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William R. Ware, PhD - Editor

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The arsenal of modern medicine is limited—surgery or other invasive procedures, radiation, mostly ionizing, and prescription drugs, which because of patent laws, must almost universally be chemicals not found in nature and therefore foreign to human biochemistry. To this short list should be added the variety of diagnostic procedures, some of which represent levels of sophistication unimaginable 50 years ago. The so-called war against disease which is waged with these tools and weapons comes at a high cost, both financially and as measured by adverse effects and human error which impact the quality of life and even mortality. Profits in the pharmaceutical and device sectors drive innovation that reaches the consumer level and any increase in the population that can be described as having a treatable condition becomes a disease and is accompanied by a potential increase in profits. Thus there is constantly a search for new applications of existing drugs to expand the potential customer base. During just the past 12 months, Medline (PubMed) lists 33 publications describing the results of clinical trials using the statin Crestor (rosuvastatin).

In this issue the new action by the U.S. Food and Drug Administration regarding an expansion of the indications deemed appropriate for Crestor is reported. The FDA's approval of the indications for Crestor is based on the JUPITER trial and should be read in the context of the Perspective concerning this trial presented in the February 2009 issue of IHN www.yourhealthbase.com/ihn194jn.pdf. There is also new information discussed regarding the unusual ability of Crestor to dramatically elevate the vitamin D status marker, 25-hydroxyvitamin D, a confounding effect with the potential to seriously impact the interpretation of the JUPITER results.

Other aspects of cardiovascular disease and blood lipids are discussed. In particular, there is no evidence that lipid-lowering has any impact on subclinical atherosclerosis, and lipoprotein(a) is now getting more attention in the context of being a risk factor for adverse cardiovascular events, although the growing consensus that it is a cause can be challenged.

Natural treatments that might benefit Parkinson's disease patients are discussed and as well, an attempt is made to put into perspective the recent study showing only small benefits from fruit and vegetable intake and cancer prevention.

In the News Briefs section, a variety of subjects are touched upon which should be of interest to many readers. These involve mammography, macular degeneration, colon cancer prevention, alcohol and the risk of diabetes, and statins for women.

This issue also contains The Prostate Monitor.

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

Wishing you and your family good health and well-being,

William R. Ware, PhD, Editor

Highlights

BE PREPARED FOR A CRESTOR ADVERTISING BLITZ

The U.S. Food and Drug Administration has just approved an extension of the "label" for the statin Crestor (rosuvastatin) allowing it to be prescribed for men over 50 and women over 60 who have one risk factor for cardiovascular disease like smoking or hypertension and in addition, have elevated inflammation as ascertained by a blood C-reactive protein (CRP) determination. In the U.S. alone, it is estimated there are 6.5 million individuals who would qualify. This is all based on the JUPITER trial. The reader is referred to the February 2009 issue of IHN www.yourhealthbase.com/ihn194jn.pdf for a perspective concerning this trial and the many issues surrounding using CRP in this context. In JUPITER, the absolute benefit was barely measurable. Out of 8901 who took the placebo, 68 patients had a heart attack (0.37%) whereas for those on the drug the number was 31 (0.17%). In absolute terms the often quoted relative risk reduction of 55% benefit becomes 0.2% and 500 people would need to be treated with Crestor to avoid one usually survivable heart attack. The numbers for stroke were similar. As discussed in the Perspective, the absolute benefits, while still very small, were somewhat larger when the primary combined endpoint was used. Thus by the standards of some, this may be a statistically significant benefit but it is not clinically significant. The annual financial cost comes to about $1300 U.S. As pointed out in the perspective, the reduction in CRP only lasts while one is on the medication and may return to baseline upon termination of the therapy. The root cause of the inflammation is not being addressed. Thus normal, healthy individuals with normal cholesterol are being converted into patients prescribed a lifelong regime of statin therapy since for one reason or another, their CRP is elevated. Once on the drug, which reduces CRP, the possibility that the elevated CRP would disappear spontaneously or due to other interventions is no longer as easily followed and the rationale for using the drug could no longer be present but its use continued indefinitely.

Aside from the issues discussed in the Perspective concerning the many reasons why CRP can be elevated and the power of dietary and other non-drug interventions to permanently reduce levels to normal for many individuals, a paper just published in *The Lancet*[1] found that in a meta-analysis of studies involving almost 100,000 patients, statin therapy increased the risk for incident diabetes by 9%. It is well known that diabetes increases the risk of cardiovascular disease. Add this to the probably vastly under-reported side effects such as muscle damage and pain, in rare cases serous enough to be fatal, and consider the 500 needed to treat to prevent one heart attack, and perhaps this new wave of enthusiasm for Crestor may not be so attractive. See the book *The Statin Damage Crisis* by Duane Graveline, M.D. for a discussion of statin side effects.

Finally, as mentioned in the December 2009/January 2010 issue of *International Health News* www.yourhealthbase.com/ihn_december2009.pdf, Crestor appears unique among the statins for its remarkable power to strongly elevate the vitamin D status marker, 25-hydroxyvitamin D.[2] In fact, the changes are large enough to account for most of the risk reductions found in JUPITER for a number of the endpoints examined! No one seems to be talking about this potential confounding of a so-called landmark study. Thus JUPITER with its exceptional although very small primary prevention benefit compared to other statins may in fact have been a study of the benefits of elevating vitamin D status! As all readers of this Newsletter know, one can bring their vitamin D status up to a sufficient or optimal or even super-optimal level for pennies a day with zero side effects and it is an understatement to point out that the benefits go way beyond the reduction in the risk of cardiovascular events.

LIPID LOWERING DOES NOT INFLUENCE PROGRESSION OF SUBCLINICAL ATHEROSCLEROSIS. A LONG-TERM STUDY

Almost all individuals who experience acute coronary events have had subclinical coronary atherosclerosis for years and it has also relentlessly progressed. A paper in the *International Journal of Cardiology*[3] has just reported a study of 510 patients with stable angina, mean age 63 years. At baseline, 372 were put on a statin and/or fibrate (the lipid lowering therapy group--LLT) and 138 were not (no lipid lowering). Coronary calcium scores were obtained every two years for a median of 5.6 years using non-invasive CT in order to monitor atherosclerosis. Cholesterol levels decreased in both groups, but the drop was more pronounced in the patients on LLT. Changes in cholesterol levels during follow-up were not associated with coronary calcification with calcium scores increasing in all quartiles of cholesterol level changes. Neither baseline calcium score nor its change was correlated with baseline cholesterol level or its changes. Twenty-eight percent of the patients exhibited new calcified lesions during the follow-up with no difference between the treated and untreated groups. In summary, a totally null result. This results is consistent with the studies discussed by your editor in a recent paper,[4] and adds to the evidence that falsifies the hypothesis that LDL cholesterol drives atherosclerosis.

A systematic review has also just been published which examined the impact of statin treatment on the annual progression of coronary calcification in individuals with cardiovascular disease or chronic kidney disease.[5] In some cases there were placebo arms to the studies included in the review. The researchers found no consistent or reproducible treatment effect of either statins or antihypertensives on the annual coronary calcification progression. The abstract concludes with the rather odd statement that the 1-year change in coronary calcium does not appear to be a suitable surrogate endpoint for treatment trials in patients with CVD or chronic kidney disease. Does this translate into the suggestion not to use coronary calcium imaging because you won't get the results you are looking for?

