# INTERNATIONAL HEALTH NEWS

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*The featured subject this month is related to the concern that children and adolescents are overmedicated, especially with psychiatric drugs. The number of children and adolescents taking powerful drugs for Attention Deficit Hyperactivity Disorder (ADHD) has increased dramatically in the last two decades suggesting a remarkable, if not astounding, increase among this age group in the problems these drugs treat. The Centers for Disease Control recently reported that currently one in 8 boys between 3 and 17 years and one in 18 girls between 3 and 17 years have ADHD. Why is this not considered a huge crisis? Among children, this is the greatest epidemic ever, considering that it is not transient like influenza. Is it being shrugged off because it can be treated, even though, as we will discuss below, there are great problems with the treatments, especially over the long term. This whole scenario, which is being played out before our eyes, should be profoundly frightening to parents, public health officials and physicians. What is going on? The situation may get worse with the publication of the new guide to mental disorders, the bible used by the psychiatric profession. In a few years we may have a pill for DDHS (disinterest in doing homework syndrome).*

*Children and adolescents are no doubt viewed by the pharmaceutical industry as a far from fully exploited market. Evidence that they are working hard on it comes from the recent announcement that the European Commission has approved a chewable version of the cholesterol lowering drug Lipitor for use by children over age 10. While Lipitor is approved for children with the genetic condition which leads to very high cholesterol levels, an intervention which is debatable, it is now regularly prescribed off-label for children simply with elevated cholesterol, in spite of the fact that there is no evidence of long-term benefit, and as well the untreated condition fluctuates naturally and tends to normalize with increasing age, something which would be masked by drug intervention, presumably for life. Successfully convincing prescribers that benefits outweigh risks, or simply downplaying or concealing risks, has become a highly developed and refined art in the industry whose conduct is only now beginning to be exposed in court documents forced into the public domain.*

*The special situation represented by young people may not be fully or properly appreciated in medical practice or pharmaceutical marketing. Children do not provide informed consent and it is not clear at what age this is possible. Governments have the power, which they on occasion use, to force medication treatment on children despite resistance from the parents, the child or both. In some cases the risk vs. benefit is debatable or perhaps even unknown. Benefit may even be argued on the basis of fraudulent studies. Long-term risks in medication for children, which may be used for a decade or more, are of necessity totally unknown. The practice of pediatrics is rife with off-label drug use where there are only adult or late adolescent trials, some of which are small and most of which are short-term. Children obviously represent a very special case since they are undergoing development, and along with this comes a very special challenge to do no harm, a challenge that the current drug testing and approval system is incapable of meeting. The potential for the present system to do the youngest members of our society a huge disservice seems beyond question, but only a small minority seems to care.*

*This issue also includes several book suggestions for holiday reading and the latest issue of* ***The Prostate Monitor****.*

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

*Wishing you and your family good health,*

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

**Highlights**



# DIAGNOSIS AND TREATMENT OF ADHD AND DEPRESSION IN CHILDREN

***ADHD***

This is an interesting area because children and adolescents represent a huge market for ADHD (attention-deficit/hyperactivity disorder) and antidepressant drugs which is being aggressively exploited by the industry with the nearly full cooperation if not encouragement of the psychiatry community and the regulatory agencies. Questioning the conventional wisdom in the peer-reviewed literature appears rare, but over the last decade there have been a number of voices raised to question the evidence base and the wisdom of using these drugs to treat children, especially stimulants and the selective serotonin reuptake inhibitors (SSRIs)

Recently Evans *et al* used a rather unique approach to examining the question of inappropriate diagnosis and overtreatment of ADHD.[1] They examined the incidence of diagnosis in kindergarten classes which of necessity contain a range of ages due to the use of a cut-off. They found a significantly lower incidence of both diagnosis and treatment for children born just after the cut-off (relatively old for the grade) as comported to similar children born just before the cut-off (relatively young for the grade). If one believes there is an underlying neurological biochemical problem represented by ADHD, then the incidence rates should not change dramatically from one birth date to the next. They regard their results as suggesting that the driving force is age relative to peers in the class which result is behavioural differences which influence the child's probability of being diagnosed and treated for ADHD. Thus there is an indication of overdiagnosis. The authors discuss both this and the potential for under-diagnosis in the oldest members of the class, and while they consider accurate diagnosis and treatment of ADHD important, they also point out that research suggests many children given stimulant medication may suffer from toxicity that will hamper rather than improve their present and future cognitive function. They also comment that in the US, 5-10% of children 6-18 years of age have been diagnosed with ADHD and it is estimated that this number has increased by 500% between the late 1980s and the early 2000s.

There appears to be only one long-term randomized trial of drug treatment for ADHD, the Multimodal Treatment Study of Children With ADHD (MTA).[2] The results of 8 years of follow-up have been reported. The children were dividend into four groups: medication, intensive psychotherapy, both or usual community care. There was considerable contamination with regard to medication especially during later years of the follow-up where each group had about the same number of participants on medication even though one group was originally just to have psychotherapy. Furthermore, there was a significant discrepancy between parent-reported medication intake and that found with spot saliva tests.[3] The principal medication was Ritalin. There was no untreated arm and fifteen of the twenty-two investigators had very strong ties with the pharmaceutical industry.

The results at the end of 14 months intensive therapy showed benefit in all four groups with the best results from the combination of medication and psychotherapy. However, the

benefits from medication were not sustained and by the end of three years it was apparent that there were no beneficial effects. This picture persisted over the next 5 years. During the follow-up period, the distribution of medication throughout the four groups evolved to be similar. One of the investigators was quoted as saying: "Is this going to make a benefit for my child long term? The answer is no. Behavioural treatments are going to have much bigger benefit in the long term." However, he pointed out that behavioural therapies used without medication have not been studied over the long term. The MTA study also found that stimulants stunt growth.

Adverse side effects of stimulant medication were not examined to any extent in the MTA study. But they surely enter into the risk-benefit equation. Side effects appear to include drowsiness, appetite loss, lethargy, insomnia, headaches, abdominal pain, motor abnormalities, facial and vocal ticks, skin problems, liver disorders, hypertension, and sudden cardiac death. Some stimulants reduce blood flow to the brain and inhibit glucose metabolism. These lead to neuropathological changes.

