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William R. Ware, PhD - Editor

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This issue deviates a bit from the usual format and content by discussing general issues in modern medicine rather than specific clinical and nutritional studies. Included is a discussion of problems associated with the process and even the concept of diagnosis. Attaching labels to health problems has many ramifications, both psychological and as part of the mechanism of managed care and insurance billing. It is suggested that the uncertainties and a huge gray area in the process of assigning diagnostic labels to the millions that present each year with a myriad of symptoms are not fully understood or recognized by patients.

The second topic was inspired by a paper which addresses the problem confronting the pharmaceutical industry, the pesky and inconvenient placebo effect. Many drug studies are randomized against a placebo, and this paper suggests a new approach to reducing the null results of such clinical trials. The approach appears arbitrary and self-serving but may indicate a trend.

This is followed by a discussion of a very interesting paper concerning the well known widespread failure of vitamin and mineral intervention trials in spite of positive evidence from observational studies. The paper attempts to expose a serious flaw in the design of many intervention trials. Closely related to this is a discussion of the triage theory advanced by Bruce Ames, a name that should be familiar to followers of this newsletter.

Finally, there is a discussion of an article in the journal Health Affairs which makes one wonder how bad things really are in hospitals. A number of years ago Robert Mendelssohn. M.D. pointed out that in his opinion hospitals were among the most dangerous places on earth, an opinion which strongly annoyed mainstream medicine. It was put forward in a best selling book critical of the system. The article reviewed discusses different measures of adverse event rates in the hospital setting and comes up with some startling differences. Also discussed is the remarkable success achieved in one of the largest health care delivery systems in the US when a very serious and concerted effort was undertaken to reduce events causing harm to patients.

This issue also contains the Prostate Monitor. The discussion of the treatment of enlarged prostate (BPH) should be of interest to all men over the age of 40 years.

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.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

DIAGNOSIS. WHAT DOES IT REALLY MEAN?

The March Newsletter discussed problems concerning thresholds and diagnostic criteria in hypertension, diabetes and mental health. There is an underlying fundamental problem exposed in those examples. At issue are parameters that are continuous such as systolic blood pressure, blood sugar, blood lipids and serum hemoglobin, just to name some high profile examples. These parameters can be thought of as associated with so-called continuous diseases and reflect a range of severity. There are also situations where it is a matter of yes or no, with perhaps some reservations, and these are sometimes termed binary disorders. When a pathogen is positively identified during the work-up of a patient for a set of symptoms, and the pathogen is directly and positively associated with the symptoms, then it is possible to say yes for the associated disorder with a level of certainty that depends mainly on what needed to be ruled out, and that list might be quite short, and in addition how definitive the pathogen identification was. Thus when one is properly diagnosed with a strep throat, chances are that this is what is going on. The diagnosis of a broken bone is almost always definitive. This is what you have, the patient is told, and this is what we do or no, you have no broken bones. Modern medicine seems at its best, sometimes sensationally so, when doing repair work.

Consider hypertension. The numbers on parade in any doctor's office represent a continuum. Thus the need for a threshold for declaring someone hypertensive. A threshold implies that above it is bad, below it is OK. For hypertension this is based on a judgement call as to when systolic and/or diastolic pressure represents an enhanced risk of cardiovascular, kidney and other problems. But these problems do not just abruptly rise at the threshold, they also represent a continuum, and thus there is a significant arbitrariness about the whole process of identifying a threshold. A continuous variation in risk is addressed by a threshold and when dictated, a diagnosis, and generally medication.

Thresholds are used in diabetes to identify prediabetics and diabetics. The same problem exists. There is a continuum of results seen in any physician's office every day. Thresholds are determined by the vascular risk associated with hyperglycemia, but again, these risks do not rise up like the first step of stairs but also represent a continuum, and again the definition of prediabetes or diabetes becomes arbitrary and based on arbitrary notions about when a risk level becomes important. But the patient diagnosed with diabetes does not generally know this. Above a certain fasting blood glucose or glycated hemoglobin (HbA1c) one is declared diabetic. But the thresholds are merely arbitrary points in the continuum of hyperglycemia and dysfunctional carbohydrate metabolism.

Cancer is another example of a continuous disease, although some might be surprised to hear this and instead imagine that it is a disease you either have or do not have. Cancer develops in a continuous manner over many years and thus there are stages from initial mutations that are not successfully addressed by defence mechanisms, and then a preneoplastic lesion, a small cluster of tumor cells, a local tumor of significant size and finally metastatic disease. This can occur over 20-40 years. Thus there is a gray area where in many cases the nature of the early stage after detection is unclear, discordant opinions can be obtained from pathologists and the long-term risk of progression is unclear and perhaps even nonexistent. Yet it is not uncommon that the diagnosis of cancer is delivered and therapy initiated. Some breast ductal carcinomas In situ or low Gleason score results on prostate biopsy are examples.

