-33</sup> In terms of trials, IFG appears ignored. These studies provided evidence that such changes can dramatically reduce the incidence of diabetes and reduce HbA1c progression or reverse its progression in non-diabetic individuals. Dietary interventions in these studies, which reported in the period 1997 to 2002, were influenced by the “fat is dangerous to your health” dogma and thus it is possible that even more dramatic results could have been obtained by using judicious choice of carbohydrate type and quantity to limit post-meal blood glucose swings. While low-fat diets may have helped some to reduce weight, as discussed in the above mentioned research review, this strategy frequently enhanced other symptoms of the metabolic syndrome.

The book *Dr. Bernstein’s Diabetes Solution, The complete Guide to Achieving Normal Blood Sugars* (Little Brown, New York, 2003. Reviewed in the Newsletter of February 2007 along with his diet book) should also be

of interest to anyone with blood glucose problems, even if not diabetic. Bernstein is somewhat of a maverick M.D. and a strong believer in carbohydrate restriction and selection for blood glucose control that goes way beyond the ADA recommendations. He is a Type 1 diabetic himself who specializes in diabetes. Patients come to his clinic from all over the world. His book provides useful information on the use of diet to control post-meal hyperglycemia and normalize HbA1c levels in both diabetics and pre-diabetics. His aim is to achieve in his patients HbA1c levels similar to lean non-diabetics, which are in the range of 4.2% to 4.6%. This is in sharp contrast to the target of 7% advocated by the ADA for diabetics. He regards the 7% target as “out of control” rather than tight control, the ADA view. He considers the HbA1c levels associated with IFG and IGT to also be dangerously high if micro- and macrovascular damage is the issue, i.e. he believes the threshold for long-term vascular damage is lower than the generally believed.

Readers of this newsletter will be aware of the constant stream of studies which are concerned with reducing the risk of heart disease and diabetes. The general theme that emerges in all these studies is the avoidance of refined grains and sugar and the emphasis on fruits, vegetables, beans, nuts and fish, moderation in red and processed meat consumption, weight control or reduction and exercise. The importance of preventing hyperglycemia in the context of both heart disease and diabetes is highlighted in many studies that emphasize low glycemic load diets or low glycemic index diets and as well, the Mediterranean diet. It is becoming clearer by the day that defective glucose metabolism and hyperglycemia represent a serious threat to living a long, healthy life.<sup>34</sup>

## CONCLUSIONS

At issue here is the risk of serious eye and kidney disorders, peripheral circulation problems and the risk of amputation, coronary heart disease and stroke. It seems clear that hyperglycemia even in non-diabetics should not be ignored. A fasting glucose of > 100-124 mg/dL (5.6—6.9 mmol/L) or an HbA1c greater than about 5.5% should prompt concern and further testing. Impaired glucose tolerance is much more prevalent than impaired fasting glucose and can only be identified by a 2-hour oral glucose tolerance test. Diet, weight loss and exercise represent a trio of interventions that have been shown to strongly impact the progression to diabetes. This of necessity translates to the prevention of progression of impaired glucose tolerance and impaired fasting glucose to the cut-offs for the “diagnosis” of diabetes. These are the abnormal intermediate states, and the reversal of the progression of these two disorders prevents diabetes. Since post-meal blood glucose fluctuations impact the average blood glucose level, the carbohydrate content of the diet becomes a central issue although it appears to be downplayed by mainstream medicine which still seems obsessed with dietary fat.

