In this issue a number of studies are summarized which address issues deemed important and significant. We start with an unusually detailed discussion of a paper just published which challenges the conventional wisdom regarding who should be treated with statins. This is an important matter because the threshold for recommended intervention keeps decreasing and because of the long-term nature of a prophylactic treatment that is not free from adverse side effects. The last major revision of the U.S. guidelines increased the number of Americans for whom statins are recommended from 13 million to 36 million, the latter being over 10% of the total population. People who joke about this suggest that eventually statins will be put in municipal drinking water. The Newsletter continues to highlight the importance of vitamin D with a discussion of two recent articles. Those interested in breast cancer and ovarian cancer risks will find two studies included in this issue. Also, an interesting international anomaly associated with the use of fish oil in secondary prevention of heart attacks is described. There is also good news for both chocolate and coffee lovers.

This issue also includes the first issue of The Prostate Monitor. It is anticipated that this will be a monthly feature. Presented in the style of a research report, it endeavors to supplement our book The Prostate and Its Problems by presenting recent developments concerning benign prostate hyperplasia and prostate cancer. This report should be of interest not only to those who have read part or all of our book, but the topics covered, it is hoped, will be of general interest to men concerned about these two very serious threats to their wellbeing and quality of life. In fact, it seems that wives should seriously consider acquiring an understanding of prostate health and disease since many of their husbands are in an unnecessary but understandable state of denial and embarrassment regarding this subject.

Please bear in mind that the cost of publishing this newsletter is solely defrayed by income made from the on-line vitamin store. Without this, there would be no IHN. So, if you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and database, and the publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you continuing good health,

William R. Ware, PhD, Editor

Highlights

- Who should take cholesterol-lowering statins? p. 2
- Does radiation therapy cause new cancers? p. 4
- More studies on the importance of vitamin D p. 4
- Breast and ovarian cancer risks p. 6
- Put on the coffee pot p. 7
- NEWS BRIEFS p. 8
- THE PROSTATE MONITOR p. 10
WHO SHOULD TAKE CHOLESTEROL-LOWERING DRUGS (STATINS)?

In the January 20th issue of the journal *Lancet* two researchers, one from Harvard (J. Abramson) the other from the University of British Columbia (J. M. Wright) raise serious questions about the extent of the evidence supporting the use of statin drugs for true primary prevention of cardiovascular events or life extension. The authors acknowledge that for individuals between 30 and 80 years of age with occlusive vascular disease, secondary prevention with statins confers total and cardiovascular mortality benefit. What is at issue here are individuals who exhibit no evidence of occlusive vascular disease. They point out that about 75% of those taking statins are in this category, i.e. pure primary prevention. On the basis of analysis of pooled data published earlier (Jauca, C. and Wright, J.M., *Int Soc Drug Bull Newsletter*. 2003, Vol. 17 No. 3 pp. 7-9, available free online) and as well, reference to specific studies, they conclude that there is no statistically significant evidence favoring the use of statins for pure primary prevention for the following subsets: (a) women of any age; (b) men older than 69 years. The authors claim that in justifying primary prevention with statins in women and in people over 65 years of age, the U.S. guidelines for treatment cite 16 randomized trials and yet not one provides evidence of benefit from statin therapy for these two groups. In addition, they find that high-risk men between 30 and 69 with no apparent vascular disease should be advised that about 50 patients need to be treated for 5 years to prevent one adverse event.

The pooled studies used by Abramson and Wright consisted of five large trials of statins which mostly involved primary prevention (average percent primary prevention—83% of participants, range 56-100%) In the pooled studies, total mortality was not reduced by statins and while the 5-year frequency of total heart attacks and stroke was reduced (relative risk 0.84) the absolute risk reduction was only 1.4%. This is equivalent to needing to treat 71 individuals for 5 years to prevent one adverse event. They also quote the results of the PROSPER randomized controlled trial which involved over 5800 men and women over 69 years of age. In a subset of 3239 men and women with no evidence of previous vascular disease and viewed at risk because of smoking, hypertension or diabetes, this study found that statins did not reduce total cardiovascular events. When the PROSPER results were stratified just by gender only, among women there was no significant benefit from statin treatment and an unspecified number of the total female cohort had prior vascular disease. In the interpretation part of the abstract of the PROSPER paper no mention was made of the absence of benefit for primary prevention or for elderly women in general (primary or secondary prevention), but rather, it is simply stated that the statin in question given for 3 years reduced the risk of coronary disease in elderly individuals, thereby omitting an important result. This is in spite of the fact that of the 5804 individuals included in the analysis, about 56% were in the “no previous vascular disease” category, i.e. a significant fraction of the total study population. This data has been in the literature since 2002. Finally, the paper published in 2004 in the *Journal of the American Medical Association* to which Abramson and Wright make reference found that for women without cardiovascular disease, cholesterol lowering with a statin drug did not affect total or coronary heart disease mortality. For fatal heart attacks, revascularization or coronary heart disease events, only one out of nine study results showed significant treatment benefit and this was just for one outcome. Even for those with known cardiovascular disease, lipid lowering did not affect total mortality. This was a study of analyses (meta-analysis) which included six trials involving 11435 women of various ages without cardiovascular disease.


