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The main theme of this month's issue is the threat of the H1N1 virus. While reports continue to indicate that the swine flu is rather mild in most cases, it is nevertheless desirable to avoid becoming sick. While mainstream medicine's first line of defence is vaccination, it seems important to consider the body's natural defenses provided by the innate immune system. Methods for increasing the chances that this system is functioning properly are discussed and include a number of supplements. Evidence that high levels of 25-hydroxyvitamin D are highly protective continue to accumulate, but since severe deficiency is extremely common, only a limited number of individuals will benefit from having a protective vitamin D status. In fact, your editor has never heard even a whisper in any U.S. network news discussion or in the Canadian national press regarding high vitamin D status as protection from the coming pandemic. Mainstream medicine has always been against taking supplements and there are no large, randomized, placebo controlled (and very expensive) studies that provide statistically significant evidence that maintaining 25-hydroxyvitamin D levels above some threshold provides protection from influenza. Anecdotal and circumstantial evidence does not count.

In this issue other aspects of the swine flu pandemic are discussed including concerns regarding the widespread use of a vaccine with minimal safety testing, and the potential for anti-inflammatory drugs such as aspirin and non-steroidal anti-inflammatory drugs to enhance the virulence of the flu virus.

Other topics include an update on the use of salvestrols in targeted cancer therapy, problems with permanent muscle damage associated with statin use, study results that provide guidance on how to avoid becoming hypertensive and the latest on preventable causes of death in the U.S. population.

Finally, recent disclosures and studies are discussed which further undermine the credibility of published clinical studies and expose the ethics of those involved.

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 good health,

William R. Ware, PhD, Editor

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IMMUNE SYSTEM BOOSTING IN RESPONSE TO THREAT OF H1N1 PANDEMIC

In the context of influenza, mainstream medicine thinks of immunity and immune boosting in terms of vaccines. This translates into artificial active manipulation of the adaptive immune system.

Traditionally the new flu vaccine offered each year is composed of strains determined by a consensus reached months before the season starts and to some is akin to using a crystal ball to forecast the future. H1N1 is different in that a vaccine can be made from the currently active strain although time is short, and the vaccine will receive only limited testing over a very short period. Given the circumstances, it is quite impossible to test for adverse effects that might occur months after inoculation. The recommendation that all pregnant women be vaccinated is a pure act of faith based on earlier experience that there will be no adverse effects on either the mother, the fetus, or the child, either in the near or long term. Some expectant mothers may find this worrisome. Also, flu vaccines drawn from multi-injection bottles generally contain the famous mercury preservative. H1N1 vaccines is also said to contain a chemical or chemicals that augment the effectiveness but these have not been used before and thus not extensively tested.

The approach which impacts the adaptive immune system is of course practical but ignores the innate immune system which may well be more important if the N1H1 virus mutates or if other vaccines do not contain the appropriate strains for the coming flu season. For those who do not believe in vaccines for one reason or another, the innate immune system becomes paramount to their defence against this and other flu viruses. Mainstream medicine tends to ignore protocols that boost the innate immune system because they involve mostly

- Selenium, 200 micrograms/day (maximum)
- Zinc, 30 mg/day (maximum)
- Probiotic sources guaranteed to contain significant levels of beneficial bacteria (billions of cells) such as some yogurts, e.g. *Activa*®
- Omega-3 fatty acids (fish oil) 1-2 g/day
- Garlic extract, 1 g/day
- Grape seed extract 100-200 mg/day
- Green tea extract, 325 mg of EGCG/day
- N-acetyl cysteine, 600-1000 mg/day
- Alpha Lipoic acid, 200-500 mg/day
- Active Hexose Correlated Compound (AHCC) such as *ImmPower*®, 1-2 g/day
- Vitamin D3, 4000-5000 IU/day,
- Beta 1,3/1,6 glucan, 750 mg twice daily. The preparation derived from baker's yeast cell walls appears popular, e.g. *Immuto*®
- Black elderberry extract, dose as suggested by supplier.
- Vitamin A, 5000 IU/day maximum
- Vitamin C, 200-500 mg 3 times a day
- Vitamin E (natural source), 400 IU/day
- Vitamin B6, 50-100 mg/day

non-prescription substances obtained at the health food store and because the research available does not meet their standards. The latter factor is not surprising. Using the profits of the drug companies as a standard, there is no significant money to be made and thus no money for trials that would satisfy those who insist that every intervention be backed by large randomized clinical trials that follow after phase I and II trials. This philosophy ignores the fact that a significant fraction of the modern medicine is not evidence based, a situation which one or two major peer reviewed journals have recently had the courage to document. And it obviously is ignored in the case of seasonal vaccines.

The innate immune system comprises the mechanisms and cells that defend an organism from infection by other organisms by recognizing and responding to pathogens in a generic manner, recruiting immune cells to the sites of infection, activating processes that identify invaders, and promote the clearance of dead cells or antibody complexes. Involved is the identification and removal of foreign substances present in organs, tissues, the blood and lymph by specialized white blood cells. Thus the healthy immune system distinguishes between self and non-self. Recommendations commonly encountered suggest the immune function may be protected and enhanced by supplementation.¹⁻³ Included are the following which are readily available in most health food stores or from

<http://www.yourhealthbase.com/vitamins.htm>:

The reader is cautioned that the scientific evidence of immune function enhancement associated with the above supplements is limited, mostly dependent on rodent studies which may or may not be applicable to humans, and in some cases (e.g. AHCC) the evidence mostly involves individuals with cancer or other disorders and when normal healthy individuals are studied, only some immune functions are enhanced. The strongest evidence appears to exist for vitamin D (see September issue <http://www.yourhealthbase.com/ihn200sg.pdf>). But the silence regarding vitamin D remains deafening. On the current vitamin D Council website there are two anecdotal emails from physicians regarding the apparent remarkable power of vitamin D to prevent flu. On the home page, click on the link "vitamin D and the H1N1 swine flu."