***DEPRESSION***

A recent meta-analysis has examined the question of whether the popular selective serotonin reuptake inhibitors (SSRIs) work for children and adolescents and if they are well tolerated. They found evidence for effectiveness in improving response and depressive symptoms in children and adolescents compared with a placebo for only one drug, fluoxetine.[4] However, there were serious problems with the trials in general. Most children participating were not typical of those presenting with problems. Already in 2004 it became clear that there was another big problem with SSRI clinical trials in that a number of unfavourable trials were not only suppressed but that this was simply business as usual. In that year Whittington *et al*[5] undertook a meta-analysis of SSRI trials concerning children and adolescents that included as many unpublished results as they were able to obtain. After all, meta-analyses are only informative if they contain all appropriate studies. Whittington *et al* concluded that only the published data suggested a favourable risk-benefit profile but addition of unpublished data changed the picture and indicated that risks could outweigh benefits for these drugs, with fluoxetine being an exception. In an editorial accompanying this paper, the author took the strong and highly justified position that it was unacceptable and should be unimaginable that a drug's use would be based on selective reporting of favourable research. He viewed this as an abuse of the trust that parents place in the system and an abuse of the trust of trial volunteers in the pharmaceutical establishments in question. Furthermore, the benefits of fluoxetine were only "modest." a term used in studies to indicate barely significant with questionable clinical significance. The analysis found evidence of increased risk of suicidal notions and behaviour, something which has always been an issue with SSRIs. Study design prevented gaining insight into the important question of effectiveness and risks in those with more severe and complex presentations. In addition, what was not studied was whether or not the subjects, especially those on long-term medication, fared better or worse than a comparison group totally unmedicated. There was no such group. Since the analysis of Whittington *et al* was published, documents made public during litigation have exposed details of study design that are shocking. Studies enrolled subjects with low rates of comorbidity who were at low risk of suicide or self-harm. The designers of the studies typically screened out placebo responders as a preliminary to selecting the placebo group in order to maximize the resultant benefit.

In his book *Anatomy of an Epidemic* which is reviewed in this issue, Robert Whitaker describes the development and marketing of the first antidepressants. This provided a game playbook for not only the psychological drug industry but the drug industry in general. He also describes a two-day visit to the center in California which, among a number of services, offers the "last stop" for severely disturbed youth. The children, ranging in age from five to thirteen, typically had a history of cycling through several foster homes, had multiple hospitalizations, and had behavioural difficulties which made additional placement or treatment difficult. The short version of the story is that the "aggressive treatment approach" used at the center featured getting these children off all mental-disease related drugs. All of these children were on heavy

medication and many had been reduced to zombies. Behaviour modification was substituted for medication. This approach, while very difficult in its initial stages, was used because it worked better than anything else and because otherwise, these kids had a grim future. The lesson here speaks volumes about the mainstream approach. These children and young people were on multiple drug treatments that, in the view of critics, were over the years, destroying them mentally and socially rather than helping them and curing them. This puts the adverse effects of the antidepressants in perspective. In fact, as Whitaker discusses and documents at length in his book, most drugs used to treat depression and other mental problems frequently result in long-term deterioration in spite of short-term initial evidence of benefit. In fact, the short term nature of most studies which are used to justify the long term use of SSRIs in children illustrates this problem. A recent paper designed to justify the current standard of care listed forty studies.[6] The average duration was 11 weeks. These studies were held up as the evidence that SSRIs were effective in children and adolescents. This totally ignores the real question, what about the long term? It appears that when the long-term is examined, all the benefit disappears and one is left with the downside. The downside Whittaker describes in detail with documentation is not pretty.

The big question in the areas explored above is whether or not stimulants, anti-anxiety agents, antidepressant and antipsychotic drugs so widely used by both children and adults cause *permanent* long-term harm. Whittaker's book, examines this question in great detail for all four classes of drug with extensive documentation and quotations from well know psychiatrists critical of the mainstream thinking. The evidence of long-term permanent harm seems overwhelming and the fact that this evidence is actively ignored or downplayed is both significant and frightening.

A commonly held opinion regarding the dramatic increase in such disorders as ADHD and depression is in part due to aggressive diagnosis and the application of criteria which are too general. Furthermore, there are rumors that the new Fifth Edition of the *Diagnostic and Statistical Manual of Mental Disorders,* the psychiatrist's bible, will push this approach beyond all reason. In the contest of depression diagnosis, The journal *Pediatrics* has recently published studies favourably evaluating two questionnaires designed for the rapid screening of adolescents.[7,8] The questions are interesting--over the last 2 weeks, how often have you been bothered by any of the following problems?

1. Little interest or pleasure in doing things
2. Feeling down, depressed or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Felling bad about yourself—or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual.
9. Thoughts that you would be better off dead, or hurting yourself in some way.

The respondent checks off one of 4 boxes for each question which are headed: (a) not at all; (b) several days; (c) more than half the days; (d) and nearly every day. The quick assessment uses only the first two questions. The long—form involves all nine. They probe only the most immediate past—two weeks. For the long form, four checks in either of the (c) or (d) boxes, including the first two questions, and you are diagnosed as potentially having a depressive disorder. Five checks in the (c) or (d) boxes including either question 1 or 2, and you may have a major depressive disorder. It was found that this approach was much more successful in ruling out depression than in accurately identifying it but the questionnaire was viewed as a success. Critics would view positive answers to some of the questions as reflecting the variety of childhood behaviour that was traditionally associated with growing up and is normal. Poor diet, home environment, metabolic disturbances and micronutrient deficiency could be responsible for positive answers to some of these questions. Also the

side effects of stimulants used to treat ADHD could be confused with depression if the above questionnaire is used. Indeed, as Whittaker discusses in his book, there seems to be a path leading from the treatment of ADHD to the diagnosis of depression. The modern, enlightened view is that these questions tease out underlying biological-biochemical disorders in the adolescent brain that need to be corrected by drugs that manipulate levels of brain chemicals and receptors. In the context of depression something like this was already described in *The Brave New World*. In fact, Cutcliffe and Lakeman[9] in their challenge to the "normative orthodoxies" liken the pharmacologically induced depression-free state to Huxley's famous utopia**.** This is not quite accurate since many medicated individuals have, in the end, not found utopia but something quite different.

## HOMOCYSTEINE AND MILD COGNITIVE IMPAIRMENT AND DEPRESSION

Studies suggest that elevated blood levels of homocysteine represents a risk factor for both dementia and Alzheimer's disease.[10,11] Early stage disease is characterized by mild cognitive impairment (MCI) and brain atrophy (shrinking). While progressive brain atrophy is associated with aging, it is much accelerated in individuals suffering from Alzheimer's disease and an intermediate rate of atrophy is found in those with mild cognitive impairment. Furthermore the rate of atrophy is greater in individuals with MCI who convert to Alzheimer's disease (about 50%).