It is important to recognize that dietary carbohydrate may well be the key to the whole problem, although weight loss and subsequent control may also be critical. Carbohydrate addiction or heavy carbohydrate consumption, which are very common, especially if one is advised to limit fat, results in fat storage which results in weight gain which results in increased insulin resistance which results in hyperglycemia. The end result is obesity and pre-diabetes leading to diabetes. Not everyone agrees. Some consider carbohydrates benign. The ADA suggests that less than 120 g/day is not advisable. Bernstein, who tries to regulate blood sugar levels in both diabetics and pre-diabetics, suggests 30 g/day and in some cases achieves HbA1c levels well below 5%, even in diabetics! Most individuals would find 30 g/day unacceptable if not impossible except over a fairly short term. Such extreme restriction is also probably not necessary to normalize FPG and the OGTT in many individuals. Strongly elevated post-meal glucose levels are almost invariably the result of heavy carbohydrate consumption, especially rapidly digested carbohydrates (from high glycemic index foods such as most bread, rice, potatoes, carrots, corn, candy, many breakfast cereals and most deserts). They in fact tend to make one feel good and the physiology is well understood. Finally, HbA1c can be a useful measure of progress in glucose control even in non-diabetics, although for individuals with IGT, it seems reasonable that success should be measured by a return to a normal OGTT, independent of FPG, given that the absence of insulin resistance is the ultimate goal.

The reader is also referred to the December-January 08-09 Newsletter for a discussion of the role of carbohydrate restriction and exercise in normalizing glucose metabolism in Type 2 diabetics. The Studies of Westman, Vernon and coworkers are particularly pertinent and apply equally well- to prediabetics.<sup>35,36</sup>

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# The Prostate Monitor

Editor: William R. Ware, PhD

*Reviews of recent studies from the peer-reviewed literature*

NUMBER 17

DECEMBER 2008/JANUARY 2009

3<sup>rd</sup> YEAR



*The top news story this month seems to be the failure of the SELECT trial which examined the ability of vitamin E and selenium to prevent prostate cancer. As will be seen, there are several issues regarding this trial that are disturbing and suggest the possibility of a fundamental flaw in the design.*

*An important subject covered in this issue concerns the use of hormone therapy as an initial monotherapy when the diagnosed prostate cancer is localized but surgery or radiation therapy is declined or not considered appropriate. At issue here is mainly survival time vs. side effects.*

*Three studies concerning PSA are reviewed which deal with the use of the percent free PSA to estimate the risk of prostate cancer in men with PSA  $\leq$  2.5 ng/mL, prostatitis and elevated PSA levels, and the impact of progressive prostate enlargement due to benign prostatic hyperplasia on the interpretation of PSA velocity.*

*Finally, new studies concerning the long-term risks of nerve sparing surgery and vasectomy are reviewed.*

*Wishing all the best for a Happy Holiday Season and continuing good health in the New Year,*

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

You can order *The Prostate and Its Problems* at <http://www.yourhealthbase.com/prostate/book.htm>

## **DISCOURAGING NEWS FROM THE SELECT TRIAL**

SELECT is a double blind randomized clinical trial that is testing an intervention of vitamin E (400 IU/day of dl-alpha tocopherol, the synthetic form) and selenium (200 microg/day) in order to test the hypothesis generated by earlier studies that such a combination reduces the risk of prostate cancer. This is a large multinational study involving 35,000 men age 50 and older. According to a press release from the National Cancer Institute on October 28, an initial, independent review of the study data has revealed that neither the combination nor the supplements used individually reduced the incidence of prostate cancer. The trial has been terminated but there will be continued follow-up that will remain blinded. This comes as a disappointment to those who regarded the earlier work as providing a fairly strong argument for the use of this pair of supplements in prostate cancer prevention. (As reported by <http://www.urotoday.com>).

When the trial design was announced, there was discussion in the literature regarding the form of vitamin E used since natural vitamin E is much more effective in general and the form in food is in fact gamma tocopherol. It is doubtful that the trial will be repeated with either the natural form or the gamma form and thus we will never know if the null result was due to the use of the synthetic E. Nevertheless, the form of selenium used is generally considered to be satisfactory from the point of view of bioavailability (L-selenomethionine), and it alone was not effective in this trial. But, it has been pointed out that statin drugs interfere with the synthesis of selenoproteins, glutathione peroxidase and in particular selenoprotein N.<sup>1</sup> But the SELECT trial has not indicated results from stratification to see if selenium alone was effective in statin non-users. In the age group studied, there were no doubt a large number of statin users who may have had the beneficial effects of selenium blocked by the statin enzyme inhibition. In fact, it has been postulated that the inhibition of selenoproteins may be related to the side effects of statins such as rhabdomyolysis and polyneuropathy.<sup>1</sup> Thus this study was far from ideal to answer the target question and in fact may have been fatally flawed.