Elderberry flavonoids have actually been tested *in vitro* for anti-H1N1 activity and found effective. Certain flavonoids in this berry bind to the virus and inhibit its action.⁴ This study found elderberry extract equivalent in anti-influenza activity to Tamiflu®, the famous antiviral that governments are stockpiling. This is consistent with a randomized, placebo controlled trial of oral elderberry extract in the treatment of influenza A and B virus infections which found it effective.⁵ A variety of extracts are commercially available. Perhaps alternating between two or three brands would be wise since there is little guidance regarding dose or extract type.

Precautions: Individuals taking warfarin (Coumadin) should consult their doctor before taking large amounts of fish oil, although the risk of enhanced bleeding is debatable. A number of mainstream guidelines recommend 1 g/day for heart health or other benefits. Garlic has blood-thinning and anti-clotting properties, but is of course consumed in large amounts in many cultures. Green tea extract combined with aspirin or warfarin can increase the risk of bleeding. N-acetyl cysteine is contraindicated for individuals with chronic liver disease, a history of kidney stones or peptic ulcer. If one also takes a multivitamin, check the zinc and selenium content and do not exceed the maximums given above. Many multivitamin preparations already include the indicated amounts of these two minerals. AHCC has been widely used in Japan for some time with no adverse effects.

If an individual has gut dysfunction this can greatly weaken the immune system, cause nutritional deficiencies and presumably make one more susceptible to influenza. This is a complex issue

and symptoms can range from subtle to acute. Symptoms include chronic constipation or diarrhea or an alternation between the two, excessive gas or bloating, anemia, sugar intolerance and chronic fatigue. A common cause is the heavy use of antibiotics which can severely disturb the balance of good and bad gut flora. Frequently this can be addressed with probiotics either from yogurt or in capsule form or both. But many commercial yogurts in fact are essentially probiotic free due to pasteurization. Lactose and gluten intolerance may play an important role and can be addressed with diet modifications. Small bowel bacterial overgrowth (e.g. candida) may also play a critical role in gut dysfunction and immune impairment and can be challenging to diagnose. Frequent infections may also suggest an impaired immune system. Readers are referred to the book *Gut and Psychology Syndrome* by Dr. Natasha Campbell-McBride (Medinform Publishing, 2004) for a detailed discussion of gut dysfunction and its treatment with diet and other therapies. While the emphasis in this book is on children and the gut-brain connection, much of the material is equally applicable to adults. The chapter on probiotics is highly recommended.

Regular exercise should also not be ignored as a component of an immune boosting program. This is particularly true for older individuals who are at risk of so-called immunosenescence, the change in the immune system associated with aging. One of the most important findings to emerge from study of the relationship between exercise and immunity is that positive immune changes appear to occur during each session of moderate physical activity. It has been found that over time this results in fewer days of sickness associated with the common cold, influenza and other infections, and is consistent with public health guidelines recommending near-daily physical activity of 30 minutes or more.⁶ However, vigorous exercise in young individuals can have the opposite effect on the immune system, but this is not seen in older persons.⁷ In addition, aging can have a negative effect on immunity due to stress and exercise may be an effective intervention to limit the impact of stress in chronically affected older populations.⁸ The observed exercised-enhanced influenza immunity in older adults may in fact be mediated in part by improvements in psychosocial factors.⁹ In the case of upper respiratory tract infections, the amount of physical activity required to achieve protection is not clear since incidence, seriousness and duration are issues. In one study walking for 90 minutes a day was associated with the greatest protection. But data is limited. Daily exercise such as a 30-60 minute walk appears to be

one of the most challenging interventions to implement, given the hectic modern pace and complexity of daily life. But the benefits go well beyond immune boosting and it seems clearly worth the effort to program such activity into ones daily routine, difficult as this may be. For retired individuals or those no longer raising children, exercise programs should be much easier to implement, and they may stand to achieve the most benefit. The synergism of exercise with diet has come up a number of times in studies discussed in this Newsletter, most recently in connection with reducing the risk of progression to diabetes.

Finally, several observational studies suggested that statin drugs protect against pneumonia. A

recent population based case-control study failed to find any association with decreased risk of pneumonia among immuno-competent community dwelling older individuals and suggest that previous studies may reflect “healthy user” bias, a serious problem in observational studies related to the particular population willing or enthusiastic about participation.¹⁰

There is of course no guarantee that if one engages in a program of immune boosting that they will not contract or even die from H1N1. But it is hard to believe that the above interventions will be other than beneficial.