METFORMIN AND PERIPHERAL NEUROPATHY

The prevalence of diabetes is large and increasing. Diabetic peripheral neuropathy is present in up to 50% of diabetic patients. Metformin in a very commonly used drug aimed at glucose control. Presumably one of the reasons for the focus on glucose control is to minimize such comorbidities as peripheral neuropathy and other vascular complications. However, it appears to have been known since 1971 that metformin usage is associated with a vitamin B12 deficiency and it is well known that this deficiency is associated with peripheral neuropathy. A study from the University of Calgary which has just appeared[6] looks for clinical evidence of the suggested connection between metformin-worsened diabetic peripheral neuropathy. This was a prospective case-control (snap-shot) study of diabetic patients with concurrent symptoms of peripheral neuropathy and compared those on metformin for > 6 months (n = 59) with those not taking the drug (n = 63). Levels of vitamin B12, homocysteine and a marker of B12 deficiency, methylmalonic acid (MMA) were measured and electrophysical measurements were carried out to quantify the neuropathy.

The results were as follows:

- In the drug group, 31% were B12 deficient compared to 3% in the control group.
- Homocysteine was elevated in 25% of the drug group vs. 2% in the controls.
- The B12 deficiency marker MMA was elevated in 73% of the drug group vs. 11% of the controls.
- There was a strong, significant and linear relationship between the two electrophysiological measures of the extent and severity of peripheral neuropathy and the cumulative metformin dose, with data up to 12,000 g cumulative intake. Correlation coefficients of 0.79 and 0.80 were obtained, numbers that are unusually high in clinical studies.
- There was also an inverse correlation between serum B12 and cumulative dose as well as a positive correlation between serum homocysteine and cumulative dose, but the correlation coefficients were lower but still large

enough to be strongly suggestive (0.41 and 0.50 respectively).

The authors comment that it is at this point unclear whether B12 supplementation will prevent clinical worsening. Both B12 injections and oral intake are commonly used, and many regard the former as a more reliable approach. They also point out that oral calcium supplementation has also been effective in reversing B12 deficiency due to low bioavailability in metformin patients. They conclude that more research is needed to sort out the various actions of metformin, but that since B12 deficiency is correctable, this possibility should not be ignored.

This seems to be another example of the mix of benefit and harm associated with introducing a biochemically active chemical unknown to human biochemistry into a system that is complex and only partially understood and where there are huge financial benefits from downplaying or ignoring adverse effects and emphasizing the benefits. Nevertheless, this happens repeatedly every day to a significant fraction of the world's population.

DOES LIPOPROTEIN(a) CAUSE HEART DISEASE?

In the past few months there has been a flurry of reports regarding lipoprotein(a), generally designated Lp(a), in the context of coronary heart disease (CHD). Lp(a) consists of low-density lipoprotein attached to a protein called apolipoprotein(a). Initially described in 1963, it was already being proposed as a risk factor for CHD in 1972. The big question is whether or not elevated blood levels of this protein are a cause or a marker of coronary CHD. In what is described as the "strongest evidence yet that Lp(a) causes heart disease" (theheart.org, December 23), results from a case-control study identified two genetic variations that were strongly associated with both an increased level of Lp(a) and an increased risk of CHD.[7] Since the risk of CHD increases with increasing levels of Lp(a), the conclusion was taken as evidence of causality. The authors state that "These finding are consistent with a causal association of elevated lipoprotein(a) levels with increased MI." Whether or not this represents an oversimplification of complex human microbiology and biochemistry remains to be seen, since when a gene sets in motion the synthesis of a single protein, in this case an apolipoprotein(a) *component*, this does not initially result in the fully formed Lp(a). Furthermore, there is already rather extensive evidence from a meta-analysis of 36 prospective studies that Lp(a) levels are positively associated with CVD risk.[8] Does it really constituent proof of causality to show that the genetic variations that are associated with increased Lp(a) production are also associated with the risk of CHD? But the new genetic results have created excitement in the heart disease research community and an editorial accompanied this study contained the title phase "From curious molecule to causal risk factor."[9] Nevertheless in this editorial the author also states that "To close the loop for plasma Lp (a) lipoprotein from a curiosity to a causal risk factor, a therapeutic intervention that selectively lowers plasma Lp(a) lipoprotein level will need to be tested in a randomized trial." This is somewhat inconsistent with the use of the term "cause." A statement from the British Heart Foundation was even more explicit, claiming the latest genetic study indicated that Lp(a) "caused" heart disease (www.bhf.org.uk December 23).

The almost obligatory statement in observation studies is that associations do not prove causality and randomized clinical trials are required. One is reminded of the homocysteine saga. As discussed in an earlier Newsletter, after strong observational evidence had accumulated that elevated levels of homocysteine were positively associated with CVD, three intervention trials with folic acid and vitamins B6 and B12 all lowered this amino acid but failed to impact the incidence of CVD events. Many experts were surprised. Even the causal issue with CRP and CVD does not appear settled since JUPITER changed two variables at once, and while there is evidence that the statin used is independently influencing events through the reduction of CRP, this still does not eliminate the need for a study where the drug or intervention used only impacts CRP levels, something very difficult to prove given the complexity of human biochemistry. In fact, as mentioned in the last newsletter, the statin used in the JUPITER trial has a remarkable if not unique impact among this class of drug on vitamin D levels and the increase in 25-hydroxyvitamin D could account for all or even most of the benefit of the intervention. There have as yet been no such trials reported that used an intervention to reduce Lp(a) with CHD or overall mortality endpoints and yet we are told that causality has been established.

The question which always should be asked relates to subclinical atherosclerosis vs. CHD events and what is really being studied according to the endpoints. It almost always turns out that studies of CHD are really studies based on acute events and not subclinical atherosclerosis in the coronary arteries, and to describe them as directly related to true primary prevention leaves a lot unsaid. A recent study examined this question by measuring Lp(a) and coronary artery calcium (CAC) in both diabetic and non-diabetic men and women.[10] It was found that Lp(a) was a strong predictor of CAC in type-2 diabetic women regardless of race, but not in men and there was no association for either men or women without type-2 diabetes. The authors cite four studies, two consistent and two inconsistent with this latter result, which when added to the present study probably means that Lp(a) is not an issue in the prevalence of coronary plaque and instead the risk is related to adverse events.

Another recent study attempted to establish where the significant risk levels might be for fasting serum Lp(a).[11] The researchers found that a level of more than 1100 mg/L seemed to be an important predictor for the occurrence of significant CV risk. When a level of 322 mg/L was compared to 1235 and 2068 mg/L, the risk increased 2.8 and 6.2 times. This sharp rise in risk was independent of other dyslipidemias, BMI, sex, age, diabetes, hypertension and liver disease. Sinatra and Roberts [12] give 300 mg/L as a healthy level which is consistent with these results. Finally, it is important to point out that there may be a problem with standardized assays for Lp(a) and studies need to be viewed with caution.

The only recognized intervention to lower Lp(a) is niacin, although Sinatra and Roberts also suggests vitamin C and fish oil.[12] But niacin impacts not only other blood lipids including raising HDL and lowering triglycerides, but it also is involved in a large number of biological processes associated directly or indirectly with CHD,[13] and thus studies that use niacin will have to be carefully designed and it may be very difficult to rule out pleiotropic effects and prove direct causality.

ARE THERE NATURAL TREATMENTS FOR PARKINSON'S DISEASE THAT MIGHT WORK?

In its initial stages, Parkinson's disease (PD) can be merely inconvenient and aggravating, but as it progresses there can be a profound decline in quality of life, a considerable increase in the burden on caregivers, and in the last stages, a very grim picture. There is no cure and mainstream treatments appear somewhat limited and variable in efficacy and in their ability to halt progression. While there are a number of studies underway, some of which may eventually yield approved treatments, this may come too late for many who now have the disease. Thus the question: are there "natural" treatments that are promising enough to be in or considered for clinical trials, but which are still a long way from meeting the standards of either working or not working according to modern evidence-based criteria? If these approaches employ supplements having few if any safety issues, then perhaps they are worth considering.