Editor’s comment: The results that Abramson and Wright quote as well as the earlier meta-analysis are obviously being ignored if one assumes statin users include elderly individuals and women of all ages, both with no prior vascular disease. However, the meta-analysis of Jauca and Wright was not published in a peer-reviewed journal. The commonly held view is that cardiovascular disease is a continuum and therefore it is valid to extrapolate from studies on individuals who are symptomatic or
have experienced adverse events to those deemed at risk but appear free from this disease. As Abramson and Wright point out, the validity of this extrapolation has never been established and studies frequently fail to present results stratified by primary vs. second prevention. Also, many studies combine primary and secondary prevention and produce evidence of benefit which is used to justify therapy, but the important point of Abramson and Wright is that this does not justify application of the combined results just to primary prevention or assuming that studies that involve mostly men can be extrapolated to women. In many studies, this stratification was possible but just not published, which essentially ignores what are apparently important issues.

Those who believe in the continuum theory also apparently believe that risk can be measured and a cut-off established beyond which intervention is indicated. If the Framingham model is used, then cholesterol levels are part of the calculation, and cholesterol levels play a key role in statin guidelines. Yet in all of the studies discussed above that found no benefit for primary prevention, significant cholesterol lowering took place. Even when a study involves or includes primary prevention, the subjects have other risk factors than hyperlipidemia such as smoking, diabetes, hypertension, etc, which are used to justify the intervention with statin drugs. The issue addressed by Abramson and Wright questions this justification when based on risk factors in the elderly and in women, and with some qualifications, even in men between 30 and 69 years of age, when the intent is primary prevention. Also, in a meta-analysis of primary prevention studies published in 2000 (British Medical Journal, 2000; 321:1-5) which included more than 90% men, the number needed to treat for about 5 years to prevent one coronary heart disease event was 74 which translates into a difference in the percentages of events between treatment and placebo groups of only 1.35 percentage points (the absolute risk reduction). Likewise, a primary prevention study (Lancet, 2004;364:685-96) of a statin for a cohort with diabetes and one additional risk factor such as hypertension or smoking, found an absolute risk reduction of 1.9% for acute coronary events which translates to 53 individuals needed to treat to prevent one event. In this study, 68% were men.

In another recently published meta-analysis of seven trials going back to 1995 which were predominantly for primary prevention, benefit was found from statin therapy for major coronary and cerebrovascular events and revascularizations but not for coronary heart disease or overall mortality. Relative risks were similar to those quoted above. Gender breakdown was possible in almost all the studies, and together they included only 27% women. The abstract does not mention the low percentage of women and the results were not stratified by age or gender (Archives of Internal Medicine. 2006;166:2307-13). Results from these studies appear consistent with those of discussed in the paper of Abramson and Wright.

Those who have a personal interest in this subject and consider these benefits to be small when viewed this way may want to explore in some detail question of side effects. The conventional wisdom appears to be that these benefits are very large and so they might appear if one looks at the relative risk rather than the absolute risk!

Finally, in the 2004 suggested revisions of the U.S. cholesterol treatment guidelines (Circulation 2004:110:2227-39) the PROSPER trial is offered as evidence for treating older individuals without established cardiovascular disease, but this trial found no benefit for this group when the endpoint was coronary death, non-fatal heart attack, or fatal or non-fatal stroke (Table 3, PROSPER study). Also, there are no separate recommendations for men and women. This goes directly against the large meta-analysis focused on women which is discussed above. It is true, however, that gender enters into risk assessment when the current guidelines are used, but it is only if the 10-year risk is calculated. The Framingham data is generally the basis of the estimate. For an online calculator (see http://www.nhlbi.nih.gov/guidelines/cholesterol). If one just counts risk factors, these are gender neutral. But the issues Abramson and Wright raise are independent of risk factors as long as cardiovascular disease is absent. The studies on which they base their arguments all enrolled individuals with risk factors.
DOES RADIATION THERAPY FOR BREAST CANCER CAUSE NEW CANCERS?

It is well known that radiation is implicated in the process of carcinogenesis. An increase of breast cancer has been linked to ionizing radiation used for treatment of non-malignant and malignant diseases and in addition, excess cancers were documented among atomic bomb survivors. Thus an interesting question involves what if any risk of new primary cancers might be due to the therapeutic use of radiation along with surgery for breast cancer. A very large study has been recently reported in a document from the National Cancer Institute (in press) which is based on a huge database known as Surveillance Epidemiology and End Results (SEER), which in the case of this study covered the period from 1973 to 2000 with follow-up on over 300,000 women. Increased cancer rates for women having had radiation as part of their initial treatment were calculated by comparing with rates observed for non-irradiated patients. For those surviving 5-10 years, risk of cancer of the esophagus was increased 3-fold, bone 6-fold, and soft tissue 3-fold. For angio-sarcoma the ratio of observed to expected cases was over 17 and there was a correlation between the side irradiated and the location of the soft tissue sarcomas. This same correlation was observed with lung cancer where the 10-year relative risk was about 1.5. These increased risks were in general consistent with those observed in smaller studies. The authors do not discuss the risk-benefit aspect issue raised by this study.