A recent study addresses the issue of using B vitamins, the classical approach to homocysteine lowering, to slow the rate of brain atrophy in individuals with MCI.[12] The study was a single-center, randomized, placebo controlled double blind trial of high-dose folic acid and vitamin B6 and B12 in over 167 individuals over 70 with MCI who agreed to have brain MRI scans at the start and finish of the study. They were randomly assigned to two equal groups, one treated with vitamins, the other with a placebo. The mean rate of brain atrophy per year was 0.76% in the treatment group, 1.08% in the placebo group, a significant difference. The treatment effect was greatest for those with the highest baseline homocysteine level and interestingly, there was no effect of treatment on those in the bottom quartile of baseline homocysteine. The authors point out while these results lead one to regard elevated homocysteine as causative, they do not exclude the possibility that low levels of one or more of the vitamins used might be causative. They also comment that these results suggest the merits of a study to see if the same treatment will delay the development of Alzheimer's disease.

It has been known for a long time that low levels of vitamin B12 are related to the risk of cognitive problems and in fact careful patient evaluation requires assessing the possibility of such a deficiency.[13] It is interesting in this context that the anti-hyperglycemia drug metformin, the cornerstone of the pharmaceutical approach to diabetes treatment and the most frequently drug given initially to type 2 diabetics, has the highly undesirable side effect of enhancing the risk of vitamin B12 deficiency.[14] It should be noted that correcting vitamin B12 deficiency orally may be only partially successful due to a deficiency in what is called the intrinsic factor. The form of the vitamin that appears best is cobalamin since a fraction is absorbed independent of the levels of this factor and 2000 micrograms twice daily has been found to provide rapid replenishment in, for example, those with pernicious anemia.[15]

It turns out that a folate and vitamin B6 are also associated with "mental" problems,[13,16] and we have closed the circle in the sense that homocysteine, B12, B6 and folate are connected physiologically. Thus it might seem reasonable that the first step in the assessment of anyone with cognitive impairment or depression or some other mental problem would be to look into the possibility of a deficiency in B12, the classical vitamin deficiency related to the problems in question. But B12 presents a problem in that the lower limit of the standard reference range for normal may conceal a B12 deficiency serious enough to merit treatment. Since the

results of such an intervention are generally rapid and the treatment simple and inexpensive, a strong argument can be made for first trying vitamin B12 therapy before the conventional pharmacological and behavioural approaches. In his recent paper *How I treat cobalamin (vitamin B 12) deficiency*, Dr. Ralph Carmel of the Weill Medical College, Cornell University, states that he usually provides 8 to 10 injections over the first 2-3 months before considering monthly injections.[17] He elects the intramuscular route rather than oral treatment because it removes issues concerned with absorption. Cyanocobalamin is the usual form available in North America whereas hydroxycobalamin is preferred in parts of Europe and requires fewer injections. If B12 is the problem, neurological improvement should begin within the first week and is typically complete in 6 weeks to 3 months.[17] However, if the problem is not caught early enough, residual disability can be occur which is generally associated with a therapeutic delay of over 6 months. This urgency is probably underappreciated, given the knee-jerk response that results in a prescription dictated by modern psychopharmacology.

The neuropsychiatric effects of folate deficiency are similar to those attributed to B12 deficiency.[13] Folate and B12 deficiency produces about the same incidence of cognitive decline, but depression is more than twice as common in folate compared to B12 deficiency. Incidentally, both can cause peripheral neuropathy, with twice the incidence attributable to B12 as compared to folate. Several controlled trials lasting for up to a year have demonstrated the effect of folates on mood, cognitive function and social recovery either when used directly or in addition to psycho-pharmaceuticals. To avoid unmetabolized folic acid, methylfolate can be used. It is important to recognize that treatment with folic acid or folate must be done with care in the presence of B12 deficiency since the therapy may have the opposite of the desired effect. Similar problems are seen with those with epilepsy.[18] Thus eating foods high in folate or taking small doses of folate (probably < 1 mg/day) over a long term may be the best approach, but there does not appear to be much guidance in the modern literature. The potential is that large doses of folic acid frequently used to drop homocysteine levels may be inappropriate for individuals with B12 deficiency. It is interesting that some multivitamin formulators have switched to folate from folic acid. They must read the literature discussing concerns about unmetabolized circulating folic acid.

One might wonder if the results of population studies finding the rapid increase of depression over the past two decades are due to increasing homocysteine or decreasing folate levels, but the opposite has in fact occurred, presumably due to the advent of folic acid food fortification.[19] But this fact does not diminish the importance of considering levels of these biochemicals as potential contributors or markers of mental problems. Finally, the above results point to a natural approach to neurological problems both mental and peripheral, which might merit trying prior to the conventional pharmaceutical approach.

## TREATMENT OF RISK FACTORS FOR PRIMARY PREVENTION OF CHRONIC DISEASE

It is rapidly becoming apparent that the decades-old paradigm that one can prevent chronic diseases by treating risk factors is both seriously flawed and a severe impediment to progress in this challenging area. In a recent perspective in the journal *Alternative Therapies in Health and Medicine*, Dr. Mark Hyman, MD presents a penetrating analysis of this subject which carries a strong message that neither the pharmaceutical industry nor the expert writers of guidelines want to hear.[20] His position is simply that this failed paradigm for primary prevention means that treatment in many cases is focused on symptoms rather than causes and therefore is ineffective while producing adverse side effects with a wide spectrum of morbidity. Until this is admitted and there is a paradigm shift, we will continue to be exposed to ineffective therapy at great cost both financial and physical. The examples he cites in the areas of diabetes and cardiovascular disease nicely

highlight the current state of affairs. The NAVIGATOR and ACCORD studies discussed by Hyman confirmed that the current approach may not only be ineffective in preventing cardiac events, diabetes and mortality but is causing harm. Lipids, glucose and blood pressure were all effectively reduced in these trials, but there was no reduction in mortality or morbidity. Furthermore there were significant side effects. Hyman points out that two other large trials targeting blood pressure, lipids and glucose came to the same conclusion.