ANTI-INFLAMMATORY DRUGS AND H1N1 INFLUENZA

A letter in the *British Medical Journal* calls for immediate research regarding the risks associated with the use of aspirin, ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) in treating symptoms of the H1N1 flu. The authors point out that aspirin may have enhanced the virulence of the flu virus in the 1918 pandemic, an observation that has implications for the present situation. They also point out that NSAIDs in general have potentially harmful effects since they

may aggravate severe sepsis with multi-organ failure. They also comment that since the flu pandemics of the 20th century, aspirin use for children with flu symptoms has been contraindicated due to a link with Rey's syndrome but other NSAIDs are still used. When the use of diclofenac and mefenamic were restricted for use in children in Japan in 2000, the case fatality rate of flu associated encephalopathy fell dramatically.¹¹

AUSTRALIAN EXPERIENCE—AN INTERIM REPORT

It is well known among flu experts that the seasonal variation of influenza in the southern hemisphere mirrors that in the northern hemisphere with both peaking in the respective winter months. Thus there is a 6-month phase shift. The experience thus far in Australia is thus of interest because it may offer clues as to what to expect this coming winter north of the equator. A recent report appeared in the journal *Eurosurveillance*.¹² The following observations are of interest: (a) The expected

seasonal flu activity is similar to other years of high activity (2003 and 2007); (b) the H1N1 virus has been responsible for most of the cases where nose swabs were taken and the virus identified; (c) there was no evidence of significant protection against H1N1 from traditional seasonal vaccines in any age group; (d) the age group 20-49 had the highest proportion of seasonal H1N1 influenza, and 5-19 was next. Very low incidence was seen in the 0-4 and 65+ age groups.

SWINE FLU VACCINE DEBATE

This issue will not attempt to discuss in detail the scientific aspects or take a position on the flu vaccination question, either in connection with the swine flu or flu in general. The available data is of necessity incomplete and subject to strong governmental and industrial bias and a high level of emotional input. Nevertheless, your editor is looking

for a nice color picture of guinea pig “suitable for framing” to hang in his study. This is motivated by the concerns raised regarding safety, the short duration of testing, the history of the last swine flu vaccination program and problems inherent to side effect monitoring.

The H1N1 virus is unlike any previously isolated and has an unusual combination of sequences from bird, human and swine flu virus lineages from both North America and Eurasia. It has been suggested that such a strikingly unusual virus may have been created in the laboratory and released by accident.¹³ The flu risk it is perceived to present has been classed by the WHO as a pandemic and the rush is on to develop vaccines, test them, and then inoculate as many occupants of the planet as possible, starting with, so we are told, children (newborns as well??), young people, pregnant women, and health care workers. Testing must be finished quickly since influenza is well known to have a very strong seasonal pattern (nicely explained in detail by vitamin D deficiency incidentally). Since the goal is to start mass immunization early in the fall, the testing for adverse effects is of necessity very short term and a much larger sample is needed to detect rare but potential deadly side effects. But this is not possible. Exhibit A is the Guillain-Barre Syndrome (GBS) which was associated with the 1979 swine flu vaccine. GBS attacks the lining of the nerves causing paralysis and the inability to breath and can have fatal results. In 1997 it is estimated that more people died from the vaccination than from swine flu. About 500 cases of GBS were reported

In the UK, the newspaper the *Daily Mail* published a leaked letter from the Health Protection Agency which informed neurologists that they must be extra vigilant regarding possible GBS cases. The *Daily Mail* also quoted from a second letter from the Association of British Neurologists that had the same theme. Thus there is concern among experts regarding the threat of GBS. In the US, 40 million individuals were vaccinated in 1997 before the

program was stopped at 10 weeks. To get statistically significant data, it again will require inoculating a large number of "guinea pigs" before the vaccine can be declared free of the GBS side effect. Will all these individuals be provided with what is required for an informed consent? In the case of children, will be their parents receive such information. How can one describe the unknown risk to an unborn child or a pregnant woman? Can several million or more individuals in the age groups targeted be vaccinated, side effects documented and reported to central agencies, and the general picture developed before mass vaccination starts? Hardly in just a few weeks. Certainly adverse prenatal and neonatal effects can not be determined at all, and what about years down the road? The Internet provides a growing source of opinion concerning this debate.

A useful source for readers living in the U.S. is the National Vaccine Information Center.¹⁴ This website is currently indicating that in the U.S. the required testing period for the new swine flu vaccine will be one to three weeks with testing on less than a thousand children and adults. The website also contains a discussion of so-called adjuvants, chemicals added to enhance the effectiveness of the vaccine, and the possibility is discussed that that the vaccines used in the U.S. will contain oil-based chemicals which are untested, potentially very toxic, and thought to have caused serious problems with previous vaccines. Adjuvants allow the use of lower amounts of the viral component in each dose. According to a U.S. law passed after 9/11, once an emergency has been declared by the government, the vaccine manufacturers are not liable for harm caused by the vaccines and can not be subjected to lawsuits.

SALVESTROL UPDATE

At a one-day *Cancer Prevention and Healing Conference* held in North Vancouver, B.C., Michael Wakeman, executive director of the U.K. company Nature's Defence, gave a lecture on salvestrols which included recent results from the laboratory of Dr. Gerald Potter (see the June 2008 issue for a discussion of Salvestrols). They have developed analytical techniques which permit the identification of Salvestrols in the circulation and as well the metabolites from the enzyme action unique to cancer cells due to the presence of the enzyme CyP1B1. The appearance of the metabolite of the salvestrol is a marker for the expression of the

enzyme and thus the presence of cancer, and its decline with treatment a measure of success. The diagnostic implications alone are impressive. Waldman also showed impressive slides of cancer and normal cells where fluorescence techniques were employed to highlight the presence of a metabolite of CYP1B1. Under fluorescence microscopy, the cancer cells light up brilliantly while normal cells are dark. One of the slides showed prostate cancer cells vs. normal prostate cells to illustrate the fluorescence visualization. In a paper by your editor recently published in the journal *Medical Hypotheses*, it was suggested that

fluorescent metabolites of CYPB1B have potential utility in providing visualization of cancer tumors, for example in the bladder wall, and the fluorescence concentrated just in the tumor cells may help outline surgical margins, a particularly serious problem in brain tumor surgery. In addition, there may be some metabolites which will provide targets for photodynamic therapy, where light is used to induce cytotoxicity.