Curtis, R. E. et al. New Malignancies among Cancer Survivors: SEER Cancer Registries, 1973-2000. NCI Publication # 05-5302, Chapter 7. (Free download available—“Google” NIH Publication 05-5302, identify the document and click “PDF available”)

Editor's comment: Radiation as a risk factor for breast cancer is also discussed in the Research Report on primary prevention of breast cancer that appeared in the previous three issues of International Health News. For modern diagnostic x-ray exposure such as from chest x-rays, there appears to be an increased risk of breast cancer only among women with the genetic predisposition indicated by the BRCA 1/2 gene mutations, but for this population it appears to be a serious issue. The risk of cancer from the high intensity radiation associated with CT scans is another matter. In the case of trauma patients, a recent study used dosimetry at the neck, chest and groin to measure doses delivered during trauma assessment (Journal of Trauma, 2007;62;151). The authors calculate that the doses observed could result in 190 additional cancer deaths per 100,000 individuals exposed. While the benefits presumably outweigh the risks in selected trauma cases, the authors suggest that as more CT examinations are performed, the associated cancer risk may become a greater public health issue and that unnecessary CT scans should be avoided. This presumably also applies to CT scans used for screening of asymptomatic individuals, which appears to be growing in popularity, and is patient driven.

MORE STUDIES HIGHLIGHT THE IMPORTANCE OF VITAMIN D

VITAMIN D AND MULTIPLE SCLEROSIS

It is estimated that 350,000 individuals in the U.S. and 2 million worldwide are afflicted with multiple sclerosis (MS). This terrible disease is more common in young adults. One high profile victim well known to classical music fans was the famous cellist Jacqueline Dupre, for whom the disease proved fatal by the time she was in her early 40s, long after she was forced to stop performing. A study reported in the December 20th Journal of the American Medical Association found high circulating levels of vitamin D associated with a lower risk of MS. The authors point out that a striking feature of MS is a multifold increase in incidence with increasing latitude both north and south of the equator. Such a geographic variation points to vitamin D as a potential factor. Because food provides little vitamin D, most people must obtain this vitamin through the action of ultraviolet (UV) sunlight on the skin which generates vitamin D from cholesterol by a photochemical process. In the temperate latitudes (>40°) there is a huge seasonal variation in sunlight-generated vitamin D because during the winter months there is little or no ultraviolet radiation of the necessary wavelength. Thus seasonal vitamin D deficiency is not only common but almost the norm for those living in the temperate zones, and this includes a significant percentage of the world’s population. Also, dark-skinned individuals generate lower levels of vitamin...
D from the same sunlight exposure due to the blocking of UV by skin pigments.

The study in question made use of a unique source of data from more than 7 million blood samples left over from routine blood tests which were stored by the U.S. military. Military personnel generally provide one sample at entry and on average, one every two years thereafter. This allowed a prospective nested case control study that related vitamin D status to the risk of MS. Controls were randomly selected and 2 controls were matched to each MS case by age, race/ethnicity, and dates of sample collection. The metabolite 25-hydroxyvitamin D was used as a measure of vitamin D status. In addition, information was collected on latitude of place of residence at time of entry into the military in order to account for variability caused by sunlight exposure. Among white skinned individuals, when the lowest quintile (fifth) of serum 25-hydroxy vitamin D was compared with the highest (>99.2 nmol/L), a statistically significant 62% reduction in MS risk was observed, and there was a 41% decrease in risk for every 50 nmol/L increase in this serum marker. This inverse association between 25-hydroxyvitamin D levels and MS was particularly strong in individuals where the vitamin D status was measured before the age of 20. No protective effect was observed among blacks or Hispanics. but in this cohort, black skinned individuals had much lower levels of the serum marker.

The authors discuss the possibility of reducing the risk of MS by raising the circulating levels of 25-hydroxyvitamin D. They point out that almost half of white and two-thirds of black adults in the U.S. have 25-hydroxyvitamin D levels below 70 nmol/L and that according to recent evidence, the best levels are between 90 and 100 nmol/L. However, the authors appear reluctant to specify a supplement intake level and comment that “several-fold increase in vitamin D intake among adolescents and young adults requires stronger evidence than provided by observational studies alone.”


Editor’s comment: It is not surprising that no recommendation is made regarding supplementation. Such recommendations are now generally made by representatives of mainstream medicine only on the basis of overwhelming and compelling data meeting the highest standards of randomized, controlled clinical studies. In many situations such studies will never be conducted for reasons too lengthy to enumerate. However, there are experts in the field of vitamin D research who are willing to publicly go on record as being in favor of the merits of raising the vitamin D status of the general public through supplementation and who point out that the U.S. official maximum intake considered to be safe is 2000 IU of a vitamin D3 supplement. Such supplementation would raise many individuals to a vitamin D status equivalent or better than 75-100 nmol/L, but some of these experts consider the 2000 IU limit to in fact be too low. In a paper that just appeared, Hathcock et al in fact recommend a revision of the upper limit to 10,000 IU/day (American journal of Clinical Nutrition, 2007; 85:6-18). Interested readers should also look at the paper by Reinhold Vieth (American journal of Clinical Nutrition, 1999;69:842-56). Both are available free at the journal website, www.ajcn.org. In general, the lower the starting level of 25-hydroxyvitamin D, the longer the time required to bring the levels up and the higher the dose, the faster the increase and the higher the achievable level.