Now that the JUPITER trial has propelled C-reactive protein (CRP) to a new level of importance, we have a CRP threshold above which statin treatment is indicated. CRP provides a continuous measure of inflammation. But the casual CRP level comes with serious reservations since there are any number of reasons why it can be

elevated. Finding them and treating or eliminating them should be of primary concern, not automatically prescribing a statin. After all, the entire problem may caused by poor oral hygiene which a statin will obviously not correct.

When psychological symptoms suggesting a mental problem are noted, various potential diagnoses are identified, and then with the help of the diagnostic manual the symptoms and characteristics are counted and the duration assessed and a "diagnosis" is created. Patients now have some recognized psychological disorder, generally incorrectly believed to have associated brain pathology, and are assigned specific diagnoses, which may haunt them for the rest of their lives. If the condition worsens, it may be redefined with a new diagnosis. For example, ADHD may evolve to meet the criteria for major depression. However, saying that meeting for example 4 out of 6 criteria and exhibiting the symptoms for in excess of so many weeks is convenient but arbitrary and done simply because of the absence of a better approach. Patients are not tuned in to the uncertainties and difficulties of figuring out what is wrong with humans when they present with a problem, and they frequently accept and even expect a definite diagnosis. Thresholds and counting symptoms and episodes do not take into account the large degree of human variability. Patients go home believing that they have major depression or AHDH or OCD, or any of a huge number of defined disorders. Many fill a prescription to combat their now diagnosed illness. In some cases, the side effects are so bad they dump most of the stuff down the toilet, a response that is dangerous to the environment.

Thresholds also imply the notion that more or less exact meaning can be attached to the laboratory results, other measurements or clinical observations or the results of histological examination. Yet there is the potential for laboratory measurement error, sample or x-ray identification, the white coat effect, variations from morning to afternoon, pathologist error and as well, errors in judgement. Then there is the inevitable human variability, both short and long term, which introduces considerable uncertainty into diagnostic and screening tests. The arbitrary nature of thresholds is similar to that of speed limits. The message all this virtually screams is "be careful," the path you are being taken down may be the wrong one.

Guidelines also make extensive use of thresholds. The Framingham risk score is a good example. In addition, the American Heart Association (AHA) has recently presented guidelines for defining "ideal cardiovascular health, using seven simple measures.[1] The idea is to define goals in the hope that over the next decade a significant reduction in cardiovascular mortality and morbidity can be achieved if everyone knows what is ideal. Six measures use thresholds and only smoking is dichotomous. The National Cholesterol Education Program uses thresholds extensively and gives the impression of evidence-based fine-tuning the management of LDL cholesterol to prevent primary or secondary cardiovascular acute events. Yet half those admitted for a heart attack have low to very low cholesterol. Careful examination of the basis for thresholds will always reveal gray areas, uncertainties in the evidence and indications that the thresholds are not universally applicable but have ethnic, gender, age and comorbidity qualifications. In the AHA scheme of the ideal world, there is no stratification by adult age or gender. Just 7 simple questions about smoking, weight, physical activity, diet, cholesterol, blood pressure and fasting blood glucose. It is fascinating that in a study group of about 2000 individuals with a mean age of 59 years, only one person met all seven criteria for ideal cardiovascular health![1] Ideal indeed!

In an article in the *Annals of Internal Medicine* in 2008, Vickers and colleagues discuss the continuous disease problem.[2] They point out that in many cases the use of diagnosis for X should be replaced with a discussion with the patient regarding the enhanced risk of the associated disorders and problems rather than merely the assignment of label, an entry into the chart, and frequently the advice to take a prescription drug and alter lifestyle. This of course opens a Pandora's box and may involve the discussion of the precision and accuracy of laboratory measurements and bacteriologic diagnosis, the nonsense that thresholds hold quantitative meaning, clinical or otherwise, and the whole exercise tends to undermine the belief implanted in patients of

evidence-justified medicine based on thresholds and studies that use thresholds.

THE INCONVENIENT PLACEBO

As has been discussed in this Newsletter and in the recent Research Review concerning psychiatric drugs, a recent meta-analysis based on a FDA database and including suppressed trials found that essentially half of all trials of antidepressants for major depressive disorders actually failed. The analysis included 12 approved drugs, 74 randomized clinical trials, and over 12,000 patients. A recent paper takes the position that there is a urgent need to improve the efficiency and accuracy of randomized controlled trials (RCTs) concerning major depressive disorders, which apparently translates into getting more drugs approved with less cost and effort.[3] The authors point to four reasons why these RCTs fail: (1) low sensitivity of the methods used to detect clinical improvement; (2) modest efficacy of the drug; (3) heterogeneity of the study population; and (4) a high placebo effect. The first point suggests it is hard to detect significant improvement above the noise. In fact, the improvement may not be there at all. The second point implicitly indicates a belief in the efficacy. They then propose a data analysis method to "enhance the signal" which translates, it would appear, into dealing with the data such that the effect believed to be there is selectively amplified.