A recent paper by M. Flint Beal from Weill Cornell Medical College in *Parkinsonism and Related Disorders*[14] examines one aspect of this problem, therapeutic approaches to mitochondrial dysfunction in PD. There is considerable evidence from post-mortem brain tissue and genetic studies in humans, as well as studies in animal models of neurodegeneration, that suggests mitochondrial dysfunction as a key pathological mechanism in PD. The details are complex and beyond the scope of this note. In human intervention studies, the results are frequently judged by what is called the *Unified Parkinson's Disease Rating Scale* (UPDRS) which increases with the severity of the disease. Beal only discusses in any detail two interventions in the context of mitochondrial dysfunction, creatine and coenzyme Q-10 (CoQ10),

Creatine. This is a naturally occurring compound in vertebrates and helps supply energy to muscle and nerve cells. Experimental studies suggested benefit, but there appear to be two clinical trials, one of which was designed to rule out futility. It was found that progression of the UPDRS was slowed by almost 50% at one year in creatine-treated patients. In a run-up to a phase III trial, a randomized double-blind placebo controlled trial on 64 subjects indicated that oral creatine at 8 g/day for 16 weeks was well-tolerated, safe and bioavailable and reduced a marker for oxidative stress. Creatine is available as a supplement from health food stores and online.

Coenzyme Q 10. CoQ10 is an essential biologic factor in the mitochondrial membrane. It is probably one of the most popular supplements used by integrative cardiologists.[12] In experimental studies CoQ10 has been found to be neuroprotective due to the reduction of mitochondrial free radical generation, but it has a number of other important functions. Beal and coworkers have shown that a combination of creatine and CoQ10 provide neuroprotective effects in three models of PD. Furthermore, patients with PD were found to have reduced levels of the oxidized or reduced form of CoQ10 in spinal fluid. Furthermore, they found a reduction of CoQ10 in platelet mitochondria isolated from PD patients. In a multicenter randomized placebo controlled double-blind phase II trial designed to examine safety and tolerability, CoQ10 was found safe and well-tolerated at doses up to 1200 mg/day and the same result was also found for 3600 mg/day, although the blood levels plateaued at 2400 mg/day. A significant dose-dependent reduction in the UPDRS score in subjects assigned to CoQ10 compared to the placebo was also found. Phase III trials are now underway. There is, incidentally, a considerable variation in bioavailability associated with various commercial CoQ10 formulations.

Beal also mentions that nicotinamide, riboflavin and lipoic acid are being tested for neuroprotective efficacy in disorders involving neurodegeneration. He also mentions sulforaphane and curcumin as having been shown to have neuroprotective properties, but in the case of all of these readily available substances, he cites no clinical trials. Sulforaphane is found in vegetables such as broccoli, and is available as a concentrate combined with other ingredients found in cruciferous vegetables.

Vitamin D. A recent study found that significantly more PD patients as compared to either healthy controls or Alzheimer's disease patients had vitamin D insufficiency.[15] The comparison with Alzheimer's patients was used to rule out confounding. However, there do not appear to be any intervention studies, although it is not unreasonable to maintain, given all that is now known about vitamin D and the merits of sufficiency and optimal year-around levels, that bringing PD patients up to good or ideal levels is probably safe and might provide benefit.

FRUITS, VEGETABLES AND CANCER PREVENTION

First a bit of history. Twenty years ago it was strongly believed that increased consumption of fruits and vegetables would substantially reduce the risk of many cancers, in some cases by as much as 50%. This inspired public health recommendations. The evidence behind this position was mostly from case-control studies which are notoriously vulnerable to confounding, especially with regard to the control group. In the late 1990s, large prospective studies which avoid some of the problems associated with the case-control approach failed to confirm the large risk reductions, and the picture did not improve with pooled analyses. This resulted in a position statement from the World Cancer Research Fund/American Institute for Cancer Research in 2007 which reversed the earlier conclusions of strong benefits resulting from the consumption of fruits and vegetables for many cancer sites.[16,17]

A large European prospective study has just reported that provides additional insight into this matter.[18] The study involved nearly 400,000 men and women who developed approximately 30,000 cancers during about 9 years of follow-up. The results for all cancers combined were disappointing, with a 4% lower incidence for an increase of 200 g of total fruits and vegetables, i.e. about two extra servings per day. Stratification by quintiles of intake found significant trends toward lower risk with increased intake. When the highest vs. the lowest quintiles were compared, for combined fruit and vegetable intake, a risk reduction of 11% was found for men and 10% for women. For vegetable intake, the corresponding numbers were 5% and 8% and for fruit intake they were 11% and 3% respectively. Only the last number (3%) failed to reach statistical significance and the decrease in risk with increased intake (trend) was highly statistically significant. The highest quintile for combined fruits and vegetables consisted of intakes ≥ 647 g/day, which corresponds to a minimum of about 23 ounces. If one looks at an 11% reduction on a population basis, if everyone in the U.S. adopted a diet containing over a pound of fruits and vegetables, the number of cases prevented would exceed 150,000. Worldwide, using World Health Organization numbers for cancer incidence, the number of cases prevented would be about 1.3 million. From an individual point of view, 5-10%

does not seem very large, and when risk reductions drop below 10% some epidemiologists suspect that there is any effect at all.

Something not discussed in this or other studies is the presence in fruits and vegetables of chemicals, mostly polyphenols, which target a certain enzyme only in cancer cells and produce a cytotoxic product which kills the cell, i.e. the classical magic bullet. Studies discussed in the Newsletter (June, 2008 and Oct 2009) in connection with the commercial supplement Salvestrol find that when fruits are screened for active ingredients, those that are found are in high concentrations only in organically grown fruits as compared to those grown with the standard modern chemical-based agriculture. These active polyphenols from fruits are thought to have evolved to be a primary defence against the initiation of cancer. Thus it is possible that if studies of cancer and fruit and vegetable consumption were conducted using organic produce, the results might have been much better. However, it is highly unlikely that such prospective studies will ever be carried out. In addition, some supplement vendors have a large number of different fruit and vegetable concentrates as well as tea extracts, and one wonders if the benefits derived from taking these extracts are also diminished in the context of cancer prevention if the extraction process starts with standard non-organic produce. It also follows that the Salvestrols may be the ideal preventive agents if one wishes to take advantage of the protective features of fruits and vegetables.[19] Another approach is to juice organic produce.

Cancer epidemiology is probably one of the most challenging areas of this discipline. Given the long latent period, perhaps as long as 20-30 years, studies with any meaning are hard to design, execute or finance. If the impact of micronutrients in fruits and vegetables is on the initial process where they prevent free radicals from damaging oncogenes, cancer tumor suppressor genes, and repair genes, then studies are likely to fail unless they are very long term. Thus the above results should not discourage anyone from consuming ample fruits and vegetables. Salvestrols are targeted on tumor cells and appear to have activity at most stages of the disease, and therefore may be unique.

NEWS BRIEFS

MORE ON THE MAMMOGRAPHY DEBATE

The February 2010 issue of IHN www.yourhealthbase.com/ihn204.pdf contained a fairly lengthy discussion of the debate concerning Mammography. A paper just published in the *British Medical Journal* adds significantly to this debate. A government data base in Denmark allowed the comparison of mortality before and after the institution of mammography screening which covered the period 1971 to 2006 and provided breast cancer mortality figures in both screened and non-screened regions of the country. This data allowed the investigators to examine the question of the effect of the Danish screening program on breast cancer mortality. They were unable to detect any effect. Reductions in screening regions were similar or less than those in non-screened areas. The authors suggest that the declines in mortality were due to changes in risk factors and improved treatment rather than to mammography.[20]

Just after the above paper was published, a report in the March issue of *Journal of Medical Screening*[21] reported on a Swedish screening study with a maximum follow-up of about 21 years. Individuals between 40 and 74 were randomized to an invitation to participate in screening. The endpoint was breast cancer mortality for cancers

diagnosed *only during the 6-7 year screening period.* Thus there were two groups with a diagnosis of breast cancer, those produced in the screening group and those in the group that were not screened. In the former group, the mortality rate per 1000 individuals was 4.3 whereas in the unscreened group it was 6.9. The investigators attempted to estimate the extent of overdiagnosis and concluded that 2 to 2.5 lives are saved for every overdiagnosed case. However, overdiagnosis estimates, as admitted by the authors, vary considerably. Going back to the raw data, a simple explanation is that in the screening group; among the cancers found there were some that were not significant but still labelled as cancer although they never resulted in mortality and some might have never been noticed. In the unscreened group, diagnosis was presumably based on cancers sufficiently advanced to provide a clinical presentation. Herein lays the central problem.