VITAMIN D AND THE RISK OF PANCREATIC CANCER
While there do not appear to be geographic studies suggesting sunlight protects against pancreatic cancer, scientists from Harvard Medical School and Northwestern University Medical School have recently reported on a very large study involving two cohorts that addresses the role of vitamin D. This study made use of data from the Health Professionals Follow-up Study and the Nurses’ Health Study. Food-frequency questionnaires which included questions regarding supplementation were employed to determine the total oral intake of vitamin D and examine its relationship to the risk of developing pancreatic cancer. Controlling for confounding by UV exposure was accomplished by taking into account the location of residence. Multivitamin intake as well as intakes of calcium and retinol were also taken into account in the final, pooled multivariate analysis. It was found that when the lowest category of total vitamin D intake was used as the reference point (< 150 IU/day), the relative risks for pancreatic cancer were 0.78 for 150-299 IU/day, 0.57 for 300-450 IU/day, 0.56 for 450-599 IU/day and 0.59 for ≥ 600 IU/day. All but the first result were statistically significant, Supplement use ranged from 8-11% in the < 150 IU/day group to 94-94% in the ≥600 IU/day, a result that confirms that it is difficult to achieve higher levels of intake from
food alone. The authors conclude that this study points to the potential role for vitamin D in the prevention of pancreatic cancer. They also point out that because there is no effective screening available for this cancer, identifying modifiable risk factors is essential for developing preventive strategies.


Editor’s comment: These results show a leveling off of effectiveness above about 400 IU/day, which is currently the U.S. Recommended Daily Allowance. Many multivitamin preparations contain this amount. Thus the indicated preventive action is simple and inexpensive. This is a serious matter since pancreatic cancer is the fourth-leading cause of cancer death in the U.S. There is also a recent study (Cancer Research, 2006;66:10213, commentary pp.9802) that found higher vitamin D status was associated with increased risk of pancreatic cancer, but this study was restricted to smokers and will not be discussed.

**BREAST AND OVARIAN CANCER RISKS**

**WEIGHT GAIN AND BREAST CANCER RISK**

Over the years there has accumulated considerable evidence concerning the association between indicators of body size and postmenopausal breast cancer. However, little is known about the importance of the timing of weight gain in adult life. This issue has recently been addressed in a large international population-based case control study. Included were 1166 cases of primary histologically confirmed postmenopausal breast cancer and 2105 controls matched on age, race and country of residence. Data on weight gain and fat distribution were collected through in-person interviews and questionnaires. Participants were asked to recall their body weight for each decade from age 20 to one year before diagnosis for cases and to 1 year before interview for controls. Information was also collected on weight gain during first pregnancy and body shape at menarche. Current height, weight and measures of central adiposity (abdominal fat collection) and hip and waist circumferences were also noted. For the cases, the estrogen and progesterone status of the breast cancer was obtained from pathology reports.

For lifetime adult weight gain it was found that there was a 4% increase in risk of postmenopausal breast cancer for each 5 kg (11 lbs) increase in adult weight. In addition, there was a tendency for a stronger association for those with a higher waist circumference which suggested that fat accumulation around the waist was of greatest significance. Only those with estrogen/progesterone positive tumors exhibited weight-related increases in risk. Weight gain from age of first pregnancy to age of menopause was associated with increased risk with a significant trend associated with the amount of weight gain. Other than this, there were no significant associations with the time of life in which weight gain occurred. This study also confirmed what others have observed, i.e. there is a protective effect of higher body weight at age 20, with women in the highest quartile having a significant reduced risk of 27% as compared to those in the lowest quartile. No association was found for weight gain during pregnancy and the risk of postmenopausal breast cancer.


**OBESITY AND OVARIAN CANCER RISK**

Ovarian cancer is most frequently diagnosed at a late stage with 5-year survival rates of around 30%. Only a small number of positive risk factors have been identified. These include age, family history of breast or ovarian cancer, and genetic predisposition associated with carrying the BRCA 1/2 tumor suppressor gene mutation, and all are not modifiable. Actions that can reduce risk include pregnancy and taking oral contraceptives. Studies of the association of risk with body weight have been inconsistent but suggestive. A recent study from the Roswell Park Cancer Institute in Buffalo, NY has attempted to clarify the role of body size in the context of ovarian cancer risk. In a hospital-based case control study, 4427 women with primary ovarian cancer and 854 women acting as cancer-free controls completed a comprehensive
epidemiological questionnaire which included height and usual weight prior to the study. Normal or underweight was defined as a BMI ≤ 24.9, overweight 25-29.9 and obese as ≥30 kg/m². For postmenopausal women (≥ 50 years of age), BMI was not associated with ovarian cancer risk. However, for premenopausal women, those classified as obese had over a 2-fold increase in risk compared to those who were normal/underweight. This result is important because body mass is a modifiable factor. While the biological mechanism is unknown, body size is thought to influence the hormonal environment and is known to influence androgen and growth factor levels that may be involved in ovarian carcinogenesis. BMI is calculated by dividing weight in kg by the square of height in meters.