Westman also discussed recent work which further confirms the impact of herbicide and insecticide use on the levels of Salvestrols in fruits, where organically grown fruits have a much higher content of active substrates for CYP1B1. This may be underappreciated by manufacturers of fruit extracts sold as dietary supplements since the benefits of

these extracts in the context of cancer may also operate in part if not significantly via Salvestrols, and the levels will be much reduced.¹⁵

Of course, the most interesting aspect of Salvestrols, the results of clinical trials, is awaited with great interest. It may turn out that the first extensively tested compounds will be synthetic rather than natural, will be patentable, and if successful will end up in the same category as chemotherapeutic drugs. Meanwhile, all we appear to have are the case histories discussed in an earlier newsletter and the ready availability of natural Salvestrols from Nature's Defence. This product appears to be under constant improvement as new and more potent Salvestrols are identified.

MEDICAL LITERATURE—PROBLEMS CONCERNING CREDIBILITY AND ETHICS

In the May issue of the open access journal *PLoS ONE*, a paper appeared which presented a systematic review of the practice of fabricating and falsifying research.¹⁶ The literature examined involved published results of surveys which asked scientists about their own actions and what they had observed in colleagues. In surveys asking about the behaviour of colleagues, over 14% of respondents claimed knowledge of falsification and up to 72% claimed to be aware of other questionable research practices. In spite of the obvious limitations of such a study, the author considers the results a conservative estimate of the true prevalence of scientific misconduct. This study comes after several reports in the past year or so of peer review journals "withdrawing" or "disowning" articles found to be fabricated,

Another phenomenon that eats away at credibility is the practice of ghostwriting. In the August 5 issue of the *New York Times* it was revealed on the basis of court documents that ghostwriters paid by a pharmaceutical company played a major role in producing 26 scientific papers backing the use of hormone replacement therapy for women. The magnitude of this operation was taken as suggesting that the level of hidden industry influence on medical literature is broader than previously recognized. The firm in question contracted with a so-called medical communications company, i.e. a firm that writes medical papers from drug company-provided outlines and data. Recognized physicians who had little or nothing to

do with the paper or the underlying research were then paid to attach their names to the papers and in the process introduce the associated prestige of their institutions in support of the importance and validity of the work. This comes on the heels of the revelation mentioned in an earlier Newsletter that one highly regarded medical journal publishing company actually created fake journals with convincing titles which contained nothing but industry written papers, the sole purpose for which these journals were created.

Ghostwriting has come to the attention of some members of the U.S. congress who are disturbed about the implications. The August 19 issue of the *New York Times* carries an article describing a letter from a senator to the National Institutes of Health requesting information on how they propose to control such practices among researchers supported by the NIH, i.e. the taxpayer. This follows a similar letter to journals addressing the issue of detecting and rejecting ghostwritten papers. The article quotes a professor of cardiology from the University of Wisconsin School of Medicine saying that he recently turned down a request to be a ghostwriter for a paper about the effectiveness of a cholesterol-lowering drug. What is interesting is that he was quoted as also saying "This happens all the time." The good news is that some of the major journals are taking positive action to identify and reject ghostwritten papers and to require detailed statements from all authors as to their contributions. But there are hundreds of journals and many do not

require any declaration of conflict of interest or author contribution disclosure. It is hard to be very optimistic. The name of the game is to get papers favourable to a product published, obtain thousands if not tens of thousands of reprints, and then distribute them to the profession during drug rep office visits. Unfortunately, this is the primary mechanism whereby the profession stays abreast of "progress" in medicine. Some readers may not realize that a major and in some cases vital source of income for publishers of medical journals comes

from the money made selling reprints to pharmaceutical companies. See the recent book by Richard Smith titled *The Trouble with Medical Journals*. Smith worked for the *British Medical Journal* for 25 years and was Editor and Chief Executive of BMJ Publishing from 1991 to 2004. The book is of considerable interest at present because it discusses problems not only with industry influence but also with the whole peer review process.

STATIN-ASSOCIATED MUSCLE DISORDERS AND SKELETAL MUSCLE DAMAGE

A study has just appeared in the *Canadian Medical Association Journal* which associates persistent myopathy (pain and weakness) with structural muscle damage.¹⁷ The researchers examined 44 patients with clinically diagnosed statin-associated myopathy of which 29 were currently taking a statin and 15 had discontinued statin therapy. Also included were 19 patients taking statins who had no myopathy and 20 who had never taken the drug. Biopsies were used to assess muscle damage. Muscle injury was observed in 24 of the 44 patients with myopathy and in 1 patient without myopathy. Only one patient had a circulating level of the standard marker which exceeded the threshold used as a warning sign (creatinine phosphokinase \geq 1950 U/L). The authors conclude that the current cut-off for this marker fails to exclude potential structural muscle damage.

This study directly relates to the problem of permanent myopathy. For a discussion of this subject we turn to a just published book *The Statin Damage Crisis* by Duane Graveline, M.D., an USAF flight surgeon, and a NASA astronaut. He is currently a retired family physician suffering from what he believes are side effects of statins which for him have been physically devastating. His book has a section on permanent muscle damage which is of interest in connection with the above paper. Acute muscle problems associated with statin use involve rhabdomyolysis which can be fatal. The statin Baycol caused at least 100 deaths before it was recalled. Permanent muscle damage is not fatal but a serious side effect. Graveline quotes Dr. Beatrice Golomb of the University of California San Diego as reporting that 68% of her statin myopathy patients have permanent damage. Graveline collects statin side-effect reports and points out that there is small but growing subgroup of patients with the primary

complaint of muscle aches and pains persisting for months or even years after they stopped statin therapy. In fact, 25% of his myopathy reports are of the persistent type. He points out that Golomb's higher number reflects individuals who have come to her seeking further evaluation.