The whole idea of the RCT is to eliminate any bias in selecting treated vs. placebo subjects and if the study is blinded, to design it so that neither the subjects nor the investigators know who is getting the drug. These studies generally involve multiple sites and it has been observed that the magnitude of the placebo effect varies considerably form site to site. In what the authors describe as a new "population-enrichment strategy," they propose that the data should be filtered to eliminate that from sites that have either high or low placebo rates. It turns out that in practice, their method mostly eliminates sites with high placebo rates (treatment group has a low % with benefit and the placebo group a high % with benefit), which one might, expect, would increase the evidence for efficacy and reduce the trial failures. This is called generating an "enriched window." They liken this approach to the use of a so-called band-pass filter, a common practice in economics, physics, engineering and physiology as an enrichment strategy to optimise signal detection. It seems that there is an implicit belief present that there must be a benefit and all one has to do is look harder. The above procedure would be relatively transparent. This is in contrast to many of the statistical manipulations carried out with great ease using standard software packages which provide, according to critics, considerable latitude to massage results. The competing view of the above meta-analysis is that there is no benefit and that the 74 RCTs with over 12,000 subjects are in fact giving the correct picture.

In an editorial, concern was expressed over the obvious question and the "need for proof of what happens when no signal exists."[4] In the trade this is called a Type I error, e.g. finding that a drug appears to work when it does not. The editorialists did their own test and found that using an enhancement window increased the Type I error with a doubling of the support of the supposition that the drug was more effective than the placebo. While they point out that this is not definitive, they use this as an example of the merit and need for further investigation of the enrichment window approach. Note, as mentioned above, that the process of discarding sites is not symmetrical but removes from the data base studies with strong evidence of benefit from the placebo and weak evidence for benefit from the drug. They also suggest that the pre-specification of the cut-off points used for site exclusion would introduce its own bias since the investigators would know at the start what the ground rules were and might be concerned least their results were discarded and they then might suffer financial damage by being excluded from future trials. In addition, if the window protocol were widely adopted, this might increase the number of studies that really demonstrated ineffectiveness being used, perhaps successfully, to justify drug approval and/or influence practice.

The authors of the "window" proposal declared they had no conflicts of interest, but two where listed in the affiliation sections as being directly associated with a major drug company involved in the antidepressant business. This seems to be an odd notion of the absence of conflict of interest. Also, the editorialists both were employed by a major drug company in the same business. Why is it that the journal could not come up with two expert editorialists in the field of biostatistics who were totally independent? Surely there are a number of such individuals who would qualify.

The reader is referred to Part I of the research review in the February and March issues for a discussion of a closely related issue, namely that there is no initial pathology in most of these mental problems to which one can direct targeted psychiatric drugs, and thus the basic paradigm for drug discovery in this field is defective.

Finally some comments on the current status of the placebo effect seem in order. While the placebo effect has been known since the end of the 18th century, only recently have the high powered techniques of whole brain imaging been applied to examine the phenomenon. A recent perspective addresses some of the issues and discusses the recent study of Bingel *et al.*[5,6] Bingel and coworkers used the treatment of constant pain induced by heat to examine the impact of positive and negative treatment expectancy. Positive treatment expectancy substantially enhanced (doubled) the analgesic effect of the drug used whereas negative treatment expectation totally eliminated the analgesic. The researchers were able with whole brain imaging to correlate these observations with neural activity in regions involved with the coding of pain intensity.

WHY VITAMIN AND MINERAL INTERVENTION TRIALS OFTEN FAIL

Most readers are aware of the fact that many epidemiological studies (follow-up, case control etc.) that indicate the importance of micronutrients in prevention and treatment of various chronic diseases frequently are not confirmed by randomized controlled intervention trials. Since the latter are regarded as the gold standard for proof of effectiveness, the net result has been the widespread belief that vitamin and mineral supplements are not beneficial. We constantly hear the mainstream chorus chant about the necessity of successful randomized trials before any intervention can be accepted. Such trials are very expensive, and in the context of primary prevention, must involve either huge numbers of subjects or subjects selected for very high risk or not enough cases will be observed to achieve the statistical significance required by convention. Furthermore, such studies must be very long term to pick up benefits in many chronic disorders with long latency periods and compliance can be a serious and even invalidating problem. It is inherent in the RCT that the control group offer a valid comparison. In RCTs of micronutrient supplementation, this is a significant problem since the controls must have a distinctly inadequate intake of the nutrient which must not change during the long follow-up—sometimes a totally unrealistic expectation. These and other shortcomings and problems with RCTs in micronutrient studies have been pointed out on several occasions.[7-9] The RCT may be a suitable gold standard for drug trials, since in this case one can safely assume that most if not all of the controls do not take the drug, especially, if it is only available for trials. This is in sharp contrast to supplements. Since the pharmaceutical industry is not interested in natural micronutrients, widespread testing of vitamin and mineral interventions with randomized controlled trials (RCTs) will, with a few exceptions, never be more than a token effort, mostly supported by government agencies. Furthermore, judging from past efforts, there is probably a considerable risk that the results will be meaningless. But most of those that have been done have contributed to the current mainstream disdain for supplements and strengthened the belief that the answer to mankind's health problems is behind the prescription counter, not the health food store.