Hyman devotes considerable space to cholesterol lowering in the context of primary prevention and agrees with the critics that there is no good evidence for statin therapy in the context of primary prevention except for high-risk younger males, but for this subgroup, the number needed to treat to prevent one event is very high (50 to 100). He interprets the JUPITER lipid lowering trial for individuals with high C-reactive protein as indicating that lowering LDL without reductions in inflammation showed no benefit. Yet this study is held up as proof of the effectiveness of statin therapy in primary prevention. He also points to the ENHANCE trial which showed that adding a second drug (ezetimibe) to statin therapy lowered cholesterol much more than the statin drug alone but led to more arterial plaque and no fewer cardiac events. He also mentions the observation that convinced many professionals regarding the cholesterol myth, namely that 50% to 75% of individuals who have a heart attack have normal or low cholesterol and that in older patients, the lower the cholesterol, the higher risk of death.

Another example could be added, namely the failure of homocysteine lowering to impact the enhanced morbidity associated with elevated levels of this amino acid. This has been discussed in the Newsletter.

The notion that treating risk factors in the context of primary prevention is appealing because of its simplicity and because it provides a *modus operandi* for drug development which is vastly easier to implement than research aimed at identifying and eliminating the true causes. It can also be described as naively simplistic and a paradigm prone to generating dogma and the frequent need for the suppression of dissent, and there is ample evidence that this is indeed the case.

Hyman calls for a new paradigm of prevention for heart disease. He points to the EPIC study which found benefits from adherence to simple behaviours (not smoking, exercising 3.5 hours per week, eating a healthy diet [fruits, vegetables, beans, whole grains nuts, seeds and limited amounts of meat], and maintaining a healthy weight [BMI < 30]. The result was that 93% of diabetes, 81% of heart attacks, 50% of strokes, and 36% of all cancers were prevented. Also, the INTERHEART study found that changing lifestyle could prevent at least 90%of all heart disease. He suggests that the reason for these successes is simple—the protocols address fundamental causes and biological mechanisms leading to disease. Inflammation and insulin resistance are thought to be the primary drivers of cardiovascular disease and are driven by what we eat, how much we exercise and how successful we are in dealing with stress and reducing the body burden to environmental toxins. The interaction between risk factors and the existence of drugs which impact them appears to have trumped this more rational approach to dealing with chronic disease.

Meanwhile, the machine moves forward. The European Commission has approved a chewable version of Lipitor for children, Pfizer's blockbuster cholesterol lowering drug, a drug which Dr. Duane Graveline, MD claims in his books and on his website, has damaged his life almost beyond repair (www.spacedoc.net).

## NEW RESULTS ON THE MERITS OF TEA AND COFFEE

The evidence continues to accumulate that drinking caffeinated coffee and tea is in general beneficial. Four recent studies address the benefits in four different disorders.

- *Brain tumors.* A large follow-up study (520,000 subjects, age 25-70, follow-up average 8.5 years) found that among

those consuming > 100 mL of coffee and tea per day as compared to those with lower consumption, the risk reduction was 56% for brain cancer (glioma). The authors point out that this was consistent with a study in the US which combined 3 prospective cohort studies and found both coffee and tea protective for glioma (40% risk reduction). In both studies, the results were statistically significant and large enough to qualify for clinical significance.[21]

- *Cardiovascular morbidity and mortality.* In a follow-up study, over 37,000 individuals were studied for 13 years. For coffee a risk reduction for coronary heart disease (CHD) of 19% was found for consumption of 2-3 cups per day. For tea, daily consumption of more than 6 cups was associated with a CHD risk reduction of 36%. No associations were found for stroke. Coffee only slightly reduced the risk of CHD mortality whereas for tea, 3-6 cups per day reduced CHD mortality by 45%. There was no impact on all-cause mortality.[22]
- *Type 2 diabetes.* In a 12 year follow-up study of 47,000 African American women, when compared to no coffee consumption, intakes of 3 and ≥ 4 cups per day of caffeinated coffee was associated with reduced risk of type 2 diabetes of 18% and 17% respectively, but the results for the larger consumption rate just missed statistical significance.[23] While these are not large risk reductions, at least no enhanced risk was observed.
- *Cognitive decline.* In a paper recently presented at the Alzheimer's Association International Conference, researchers reported on a follow-up study of 4800 US residents aged 64. Follow-up was up to 14 years. Standard tests were used to assess cognitive decline. In comparison to those who never drank tea, it was found that those who drank tea five or more times per week had a 26% lower risk. For one to four times per week the reduction was 37%. Coffee was protective at intakes of five times per week where the decrease in cognitive decline was 20%. The authors point out that the coffee consumed had three times more caffeine than the tea, whereas tea was more protective.
- *Depression.* A follow-up study just published examined the impact of coffee and tea consumption on the risk of severe depression. It was found that compared to non-drinkers, those who consumed >4 typical North American cups of coffee had a 72% decreased risk for depression, a result that remained essentially unchanged after extensive adjustment for confounding. There was no association with either tea or caffeine.[24]

## NATIONAL LUNG CANCER SCREENING TRIAL

In early November the media carried an announcement concerning this trial sponsored by the National Cancer Institute. The cohort consisted of heavy smokers ages 55 to 74 years. The trial compared chest X-rays with CT scans, using death from lung cancer as the primary endpoint. The cohort was randomly divided into two groups, each of which received three scans over two years and were followed for up to 5 years. The Institute considered the results so important that they provided early results, not in a paper, but via the media which provided widespread coverage. Those who received the standard X-ray screening suffered 442 lung cancer deaths compared to 354 among those who received CT scans. All cause mortality was also lower in those receiving CT scans. The majority of the suspected cancers found by CT proved false, resulting in unnecessary invasive procedures and some deaths. According to the conventional wisdom, the CT scans with 20 times the radiation exposure of X-rays should increase the risk of cancer. In their press release, the NCI took the position that the benefit of potentially finding more treatable cancers using CT scans appears to outweigh the risk from receiving what they describe as low-dose radiation. They also admit that screening with chest X-rays does not reduce lung cancer mortality.

Screening for lung cancer with the modern low-dose spiral computed tomography which was employed in this study is not new but the results so far have been controversial. Until the results of the NCI trial are actually published in a peer reviewed journal, it is not

possible to put them is perspective or compare to earlier non-randomized studies. Two of the most recent non-randomized studies came to diametrically opposed conclusions as to the merits of screening.[25,26] It appears that this type of screening has variable ability to detect very early stage cancer, some of which is indolent, and this impacts the endpoint and results in overdiagnosis and overtreatment.