Readers interested in statin side effects are encouraged to acquire Graveline's book which is the third in the series on statin side effects (www.spacedoc.net or Amazon.com.) He was first drawn into studying this subject after two incapacitating episodes of global transient amnesia. Those resolved upon statin treatment termination, but he has suffered progressive degeneration to the point of using a walker. This book describes a number of side effects including the mimicking of ALS (Lou Gehrig's disease), permanent peripheral neuropathy and chronic neuromuscular degeneration. He also deals at length with the ramifications of the inhibition by statins of the acetyl and mevalonate pathway which impacts a large number of critical biological process and at least six critical biochemicals, of course including cholesterol. How important these inhibitions will turn out to be in the final analysis remains to be seen. The experiments are ongoing with the general public acting as guinea pigs, incidentally without giving informed consent. He also describes his recent protocol which seems to be slowly reversing his disability. Graveline's website www.spacedoc.net is one way to keep up to date with this aspect of statins.

In late 2008 Golomb and Evans from the University of California San Diego published a comprehensive review (893 references) in the *American Journal of Cardiovascular Drugs* of the literature and evidence for a mitochondrial mechanism for statin adverse

side effects.¹⁸ They conclude that adverse effects of statins are neither vanishingly rare nor of trivial impact. They find convergent evidence supporting the role for mitochondrial predispositions and mechanisms for statin muscle adverse effects and

suggest that mitochondrial dysfunction may underlie additional adverse effects reported on statins.

Dr. Golomb is also actively collecting reports of statin side effects and those interested in this subject no doubt eagerly await further publications.

MODIFIABLE RISK FACTORS FOR HYPERTENSION IN WOMEN

A recent study has just appeared in the JAMA which examined the potential risk reduction for developing high blood pressure associated with diet and lifestyle changes.¹⁹ This was part of the Second Nurses' Health Study from Harvard. Almost 84,000 adult women between 27 and 44 years of age who did not have hypertension, cardiovascular disease, diabetes or cancer in 1991 and who had normal blood pressure were followed for 14 years. Six modifiable lifestyle and diet factors for hypertension were identified which were protective. They were a body mass index (BMI) of < 25 (not overweight), a daily mean of 30 minutes of vigorous exercise, a high score in adherence to the so-called Dash diet, modest alcohol intake, use of non-narcotic

analgesics (e.g. aspirin or acetaminophen) less than once per week, and an intake of 400 or more micrograms of folic acid daily. A high DASH diet score was achieved with a high intake of fruits, vegetables, nuts and legumes, low-fat dairy and whole grains, and a low intake of sodium, sweetened beverages and red and processed meats. The risk factors were then grouped as follows: 3 factor group—3 highest quintiles of the DASH diet plus exercise plus BMI < 25; 4 factor group—add alcohol intake 0.1-10 g/d, i.e. less than one drink maximum; 5 factor group—add low analgesic use; 6 factor group—add folic acid supplementation. The results of statistical analysis which yielded large risk reductions were:

| <u>FACTORS</u> | <u>HR</u> | <u>NNT</u> |
|----------------|-----------|------------|
| Group of 3 | 0.46 | 16.6 |
| Group of 4 | 0.42 | 15.9 |
| Group of 5 | 0.28 | 12.9 |
| Group of 6 | 0.22 | 11.9 |

HR = hazard ratio approximately equivalent to the odds ratio
 NNT = number needed to treat to prevent one case

These are very favourable hazard ratios suggesting risk reduction of from about 54% to 78%. When adjusted for the absence of family history of hypertension or oral contraceptive use, HRs were even lower. Those in Group of 6 without family history of hypertension had a risk reduction of 90%. Also, compared to many popular interventions, the above numbers needed to treat are quite low and favourable. In their discussion, the authors point out that each of the risk factors considered has been studied separately and found to be important in the context of hypertension. In addition, intervention trials found that reductions in blood pressure resulted from weight loss, physical activity, the DASH-type diet, alcohol reduction and folic acid supplementation and increases resulted from the administration of acetaminophen, aspirin and non-steroidal anti-inflammatory drugs. They also found

that BMI was the most powerful predictor of incident hypertension. In addition, it was found that obese women might not benefit from the other low-risk behaviours unless weight loss was addressed as well. But achieving and maintaining a low BMI and exercising vigorously for 30 minutes a day are unfortunately not realistic for many individuals. But the potential appears to be there for dramatic risk reduction.

These results are not only of interest in connection with the risk of cardiovascular events, but in addition, when one looks at the factors associated with the progression of coronary atherosclerosis measured by the calcium score from non-invasive imaging, hypertension is the only traditional risk factor to be consistently significant.²⁰

PREVENTABLE CAUSES OF DEATH – COMPARATIVE RISK ASSESSMENT

Data available from the National Health and Nutrition Examination Survey (NHANES) and the National Center for Health Statistics plus the vast number of studies and meta-analyses in the medical literature permit the estimation of the relative contribution of various risk factors to mortality. A recent study reported in the open access journal *PloS Medicine*²¹ has examined the comparative mortality risk of a number of dietary, lifestyle and metabolic risk factors. The results are reported in terms of excess deaths in the population due to elevated risk factors. Inputs involved were the

current population distribution risk factor exposure, the etiological effect of the exposures on disease specific mortality, an alternative exposure distribution, and the number of disease specific deaths in the population.