A recent commentary by Morris and Tangney published in the *Journal of the American Medical Association* directly and significantly relates to this matter.[10] They forcefully point out with a diagram that physiological function is far from a linear function of nutrient status level. Quite the contrary, in general there is a range (plateau) they term adequate or optimum and on both above and below this level there is marginal function followed at the extremes of status characterized by dangerously deficiency or high dose toxicity. This relates to large intervention trials targeted at primary prevention, which enrol more or less healthy individuals. If the majority of subjects are on or near the plateau region of the physiological function curve, then increasing the level has no significant impact. Intake of the micronutrient being tested was already close to or in the plateau (optimal) range, and increases were irrelevant and toxicity was never reached. A second possibility is that the even with a population deficient in the nutrient being tested, the dose involved in the intervention may be inadequate to produce a significant benefit. Vitamin D, incidentally, is now the classical example. The authors sum up their commentary by the statement that "…most RCTs of vitamin supplementation are designed to test the hypothesis that supplementation, no matter the nutrient status, is protective." This they describe as a potential design flaw. They go on to provide examples from the field of dementia where the interventions involved vitamin E, B-vitamins and docosahexaenoic acid. In these trials, null results were obtained. Only when post-hoc or sub-group analysis focused on individuals who had very low micronutrient intakes, were significant beneficial outcomes observed. Perhaps space limitation prevented their inclusion of a dozen or so other recent studies that appear to suffer from the same flaw and have contributed to what critics and some observers describe as the war on supplements.

An excellent example by Bolland *et al* of the point being made in this paper just appeared *in the British Medical Journal*.[11] The issue is the cardiovascular risk for women that may be associated with calcium supplementation. This meta-analysis plus an earlier one from the same group found a statistically significant increased risk. When the first analysis came out in 2010 it was met with considerable scepticism because the Woman's Health Initiative (WHI) study failed to find any association at all. However, it turned out that in the WHI study, subjects were allowed to continue with any supplements they were already taking and were randomized into the placebo and intervention groups, the latter involving calcium supplementation. Thus critics of the WHI study pointed out that that some in both the placebo group and the intervention group were already taking calcium supplements and this was not taken into account and could produce a null result. When Bolland and colleagues obtained the WHI data and separated the subjects into two groups, one where no participant in the intervention or placebo grope was taking calcium supplements, the results showed the increased risk for the comparison of the calcium subgroup vs. the placebo subgroup. This appears to resolve the inconsistency. This example illustrates a flawed study design that failed to reveal evidence of risk rather than benefit, but the same principle applies.

Thus there may indeed by some risk of cardiovascular adverse events associated with the common practice among women of taking supplementary calcium or calcium and vitamin D for bone health, a recommendation of long standing. Incidentally, it appears that the elevated risk is independent of the presence or absence of simultaneous vitamin D supplementation. A study to settle this question may never happen due to the low event rates and high costs.

VITAMIN AND MINERAL SUPPLEMENTATION AND THE TRIAGE THEORY OF BRUCE AMES

Closely related to the above is the triage theory proposed in 2006 by Bruce Ames, one of the world's leading experts on the role of micronutrients in cell function and metabolism.[12] Readers are referred to the September and October, 2004 Newsletters for a review of Ames' work on what he terms "a metabolic tune-up." The triage theory holds

that when there is an inadequate availability of a micronutrient, nature ensures that micronutrient-dependent functions required for short-term survival are protected at the expense of biochemical functions that are associated with only long-term consequences of this deficiency. These long-term consequences include diseases associated with aging. More specifically, this theory proposes that micronutrient-dependent protein synthesis required for short-term survival and/or reproduction is protected during micronutrient deficiency over other non-essential micronutrient dependent protein synthesis processes needed only for long-term health. Thus, micronutrient deficiency contributes to subclinical damage and increases the long-term disease risk. The theory focuses on vitamins and minerals as the critical micronutrients. It is important in this context that virtually every metabolic pathway includes one or more enzymes that require vitamins or minerals as essential cofactors in order to function.

While it is a common mainstream belief that we should be able to get all the vitamins and minerals we need from our diet, study after study suggests widespread inadequacy in intake that falls well below the estimated average requirement (EAR) or recommended dietary allowance (RDA), and these values themselves may be low. Furthermore, the normal range of intake of vitamins and minerals for optimum health is unknown for humans, and the EAR and RDA, which do not really relate to optimum levels, are based only on crude estimates or outright guesses. Furthermore, there is substantial human variability, which has genetic, gender and age-related components. Therefore, judgements based on animal models and a very detailed understanding of a large number of pathways may be the only guidance we will have for some time, if ever, given the great difficulties associated with relevant human studies at the mechanistic or epidemiological level. Bruce Ames and his group have made large and significant contributions while addressing these issues and testing the triage theory. The initial focus has been on micronutrients that are required for relatively few functions (biotin, folate, iodine, molybdenum, selenium, vitamins B-1, C and K). Thus far studies involving vitamin K and selenium[13,14] have successfully tested the triage theory against published literature. Both studies provide evidence associating deficiency-inadequacy with diseases of aging, but they are not definitive human studies.