The November 2008 Newsletter contained a Research Review questioning the conventional wisdom that low-dose ionizing radiation such as from CT scans and X-rays was dangerous and pointing out (a) that there was no acceptable evidence of risk and (b) that there was considerable evidence that low-dose ionizing radiation conferred benefits of unproven origin but possible associated with enhanced immune systems. The review contained a lengthy description of the apartment house episode where the occupants were unknowingly exposed to low-dose radiation over an extended period due to contaminated building materials. It documented their dramatic *decrease* in cancer incidence. This is called *Hormesis* and is the subject of a just published scholarly work (*Radiation Hormesis and the Linear-No-Threshold Assumption*, by Charles L. Sanders) carrying a price tag consistent with medical textbooks (about $200). In 2008, the *Journal of American Physicians and Surgeons* published a paper titled *CT Scans May Reduce Rather than Increase the Risk of* Cancer which reviews the existing hormesis literature in the context of CT scans.[27] The position implied by the title strongly challenges the conventional wisdom. Hormesis may provide a simple, evidence based explanation for at least part of the NCI study's observed mortality benefits, given that three CT scans were done over 2 years.

The belief that CT scans are dangerous in the context of cancer initiation now occupies the position of a super dogma. Every year there are number of papers that employ the linear-no-threshold model to come up with dire predictions about the population impact of diagnostic radiation, presenting the results as evidence based when they are not. Such studies discourage individuals from having, for example, so-called coronary artery calcium scans and are responsible for the caution exhibited in guidelines. It seems also clear that the dogma will have a long lifetime. Most in mainstream medicine have probably never heard of hormesis or even thought to question the models used for predicting radiation-induced cancers.

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## READING SUGGESTIONS FOR THE HOLIDAY SEASON

***Wrong. Why Experts Keep Failing Us—And How to Know When Not to Trust Them.*** **David H. Freedman. Little, Brown and Company, New York, 2010. ISBN 978-0-02378-8**

David Freedman is a well known science and business journalist, writes for major magazines and newspapers and is the author of a number of books. This is a timely work since over the past year respect for and trust in one group of experts, the economists, has been in decline. But the book covers the whole spectrum of experts and how they interact with government, the media, and

organizations. The two chapters titled “The Trouble with Scientists,” Part I and Part II, should be of particular interest to readers of this newsletter since they mostly concern medical science. The author provides an in-depth analysis of the deep biases and career pressures that corrupt and distort research and the sloppy and manipulative acquisition of data common even in the most prestigious institutions. He investigates what is termed foolish thinking that permeates many areas that impact all of us with the result that the most acclaimed advice is in fact the most disastrous. Freedman ends the book with a chapter titled “Eleven Simple Never-Fail Rules for Not Being Misled by Experts.” This is followed by four appendices, the last a dealing the now obvious question, “Is This Book Wrong.”

***Anatomy of an Epidemic*. *Magic Bullets*, *Psychiatric Drugs, and the Astonishing Rise of Mental Illness in America.* Robert Whitaker, Crown Publishers, New York, 2010.**

This book by a respected and award winning investigative journalist may drive readers to depression, but one thing is almost certain, no one who has read this book will willingly take or give to their children any of the vast number of pharmaceuticals designed to treat mental illness unless it is either forced on them by the courts or as a last desperate resort. Whitaker tackles the question of why the number of officially disabled mentally ill in the US has tripled over the past two decades and why psycho-pharmaceutical treatment is spreading most rapidly among the nation’s children. These are obviously important questions. According to the US government figures, one in every fifteen young adults, eighteen to twenty-six is now seriously mentally ill. The numbers are astounding with 680,000 in that age group declared bipolar and 800,000 ill with major depression, and these numbers were regarded as a significant underestimate since they do not include youths in this age group that were homeless, incarcerated, or institutionalized, almost all of whom are functionally impaired to some extent.

This is a scholarly and well documented examination of the title subject and issues. One of the critical questions examined thoroughly involves how well in the past fifty years psychiatric drugs have affected long-term outcome. The overwhelming evidence for poor outcomes, results the author demonstrates were concealed from the general public, provides a shocking and sad story of deceit, manipulation, fraud, and in the end litigation. Readers of this newsletter will perhaps recall the recent study where antidepressives were found no better than placebos for the relief of symptoms of either mild or moderate depression, is spite of the huge worldwide use for this indication. As Whitaker explorers in horrific detail, this is only a small part of a terrible history which has involved drug companies, academics, the media, and governments.

Whitaker’s work, which involved a critical examination of a vast literature going back over 50 years, provides significant insights into the harms and benefits of the drugs in question. He appears to provide an unbiased review of the literature and includes quotations or interviews with high-profile psychiatrists. The net result is a highly disturbing picture of the long-term effects of this whole class of drugs on both children and adults, adverse effect that are disastrous now and will continue to be disastrous if the conventional wisdom of psychiatry prevails and the companies making and marketing these drugs are successful in maintaining what currently appears to be a huge hoax and a highly developed mythology. What can not be questioned is the skill that has characterized the last 30 years of marketing. The example of Prozac provides a universal guide with a remarkable track record for pharmaceutical companies intent on promoting their product irregardless of its merits or risks.

One of the most interesting sections of the book describes a home for seriously disturbed children, a place of last resort accepting only the most intractable cases. Many had been drugged into a zombie state. They treated them aggressively—by eliminating all drugs! The success rate was astounding.

One of the most disturbing aspects of the book is the constantly recurring and very well documented theme that long-term use of antipsychotic and antidepressant drugs cause permanent harm, and that minimization of exposure to these drugs appears highly advisable. The chapter *The Hunt for Chemical Imbalances* provides support for this observation since there in fact appears to be no evidence that mental disease is caused by chemical imbalance of the sort that is targeted by the drugs in current use.

Your editor is reminded of a casual conversation he recently had with a clinical psychiatrist. This doctor had recently returned from a large international conference where he heard a talk by a well known member of the fraternity who pointed out that many of the drugs currently used in psychiatry simply did not work any better than a placebo. After the talk, he wandered into the exhibition hall and found a stark contrast where a number of companies were flogging the same drugs as effective, a view held apparently by the related professional organizations who apparently find it convenient to ignore the numerous studies. Is there any hope, given the tight grip of Big Pharma in this area?

The reader needs to examine this comprehensive history of psychiatry over the past 50 years and decide if he or she regards the evidence presented regarding crumbling foundations of the current standard of care and the active propagation of frank mythology as credible.