SUNSHINE AND DARK, OMINOUS CLOUDS

As many readers know, Canada has "universal" health care where everyone is insured and although not everything is covered, the insurance is by any standard comprehensive. The Health Act is federal but is implemented by the provinces with some variations. On Jan 6, 2010 the *Toronto Globe and Mail* carried the announcement that the Ontario government is considering ending the coverage for routine vitamin D tests, even while examining a report that 5% of the population is so deficient as to be at risk for bone disease. The problem is the surge in 25-hydroxyvitamin D tests. In Ontario, the rate has gone from about 70,000 in 2005 to over 700,000 in 2009 and each test costs the province about $52. With 13 million living in Ontario, one can see the mental bureaucratic wheels turning. If a third of the population gets the test, that is almost a quarter billion dollars! The government referred the question to a medical advisory committee which last month recommended against paying for routine testing in "otherwise healthy people." This is in keeping with the general philosophy that health care is really sickness care and prevention something that gets only lip service. It is too complicated anyway for the 5 to 10 minute office visit. The committee report also took the position that in the context of cancer, multiple sclerosis and other diseases, the evidence is "inconsistent." Many experts of course strongly disagree. This is a splendid example of the interplay between cost control and public health.

Now the good news. The above story seems to provide convincing evidence that the word is getting out to both the general practitioners and the general public, i.e. there is a big health problem associated with low vitamin D levels in people living in Ontario and there is a blood test that will indicate where they stand. The same appears to be happening in other provinces. So apparently a lot more doctors are writing in the request for 25-hyroxyvitamin D along with other blood work, and some no doubt are responding to specific patient requests.

OMEGA-3 FATTY ACIDS AND MACULAR DEGENERATION

A recent study examined the effect of dietary long-chain omega-3 fatty acids (e.g. those from fish and fish oil) on the progression of age-related macular degeneration (AMD) in individuals already at high risk with symptoms in one or both eyes.[22] The results were presented in terms of quintiles of intake expressed as a percentage of total energy intakes. Since there was a wide range of energy intake this makes it hard to apply the results in a simple fashion as regards recommended intakes based on the data. It was found that in comparison between those in the highest intake quintile and those in the lower four quintiles, there was a 30% decrease in the risk of progressing to advanced AMD. For someone with an energy intake of 1800 cal, the highest quintile for docosahexaenoic acid (DHA) was 120 mg/day and for eicosapentaenoic acid (EPA) it was 88 mg/day, based on 9 cal/g of fatty acid.

These results make one wonder about the benefits if much larger amounts had been consumed by supplementation with fish oil capsules. Individuals taking fish oil for cardiovascular protection typically take 1-2 g of fish oil giving them 400 mg of EPA and 200 mg of DHA per gram of oil. However, the authors point to an ongoing trial that will include supplementation with 350 mg of DHA and 650 mg EPA per day, amounts which clearly represents a big advance over typical amounts obtained just from the diet. This study will also look at supplementation with lutein/zeaxanthin (10mg/2mg day) alone or in combination with the above dose of EPA/DHA. This is a 4000 person, 5-year randomized clinical trial and also involves individuals at high risk of AMD. The study was started in late 2006. Readers are referred to the December 2009-January 2010 issue of IHN www.yourhealthbase.com/ihn_december2009.pdf for a discussion of a study that used eggs to enhance the intake of retinal pigments in the context of preventing AMD. Eggs are rich in lutein and zeaxanthin. Incidentally, so-called omega-3 eggs typically contain about 400 mg of omega-3 fatty acids per egg but this includes the short chain omega-3 fatty acids which are inefficiently converted to the long-chain acid in human biochemistry.

PREVENTION OF COLORECTAL CANCER

Two studies, one involving an antioxidant cocktail and the other omega-3 fatty acids, were presented in early December at the Research Frontiers in Cancer Prevention conference sponsored by the American Association for Cancer Research (Reported on Medline Plus, December 8, 2009). The antioxidant study involved 411 individuals 25 to 75 years old who had had one or more colorectal polyps removed. The intervention involved a combination of selenomethionine (200 microg), zinc (30 mg), vitamin A (6000 IU), vitamin C (180 mg, and vitamin E (30 mg). Colonoscopies were performed one, three and five years after starting the regimen. It was found that 4.2% of those on taking the supplements had recurrence of polyps vs. 7.2% of those on a placebo. A weakness of this study was that it does not allow one to determine the relative effectiveness of the components in the intervention.

A second study examined the dietary habits of over 1500 white and 380 black Americans. Half had colorectal cancer. Among the white participants, those who were in the highest quartile for omega-3 fatty acid intake were 39% less likely to have cancer in comparison to those in the lowest quartile. For unknown reasons, this benefit was not found among the black participants. The authors conclude that the results support taking omega-3 supplements and eating oily fish. However, the investigators admit that they did not correct for the possibility that those who ate more fish might have had a healthier diet overall.

Even with these uncertainties, making sure that one has an adequate intake of selenium and the other components of the above intervention and as well consumes adequate amounts of the long-chain omega-3 fatty acids should have multiple health benefits, and possible significantly reduce the risk of this prevalent and serious cancer.

STATINS FOR WOMEN?? SEE *TIME* MAGAZINE, MARCH 29

One quote from this article available free online nicely summarizes its thrust. Dr. Rita Redberg, a prominent cardiologist at the University of California, San Francisco, asks “There are millions of women on a drug with no known benefit and risks that are detrimental to their lifestyle—and no one is talking about it. Why?” This will not come as a surprise to readers of this Newsletter! In addition, while the JUPITER trial is held up by experts as evidence that there really is benefit for women, the reduction in cardiovascular events that were statistically significant were restricted to less extreme endpoints such as hospitalization for unstable chest pain and arterial revascularization, and the absolute benefits were very small. But the JUPITER cohort was unusual in that all had quite high C-reactive protein. Thus this study, which was the first to show any benefit for women in true primary prevention, applies to a limited population. The *Time* article also includes descriptions of serious side effects experienced by two women. One involved incapacitating muscle problems, the other severe cognitive problems.

The *Time* article produced the expected response from the cardiology community, especially a concern that women would stop their statins. In March 29 issue of the heart.org (www.theheart.org) which provides current information for cardiologists, a common comment suggested that the problem was two few women in studies. With more statistical power, some cardiologists appeared convinced the gender difference would disappear. But as has been pointed out several times in this Newsletter, there are two recent meta-analyses which both gave null results. These are universally ignored.

IS ALCOHOL A RISK FACTOR FOR TYPE 2 DIABETES?