## **HORMONE THERAPY—IT'S USE WHEN NOT INDICATED. RISKS VS. BENEFITS**

Androgen deprivation therapy (ADT, hormone therapy) is not an approach for the treatment of localized prostate cancer sanctioned by major groups or guidelines and yet an increasing number of clinicians and patients have turned to primary ADT as an alternative to surgery, radiation or conservative management. A group of urologists and oncologists from six countries have just joined together to present a review in the journal *European Urology* of the risks and benefits of ADT for prostate cancer with special emphasis on uses where, according to the authors, there is no evidence-based proof of prolonged overall survival.<sup>2</sup> Medical ADT uses drugs whereas surgical ADT involves castration. The net result is that testosterone levels drop to very low values. ADT is discussed at length in our book *The Prostate and Its Problems*. ADT was initially used for the treatment of metastatic disease, but now it is the second most common approach, after radical prostatectomy, for the treatment of organ-confined prostate cancer in the U.S. Nevertheless, according to the authors of the review, there are only three clear indications for the use of ADT; (1) along with radiation therapy in high-risk patients which prolongs overall survival; (2) to decrease the size of the prostate before starting brachytherapy even though in this setting it does not increase overall survival; (3) To minimize the risk of fatal cancer-related complications and for palliation of symptomatic disease in patients with advanced metastatic disease. The authors add that ADT may also prolong survival in patients with node positive disease after radical prostatectomy but when to start therapy is not clear and studies have produced conflicting results. Also, there continues to be a debate about continuous vs. intermittent ADT.

Not included in the above review was mention of a recent study from the U.S. which compared a population of over 19,000 men 66 years or older with localized cancer (T1-T2) who did not receive definitive local therapy but rather either ADT monotherapy (41%) or simply conservative management. Subjects were enrolled between 1992 and 2002 and followed through the end of 2006. Survival analysis covered a 10-year period. It was found that primary ADT was not associated with improved survival when compared with conservative management. However, there was a slight benefit regarding prostate cancer-specific survival in a subset with poorly differentiated cancer (59.8% vs. 54.3%).<sup>3</sup>

The concern regarding the use of ADT as monotherapy in the case of organ confined or locally advanced disease in the absence of evidence of any significant impact on overall survival is based on the following adverse effects associated with this therapeutic approach. Included are anemia, decreased cognitive function and libido, impotence and osteoporosis. ADT is also associated with loss of muscle mass, obesity, metabolic

dysfunction and insulin resistance and greater risk of diabetes and cardiovascular disease. A review of these metabolic and cardiovascular side effects was described in the title of a recent review from Johns Hopkins as "An Inconvenient Truth."<sup>4</sup> The risk of these adverse effects of ADT are not exclusively associated with its long-term use since there is evidence that even short-term use may induce some of these conditions. Insulin resistance can develop without hyperglycemia in as little as 3-6 months.<sup>4</sup> Finally, the authors point out that early use of ADT after failure of first-line therapy is associated with a clonal selection of aggressive, androgen dependent prostate cancer cells which may lead to an earlier occurrence of androgen-independent disease. They also comment that if surgical rather than medical castration were still the only approach to ADT, a substantial number of present indications would certainly be reconsidered!

In the second review cited above,<sup>4</sup> Basaria suggests that physicians should conduct detailed discussions regarding the complications of ADT, especially with men who have early stage prostate cancer and those with biochemical recurrence, because they are the ones who stand to have the least favourable risk/benefit ratio. Furthermore, it is suggested that all patients on ADT be screened for diabetes every three months using both fasting glucose and HbA1c. Men with impaired fasting glucose prior to initiating treatment should have an oral glucose tolerance test, the only way to diagnose insulin resistance. However, there does not appear to be any evidence to guide in the prevention of the above-described complications when they are promoted by ADT. After all, it is not simply a matter of lifestyle and diet driving the problems.