***Why Your World Is About To Get A Whole Lot Smaller*. Jeff Rubin. Vintage Canada (Random House) 2009-2010.**

While one would never know from the title, this book is all about oil. Anyone who thinks so-called peak oil is either a fantasy or too far in the future to be of concern needs to read this fascinating book. The author was Chief Economist at the CIBC World Markets for almost twenty years. He was the first to predict the sharp rise in oil prices in 2000 and is now one of the world's most respected energy experts. The book presents a careful but very readable analysis of the changing patterns and politics of oil production, oil consumption for energy, and oil consumption for petrochemicals. The author takes the position that the recent economic meltdown was triggered by the spike in oil prices that preceded it rather than the current popular explanation, and points to a similar pattern in other recent recessions. If the prediction is true that much higher oil prices are absolutely inevitable, then this becomes an important factor to be reckoned with in the context of investment strategy and retirement and estate planning.

***The Mind's Eye*. Oliver Sacks. Alfred A. Knopf, New York, 2010**

Some readers of this Newsletter are already familiar with the writings of Dr. Oliver Sacks. Memorable was *The Man Who Mistook His Wife for a Hat.* Sacks is a professor of neurology and psychiatry at Columbia University Medical Center. His latest book deals with the stories of people who have lost a single but vital aspect of their brain function, for example, the inability to read or even recognize the letters of the alphabet, and yet being able to write and converse normally. Others are unable to recognize faces but otherwise are normal, or have no the sense of three-dimensional space. He describes both successful and unsuccessful coping with these highly selective mental disorders, some with a genetic component but many precipitated by a highly localized stroke or subtle brain pathology. He describes ingenious ways some compensate for these disabilities but in many instances, the problem is permanent and even progresses. One of the most fascinating stories is that of a concert pianist who became unable to read the printed page or music or labels in the grocery store. Yet she continued to travel, perform, and was still able to mentally transcribe a string quartet into a piano version. What many may not know is that Sacks can personally relate to one of these syndromes since he himself suffers from the inability to remember faces, a disability which causes him considerable grief.

Sacks' story about Sue Barry, who for thirty years endured and successfully coped with only two-dimensional vision while pursuing an academic career in neurobiology, is one of the highlights of the book. Suddenly through visual therapy, she regained stereovision, was able to see in three dimensions and was able to maintain this new state with constant visual exercises. For those with normal stereoscopic vision, it is hard to imagine what the world looks like on a daily basis without it. Sue described falling snow as appearing in a plane and when she again could see in 3D, the first snowfall appeared so amazing that it she just stood and looked at it for several minutes. Her description of the many experiences associated with this return to normal vision makes fascinating reading. And this is just a sampling of the case histories this book contains.

Near the end of the book is a chapter which describes in great detail the author's own personal experiences with melanoma. The tumor was near the retina. His story of its treatment and his subsequent problems makes the book in part a very personal history. Among other consequences, it

is ironic that he lost stereovision. The last chapter deals with many aspects of total blindness and the interaction between the absence of vision and the brain and provides the reader with the titles of a number of relevant books.

Sacks' book presents an interesting problem for readers to contemplate: "Why should human beings have the built-in facility for reading, when in sharp contrast to the evolution of verbal communication, writing is a relatively recent cultural invention?" It in fact dates back only about 5000 years. He provides insight into the phenomenon of reading, and especially the speed with which many scan the written page and extract complex and abstract meaning, when there does not appear to be an evolutionary path to this ability. Interestingly, the defect that appears associated with the onset, generally rather sudden, of the inability to read at all appears to be highly localized.

This is a very readable and entertaining addition to a long series of wonderful books by this author. Incidentally, Sue Barry published a book in 2009 on her experiences, *Fixing My Gaze: A Scientist's Journey into Seeing in Three Dimensions*.

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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 the past two months almost 1000 papers have appeared in the literature with "prostate" in the title. About 150 directly pertain to humans, the rest being animal and cell culture and studies of other aspects of the problem. What is distressing is that so few of the papers pertaining to humans carry messages of interest or utility. Prostate problems and in particular prostate cancer have been the subject of a vast amount of research over several decades and some would regard it as a mature field. The net result is that many studies add little to what is already known and to some extent represent simply the dotting of "i"s and the crossing of "t"s. Studies of the differential benefits of some procedure or drug frequently boil down to small statistical differences which are good enough for editors and peer reviewers but seem to lack much clinical significance or relevance to the individual who is just part of some broad distribution. The screening debate goes on, but the tools remain highly imperfect. Active surveillance is a hot topic, but there are so many different protocols and the disease is so complex that it is difficult to go beyond broad generalizations. Extending life by 2 months out of 18 with chemotherapy is still a big deal for those in the business and considerable effort goes into fiddling with combinations, order of treatment, and dose. This is not to say that there is no activity in developing new therapies or better ways to screen for prostate cancer, but the journey from "bench to bedside" is painfully slow. Interest in natural therapies can be described as alive but hardly robust. Rather, it suffers from chronic financial starvation and scepticism from the establishment.*

*This issue presents highlights from the recent literature, but your editor regrets that there does not appear to be anything particularly sensational to report, as Erich Remarque said in the title to his famous novel, Im Westen nichts Neues (All Quiet on the Western Front). But perhaps your editor's view is based on unrealistic standards.*

*Wishing you good health,*

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

## PREVENTION OF PROSTATE ENLARGEMENT (BPH)

BPH is one of the major curses associated with male aging and results in progressively bothersome urinary symptoms and eventually in some cases acute urinary retention. BPH can cause to prostate to enlarge to two to three times its normal volume and in the process constrict the tube draining the bladder. It is not uncommon to hear general practitioners comment that many men never mention this problem until they can't pee. BPH is very common and men need to educate themselves regarding the disorder. Readers are referred to the chapter in our book *The Prostate and Its Problems,* available in digital form on the IHN website.

A recent study from the University of California—San Diego has examined the role of dihydrotestosterone (DHT) in the risk of developing BPH.[1] Dihydrotestosterone, a reduced form of testosterone, is strongly implicated in the physiology of prostate enlargement and is the classical target for pharmaceutical intervention with what are termed 5-alpha reductase inhibitors, which as the name implies, inhibit the reduction chemistry. These drugs reduce the size of the enlarged prostate and provide relief for bothersome urinary symptoms. They supplement and to some extent have replaced the older alpha-blockers which also effectively reduced the symptoms but had little impact on prostate size or BPH progression.