For all of us who enjoy two or three glasses of wine with dinner, this is an important issue. A recent meta-analysis of 20 prospective follow-up studies has examined this question. The reference in all studies was the abstainer, and “sick quitters” were excluded. As expected from previous studies, men and women present a somewhat different picture. For men, consuming 22 g/day of alcohol was the most protective with a 13% risk reduction and just over 60 g/day was the threshold for increased risk. For women, the corresponding numbers were 24g/day with a 30% risk reduction and 50g/day. However, the results for women of up to about 40 g/day were bounded by 95% confidence limits that were below the null, whereas for men the upper confidence limit exceeded 1.00 at about 22 g/day. Thus both the benefit and risk associated with heavy consumption were not as clear statistically for men as compared to women. From the regression analysis it world appear that prudent limits are 3 drinks per day for men and 2 for women, assuming 15 g of alcohol per drink. The authors point out that the actual risks may be modified by when the consumption occurs and if it is with meals. They also cite a number of other studies that also found this U-shaped risk curve.[23]

Thus at present there appears to be no reason to avoid moderate alcohol consumption for the purpose of preventing the development of type 2 diabetes and moderate consumption with less for women than men may confer protection. Thus diabetes joins a number of other health issues where moderate alcohol consumption appears beneficial. However, it would be a mistake to underestimate the risk of moderate consumption evolving into heavy consumption with serious multiple consequences. In addition, some may find high to very high quality red wines to be seductively addictive, quite independent of the addictive effects of alcohol.

VITAMIN D ELEVATION WITH STATINS. CRESTOR VS. LESCOL

In the December-January issue of IHN www.yourhealthbase.com/ihn_december2009.pdf a study was reviewed which showed that Crestor, the statin used in the now famous JUPITER trial also significantly elevated vitamin D levels as measured by 25-hydroxyvitamin D. The same group has now published a comparison between Crestor and another statin.[24] The study group consisted of 134 individuals with elevated cholesterol who had never taken a statin. They were randomized into to two groups for treatment with either Crestor or Lescol (fluvastatin). Consistent with the earlier study, the effect of Crestor was dramatic. At the start of the study, the Crestor group had a median level of 25(OH)D of 11.8 (range 3.7-30) whereas for Lescol it was 9.6 (range 4.0-67) ng/mL. After 8 weeks the Crestor group had a median of 35.2 (range 4.0-101) with the 25th percentile at 20 and the 75th percentile at 57 ng/mL. Lescol had no significant impact on vitamin D status. As pointed out in the earlier Newsletter discussion, these changes could have a very significant impact on the results of JUPITER since this study was doing at least three things, lowering LDL cholesterol, lowering C-reactive protein, and raising vitamin D status. The confirmation of this effect in a second study is important, in particular with another statin as a control.

While there appears to have been no discussion of this issue in connection with JUPITER, no interpretation of JUPITER appears complete until the potential confounding by vitamins D status is introduced into the data analysis, since the changes were large and it is known that low 25(OH)D levels put one at risk and high levels lower the risk of adverse cardiovascular events. Unless the JUPITER investigators stored serum samples and 25(OH)D levels can still be determined, then millions have been spent on a study that failed to even measure what may be the most important confounding factor. But when the study was designed, the magnitude of the vitamin D effect of Crestor was probably not recognized.

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The Prostate Monitor
Editor: William R. Ware, PhD

Reviews of recent studies from the peer-reviewed literature

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Men diagnosed with localized prostate cancer who elect to be treated may be given the option of either surgery or radiation therapy. In either case, hormone therapy may be suggested, but this addition is more common in radiation therapy. Hormone therapy is also used when surgery or radiation therapy is not indicated or rejected, and in particular it is used for advanced or metastatic cancer. Hormone therapy is also called androgen deprivation, where surgery (castration) or more frequently drugs are employed to shut down testosterone production either of testicular origin or in addition from the adrenal glands through the use of antiandrogen drugs. When both sources are targeted, the elimination of testosterone is virtually complete. This is of course creates a completely unnatural state of affairs with associated side effects. The motivation for intermittent androgen deprivation discussed frequently in "The Prostate Monitor" is to minimize these side effects without seriously impacting the overall outcome.

This topic is discussed at length in our book "The Prostate and Its Problems". In this issue and in the upcoming July/August issue, Hans Larsen presents a Research Report on androgen deprivation in the context of radiation therapy with emphasis on the two critical questions, benefits (outcomes) and drawbacks (adverse effects). The report will be presented in three parts, the first which makes up this issue deals with the evidence of benefits derived from this therapeutic approach and its variations. Part 2 discusses correlations between outcomes and the clinical presentation and is available only online at www.yourhealthbase.com/ADT/Correlations.pdf

Part 3 will provide information on the adverse effects of androgen deprivation and summarize the report.

This report should be of great interest to anyone diagnosed with prostate cancer and even for those who have undergone radiation therapy and have been or may be offered hormone therapy.

Wishing you good health,

William R. Ware, PhD, Editor

RESEARCH REPORT

Radiation Therapy and Androgen Deprivation

Parts 1 and 2 – Review of Clinical Trials & Correlations

by
Hans R. Larsen, MSc ChE

Background

Three-dimensional conformal radiation therapy (3D-CRT) is now commonly used in the treatment of localized and locally advanced prostate cancer. Several clinical trials have shown that the use of androgen deprivation therapy prior to (neoadjuvant), during (concurrent), and/or following (adjuvant) 3D-CRT results in improved local control and survival.

The main fuel feeding malignant prostate cells is testosterone and its primary metabolite dihydrotestosterone (DHT). Thus reducing the availability of free testosterone and/or preventing testosterone and DHT from binding to receptors on the tumor are logical approaches to inhibit further growth and potentially shrink the tumor by starving it.

Androgen deprivation therapy (ADT) involves the use of injections of so-called luteinizing hormone-releasing hormone agonists (LHRH agonists) such as leuprolide (Lupron) and goserelin (Zoladex). The LHRH agonists work by decreasing the production of luteinizing hormone through down-regulation of LHRH receptors on the pituitary gland thus reducing or, in fact, largely eliminating testosterone production in the testes (chemical castration). During the process of down-regulation, testosterone may actually increase significantly (testosterone flare). To avoid problems related to this a course of antiandrogens – flutamide, bicalutamide (Casodex), nilutamide (Nilandron) is usually given for a week prior to and during the first month of ADT.

Antiandrogens prevent testosterone and DHT from binding to androgen receptors on prostate cells, thus further "starving" malignant cells of fuel. Although 90-95% of circulating testosterone is produced in the testes, the remaining 5-10% (produced in the adrenals) could still be problematical if not prevented from "docking" at androgen receptor sites. Thus, in cases of locally advanced and advanced prostate cancer, a combination of ADT and antiandrogens may be used; this therapy is known as complete androgen blockage (CAB).

Although 3D-CRT combined with ADT or CAB improves treatment outcome and survival it is, by no means, a "free ride". Both ADT and CAB, as well as monotherapy with antiandrogens, can result in serious adverse effects and is particularly dangerous for men with comorbidities, especially cardiovascular disease.

Determination of Treatment Outcome

The aim of definitive therapy for prostate cancer is to increase survival time while maintaining an acceptable quality of life.

Overall survival (OS) is the time elapsed from initiation of primary therapy, in this case, 3D-CRT (also known as EBRT), until death from any cause. OS is usually presented as the percentage of men still alive at a given time such as 5, 8 or 10 years from the initiation of primary treatment, in this case, 3D-CRT. Because enrolment in a trial usually takes several years, OS and other outcome measures are commonly estimated from Kaplan-Meier plots (http://cancerguide.org/scurve_km.html) so as to compensate for the variation in time each patient has actually been enrolled in the trial.

Biochemical failure (BF) or PSA recurrence is measured as the percentage of EBRT-treated patients whose post-treatment PSA level (nadir) was greater than a given value and/or increased by more than a given value over a specified period of time. There is, unfortunately, no universally agreed upon definition of BF, so the specific definition used will be indicated in each clinical trial review.

Prostate cancer specific survival (PCSS) is the percent of trial participants who had not died of prostate cancer or treatment-related causes at the end of a given time interval from initiation of primary treatment (5, 8, 10 years).