**PUT ON THE COFFEE POT**

In the February issue of *International Health News*, the effect of coffee consumption on glucose tolerance was briefly discussed. While this study looked at a marker for diabetes risk, a prospective study just published actually looks directly at the impact of both caffeinated and decaffeinated coffee consumption on the incidence of diabetes in women (average age, mid 60s). This study by Smith *et al* which appeared in the November issue of *Diabetes Care* followed 910 adults age ≥ 50 years without diabetes at baseline. About half the participants had impaired glucose tolerance. The average follow-up was 8 years after the assessment of coffee intake and the results were adjusted for gender, age, physical activity, BMI, smoking, alcohol consumption, hypertension and baseline fasting glucose. Individuals were classified as having normal glucose at baseline if they had a fasting blood glucose < 6.1 mmol/L and post-challenge glucose < 7.8 mmol/L. Impaired glucose was defined as either impaired fasting glucose (fasting blood glucose between 6.1 and 7.0 mmol/L and post challenge level of < 7.8 mmol/L) or actual impaired glucose tolerance (fasting blood glucose of < 6.1 mmol/L and post-challenge level between 7.8 and 11.1 mmol/L) Note: Multiply by 18 to get mg/dL, the unit used in the U.S. Coffee consumption was classified as follows: Past drinkers drank coffee from 18 to 45 years of age but not after 45 whereas those who did not drink coffee after 18 were nondrinkers, and the rest were classified as current drinkers.

Compared to never drinkers, past drinkers from the total cohort or those with impaired glucose had a statistically significant 62% lower risk of diabetes, respectively, whereas the same comparison with current drinkers yielded a 64% risk reduction for both the total cohort and those with impaired glucose. For those with normal glucose, there was no significant effect of coffee on the risk of becoming diabetic, i.e. coffee consumption was a neutral factor. In this study there was no dependence on the volume of coffee consumed and the observed risk reductions. Also, the number of decaffeinated coffee drinkers in the cohort was too small for meaningful analysis.


**Editor's comment:** This study is more or less consistent with the Finish study described in the February Newsletter in that coffee consumption slowed the progression of those with impaired glucose tolerance progress to abnormal glucose tolerance, i.e. progression toward type 2 diabetes. It is also consistent with a recent study (American Journal of Epidemiology, 2006;164:1075-84) which found that when the endpoint was diagnosis of diabetes or medication use, intake of ≥ 4 cups per day of caffeinated coffee resulted in a significant diabetes risk reduction for a U.S. cohort of both men and women 45-64 years of age who had normal fasting glucose at baseline. The study of Smith *et al* did not look at the progression of those with normal glucose to impaired glucose tolerance. Also, this was an American study which implies mostly the consumption of filter drip coffee whereas the Finnish generally drink boiled coffee. There are significant differences in the content of some chemical constituents, which are removed by the filtration process. In fact, as Smith *et al* discuss, it is not clear what constituents of coffee are responsible for the very large and significant protective effect against the development of diabetes found in their study. These results may be age dependent. In a recent study from Harvard (Diabetes Care, 2006:29:389-403), a cohort of young middle-aged U.S. women was prospectively studied and the investigators found similar large protective effects of...
coffee in the absence of impaired glucose tolerance (no data on glucose metabolism was available but it is unlikely that a significant number of this cohort were prediabetic). In addition, the protective effect was also seen with decaffeinated coffee but not with tea. While caffeine increases blood pressure, the effect when the intake is via coffee is small (Journal of Hypertension, 2005;23:921-28.). Thus it appears that at least in the context of diabetes risk, drinking coffee is either a good idea or at least not a bad one at any adult age.

NEWS BRIEFS

DIABETES AND CARDIOVASCULAR RISK
It is well known that individuals with diabetes are up to four times more likely to have cardiovascular disease (CVD) when compared to those without diabetes and CVD accounts for a large proportion of excess deaths related to diabetes. Middle-aged people with type 2 diabetes have a risk of coronary heart disease similar to those who have had a heart attack. In a recent Canadian retrospective cohort study, Booth et al found that the transition to a high-risk category for CVD occurred at a younger age for both men and women with diabetes than for those without the disease and that diabetes conferred a risk equivalent to aging 15 years. They also found that younger individuals with diabetes (≤ 40 years age) did not appear to be at high risk of CVD. They conclude that age should be taken into account when aggressive risk reduction is undertaken. Booth, G. L. et al. Relation between Age and Cardiovascular Disease in Men and Women with Diabetes Compared with Non-diabetic people: a Population-based Retrospective Cohort Study. Lancet, 2006, Vol. 368, pp. 29-36.

BREAST CANCER CHEMOTHERAPY AND COGNITIVE IMPAIRMENT
The authors of this paper introduce their study by pointing out that cognitive complaints among women who have received chemotherapy as part of the primary treatment for breast cancer are appearing with "concerning frequency." Of eight recently published studies involving breast cancer survivors undergoing cognitive performance assessment, half have found memory to be particularly affected. This study from the University of California at Los Angeles and the VA Healthcare System of Los Angeles used positron emission tomography to compare control subjects with women having received chemotherapy. Subjects were scanned while performing control and memory related tasks in order to evaluate cognition-related cerebral blood flow. Specific alterations in activity were found for the frontal cortex, cerebellum and basal ganglia in breast cancer survivors by this approach to functional neuroimaging 5-10 years after the subjects had completed chemotherapy. Silverman, D. H. S. et al. Altered Frontocortical, Cerebellar and Basal Ganglia Activity in Adjuvant-treated Breast Cancer Survivors 5-10 years after Chemotherapy. Breast Cancer Research and Treatment, 2006. Published electronically ahead of print.