For the following risk factors, they estimated the disease specific deaths attributable to non-optimal levels of each factor. In 2005, the following results starting with the leading cause of death in the U.S. were as follows:

| <u>FACTORS</u> | <u>TOTAL DEATHS</u> |
|---------------------------------|---------------------|
| Tobacco smoking | 467,000 |
| High blood pressure | 395,000 |
| Overweight-obesity | 216,000 |
| Physical inactivity | 191,000 |
| High dietary salt | 102,000 |
| Low omega-3 fatty acid intake | 84,000 |
| High dietary <i>trans</i> -fats | 82,000 |
| Low fruit and vegetable intake | 58,000 |

For alcohol, while 26,000 cardiovascular deaths were averted, they estimate a total of 90,000 were caused by adverse alcohol effects, including alcoholism, accidents and suicide. Together, tobacco smoking and high blood pressure accounted for one in five or six deaths among U.S. adults. This puts the figures in perspective. High blood glucose was roughly equivalent to physical inactivity. The authors estimate the impact of elevated LDL cholesterol as about half that of physical inactivity, but their source for the etiological data was one meta-analysis of statin lowering studies and it is not clear the extent to which statins lower mortality by a LDL lowering mechanisms.

Thus this figure is highly suspect. However, the lead author quoted in *theheart.org* stated that the low impact of elevated LDL was surprising and that LDL was not a major risk factor for mortality. If one were able to correct for the non-lipid lowering effects of statins, the contribution might be much lower.

Interventions are available for these risk factors and suggest that there are significant opportunities to decrease mortality in the U.S. The full paper, which is available without cost online, provides much more data and information, including a breakdown into causes of death for each risk factor.

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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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In this issue we further update the success of one individual in arresting PSA progression after failure of salvage radiation therapy following failed prostate surgery. He now has gone almost two years with a stable PSA < 1.0 after experiencing a steady increase after the RT nadir. The only intervention has been 8 oz per day of pomegranate juice.

We also discuss recent research concerning the use of hormone therapy either before or during and after radiation therapy. Of particular interest is the issue of the optimum duration of hormone therapy before RT. The results comparing duration with using PSA as a marker are very interesting, especially regarding the long term results. Also, recent research suggests that hormone therapy after RT is beneficial even for elderly individuals, but only if they are otherwise in good health.

Benign prostatic hyperplasia (BPH) is a major problem in men as they age and it is responsible for serious lifestyle problems. In this issue we discuss dietary patterns and supplement use in connection with protection from developing serious or acute BPH symptoms. In addition, evidence is discussed that moderate alcohol consumption is beneficial in the context of preventing BPH severe enough to require surgical intervention.

Finally, a number of other prostate related issues are mentioned in the News Briefs section.

Wishing you continuing good health,

William R. Ware, PhD, Editor

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

UPDATE ON POMEGRANATE JUICE

Readers will recall that we have been following an individual who had been self-treating PSA failure after salvage radiation therapy subsequent to failed surgery for prostate cancer. Pomegranate juice (POM brand, 8 oz per day) has stopped the PSA progression in its tracks for about 18 months. In February 2009, his PSA was 0.61 ng/mL. Now, six months later his most recent value is down to 0.51 ng/mL. Tests were done at the same laboratory. We will keep readers posted. His urologists continue to show no interest whatsoever in what he is doing or the results. One wonders how many of these doctors' other patients with failed salvage RT suddenly have a 2-year statistically significant halt in the advance of PSA at a level below 1.0. Your editor would be willing to bet that is either zero or very small, since this goes against the natural history of the disease, since once the PSA starts up, it advances with ever increasing PSA and eventually shows evidence of metastasis and finally death, either from cancer or from a comorbidity. The use of pomegranate juice is not based on promotions by snake oil salesmen or the pomegranate juice industry, but derives from serious and ongoing research at the University of California at Los Angeles, an institution which is regarded as first-class, and has been published in peer reviewed journals.

AHCC AGAINST HORMONE-RESISTANCE PROSTATE CANCER. A CASE HISTORY

An very interesting case history has recent appeared in the journal *Anti-Cancer Drugs*¹. A 66-year-old man was diagnosed in July 2006 with metastatic prostate cancer and was admitted to hospital for assessment and treatment of pain. He had received no prior treatment and his PSA was over 2000 ng/mL. He was started on hormone therapy (complete androgen blockage) and at discharge had a PSA of almost 1000 mg/dL. The androgen blockage resulted in a decline of PSA to 2.57 in November 2006. However, in 2007 his PSA started up with a value of 30 ng/mL in April, at which point androgen blockage was stopped to access the impact of withdrawal and by June his PSA was 70 ng/mL. At this point the gentleman took matters into his own hands and started taking a mushroom extract AHCC supplement (ImmPower). By the end of June his PSA was 3.35 ng/mL, a 95% reduction and in November 2007 it was 2.57. Repeat imaging revealed stable bone cancer and at the writing of the paper he was doing well symptomatically with improved walking due to alleviated pain. He continues to take AHCC. Normally hormone resistant prostate cancer simply progresses with relentless increases in PSA and the median survival time is 18 months. In this case the disease appears to have been at least stabilized and perhaps regression is taking place. It is to the great credit of his physicians that they published this apparent success of alternative medicine. They are associated with the Medical University of South Carolina, USA. AHCC is widely available in health food stores and the brand used in this case is available at <http://www.yourhealthbase.com/vitamins/vitamin16.htm>