The obvious question then relates to the wisdom of regularly taking a multivitamin. Already in 2001 in a short paper on clinical practice in the *New England Journal of Medicine*, Walter Willett and Meir Stampfer from Harvard were recommending a daily multivitamin where the component levels per daily dose did not exceed the RDA, and they comment that substantial data suggest that higher intakes of folic acid, vitamins B6 and B12 and as well vitamin D will benefit many people.[7] Willett reiterates this recommendation in his recent book *Eat, Drink and be Healthy*.[15] In the 2006 paper proposing the triage theory, Ames also addresses this question. Prefacing his remarks, he cites the evidence from the 2005 NHANES study that diets of many in the U.S. do not provide adequate intakes of vitamins and minerals even using as standards the recommendations by official organizations, and that efforts by public health departments to improve the American diet have not been very successful. It anything has changed since 2005, it would appear that it is in the wrong direction given the obesity epidemic and the continued ascendancy of food high in calories but low in micronutrients (aka junk food). He observes that it may be easier to convince people to take an inexpensive multivitamin-mineral pill each day than to significantly change their eating habits. He dismisses the mainstream demand for RCTs and instead suggests that all scientific evidence be taken into account, which includes biochemical, mechanistic and epidemiological studies on both humans and animals. Ames also cautions that multivitamins must be selected with certain risks in mind, which are related to excess vitamin A and iron consumption. Modern supplement formulators appear aware of these issues. In addition, he cautions against over-consumption since many minerals are toxic at high doses.

Now we come to the big problem. There have been several RCTs that examined multivitamin mineral supplementation with endpoints of cancer or overall mortality. Most gave null results.[16] The serious problems with RCTs in this context were discussed above. There have also been a number of observational

studies (mostly cohort follow-up but some case-control) that have reported over the past decade. These studies addressed the question of the impact of multivitamin mineral use on mortality, cancer incidence and cancer related mortality at various sites but mostly breast, and as well cardiovascular disease. While a some studies had a few results suggesting possible reduction in risk, mostly they were characterized by null results.[17-19] An exception was the risk of heart attack among Swedish women.[19] The Swedish studies did not suffer from the above-discussed problems with RCTs. However, there are limitations with all of the studies. These include inability to take into account the composition or intake levels of the vitamins or minerals, insufficient length of follow-up into old age, which may be important for the age-related diseases in question, too short a follow-up in general, and more or less frequent use of supplements than reported on questionnaires. With regard to minerals, the actual chemical form used may be important, controlling not only assimilation but also potential adverse catalytic and oxidative actions.[20] This failure of observational studies to provide support for the triage theory points not so much to problems with the theory as to difficulties in conclusively demonstrating the merits of its eventual application to prevention. Individuals will certainly have variable levels of micronutrient status for each essential micronutrient important for the risk of age-related diseases. In addition, there is the matter of genetic variation. Nor is the optimum level for important minerals and vitamins known or easily measured for any given individual, and it is not generally known how long it takes to achieve a significant change in level for any given micronutrient nor the dose needed. Observational studies do not correct for measured deficiencies at baseline, an impossible task given the number of components involved, and subjects consume variable amounts of micronutrient from foods. Then there is the interaction with other factors such as obesity, prescription drugs etc. While for some these null studies weaken the argument for taking a multivitamin for insurance, they definitely should not eliminate it. Nor do they invalidate the triage theory. Rather they simply indicate the complexities of implementation as research proceeds. Perhaps the strategy should be to take a good multivitamin-mineral and consume a diet known to be rich in vitamins and minerals. Even this is not simple, given the soil depletion that has been occurring for decades. It is also important to consider that prevention in terms of diet and supplementation goes beyond vitamins and minerals and includes a vast array of phytochemicals and as well, the omega 3 fatty acids.

It seems clear that we are merely at the threshold of understanding the role of micronutrients in health and in particular the diseases of aging. The triage theory provides a theoretical framework but little specific information useful in direct application to prevention in the general population. It may be that the obvious indication to take a multivitamin-mineral is not specific enough. However, the solution is not to drastically increase the intake because of toxicity considerations, although the suggested daily doses from the manufacturers provide considerable latitude below the toxicity level for many common and popular preparations. Therefore, one must be realistic in their demands for evidence and realize that the typical multivitamin-mineral as presently formulated may have inadequacies, which will only become apparent after much more research is done. Thus far, as regards the triage theory, there seems to be no evidence that falsifies it and it should provide an important incentive and vital guidance for researchers concerned with making significant contributions to preventive medicine in this context. Vitamins and minerals need to be elevated to a higher level of respect than just things we casually take to try to avoid the flu or colds. That clearly is not the name of the game. However, choosing an adequate multivitamin presents a problem, although the intake of most formulations can be increased without exceeding the toxic threshold. Finally, some important micronutrients will still be at insufficient levels.