Thus individuals offered ADT for anything other than the indications listed above should consider the risks involved since there appears to be no significant increase in overall survival to balance side effects of the treatment which clearly impact the quality of life. When ADT is being recommended, patients should demand detailed information regarding the benefits and insist on absolute rather than relative measures of increased survival.

### **% FREE PSA AND THE RISK OF PROSTATE CANCER IN MEN WITH A PSA $\leq$ 2.5 ng/L**

The famous Prostate Cancer Prevention Trial (PCPT) which has been discussed in earlier issues of this Newsletter and in our book found that 17% of patients with a total PSA between 1.1 and 2.0 ng/mL and 23.9% with total PSA between 2.1 and 3 ng/mL had prostate cancer as detected by biopsy. This prompted the suggestion that the threshold for biopsy be reduced, but the counter argument is always that this will result in a large number of biopsies which in retrospect will turn out to have been unnecessary. This is the inevitable result of having a marker, i.e. PSA, the level of which is associated with a continuously increasing risk of prostate cancer. In fact, there is no safe total PSA level below which prostate cancer does not exist. Since the publication of the PCPT there has been renewed interest in improving the selection process among men with PSA  $\leq$  2.5 ng/mL in order to reduce the number of unnecessary biopsies. If a patient with PSA  $\leq$  2.5 ng/mL has a suspicious digital rectal examination (DRE) then this is generally considered sufficient reason for recommending a biopsy, but when the DRE is unremarkable, there is obviously a problem and the need for novel biomarkers for this subgroup.

A study by Waltz *et al* has just been published in the journal *Cancer* which examines the ability of the % free PSA to stratify patients with PSA  $\leq$  2.5ng/mL in order to aid in the decision regarding the recommendation of a biopsy.<sup>5</sup> Since the probability of prostate cancer in this group is about 17%, the objective was to find a way of identifying those most likely to actually have the disease. Between 1999 and 2006, 7880 consecutive men underwent an initial biopsy at two European centers (Hamburg and Milan). Of the total cohort, 1036 had total PSA  $\leq$  2.5 ng/mL. For patients in this subgroup with an unremarkable DRE, 19% had prostate cancer at biopsy whereas overall the rate in the subgroup was 23%. The researchers comment that this is somewhat higher than would be predicted from the PCPT and that this may be due to the nature of the cohort which was referred on the basis of abnormal or suggestive PSA behaviour. The present study also used more biopsy cores as compared to the PCPT study.

The % free PSA was found to provide considerable discrimination. For men with an unremarkable DRE, those with % free PSA  $\leq$  14%, 49% had prostate cancer, whereas for those with %free PSA  $\geq$  28%, only 9% had prostate cancer. This unfortunately leaves a grey area of  $> 14%$  to  $< 28%$  free PSA. For the entire group which included men with suspicious DRE, these same two cut-offs found 59% and 13% with prostate cancer. The authors point out that the finding that the % free PSA was highly useful in identifying patients with prostate cancer was also observed in a study by Catalona *et al* in a group with total PSA between 2.5 and 4.0 ng/mL.<sup>6</sup>

Also in studies that examined the performance of free PSA at initial biopsy, repeat biopsy and saturation biopsy, % free PSA was the strongest predictor of prostate cancer. However, a Korean study found that for men 50 to 65 years of age with an unremarkable DRE and PSA between 4.0 and 10.0, % free PSA did not add diagnostic advantage.<sup>7</sup>

Walz *et al* also examined the fraction of cancers detected in the  $\leq 2.5$  ng/mL group that were deemed clinically significant among the patients undergoing a radical prostatectomy. Despite the favourable total PSA range of this cohort, 16% of the cancers had established extracapsular extension or seminal vesicle invasion and 35.6% had a pathological Gleason score of 3 + 4 (the reader is referred to our book for a complete discussion of the Gleason score both in biopsy and pathological samples). It was thought that this subgroup undergoing surgery was representative of the total cohort. The authors comment that the surprisingly elevated proportion of unfavourable pathologic characteristics indicates that low total PSA values are neither indicative of nonexistent cancer nor a favourable pathology. Obviously, the need to replace PSA and even its variants with a definitive yes or no marker for prostate cancer is urgent, but it must be recognized that even the biopsy misses a significant number of cancers. We have come a long way in this field, but we appear to have a long way to go.