The University of California researchers investigated the role of midlife serum levels of DHT and other so-called androgens before the onset of BPH in order to examine their role in promoting the disorder. They measured sex steroid hormones between 1984 and 1987 in a group of mostly white middle to upper middle class community dwelling adults. They excluded all men who reported BPH at baseline, having hormone assessment and those with prostate cancer. They subsequently examined the correlation between serum DHT and later development of BPH (between 1992 and 1996) in that portion of the group where data were available. Higher baseline DHT was associated with an increased risk of BPH. Men in the highest quartile of baseline DHT had a statistically significant 175% increase in the incidence of BPH compared to those in the first quartile. When the testosterone to DHT ratio was examined, a higher baseline ratio was associated with a 42% decreased risk of BPH when comparing the top 3 quartiles to the first.

The authors comment that these data justify the initiation of trials of 5-ARIs for the primary prevention of BPH in asymptomatic men. Given the success of this class of drug in reducing the incidence of prostate cancer, such studies should prove very interesting. However, weaker 5-alpha reductase inhibitors may be as effective in preventing BPH if use in initiated early enough. One candidate is the natural product Saw Palmetto. Unfortunately, a long-term primary prevention trial started when men were in midlife will probably never happen since this extract is not patented. But studies of the impact on the testosterone to DHT ratio would be easy and inexpensive, and while not definitive, nevertheless informative.

## PREVENTION STRATEGIES IN PROSTATE CANCER—AN UPDATE

A recent review of this subject has just appeared and provides the following information.[2]

***5-Alpha Reductase Inhibitors***. The now famous Prostate Cancer Prevention Trial (PCPT) created considerable interest in active prevention. This trial used the 5-alpha reductase inhibitor (5-ARI) finasteride (Proscar), a drug used to treat enlarged prostate, and found a 25% reduction in the incidence of prostate cancer at the end of 7 years. However, enthusiasm was dampened by the apparent small increase in cases of advanced cancer. As discussed in Prostate Monitor, this now appears to have been an artefact. Nevertheless, the results of a trial (REDUCE) with "the other" 5-ARI, dutasteride (Avodart) was awaited with great interest. The outcome after 4 years indicated a 23% reduction in the diagnosis of prostate cancer and no suggestion of enhanced incidence of advanced cancers. Consistent with the PCPT, the results of REDUCE occurred in all pre-specified subgroups (i.e. age, family history, body mass index, prostate volume, etc.) suggesting good utility for a wide range of men. Side effects were also similar to Proscar and included erectile dysfunction, ejaculatory dysfunction, and decreased sexual desire. However, in REDUCE these side effects had only a minor impact on discontinuation of the medication. A big plus was the beneficial effect on

urinary symptoms which of course was the original indication for this drug. Whether the absence of high-grade cancers would persist with long-term use is unknown.

The authors of the review list the following points that need to be considered when using 5-ARIs for primary prevention of prostate cancer:

- These drugs do not eliminate the risk of prostate cancer; they only reduce the incidence (diagnosis).
- There is still uncertainty regarding increased risk of high-grade cancer.
- The impact on mortality is unknown.
- There is the possibility of significant side effects related to sexual function.
- It is clear that there are significant beneficial effects for men with symptoms associated with prostate enlargement (BPH)

However, they point out that the REDUCE study suggests that the above concern regarding high-grade cancer probably should be modified to indicate that it is an unlikely consequence of taking this class of drug. They also point out that the adverse side effects of the medication generally disappear on cessation of the use of the drugs, but this is irrelevant if the drug is being used long-term for primary prevention.

***Estrogen Receptor Modulators***. Rodent studies have shown a decrease in the incidence of prostate cancer when the prostate estrogen receptor are inhibited. This prompted a trial with a small group of patients with a high-grade precancerous condition. At 12 months participants taking a selective estrogen receptor antagonist (toremifene) had a 22% reduced risk of being diagnosed with prostate cancer as compared to those on a placebo. There was no effect on Gleason score or prostate volume and no reported increase in adverse events. Until the results of a phase III trial are in, it is too early to tell if this approach merits adoption, but those with precancerous lesions may well become approved candidates for this treatment.

One can voice concerns based simply on the general principle that there are estrogen receptors elsewhere in the body and it will be difficult to demonstrate that there are no long-term adverse effects associated with tinkering with them.

***Statins***. The many trials of statin drugs in the context of cardiovascular disease have turned up some evidenced that this class of drug may reduce the risk of prostate cancer. However, over the years the results have been inconsistent. The most recent prospective and case control studies have failed to confirm a positive result. It has also been pointed out that a large randomized trial would be virtually impossible given the huge number of men who have been convinced of the merits to taking these drugs for cardiovascular reasons. Furthermore, if the non-lipid lowering effects of the statins play a role in cancer, it might be only in preventing advanced cancer, and this would make studies even more difficult, given that most cancers diagnosed today are localized and mostly low-grade.

***Neutraceuticals***. The authors summarize the results for five substances:

- Vitamin D. Results are conflicting when levels are normal, but modest benefit when low levels are addressed.
- Vitamin E. In randomized controlled trials no effect is found in comparison to a placebo.
- Lycopene. Meta-analysis suggests positive benefit, but none seen in a screening trial.
- Soy and isoflavonoids. Positive effects seen with non-fermented soy, mainly in non-Western men.
- Green tea. Conflicting results regarding the impact on prostate cancer diagnosis. Possible beneficial effects on the risk of diagnosis for advanced prostate cancer.

With regard to green tea, there is more to the story. A recent randomized double blind study done in Italy found that for men with high grade intraepithelial neoplasia (PIN), a high-risk precancerous condition, there was evidence of considerable benefit. Thirty men with high-grade PIN were given 600

mg of green tea catechins daily for a year, and only one patient developed prostate cancer whereas 9 in the placebo group developed the disease.[3] This result could be very important and there are a number of green tea studies currently in progress. This study used a green tea extract to achieve fairly high levels of the catechins. Green tea extracts with certified levels are readily available.

The other nutraceutical is soy extract derived from soybeans. The authors of the review point to a meta-analysis of case-control and cohort studies yielded a 24% risk reduction for prostate cancer diagnosis. Finally, the nutraceutical approach is generally free of side effects provided care is taken not to overdo the dosing.

## RADICAL PROSTATECTOMY AND RADIATION COMPARED AGAIN

A recent review of the studies over the past decade that address the above issue in the context of localized cancer has just appeared.[4] The general conclusions were as follows. The probability of a cure is similar after either RP or RT. The probability of significant treatment complications is probably higher after RP as compared to RT. Preservation of erectile function is as good or better with RT compared to RP. RT is more likely to preserve urinary continence. The patterns of adverse outcomes impacting the quality of life are worsened by obesity, large prostate size, high PSA and older age.