DIETARY PATTERNS, SUPPLEMENT USE, AND RISK OF BENIGN PROSTATIC HYPERPLASIA (BPH)

A recent review of this subject is of interest.² This review was concerned with large prospective studies that used the development of moderate to severe lower urinary tract symptoms (LUTS) as an indication. Potentially protective lifestyle, dietary habits and supplement use were examined. Factors found protective included low waist to hip ratio, high physical activity, alcohol ≥ 2 drinks /day, high vegetable intake, low fat diet, and dietary micronutrients carotene, lycopene, lutein, vitamin C and zinc. Supplemental micronutrients were found ineffective and supplemental zinc possibly harmful at high doses. Also, for some unknown reason, vitamin C from vegetables but not from fruit was beneficial. The factors that were beneficial in general provided decreases in the risk of serious or acute BPH symptoms had odds similar to the standard medical therapy provided by alpha-blockers and 5-alpha-reductase inhibitors. However, this is based on

prospective studies in comparison to intervention study results with pharmaceuticals, and the benefits associated with intervention for lifestyle and dietary factors is unknown.

ALCOHOL CONSUMPTION AND BENIGN PROSTATIC HYPERPLASIA

This is a complex subject to study since there are a number of potentially useful definitions of BPH. Men generally become aware of BPH when what are called lower urinary tract symptoms (LUTS) become bothersome. However, a number of studies investigating the association with alcohol consumption used non-cancer prostate surgery to define the disorder, i.e. acute LUTS, either alone or in combination with non-acute urinary symptoms. In a recent meta-analysis³ which included 19 studies, 14 used this definition as the primary outcome and 5 used LUTS alone. When the studies employing acute BPH as an endpoint were used, alcohol intake of 36 g/day (2-3 drinks) or greater was associated with a 35% decrease in the risk of developing BPH, a result that was statistically significant. However, the studies that used LUTS as an indicator of BPH, when pooled, suggested no significant connection. Thus it appears that moderate alcohol consumption can prevent or delay manifestations of prostate enlargement severe enough to require drastic action.

HORMONE THERAPY BEFORE RADIATION THERAPY

When hormone therapy (androgen-deprivation therapy—ADT) is given prior to radiation therapy (RT) it is called *neoadjuvant*, whereas if it accompanies and/or then follows RT it is called *adjuvant*. ADT can involve either monotherapy or combined therapy with several drugs that modify the androgen levels, in particular testosterone. These include luteinizing hormone releasing hormone agonist (LHRH-A) which decreases the stimulation of the testicles to produce testosterone, LHRH antagonists which block LHRH, and antiandrogens which block androgen receptors and prevent testosterone and dihydrotestosterone from stimulating prostate cancer growth. There is also the approach where 5-alpha reductase inhibitors are added (e.g. Proscar), but this is generally not done in the neoadjuvant or even adjuvant setting, but for ADT as a monotherapy for advanced prostate cancer. A detailed discussion will be found in our book.

Neoadjuvant ADT combined with RT is the current standard of care for men with clinically localized, high-risk prostate cancer, and those of intermediate risk may also benefit. Important issues include the duration of the neoadjuvant therapy and whether the duration should be determined by a marker such as PSA, i.e. by biochemical response. Two recent studies address these issues. In one, a cohort with a median prostate volume of 82 cc (2-3 times normal) were given a LHRH agent plus an antiandrogen and the time course of prostate volume observed. Most of the decline occurred during the first 3 months, and after 6 months there was no additional significant decline. The authors use this as an argument for 6 months being the optimal period for neoadjuvant ADT prior to RT.⁴ This study did not look at post-RT results.

A different point of view was recently put forward by Alexander *et al*⁵ based on a randomized trial of either 3 or 8 months of neoadjuvant treatment with a LHRH agonist (Zoladex) and an antiandrogen (Flutamide). Patients were assessed every 2 months during the ADT, 1 month after RT, and every 3 months for 2 years and every 4-6 months for the subsequent 3 years. A digital rectal exam and serum PSA and testosterone were measured at each visit. Outcomes included no evidence of disease, biochemical failure (PSA increasing from the nadir) and local or distant failure. Local failure was defined as an abnormal DRE along with rising PSA and/or residual disease on biopsy. Distant failure required evidence of metastasis.

It was found that the PSA response to neoadjuvant ADT before RT, not the duration, appears to be the critical and independent determinant of benefit when comparisons were made between nadirs of ≤ 0.1 ng/mL and >0.1 ng/mL. It follows from the results that

individualized determination of ADT duration based on the PSA response would maximize benefit while minimizing the duration of ADT and its related toxicities. In the 3-month arm of the study, 26.4% of the patients achieved levels of ≤ 0.1 ng/mL whereas 44.1% did so in the 8-month arm. Nevertheless, while the duration of the neoadjuvant ADT was not significantly related to the disease free survival, a higher T-stage (T3-4 vs. T1-2) and/or higher Gleason (7 vs. ≤ 6 and 10-8 vs. ≤ 6) score were significant predictors of reduced outcome benefit. Differences over time (8 years) in the PSA determined disease free survival between those starting RT with PSA ≤ 0.1 ng/mL and >0.1 ng/mL were much more pronounced in patients with high grade disease (Gleason 8-10) or those judged high-risk (initial PSA > 20 ng/mL, Gleason 8-10, and/or T3-T4 disease, the latter implying tumors extending through the prostatic capsule or invading the seminal vesicles, or invading other extra-prostatic structures).