### **PROSTATE GROWTH AND PSA VELOCITY—A SOURCE OF CONFOUNDING?**

PSA velocity is used to increase the power of PSA screening. But PSA also tends to increase with prostate size, and an increasing prostate size accompanies benign prostatic hyperplasia (BPH). Thus the question of potential confounding. A study by Loeb *et al* just published in *The Journal of Urology*<sup>8</sup> addresses this concern. The researchers identified 242 men without prostate cancer from the Baltimore Longitudinal Study of Aging who had 2 or more serial pelvic MRI studies and contemporaneous PSA tests. Prostate volume was estimated from MRI images and the median PSA was 0.9 ng/mL with a mean of 1.3 ng/mL. During the 4.2 years median follow-up, the median rate of prostate volume change was 0.6 cc/year whereas the median PSA change was 0.03 ng/mL per year. Prostate growth rates as high as 10 cc per year were encountered, and yet PSA velocity was less than 0.1 ng/mL per year in most men and showed no correlation with prostate volume. The authors point out that the National Comprehensive Cancer Network now recommends that a prostate biopsy would be considered for men with PSA  $\leq 2.5$  ng/mL if the PSA velocity were greater than 0.35 ng/mL per year. The results of the study by Loeb *et al* suggest that prostate volume changes greater than 0.35 ng/mL per year are unlikely to be due to prostate volume changes. These results suggest that progressing BPH is not a confounding factor when PSA velocity is used to indicate a probability of prostate cancer high enough to warrant a recommendation of a biopsy.

An editorial by Westphalen which is at the end of the paper by Loeb *et al* points out that in addition, there is a study in which PSA velocity correlated with MRI findings of malignancy but not BPH which also supports the use of PSA kinetics as a tumor marker. Westphalen suggests that the study of Loeb *et al* adds to others to provide added evidence for the use of PSA velocity not only in determining prostate cancer aggressiveness but also to aid in biopsy decisions.

### **PROSTATITIS AND ELEVATED PSA LEVELS**

It is well known that inflammation of the prostate alters the prostatic duct integrity causing PSA leakage into the general circulation. Many studies document a correlation between acute and chronic prostatitis and PSA elevation. The problem is aggravated by the fact that significant prostatic inflammation due to prostatitis can be present and yet not result in symptoms. It appears to be general practice that individuals with PSA elevation are not screened for asymptomatic prostatitis before a biopsy is recommended.

An Italian study by Sarretta *et al* has recently appeared in the journal *Prostate Cancer and Prostatic Diseases*<sup>9</sup> which investigates the merits of attempting to reduce the number of biopsies in patients with an elevated PSA by repeating the PSA assay after antibiotic therapy in an attempt to identify patients where the elevation is due to asymptomatic prostatitis. Ninety-nine asymptomatic men requiring urological consultation for PSA between 4 and 10 ng/mL (81 patients) or 10.2-to 200 ng/mL (18 patients) with a negative DRE who were candidates for a biopsy were enrolled in the study. An attempt was made to exclude those with merely random PSA fluctuations. No attempt was made to diagnose or rule out any type of prostatitis (the reader is referred to our book for a discussion of prostatitis). Ciprofloxacin (500 mg twice a day) was given orally for 3 weeks and PSA was again



determined 2 weeks after the end of therapy. All patients submitted to a biopsy which used 12 to 21 cores depending on the patient's age, prostate volume and ultrasound indications.