Editor's comment: This study should help to eliminate some of the uncertainty associated with reports of cognitive impairment that might otherwise be discounted. Thus what appears to be a real risk of cognitive impairment after chemotherapy must be considered when the risk-benefit analysis is undertaken prior to treatment decisions.

MORE GOOD NEWS FOR CHOCOLATE LOVERS
Researchers from Johns Hopkins have reported on a study indicating that a couple of tablespoons of dark chocolate a day could have the same benefit as aspirin in reducing blood clots and preventing heart attacks. The study reported at the annual meeting of the American Heart Association in Chicago identified a flavonoid in chocolate that lowers platelet clumping that can block blood vessels and lead to a heart attack or stroke. The effect of chocolate was discovered by accident while investigating results from disqualified participants who “cheated” and ate chocolate during a trial which examined the action of aspirin on blood platelets. Becker, D. et al. Paper presented at the annual conference of the American Heart Association, November 2006.

Editor's comment: Dark chocolate is the ideal form because it maximizes the cocoa solids, presumably the carrier of the active ingredients. It is already known that dark chocolate lowers blood pressure and has other beneficial effects on blood flow. This study provides the first biochemical evidence for why people who consume a few pieces of chocolate a day reduced their risk of dying of a heart attack.
IN EUROPE BUT NOT THE U.S, IT’S FISH OIL AFTER HEART ATTACKS

In a recent article in the New York Times, attention was drawn to the anomaly that in Europe fish oils are prescribed as part of the treatment protocol after an individual has had a heart attack, but this practice is much rarer in the U.S. The article quotes the chief of cardiology at an Italian hospital as stating that not only is this use of fish oil recommended in international guidelines, but it would be considered tantamount to malpractice to omit giving this “drug.” In fact, there is even available a prescription formulation of purified fish oil called Omacor, but it is not approved by the FDA for use in the U.S. except for very high triglyceride levels and cannot be promoted except for this single indication. Related to this subject is a paper in the Journal of the American Board of Family Medicine which reported on a survey taken among family physicians in the State of Washington to determine the frequency with which they prescribed fish oil supplements for secondary prevention after a heart attack. While 57% were aware of fish oil’s effectiveness, only 17% actually prescribed it. Only 26.5% of family physicians were even aware of one of the most dramatic effects of fish oil, reducing the risk of sudden cardiac death. This study did not include cardiologists.

Rosenthal, E. In Europe It’s Fish Oil after Heart Attacks, but Not in U.S. New York Times, October 3, 2006


Editor’s comment: Omega-3 fatty acids and heart disease was discussed in the February issue of the Newsletter and again in this issue. The disconnect between Europe and the U.S. and between accepting the currently available evidence and rejecting it or ignoring it reveals a lot about the difference in medical culture. The Times article quotes Dr. Terry Jacobson, a preventive cardiologist at Emory University in Atlanta, GA as saying that he gives the prescription for fish oil “off label” and chooses this over the fish oil capsules available over-the-counter because “Then I know exactly what they’re getting, and there is no mercury.” If the health food store product comes from a reputable firm or is “pharmaceutical grade” then such concerns are probably unnecessary. There is a huge difference in cost of about $15 vs. $150 for 120 capsules with Omacor also having about half the EPA per capsule as compared to the typical over-the-counter product. Finally, a friend of the editor who had experienced a mild heart attack a day after hip surgery relates that when he asked the hospital cardiology resident about taking fish oil capsules he drew a complete blank. The resident had never heard of such a thing!
Both prostate enlargement and prostate cancer are distressingly common, especially among men past midlife. Thus men free of these disorders should be greatly interested in primary prevention and men already diagnosed with either disease should seriously consider self-education regarding the many aspects and options associated with delaying progression and with primary and secondary treatment. Patients are frequently invited to take part in decisions regarding intervention, and without a basic knowledge of the subject and knowledge of the current status of research relevant to their problem, intelligent participation in the decision making process is unfortunately unlikely. It was this need for reliable, up-to-date information discussed in terms the layman could understand that provided the motivation for writing *The Prostate and Its Problems* (now available from the International Health News website). Men need to ask themselves questions such as “Should I have a PSA test?”, “Should I be doing something to decrease the risk of an enlarged prostate or prostate cancer?”, etc. The need for information becomes even more urgent and critical once a man has been diagnosed with prostate cancer, in part because of the variety of treatment options that are frequently offered along what can be a complex set of pros and cons. Individuals may also find detailed information on prostate enlargement and prostate cancer useful when parents, children or relatives are diagnosed with one of these disorders and come seeking information and support. Many men know vastly more about the cars they drive than about their prostate, its potential to alter their lives, and what they can do about it. Many are also unable to understand discussions of prostate issues among informed individuals. These updates are intended to provide additional information and keep readers of International Health News up-to-date. Those who have read even some parts of the book will find the following updates much easier to understand and appreciate. Those who have not should still find many of the studies discussed below to be of interest.