Disease-free survival (DFS) is the percentage of men who survived a given time interval (5, 8 or 10 years) without experiencing biochemical failure, a positive digital rectal examination or biopsy, the development of metastases, or the initiation of salvage therapy.

Distant metastasis is the percentage of men who developed distant metastasis (detectable prostate cancer migrated to the bones, lungs or other internal organs) at the end of a given time interval from initiation of primary treatment (5, 8 or 10 years).

For detailed data on patient characteristics, treatment protocols, and treatment outcomes please see the following tables:

www.yourhealthbase.com/ADT/table1.html
www.yourhealthbase.com/ADT/table2.html
www.yourhealthbase.com/ADT/table3.html

Review of Clinical Trials – Part 1

Nine major clinical trials involving 5,812 prostate cancer patients were reviewed. The goal of the trials was to determine the effect of adding ADT or CAB to EBRT. The average age of the men was about 70 years and the majority had locally advanced disease as defined by a tumor stage (1997) of T3 or higher.

A. Study A (Canada Multicenter, lead author – Juanita Crook) – This clinical trial was carried out by a group of Canadian treatment centers with enrolment starting in 1995 and the final report issued in 2009. A total of 361 men were assigned to receive either 3 months (Group 1) or 8 months (Group 2) of CAB prior to (neoadjuvant) the start of 66 Gy EBRT. The majority of study participants had localized prostate cancer with only 14% having a T3 or higher tumor stage. Most patients (89%) had a Gleason score of 7 or less and the average baseline PSA was 10 ng/mL.

Seven-year survival data is presented below:

7-year survival	Arm 1	Arm 2
Prostate-specific	94%	93%
Overall	81%	79%

Arm 1 = EBRT + 3 months of CAB
Arm 2 = EBRT + 8 months of CAB

Authors' Conclusion – *A randomized comparison of 3 vs. 8 months of CAB before conventional-dose RT failed to show a benefit in DFS or a reduction in local failures; however, a significant benefit was seen in DFS for high-risk patients in the 8-month arm.*[1]

Seven-year PCSS for a sub-group of patients with Gleason score of 8 to 10 was 88% and overall survival in this group was 75%. DFS was 33% in group 1 and 59% in group 2 (p = 0.01).

A subset analysis of the Canada Multicenter trial found that biochemical failure (BF) rate was significantly lower in patients who had achieved a PSA nadir of 0.1 ng/mL through CAB prior to starting EBRT than for those whose PSA level was above 0.1 ng/mL at start of EBRT. Thus, BF at 8 years from initiation of treatment for the first group was 45% vs. 51% in the second group (p = 0.01). However, there were no differences in survival between

the two groups. For high-risk patients (Gleason 8 to 10) the difference in BF at 8 years was more significant (36% vs. 70%). Disease-free survival (DFS) was also markedly higher in the low nadir group (57% vs. 29%). There was no significant difference in either PC-specific mortality or overall mortality between the two groups of high-risk patients. Thus, achieving a PSA nadir of 0.1 ng/mL before starting EBRT reduces the incidence of BF and increases DFS, especially amongst high-risk patients, but has no significant effect on survival at 8 years.[2]

A second subset analysis of the Canada Multicenter trial concluded that the duration of neoadjuvant CAB, age and tumor stage did not affect survival outcomes. However, a low initial and pre-radiation PSA level, and a low biopsy Gleason score were all associated with a reduced risk of BF at 5 years amongst high-risk patients. Five-year DFS was 52% for the entire group. PCSS at 5 years was significantly higher amongst patients with a Gleason score of 7 than amongst those with a Gleason score of 8 to 10 (94% vs. 86%). However, there was no significant difference in overall survival between the two groups (80% vs. 77%).[3]

HRL observations

- Increasing CAB therapy duration from 3 to 8 months resulted in no significant outcome improvement for patients with low and intermediate risk (stage T2b or Gleason score 7 or PSA level 10 – 20 ng/mL) prostate cancer.

- Longer neoadjuvant CAB duration (8 months) was clearly beneficial for patients with high-risk disease (stage 3 or Gleason score 8 to 10 or PSA level greater than 20 ng/mL). DFS at 7 years increased from 33% to 59% with 3 vs. 8 months neoadjuvant CAB in this group. PC-specific survival and overall survival at 7 years was 88% and 75% respectively for the high-risk group.

- Testosterone recovery, defined as total testosterone level, returning to a value within the normal range occurred in 92% of men at a median of 6 months following completion of EBRT.

- Although not specifically addressed in the study, the authors point out that CAB and ADT are associated with numerous side effects such as loss of libido, decreased muscle mass and bone density, anemia, weight gain, altered lipid profiles, cognitive dysfunction, and fatigue. There is now also growing evidence that even relatively short courses (1 to 4 months) of CAB or ADT increase the risk of cardiovascular disease, diabetes, fatal heart attack, and sudden cardiac arrest. Metabolic syndrome, a forerunner of diabetes and cardiovascular disease may occur within weeks of starting ADT.

B. Study B (RTOG-9202, lead author – Gerald E. Hanks) – This clinical trial was carried out at the Fox Chase Cancer Center in cooperation with several Canadian and US universities and cancer treatment centers. Enrolment of the 1514 participants with locally advanced prostate cancer began in 1992 and the final report was issued in 2008. All participants received 2 months of CAB prior to and during EBRT (a total of 4 months) and were then randomized to either cease hormone therapy or receive an additional 24 months of ADT. Fifty-five percent of patients had a tumor stage of T3 or higher and 26% had a Gleason score of 8 to 10. Five- and 10-year survival data is presented below:

5-year survival	Arm 1	Arm 2
Whole group		
PCSS	91%	95%
OS	79%	80%
Gleason 8 to 10		
PCSS	82%	93%
OS	71%	81%
10-year survival		
Whole group		
PCSS	84%	89%
OS	52%	54%
Gleason 8 to 10		
PCSS	67%	80%

OS	32%	45%

Arm 1 = EBRT + 2 months of neoadjuvant CAB + 2 months of concurrent CAB
Arm 2 = EBRT + 2 months of neoadjuvant CAB + 2 months of concurrent CAB + 24 months of adjuvant CAB

Authors' Conclusion – *Long-term androgen deprivation as delivered in this study for the treatment of locally advanced prostate cancer is superior to short-term androgen deprivation for all endpoints except survival. A survival advantage for long-term androgen deprivation in the treatment of locally advanced tumors with a Gleason score of 8 to 10 suggests that this should be the standard of treatment for these high-risk patients*.[4,5]

HRL observations

- The majority (55%) of the participants in RTOG-9202 had a tumor stage of T3 or higher and 33% had an initial PSA level above 30 ng/mL. Despite this there was no difference in survival between arm 1 and arm 2 when considering the entire group. Extended ADT did, however, benefit a subset of patients with a biopsy Gleason score above 7.

C. Study C (EORTC, lead author – Michel Bolla) – This study involved the EORTC Data Center in Brussels, the University Hospital in Grenoble and 12 other cancer treatment centers. It enrolled 412 men with locally advanced prostate cancer between 1987 and 1995 with the final report being issued in 2002. Half of the participants (198 men) were randomized to EBRT alone, while the remaining 203 men were assigned to receive ADT for 3 years starting on the first day of EBRT (70 Gy). The vast majority (91%) of participants had a T3 or higher stage diagnosis and 55% had a Gleason score above 7.

5-year survival	Arm 1	Arm 2
PCSS	79%	94%
OS	62%	78%

Arm 1 = EBRT
Arm 2 = EBRT + 36 months of ADT starting on the first day of RT

Authors' Conclusion – *Immediate androgen suppression with an LHRH analogue given during and for 3 years after external irradiation improves disease-free and overall survival of patients with locally advanced prostate cancer*.[6]

HRL observations

- It is clear that 36 months of ADT following EBRT results in better outcomes than EBRT alone in patients with locally advanced prostate cancer and T3 tumor stage. It is not clear from this study whether shorter ADT would be equally effective.