HOSPITALS CAN BE VERY DANGEROUS PLACES

A recent article in the journal *Health Affairs* addressed the question of hospital adverse event reporting and the potential for serious underestimates.[21] They examined three tools for measuring adverse event rates to track patient safety. The methods were voluntary reporting, use of the Agency for Healthcare Research and Quality Patient Safety Indicators (AHRQ) and the Institute for Healthcare Improvement Global Trigger Tool (IHIGTT). Voluntary reporting is naturally subject to influence by defensive attitudes. The AHRQ avoids this by using automated review of discharge codes to detect adverse events. The IHIGTT offers potential improvements by starting with chart reviews by two or three individuals trained to examine charts in a systematic manner by looking not only at discharge codes and summaries, but also notes or comments, medications, lab results, operation records, nursing notes, and physician progress notes in order to determine the presence of a "trigger" in the chart. Any notable trigger leads to an additional investigation regarding the possibility of an adverse event and a physician ultimately is required to examine and sign off on each flagged chart.

In the study just published, a comparison was made of these three methods in three large U.S. tertiary care centers that had a well established and respected patient safety programs. Patients were randomly selected from inpatients provided they were > 18 years of age with a length of stay of more than 24 hours. All evidence of patient identification was removed from the records examined in the study. A total of 795 records provided the data base and 393 adverse events were detected by all three methods combined.

The results were quite amazing. The IHIGTT found almost ten times the adverse events (354/393 or 90.1%) compared to the AHRQ protocol (35 or 9%) and the voluntary reporting (4 or 1%). One does not need a detailed statistical analysis of these results to decide if they are significant. The voluntary reporting protocol failed to pick any of the 4 fatalities associated with adverse events found by the other two methods. Overall, the rates documented are considerably higher than found by various methods in other studies. One reason is that this study used a broader definition of adverse events and did not require that these be judged either preventable or lead to major disability. To qualify, the *minimum* requirement for the event was that it caused temporary harm requiring intervention. Types of adverse events included were medication or procedure-related, hospital acquired infections, venous thromboembolism, pressure ulcers, device failure, and patient falls. The authors point out that the true rates are likely to be higher still, given the consistent finding that not all adverse events are documented in the patient record.

In the same issue of *Health Affairs* there is an interesting account concerning how one large health care delivery system, Ascension Health Care, undertook very aggressive action to attempt to decrease preventable in-hospital adverse events.[22] Ascension Health Care is the largest Catholic non-profit and the third-largest health care delivery system in the U.S. with 69 acute care hospitals. In 2010 the system logged nearly 700,000 patient discharges and 75,000 births. In 2003, six goals were identified: improving communication, preventing adverse drug events, avoiding birth trauma, reducing incidence of pressure ulcers, falls and fall injuries, hospital-acquired infections, and perioperative complications arising during the hospital stay. They also set a goal of decreasing the in- hospital death rate by 15% among patients not admitted for end-of-life care. This figure was based on a mean of national figures concerning the annual percentage of in hospital deaths that were judged preventable (8 to 22%). By 2010 Ascension Health Care had reduced preventable deaths by somewhere between 1500 and 5000 annually, depending on the assumptions in the calculation, compared to 2004. This was achieved during a period of rising overall severity of illness of patients cared for in their hospital system.

It would appear that in the U.S. patients have grounds for serious concerns regarding hospital care. The studies discussed illustrate both the problem and the potential for fixing it. Those with influence at any level of the health

care system need to take aggressive action to bring about change. Also time has come for the organized pressure from the general public.

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The Prostate Monitor
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Reviews of recent studies from the peer-reviewed literature

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Problems related to an enlarged prostate (benign prostatic hyperplasia or BPH) are common, impact the quality of life, and at one extreme, acute urinary retention generally means a fast trip to the ER. Surgical treatment of severe BPH is not pleasant to contemplate and incidentally it also can reveal prostate cancer. However, whether this incidental biopsy is worse than the standard transrectal ultrasound guided procedure with the needle gun is debatable.

In this issue we begin with a discussion of what is called combined therapy for BPH, which means combining an alpha-blocker with a drug which inhibits the conversion of testosterone to dihydrotestosterone. This is a serious issue since natural remedies and alpha-blockers generally eventually fail to halt the progression of BPH and the process of prostate enlargement.

The next topic involves hormone therapy prior to radiation therapy for prostate cancer. For anyone diagnosed with prostate cancer and electing radiation therapy, this option will no doubt be suggested. Thus for those individuals, a recent study discussed in some detail should be of interest. This is one area where significant progress appears to have been made.

Finally, we discuss a recent study of a monoclonal antibody directed at reducing the risk of bone problems associated with metastatic prostate cancer. This does not appear to be an area where significant progress has been made.