Wishing you continuing good health,

William R. Ware, PhD, Editor

Benign prostatic hyperplasia (BPH) represents a very serious health and quality-of-life problem with 11 million American men estimated to require treatment by the year 2020. About 20% of men at age 40 and 60 % of men age 60 show evidence of BPH at autopsy. Obviously, either avoiding BPH or slowing or reversing its progression should be a major concern, especially for those over 40. In the book The Prostate and Its Problems, the prevention, diagnosis and treatment of this disorder are discussed in detail in Chapter 2. Since publication, there have been a number of important developments.

RISK FACTORS
In recent months several interesting studies have appeared concerning potentially modifiable factors associated with the risk of benign prostatic hyperplasia (BPH). In a study from Johns Hopkins and the National Institute of Aging [1], the role of obesity, fasting blood sugar and diabetes in the development of prostate enlargement was investigated. Prostate size was determined by MRI measurements for 422 participants in the Baltimore Longitudinal Study of Aging. Based on an analysis of the characteristics of 91 participants who were found to have enlarged prostates (≥ 40 cc), it was found that severe obesity (BMI ≥ 35 kg/m²), elevated fasting glucose > 110 mg/dL (6.1 mmole/L), and diabetes were significant risk factors with enhanced risks of 3.5 fold, 3-fold and 2-fold, respectively. Since these findings remained significant after adjusting for total and free testosterone, the authors suggest that some other mechanism is operating aside from the one hypothesized to involve alterations in the androgen and estrogen balance brought about by excess adipose tissue. Since both obesity and elevated serum glucose are components of the metabolic syndrome and this syndrome is associated with systemic inflammation and oxidative stress, they suggest both are associated with unregulated nonmalignant prostate growth.

A recent study examined the relationship between the risk of BPH and lifetime occupational and recreational physical activity [2]. Prospective studies had already shown an inverse association between physical activity and BPH with the risk in one large study decreasing linearly with increased recreational physical activity with walking of particular merit. In this study recreational and occupational exercise levels were examined during different periods of life in a case control study. In this study, an inverse association was found for both occupational and recreational physical activity with the strongest association found in young adulthood (approximately a 50% risk reduction), and a 30% reduction for the 50-59 year age group. Substantial risk reductions were found when combined recreational and occupational physical activity was considered. However, their analysis adjusted only for study centers, age and years of education. Nevertheless, this study adds to the sum total of evidence favoring exercise as an important life style modification in the context of BPH risk and progression. The authors favor a mechanism based on lower basal levels of circulating testosterone.

Two studies of nutrient intake as it relates to BPH risk have recently been reported. In one [3] it was found that various carotenes were protective. In another [4] starch increased risk whereas polyunsaturated fatty acids were protective.

PHARMACEUTICAL THERAPY
BPH is frequently treated with 5α-reductase inhibitors (5ARIs) that inhibit the enzyme responsible for the conversion of testosterone to dihydrotestosterone, a hormone thought to play a role in prostate enlargement. The first drug on the market was Proscar (finasteride) and this was followed more recently by Avodart (dutasteride). Dutasteride is a so-called dual 5ARI which inhibits both forms of the enzyme whereas finasteride acts on only one form. In the past year Avodart has been heavily advertised in connection with frequent urination (the “I thought I had a going problem, but my doctor tells me I have a growing problem” TV ad). Three studies have recently been published that address the effectiveness of dutasteride in treating moderate to severe BPH [5-7]. All three studies were either directly or indirectly financed by the manufacturer of the drug, GlaxoSmithKline. In one study [7], 1667 men completed an open label phase of what had originally been a 24-month double-blind placebo controlled study. In the open-label phase, patients in both the treatment and placebo arms were eligible for dutasteride treatment for an additional 24 months. The emphasis in this study was
the importance of baseline prostate volume on treatment effectiveness. Changes in urinary symptoms and prostate volume were observed. In patients treated with the drug throughout the study, the mean reduction in prostate volume over 48 months was 30.3% for those with a baseline prostate volume of 30 cc or less, and 26.2% for those with a prostate volume of 40 cc or greater. Improvements in urinary flow were found to be independent of baseline prostate volume. The risk of acute urinary retention was reduced by 55-60% in the group on the drug for 48 months, and vs. those treated for only 24 months. The risk of needing BPH related surgery, when compared to those receiving only 24 months of treatment, was reduced by 27% and 48% for those receiving 48 months of treatment with baseline prostate volumes either equal to or less than 30 cc or equal to or greater than 40 cc, respectively.

In a smaller open-label study [6] of treatment with dutasteride, a large percentage of the patients assessed achieved a significant decrease in lower urinary tract symptoms, and improvements in patient discomfort and satisfaction scores. In this cohort of 366 patients, most had moderate to severe symptoms and had been previously treated with alpha-blockers or phytotherapy or a combination of the two. The minimum prostate volume was estimated at 30 cc. Most of the improvements in symptoms associated with urinary function were seen during the first 12 weeks of treatment. Side effects were mostly associated with sexual disorders. Of the 44 patients who had sexual dysfunction during the treatment period, 10 had these complaints at study entry.