D. Study D (EORTC22961, lead author – Michel Bolla) – This study was performed by the same group as Study C. It enrolled 970 men with locally advanced prostate cancer with enrolment starting in 1997 and the final report issued in 2009. The purpose of the clinical trial was to determine the difference in outcomes between EBRT + 6 months of CAB and EBRT + 6 months of CAB + 30 months of ADT. Hormone therapy was started on the first day of radiation treatment. The majority (78%) of study participants had T3 tumors and 20% had Gleason scores of 8 to 10.

5-year survival	Arm 1	Arm 2
PCSS	95%	97%
OS	81%	85%

Arm 1 = EBRT + 6 months CAB

Arm 2 = EBRT + 6 months of CAB + 30 months of ADT

Authors' Conclusion – *The combination of radiotherapy plus 6 months of androgen suppression provides inferior survival as compared with radiotherapy plus 3 years of androgen suppression in the treatment of locally advanced prostate cancer.*[7]

HRL observations

- PC-specific survival and overall survival rates at 5 years were impressive in both groups. Prostate cancer survival was 95% in the 6-month group and 97% in the 36-month group, while overall survival was 81% and 85% respectively.

- The small difference in PC-specific survival and overall survival between 6 months of hormone therapy and 36 months would, in light of the numerous serious adverse effects of ADT and CAB, seem to provide little justification for long-term therapy even in men with locally advanced cancer. The study provides no evidence that long-term ADT is of benefit in localized cancer. The authors themselves conclude that, "*Our results may not apply to patients with small tumors and high Gleason scores*."

- For some reason this Bolla study used the "non-inferiority" hypothesis rather than the "Null" hypothesis in determining the statistical significance of the observed differences between 6 months and 3 years of androgen suppression. This is incorrect, since the Bolla team, in 1997, could not have known of the potential for serious harm associated with the use of ADT and CAB in men with serious comorbid conditions. Thus, using the "non-inferiority" hypothesis is, when it comes to overall mortality, not justified. Had Bolla used the statistically correct "Null" hypothesis, there would have been no significant difference in survival between men who received EBRT + 6 months of CAB and men who received EBRT + 6 months of CAB + 30 months of ADT, thus significantly weakening the case for the benefits of extended ADT.

- The authors also make the following interesting statement, "*In our study, the [pre-treatment] Gleason score did not influence the difference in outcome between the two groups.*"

E. Study E (TTROG 9601, lead author – James Denham) – The TTROG 9601 clinical trial was carried out within a large group of Australian and New Zealand cancer treatment centers. The trial began in 1996 and enrolled a total of 802 patients with locally advanced prostate cancer. The final report was issued in 2005 after an average follow-up of 6 years. The trial participants were allocated to receive EBRT on its own or EBRT + 3 months of CAB (2 months pre-EBRT and 1 month concurrent) or EBRT + 6 months of CAB (5 months pre-EBRT and 1 month concurrent). About 40% of participants had T3 or T4 tumors and 17% had a Gleason score of 8 to 10.

Authors' Conclusion – *6 months' androgen deprivation given before and during radiotherapy improves the outlook of patients with locally advanced prostate cancer. Further follow-up is needed to estimate precisely the size of survival benefits. Increased radiation doses and additional periods of androgen deprivation might lead to further benefit.*[8]

HRL observations

- Specific data on overall survival is not presented; however, the authors state, "*To date, however, no significant reductions in overall mortality have been noted in either group assigned androgen deprivation*". In other words, neither 3 months nor 6 months ADT resulted in improved overall survival. It would appear that overall 5-year survival was about 80%.

- The difference in 5-year PC-specific survival between no ADT, 3 months of ADT, and 6 months of ADT is surprisingly small with survival percentages of 91%, 92%, and 94% respectively.

F. Study F (RTOG 86-10 – lead authors Miljenko Pilepich and Mack Roach III) – This study was a collaborative effort between 9 American universities and cancer treatment centers. Enrolment for the trial took place between 1987 and 1991 and involved 456 men with locally advanced prostate cancer. The final report was issued in 2008 after an average follow-up of 6.7 years. The trial participants were randomized to receive EBRT only or EBRT + 2 months of CAB prior to radiation + 2 months CAB concomitant with radiation. Eligible patients were those with bulky tumors (T2-T4), but it is not clear exactly what percentage had T3 or higher tumor stage. The majority (70%) had a Gleason score of 7 to 10. PC-specific survival and overall survival at 5 years were 80% and 85% and 68% and 72% respectively. Estimated PC-specific survival at 10 years was 64% for the EBRT only group vs. 77% in the EBRT + CAB group. Corresponding figures for overall survival were 34% and 43% indicating that prostate cancer becomes less important as a cause of death with aging.

Authors' Conclusions – *In patients with Gleason score 2-6 carcinoma of the prostate, a short course of androgen ablation administered before and during radiotherapy has been associated with a highly significant improvement in local control, reduction in disease progression, and overall survival*.[9]

The addition of 4 months of ADT to EBRT appears to have a dramatic impact on clinically meaningful end points in men with locally advanced disease with no statistically significant impact on the risk of fatal cardiac events.[10]

HRL observations

This trial concludes that 4 months of CAB primarily benefits patients with a Gleason score below 6. A comparison of 5-year PC-specific and overall survival at three different levels of Gleason score is presented below:

	Gleason score		
	2 – 6	7	8 – 10
Number of patients	129	176	124
5-year PC-specific survival			
EBRT only	83%	83%	64%
EBRT + CAB	98%	84%	67%
5-year overall survival			
EBRT only	52%	67%	59%
EBRT + CAB	70%	71%	54%

G. Study G (DFCI 95-096, lead author – Anthony D'Amico) – This clinical trial was a collaborative effort between Brigham and Women's Hospital and Dana Farber Cancer Institute in Boston. Enrolment took place between 1995 and 2001 and involved 206 men with localized but unfavorable prostate cancer. The final report was issued in 2008 after a median follow-up of 8.2 years. The trial participants were randomized to receive EBRT (70 Gy) alone or EBRT + 6 months of CAB (2 months prior to EBRT, during EBRT and 2 months post-treatment). Eligible patients had to have tumor stage less than T3, but at least one unfavorable factor such as a Gleason score above 7 or a pre-treatment PSA above 10 ng/mL.

Five-year PC-specific survival was 95% in the EBRT only group and 100% in the EBRT + CAB group. Corresponding percentages for overall survival were 78% and 90% respectively. At 8 years overall survival was 61% and 74% respectively.

Authors' Conclusion – *The addition of 6 months of AST to RT resulted in increased overall survival in men with localized but unfavorable-risk prostate cancer. This result may pertain only to men without moderate or severe comorbidity, but this requires further assessment in a clinical trial specifically designed to assess this interaction*.[11,12]

HRL observations

- In a follow-up to their original reports Dr. D'Amico and colleagues investigated the importance of using CAB rather than just ADT or part CAB during the 6 months of hormone therapy.[13] Investigating this aspect of CAB is important as 20-30% of patients assigned to anti-androgen therapy do not complete

CAB due to intolerable side effects. The researchers found that at the 8-year mark 54% of men receiving EBRT only had experienced biochemical failure (PSA recurrence). This compared to a biochemical failure rate of 38% among men who received less than 6 months of anti-androgen and 19% among men who received the full 6-month course of anti-androgen (flutamide). It is not clear what the significance of this is as the authors themselves have stated, "*Given that PSA progression does not translate into PC-specific mortality for the vast majority of patients …….*"

- The interaction between overall survival and pre-existing comorbidity (mainly cardiovascular disease) is of considerable importance. The authors observed that men with no or minimal comorbidity had an overall 8-year survival rate of 64% with EBRT alone and 90% with EBRT + CAB. In comparison, men with moderate to severe comorbidity had survival rates of 54% (EBRT only) and 25% (EBRT + CAB) indicating that CAB is not a good idea for men with pre-existing comorbidity.