Wishing you good health,

William R. Ware, PhD, Editor

COMBINED THERAPY FOR BENIGN PROSTATIC HYPERPLASIA (BPH)

Benign prostatic hyperplasia (BPH) translates to enlarged prostate, a disorder (or curse) of older men. It is present in more than half of men age > 50 and 90% of those over 80. We devote a chapter to this disorder in our book *The Prostate and Its Problems*. Those afflicted present with a range of symptoms from mild to severe, and the former are typically ignored for a significant period during which the prostate enlargement is taking place. Common early symptoms include urgency, increased frequency of bathroom trips especially during the night, and decreased flow velocity. At this point some men start taking a so-called prostate formula which includes saw palmetto, and while these preparations work best in the early stages of BPH, their effectiveness frequently declines with increasing prostate volume. At the opposite extreme is what is called an acute urinary retention (AUR) episode which of course is a medical emergency generally requiring catheterization. At this point some men undergo surgery to enlarge the urethra (transurethral prostate resection or TURP) which relieves some of the urinary symptoms and sometimes also reveals cancer in the removed tissue. The tendency to ignore symptoms until it is too late is reflected in the comment of some family doctors that most men do not bring up these problems until they "can't pee."

Mainstream medicine offers two pharmaceutical remedies. One is the so-called alpha-blocker, which was traditionally a blood pressure medicine, but today is mainly used to treat BPH, mostly in its early stages. The alpha-blocker binds to certain receptors in the prostate tissue and act mostly through a muscle relaxation mechanism. The class called 5-alpha-reductase inhibitors (5-ARI) constitute a more aggressive therapy and is commonly used as BPH problems becomes more serious. These inhibitors reduce the levels of dihydrotestosterone, which is associated with prostate enlargement. The mechanism involves the inhibition of the conversion of testosterone to dihydrotestosterone. The two popular drugs are finasteride (Proscar) and dutasteride (Avodart), both of which have the ability to dramatically reduce prostate volume over a rather short time period and as a consequence reduce significantly the symptoms of BPH. As discussed in earlier *Prostate Monitor* issues, these two 5-ARIs have also been found to significantly reduce the risk of prostate cancer, and the small increased incidence of advanced cancer while on Proscar appears to be an artefact.

Alpha-blocker therapy does not stop the prostate enlargement nor reduce its size, and as a consequence, many men reach the point where worsening symptoms prompt considering a 5-ARI in order to address their problem by reducing the prostate size. Their doctor will probably suggest it, and they will likely hear about it through a commercial during the evening news (My doctor told me I had a *growing* problem, not a *going* problem."). There then arises the question of monotherapy with a 5-ARI or combined therapy since many men start with one of the alpha-blockers.[1] A study has just been published which addresses the important question of the relative merits of monotherapy with either drug vs. combined therapy.[2] Reported are the clinical outcomes of a randomized trial (CombAT) which used combined therapy with dutasteride (Avodart) plus tamsulosin (Flomax) or either alone over four years in the context of BPH.

The study in question was multicenter and involved over 4800 men aged ≥ 50 years with symptomatic BPH, PSA levels between 1.5 and 10 ng/mL, and a prostate volume greater than 30 mL. Eligible patients received 0.4 mg of tamsulosin, 0.5 mg of dutasteride per day, or both. The primary endpoint was time to first AUR or BPH-related surgery (e.g. the TURP). Secondary endpoints included symptoms of BPH and its clinical progression. Overall baseline characteristics were similar across the three patient groups. The findings were as follows:

- The incidence of AUR or BPH-related surgery was higher in men treated with tamsulosin than those treated with dutasteride or combined therapy.
- Statistically significant superiority of combined therapy rather than tamsulosin was found in subgroups with baseline prostate volume ≥ 42 mL, in all subgroups of baseline PSA, and all other baseline subgroups.
- The incidence of clinical progression was higher in men receiving tamsulosin than dutasteride or combined therapy in all baseline subgroups except for men with prostate volume < 40 mL.
- The incidence of clinical progression was highest in men with the worst baseline clinical picture.

- Combined therapy reduced the relative risk of symptom progression compared with tamsulosin across all but one baseline subgroup (prostate volume <40 mL.).
- The reduction in the relative risk of AUR or BPH-related surgery with combined therapy ranged from 43 to 77% relative to tamsulosin therapy. The benefit from combination therapy in this context was greatest for men with prostate volumes > 58 mL.
- Differences in results for dutasteride alone or the combination therapy were small which points to the 5-alpha reductase inhibition as having the major impact.
- The incidence of BPH-related problems and complications were higher among the tamsulosin-treated patients compared to either combination therapy or dutasteride only therapy.
- Over 4 years, there were greater symptom improvements achieved with dutasteride compared to the alpha-blocker.

These results all support the superiority of combined therapy or dutasteride monotherapy over alpha-blocker therapy except for men with low prostate volume at baseline (< 40 mL).