One interesting result was that patients with testosterone recovery after ADT enjoyed significantly higher survival than those whose testosterone levels did not recover to normal. This underlines the complexity of the relationship between testosterone and prostate cancer. In fact, many aspects of the conventional wisdom concerning testosterone and prostate cancer have been questioned (see for example the new book by Abraham Mortentaler from Harvard Medical School titled *Testosterone for Life*).

RADIATION THERAPY PLUS ANDROGEN DEPRIVATION THERAPY VS. RADIATION THERAPY ALONE FOR OLDER HEALTHY MEN

Radiation therapy (RT) vs. RT followed by 6 months of androgen deprivation therapy (ADT) has been compared in a group of men over 75 who had intermediate- to high-risk localized prostate cancer. For analysis of the risk of mortality, the group was stratified by the presence of comorbidities. It was found that in patients with mild or no comorbidity, the combined therapy resulted in significant lower risk of death after correcting for confounding with a significantly lower 8-year mortality estimated at 16.5% vs. 41.5%. However, in men with moderate to severe comorbidities, combined therapy resulted in a much higher risk of all-cause death compared to RT alone.⁶ The authors point out that this result has important implications regarding screening and that screening recommendations should not be based just on unsung an age cut-off, but also take into account comorbidities since even elderly men who are in very good health appear to benefit from RT with ADT. This study used a LHRH agonist and the antiandrogen flutamide.

IS ACTIVE CELLULAR IMMUNOTHERAPY FOR PROSTATE CANCER READY FOR PRIME TIME?

A number of immunotherapeutic approaches are under development and in early trial stages. Some would describe these as vaccine based approaches. They have different hypothesized anti-tumor mechanisms and are being tested for the most part on individuals both with PSA recurrence or with advanced, hormone resistant cancer. These studies are too small and too early to provide much guidance as to their potential in the context of meaningful endpoints.⁷ However, integrated data from two randomized phase III trials have just been reported which provide some insight.⁸ These studies used sipuleucel-T, a personalized immunotherapy produced by culturing the patient's peripheral blood monocytes with a proprietary protein. The resultant product, which is hypothesized to stimulate an immune response against prostate cancer, is then introduced into the patient via IV. The combined studies had 147 individuals in the treatment arm, 78 in the placebo arm. Patients had radiologic evidence of metastases and expected survival of at least 3 months. The mean times to progression after treatment were 11.1 vs. 9.7 weeks for the placebo group, a result without significance. Progression was independent of the presence of symptomatic disease at the time to treatment. In terms of overall survival, for the treatment group it was 23.2 months (95% interval 19.0-31.0) whereas for the placebo group it was 18.9 (95% interval 13.5-25.3) months, for a difference in means of 4.3

months. However, patients in both groups received additional treatment once progression was identified, i.e. over most of the course of the study. These treatments were at the discretion of the attending physician in each case. Side effects from the immunotherapy were described as mostly minor and rapidly resolved. Four of the eight investigators either owned stock in the company making the product or were actual employees.

The small difference in mean survival, while statistically significant, emerges from two strongly overlapping distributions with many patients obtaining no benefit. The treatment also did not prevent progression and the need for conventional treatments, and thus appears to offer limited appealing features to individuals with advanced disease.

In summarizing the status of the field at present, Risk and Corman⁹ point out that immunotherapy may need to be combined with conventional therapies and may work better on individuals with lower tumor burden where the tumor is less likely to evade immune action or the immune system is not as weak as in men in the later stages of the disease. We seem far from seeing immunotherapy as a standard approach.

NEWS BRIEFS

- Neoadjuvant hormone therapy use is significantly associated with increased risk of all-cause mortality among men with a history of coronary artery disease induced congestive heart failure or heart attack, but not among men with no coronary comorbidity or a single coronary artery disease risk factor.¹⁰
- In a comparison of open and laparoscopic techniques for radical prostatectomy, similar functional outcomes associated with return to baseline were found for continence, erectile function and overall physical function. Cancer control was excellent at 1 year in both groups.¹¹
- Continuous use of androgen deprivation therapy in older men for at least 6 months is associated with an increased risk of diabetes and fragility fracture but not heart attack or sudden cardiac death.¹²
- Current smoking appears to be a risk factor for the progression and the aggressive behaviour of prostate cancers.¹³
- Radiation therapy after radical prostate surgery increases the risk of long term primary (new) pelvic cancer (e.g. bladder and rectum) but the absolute risk is very small.¹⁴
- The latest systematic review of the use of *Serenoa repens* (saw palmetto) for relief of the urinary symptoms attributed to BPH found that for 30 randomized trials involving 5222 subjects, *Serenoa repens* was not more effective than a placebo.¹⁵
- In a study from the UK of over 600 patients diagnosed with prostate cancer but judged suitable for active surveillance who subsequently underwent prostate surgery, the pathological examination of the removed prostate tissue resulted in a significant upgrading (from a Gleason score of 6 or less to a Gleason score of 7 or higher) in 23% of the group. In a group of 74 patients deemed to have “insignificant” disease, pathological examination of prostate tissue revealed that 61% of these patients actually had significant disease with 16% being upgraded to an intermediate-risk group. The investigators warn clinicians that they need to be aware that guidelines for selecting favourable cases for active surveillance do not rule out more significant disease.¹⁶
- A recent review of chemoprevention of prostate cancer found evidence justifying the recommendation of selenium, vitamins E and D, lycopene, allium vegetables (garlic, scallions, onions chives and leeks), soy/isoflavones and green tea polyphenols.¹⁷

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