For RT, they summarize 6 studies, mostly recent. The freedom from biochemical failure (post-treatment PSA rising) was 93% in the low risk group, 69% in the high-risk group. Risk assessment was based on the clinical presentation using standard algorithms. For cancer specific survival, the figures were 100% for low-risk patients, and a range of 84-95 for those with high-risk. In some of the studies, some of the patients had adjuvant androgen deprivation therapy (ADT) and the various common modes of RT were represented. The post treatment periods to which these figures apply ranged from 5 to 15 years. With regard to maintaining erectile function two years after treatment, RT was clearly superior with the percentage of patients ranging from 68% to 80%. Brachytherapy appeared to produce the lowest incidence of erectile dysfunction. For RP, the range was 13 to 22%, and this included patients treated with the nerve sparing surgery.

A comparison was also made in terms of relative risk of PSA failure when RT was compared with RP. There was considerable variation with the radiation protocol as can be seen from the following which are stratified into low- and high-risk cancer at diagnosis.

Relative risk of biochemical (PSA failure) compared to RP

| Treatment | Low-risk | High-risk |
|---|---|---|
| External Beam RT | 1.1 | 0.9 |
| Brachytherapy | 1.1 | 3.1 |
| ADT + Brachytherapy | 0.5 | 2.2 |

In other words, for patients found to have low-risk cancer at diagnosis, the risk of PSA failure was half for those treated with ADT plus brachytherapy when the comparison was with RP.

The authors were radiation oncologists, but there does not seem to be bias in this analysis or the literature selected for citation.

## ACTIVE SURVEILLANCE VS. TREATMENT IN LOW AND INTERMEDIATE RISK GROUPS

A follow-up study from Sweden has just been published in the *Journal of the National Cancer Institute*[5] which compared treatment with the intent to cure with active surveillance over a 10 year period. The cohort consisted of over 6800 men age < 70 years with Stage T1-2 cancer, a Gleason score ≤ 7, and a PSA < 20 ng/mL at baseline. Two subgroups were then identified, either low risk (Stage T1, Gleason 2-6, PSA < 10 ng/mL) or intermediate-risk (T1-2, Gleason 7, PSA < 20). Some elected active surveillance, some radical prostatectomy or radiation therapy and the researchers examined the prostate-cancer specific mortality, i.e. what many consider the most important outcome.

For the entire cohort, the mortality rates were 2.7% for treatment, 3.6% for surveillance with a number needed to treat to prevent one death (NNT) of 111. For the low-risk group, the rates were 0.7% for treatment and 2.4% for active surveillance giving a NNT of 59. The absolute difference between mortality in the surveillance vs. the radical prostatectomy subgroup was 1.2% for a NNT of 83. These differences in outcome appear very small or to put it another way, for the total cohort combining low-risk and intermediate risk, 96.4% of those on active surveillance survived 10 years without undergoing any of the risks or morbidity of treatment. There was no uniform protocol that defined indications for surveillance, follow-up procedures or criteria for initiation of deferred treatment. The study was based on data extracted from a national data base. While a limitation, it seems that this makes the results even more interesting. The study also again raises the question of overdiagnosis.

## ALCOHOL AND RISK OF PROSTATE CANCER

A US prospective follow-up study just published adds to a considerable body of conflicting information regarding this question. Watters *et al*[6] studied almost 300,000 men aged 50-71 for about eight years. Only baseline data was available on alcohol consumption and potential confounding factors. Prostate cancer incidence and its stage were obtained from databases. After adjusting for confounding, alcohol consumption was found to increase the risk of diagnosis by 18% for >3 to >6 drinks per day, whereas the risk went to 21% for ≥6 drinks per day compared to abstainers. No association was found for advanced cases. Moderate to heavy alcohol consumption appeared protective against fatal prostate cancer, a result that raises questions about confounding.

The researchers then compared their results with other observational studies. Some find an effect, some do not. Some meta-analyses find an association, some do not. When studies are able to stratify not only by type of beverage but type of wine, in one study red wine was found to be highly protective with an odds ratio of 0.45 (55 % reduction in risk) for men having 8 or more drinks per week compared to non-drinkers. Another study found no association. Two studies which examined heavy drinking both found harm, but there was a considerable difference in the observed risk (22% vs. 90% increase).

When inconsistent results characterize such a large body of evidence, there is obviously a need to be cautious in drawing firm conclusions. The reasons for the variable results are not clear but many studies were corrected for confounding as best as possible.

## PSA RELAPSE FOLLOWING RADICAL MONOTHERAPY WITH 5-ALPHA REDUCTASE INHIBITORS

In our book we discuss the approach to hormone therapy for prostate cancer championed by Dr. Stephen Strum. This involved adding a 5-alpha reductase inhibitor (e.g. Proscar) to a luteinizing hormone-releasing hormone agonist (LHRH), and an anti-androgen. A pilot study has just reported which examined the use of the 5-alpha reductase inhibitor dutasteride (Avodart) as a monotherapy for men with relapse following either surgery or radiation therapy for localized prostate cancer.[7] Relapse was indicated by a rising PSA. Some patients entered in the study received a radical prostatectomy and then failed salvage radiation therapy as indicated by rising PSA, but patients who had received any androgen deprivation therapy within 5 years were excluded for the study.

The majority of men enrolled had an initial decrease in PSA in response to dutasteride treatment. After 6 months, PSA levels were decreased from baseline in 68% of the men but increased in 28%. After a median follow-up of 27 months, 46% had PSA decrease greater than 10%, and 25% had a decrease of greater than 50%. Pre-study PSA doubling time of ≥ 12 months and Gleason score of ≤ 6 were associated with a better response to this monotherapy. No patient dropped out of the study because of drug-related side effects. There was no difference in outcomes when stratified by entry PSA or the mode of radical therapy.

The investigators conclude that dutasteride therapy may delay or prevent progression of prostate cancer in some men with PSA relapse after surgery or radiation therapy. But it must be kept in mind that a surrogate marker is being used, although it is one that has been highly successful in terms of

prognosis. Near zero or stable PSA post treatment for 5 years generally means the treatment has been successful. What is not clear is the prognosis if, for example, a drug therapy halts post-treatment progression of PSA for, say, five years.

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