It was found that there was a significantly lower cancer detection rate in patients with decreased PSA after antibiotic therapy with a correlation between PSA reduction and a negative biopsy having an odds ratio varying from 1.2 to 3.9 for PSA reductions between 10 and 90%. Out of the total cohort, if a cut-off of  $\geq 70\%$  reduction or a reduction below 4 ng/mL was used, 9% of the biopsies could have been prevented. Excluding patients with a baseline PSA > 10 ng/mL, a PSA reduction cut-off of 50% with antibiotic therapy would have avoided 11% of the biopsies. The authors emphasize that if such a protocol were implemented, follow-up would still be necessary.

In an editorial in 2007, Peter Scardino from Slone-Kettering Memorial Cancer Center points out that while antibiotics may influence the course of acute bacterial prostatitis, 90% of symptomatic and almost all of asymptomatic prostatitis are not caused by bacterial infection. While he agrees that prostatic inflammation may be associated with increased PSA levels, antibiotics have no effect on non-bacterial prostatitis. He interprets studies where PSA decreases with antibiotic treatment in some subjects as being almost entirely due to random variations and points out that in one study, there were no differences in bacterial cultures between PSA responders and non-responders to antibiotic therapy. Furthermore, he points out that there is a risk of toxicity, the propagation of unscientific medical practice and the risk of antibiotic resistance which might impact the risk of serious future post-biopsy infections.<sup>10</sup>

The study of Sarretta *et al* involved 99 patients out of which 13 had reductions > 50% and 5 had reductions > 70%. Thus it is not impossible that 10-15% of the study group had bacterial prostatitis and it is most likely in the subgroup with an antibiotic induced reduction in PSA >70%. This potentially small fraction of the treated population likely to have the target disease must be taken into account before using this study to justify the recommendation of giving "Cipro" to large numbers of men with elevated PSA. Obviously, this is not straightforward but important for those who might be able to avoid a biopsy.

## **DOES NERVE SPARING SURGERY INCREASE THE RISK OF POSITIVE MARGINS OR RECURRENCE?**

Nerve sparing surgery during the removal of the prostate is carried out in an attempt to preserve potency. The above question is not simple since the raw data from retrospective studies must be carefully analyzed to correct for confounding due to the fact that the nerve sparing operation will more frequently be carried out on individuals who would have a lower risk of positive surgical margins or recurrence whether or not the nerves were spared. Thus the question involves whether nerve sparing is an *independent* risk factor for positive margins and recurrence.

The decision to attempt nerve-sparing surgery will depend on the preoperative clinical picture and the observations of the surgeon during the operation when the region around the two nerve bundles is inspected and palpated for signs of extra-capsular tumor. The preclinical factors include age, current sexual function, and the clinical pathological observations regarding the extent, nature and location of the tumor or tumors. If the decision is made to attempt nerve sparing, then the question reduces mostly to how well surgeons accomplish the judgment call and the surgery involved in dissecting away the nerve bundles while removing the prostate. A recent multicenter U.S. study addressed this question. While there had been single institution—single surgeon studies, this one involved was more realistic in that it involved a number of institutions and surgeons. When the data was subjected to multivariate analysis to search for independent factors, neither bilateral nor unilateral nerve sparing was associated with a higher risk of positive surgical margins. The risk of biochemical failure (detected only by increasing PSA) was also not affected by bilateral or unilateral nerve sparing. It was concluded that when the procedure is restricted to appropriately selected patients, nerve sparing does not increase the probability of either biochemical failure or positive surgical margins.<sup>11</sup>

## **VASECTOMY AND RISK OF PROSTATE CANCER**

The weight of evidence shows no association between a vasectomy and the risk of prostate cancer. However, there has been concern that a risk might exist in subgroups such as men with a family history of prostate cancer, men who undergo the procedure at a younger age, or the risk might develop over a longer period than studied. A recent study addresses these issues.<sup>12</sup> Approximately 1000 men diagnosed with prostate cancer were matched

with over 900 controls. The prevalence of vasectomy was similar in the cases and controls (36.2% and 36.1%) and thus no association was found. In addition there was no association between prostate cancer and age at vasectomy, years elapsed since the procedure, or the calendar year of the vasectomy. It was concluded that prostate cancer is not an issue associated with having a vasectomy.

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