H. Study H (Phase II trial, lead author – Jonas Heymann) – This clinical trial performed at Columbia University Medical Center involved 123 men with intermediate- to high-risk localized prostate cancer who received EBRT (70 Gy) + 9 months of CAB (luprolide + flutamide). The start of EBRT was individualized to begin after maximum response to androgen deprivation, but in no case was more than 6 months of neoadjuvant treatment allowed. Enrolment to the study took place between 1997 and 2002 and the final report was published in 2007. The majority (83%) of patients had high-risk disease, 53% had a Gleason score above 8, and 51% had tumor stage T2b – T4. The results of the trial were encouraging with 5-year PC-specific survival of 99%, overall survival of 89%, and disease-free survival of 75%. Biochemical failure at 5 years was 37%.

Authors' Conclusion – *The combination of 9 months of AD and RT, with initiation of RT individualized on the basis of maximum response to AD, achieves disease control rates comparable with past studies, while preserving potency in many patients. Further studies are warranted to determine the optimal combination of AD and RT in this patient population*.[14]

HRL observations

- Patients with Gleason score above 7 were more likely to experience recurrence of clinical disease at the 5-year mark than were those with a Gleason score of less than 7 (40% vs. 0%).

- Patients who began EBRT after 6 months of CAB were significantly more likely to experience biochemical failure at the 5-year mark (82% did so) than were those who started EBRT with an undetectable PSA (33% failure rate), at nadir (29%) or when starting to rise again after reaching nadir (18% failure rate).

- Serum testosterone concentration returned to normal ($\geq$ 270 ng/dL) in 69% of patients within a median of 9 months. Patients who recovered testosterone levels after CAB were significantly more likely to survive for 5 years (95% did so) than were patients whose levels did not recover (70% survival).

- Sixty-nine percent of study participants were sexually potent when entering the study. Most lost potency during treatment, but 65% (of the 69%) recovered potency after a median of 10 months.

- Anemia was a fairly common side effect of the treatment, but most men returned to normal hemoglobin levels within a month of ceasing treatment.

- The authors make the following interesting statement – *These findings suggest that testosterone recovery may be beneficial to overall health without having deleterious effects on prostate cancer control, and further support the notion of limiting the length of time androgen deprivation is administered to the minimum necessary*.

I. Study I (RTOG 85-31, lead author – Miljenko Pilepich) – This study was performed by the same group involved in Study F. Enrolment for the trial began in 1987 and involved 977 patients with unfavorable locally advanced PC, tumor stage T3 or higher or regional lymphatic involvement. The final report was issued in 2005 after an average follow-up of 8 years. The trial participants were randomized to standard EBRT followed by ADT until the end of follow-up or death (Arm 1) or RT alone followed by observation and institution of ADT at time of relapse (Arm 2). Radiation dose was 65 to 70 Gy.[15,16] PCSS and overall survival data are presented below:

10-year survival	Arm 1	Arm 2
All patients		
PCSS	84%	78%
OS	49%	39%
Gleason 2 to 6		
PCSS	93%	88%
OS	57%	51%
Gleason 7		
PCSS	88%	82%
OS	52%	42%
Gleason 8 to 10		
PCSS	73%	60%
OS	39%	25%

Arm 1 = RT followed by ADT for duration of trial
Arm 2 = RT followed by observation and institution of ADT at time of relapse

Authors' Conclusions – *Androgen suppression applied as an adjuvant after definitive RT was associated not only with a reduction in disease progression but in a statistically significant improvement in absolute survival. The improvement in survival appeared preferentially in patients with a Gleason score of 7 to 10.*[15]

HRL observations

- It is clear that indefinite ADT following radiation results in longer overall survival compared to radiation + ADT in case of relapse for patients with locally advanced PC. This is especially true for those with Gleason score of 8 to 10. In this group, PCSS was also significantly higher in arm 1 (73% vs. 60%; p = 0.004).

- It is not clear whether results are based on intent-to-treat or on the actual number of patients who remained on their assigned protocol for the duration of the trial. However, continuous ADT is clearly not an easy protocol to follow since only 63% of patients in arm 1 managed to do so.

NOTE: This study is not included in the following discussion of correlations due to the fact that duration of ADT was indefinite.

Correlations – Part 2

From a patient's point of view the most important factors in gauging the success of prostate cancer therapy are his overall long-term survival (overall survival or OS), his odds of not dying from a recurrence of prostate cancer (PC-specific survival or PCSS), and his chances of surviving without having to deal with metastases and other symptoms of recurring prostate cancer (disease-free survival or DFS).

The above considerations are, of course, also of paramount importance to the oncologist treating the patient, but, in addition, the oncologist is also vitally interested in whether or not the patient experiences biochemical failure (BF) defined as a rise in PSA level from the lowest level achieved following the therapy.

A detailed analysis of the data presented in the studies discussed above revealed several interesting correlations between outcomes and the factors affecting them. A discussion of these correlations can be found on-line at www.yourhealthbase.com/ADT/Correlations.pdf

Part 3 of this research report deals with the adverse effects of radiation therapy and androgen deprivation. It will be published in the July/August issue of *The Prostate Monitor*.

Summary

Nine major clinical trials aimed at determining the benefits of radiation therapy (RT) accompanied by androgen deprivation therapy (ADT) or complete androgen blockage (CAB) were reviewed. The majority of patients enrolled in the trials had locally advanced PC (tumor stage T3 or higher), but 461 patients with localized cancer were also included. The following conclusions were reached:

- Patients with localized disease and a Gleason score of 7 or less derive little if any benefit from adding ADT or CAB to EBRT. However, patients with unfavorable localized disease, especially those with a Gleason score of 8 to 10, can derive substantial benefits, especially if hormone therapy is tailored to achieve a PSA nadir prior to the start of EBRT. Long-term adjuvant therapy would likely provide little additional benefit over short-term therapy in patients with localized cancer.

- Patients with locally advanced PC and a Gleason score below 7 may benefit from a short course of CAB in combination with EBRT. For patients with a Gleason score of 7 to 10, long-term therapy (28 to 36 months) may provide improved survival.

- Biochemical failure (BF) at 5 years is inversely correlated with disease-free survival (DFS), PC-specific survival (PCSS), and overall survival (OS) at 5, 8 and 10 years (from initiation of treatment) and also predicts the probability of distant metastasis at 5 years. BF, in turn, is directly associated with initial PSA value and inversely correlated with duration of androgen deprivation.

- PCSS is directly correlated with DFS and inversely correlated with tumor stage, initial PSA value, BF, and distant metastasis at 5 years.

- OS is directly correlated with DFS and inversely correlated with BF and distant metastasis at 5 years.

- There is a strong direct correlation between PCSS and OS with a Gleason score greater than 7 and a tumor stage of T3 or greater increasing the proportion of overall mortality associated with PC or its treatment.

- Continuing ADT or CAB beyond 6 months following EBRT results in a PCSS increase of less than 0.1%/month of continued therapy. In contrast, the first 6 months of therapy is associated with a 1.3% to 2.5% gain in PCSS per month of therapy. Corresponding numbers for OS is 0 to 0.14%/month improvement for treatment beyond 6 months versus 1.8 to 2.7%/month for the first 6 months.

- Long-term PCSS (8 to 10 years from initiation of EBRT) is directly correlated with DFS and inversely correlated with tumor stage, initial PSA value, BF, and distant metastasis at 5 years.

- Long-term OS is directly associated with longer DFS and inversely correlated with BF, distant metastasis, initial PSA value, and tumor stage.

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