In a large study of side effects of 5ARIs, it was found that dutasteride was well tolerated during long-term use for the treatment of symptomatic BPH. This study also confirmed that side effects associated with 5ARIs tend to diminish with the period of treatment and eventually persist in only a very small percentage of patients [5].

These studies are significant in the context of pharmaceutical treatment of BPH because research suggests that finasteride should be reserved for patients with prostate volumes over 40 cc but even men with prostate volumes between 30 and 40 cc are at increased risk for acute urinary retention which produces a medical emergency and in many cases leads to invasive action to improve urinary flow. Also, as discussed in our book, alpha-blockers, the first-line treatment for BPH, do not in general reduce prostate size or the long-term risk of acute urinary retention, a result of severe BPH that men fear the most. In addition, the effect of dutasteride on PSA has now been investigated [8] and justification found for using a multiplier of two in interpreting this marker in men taking dutasteride in order to correct for the decrease in PSA that occurs. The observed decrease in PSA stabilized between 6 and 12 months after initiation of treatment, and the authors conclude that an increasing PSA in men receiving dutasteride should be viewed with suspicion and serial measurements instituted to evaluate changes from the minimum reached.

INVASIVE AND MINIMALLY INVASIVE THERAPY FOR BPH

Transurethral resection of the prostate (TURP), the so-called roto-rooter operation, is considered to be the gold standard for the surgical treatment of BPH. On the basis of a review of the literature for the past five years concerning the use of laser based ablative/vaporization techniques to remove prostate tissue constricting urinary flow, Kuntz has recently proposed that a new gold standard should be declared, i.e. holmium laser enucleation [9]. In an associated editorial, Tubaro suggests that the potassium-titanyl-phosphate laser (KTP) should not be excluded from consideration as a competing source of energy since outstanding outcomes have also been achieved with this laser [10]. Thus laser techniques are gaining ever greater credibility as alternatives to TURP. Nevertheless, large series, long-term results, and randomized trials are lacking, and there is a significant learning curve [9,10]. Men facing the prospect of an invasive procedure because of intolerable BPH or recurrent acute urinary retention episodes may wish to investigate the availability and track record of laser ablation in the urological community to which they have access since, as Kuntz points out, there is significantly lower morbidity as compared to TURP and the holmium laser enucleation is the only laser procedure that provides a specimen for pathological evaluation, i.e. for ruling out prostate cancer. The importance of being treated in a center where laser techniques are well established and generally recognized as being executed with skill and with results comparable to the best centers seems obvious.

The use of feedback microwave thermotherapy with the Core-Therm device is discussed at some length in our book. A recent prospective, randomized, multi-center study compared this approach to treating BPH with the TURP operation [11]. The results showed that microwave thermotherapy was an effective alternative to TURP for patients with BPH and persistent urinary retention. This was true even for patients with prostate sizes
exceeding 100 cc, who in the past were generally treated by open surgery. In this study, 79% of patients treated with the CoreTherm device were permanently relieved of their indwelling catheter 3 months after treatment. The CoreTherm procedure was also accompanied by on average only 1.6% serious adverse events compared to 8.5% in the TURP group.

BOTOX TO THE RESCUE

In Chapter 9 of The Prostate and Its Problems the use of Botox injections for BPH is discussed. This unique non-cosmetic use of the botulinum toxin is starting to attract attention with reviews in 2006 in both the Journal of Urology and BJU International [12,13]. Both reviews contain the mandatory warning that this application is “off label” and caution is necessary until clinical studies are complete, which of course means randomized placebo controlled clinical trials, although recruitment might be difficult for randomized studies where 50% get an injection of saline in their prostate. Nevertheless, there are now at least 8 uncontrolled trials of Botox involving 172 human subjects, all of which have produced positive if not sensational results. The injection technique which is done under transrectal ultrasound guidance is similar to that employed for the implantation of brachytherapy seeds or the acquisition of biopsy cores, i.e. transrectal or transperineal. The picture that emerges is that one treatment involving injections into two or more locations within the prostate not only dramatically improves urinary symptoms scores, quality of life scores and residual urine, but also in most cases there is a significant shrinkage of the prostate, sometimes by as much as 50-60%. The overall positive results from only one treatment are durable at least over a number of months, and generally to the end of the follow-up, i.e. the durability may be very long. Add this to the absence of any significant side effects and one might surmise that here we have a winner. While most of the human studies are from Taiwan or Italy, there have now been studies that included scientists from the US (e.g. Dr. Michael B. Chancellor, University of Pittsburgh School of Medicine, Pittsburgh PA). Individuals with severe BPH or BPH that is no longer responsive to alpha-blocker or 5ARI intervention might want to shop around for an urologist with experience injecting Botox. Since one treatment may be all that is necessary, even traveling some distance might be worthwhile. However, having the procedure from someone with little or no prior experience might prove risky. An error in dose of a factor of 10 could have serious systemic consequences. Botox is, after all, a potent neurotoxin. It must be emphasized that this is still an “experimental treatment” but there will no doubt be trials in North America recruiting patients sometime in the near future. There is even speculation that Botox may have a role in prostate cancer treatment [12].


REFERENCES