Two questions will probably occur to most readers: (1) What happens if after experiencing a significant or satisfactory improvement in symptoms with combination therapy, one discontinues 5-ARI therapy? (2) Once combination therapy has produced a good response, can one then stop the alpha-blocker? The answer to the first question is that discontinuation of a 5-ARI results in prompt prostate regrowth which is considerable over even one year and is accompanied with an aggravation of BPH symptoms.[3] The authors suggest that this implies that 5-ARIs should be considered as a life-long therapy for preventing BPH progression and acute events. With regard to the second question, there appears to be only a short study which found that after 9 months of combined therapy, in this case with Proscar and an alpha-blocker, the control of BPH symptoms appeared to be maintained for an additional 9 months after discontinuing the alpha-blocker.[4] Since the two 5-ARIs are similar in action and effectiveness and as well the various alpha-blockers also appear to be about equally effective, these results can probably be generalized to any combination of the two types of drug. Prior to this study with dutasteride and tamsulosin, four studies all found similar results with finasteride and three different alpha-blockers with beneficial symptom changes, changes in voiding rate and prostate volume. However, dutasteride appears to achieve a considerably larger decrease in prostate volume than finasteride over a similar treatment periiod.[1]

While many readers will have a justifiable aversion to long-term use of pharmaceuticals, there do not appear to be satisfactory natural approaches to deal with the severe or acute effects of BPH. The really bad news is that 5-ARIs have a number of serious side effects. The package insert or "label" for Avodart gives the following information: *"The most common side effects of AVODART, taken alone or in combination with tamsulosin, are impotence (not being able to achieve or maintain an erection), decrease in libido (decreased desire to have sex or a reduced sex drive), changes or problems with ejaculations (including decrease in the amount of semen released during sex) and breast swelling or tenderness. Additionally, some people may experience dizziness when taking AVODART with tamsulosin."* Similar side effects are reported for Proscar. Drug-related side effects of 5-ARIs appear within the first six months and then have been reported to decrease with continued use.[1] Side effects are much less of an issue with the alpha-blockers, although there have been some reports of ejaculatory abnormalities, but tamsulosin has been reported to produce significant improvement in sexual function score compared to a placebo.[1] Some alpha-blockers can cause orthostatic hypotension (postural blood pressure drop when rising from a lying or sitting posture) and some alpha-blockers need to be "titrated" to avoid severe first-dose hypotension. Tamsulosin has a minimal effect on blood pressure.

ANDROGEN DEPRIVATION PRIOR TO RADIOTHERAPY FOR PROSTATE CANCER

A new 10-year study has just reported which examined whether 3-month or 6-month short- term neoadjuvant androgen therapy (NADT) prior to radiation therapy decreases clinical progression and mortality after radiotherapy (RT) for locally advanced prostate cancer.[5] Androgen deprivation therapy

(ADT) either short-term before (neoadjuvant) or longer-term after (adjuvant) radiation therapy came into favour in the 1990s in response to the frequency of treatment failure associated with radiation used as a monotherapy. During this period evidence accumulated suggesting that both neoadjuvant and adjuvant ADT improve survival. However, it also became apparent that prolonged ADT after RT carried serious and undesirable sequelae. These include permanent hypogonadism, osteoporosis, muscular atrophy, various aspects of the metabolic syndrome, anaemia, cognitive problems and depression, enlarged breasts and prolonged sexual dysfunction[5] (see Hans Larsen's Research Review in the May and July/August 2010 issues of the Prostate Monitor). This long list of adverse effects enhanced interest in the potential benefit of just using NADT and raised the question of the optimum duration. One of the largest trials was the Trans-Tasman Radiation Oncology Group 96.01 trial (TROG) that first examined 3 and 6 months of neoadjuvant ADT and found that 6 months provided enhanced benefit in terms of cancer-specific survival and reduction of metastases after 5 years of follow-up when compared with 3 months of treatment. The new study is important because it extends the observation period by an additional 5 years.

The study involved 818 men randomized into 3 arms, RT alone, and 3 months or 6 months of neoadjuvant ADT which was terminated at the end RT. The two ADT arms started therapy 2 and 5 months prior to the start of RT. The subjects included men with a median age of about 68 with locally advanced cancer. In this study this translates to men with T2b, T2c, T3 and T4 clinical stages but no regional lymph node metastasis or distant metastasis. The clinical stages all imply tumors detected by digital rectal examination as well as tumors that extend through the prostatic capsule and/or have invaded adjacent structures. Anyone with a positive bone scan suggesting distant metastasis were excluded at recruitment, as well as anyone with radiographic evidence of lung cancer or cancer detected with a CT scan of the abdomen and pelvic region. However, there was no upper limit on PSA and 43% had levels ≥ 20 ng/mL. Randomization was done to provide approximately equal baseline characteristics. ADT consisted of goserelin and flutamide. The RT protocol was uniform for all subjects (66 Gy), and there was no post-RT ADT. The follow-up in this latest report was over 10 years for the primary endpoints of cancer-specific mortality and all-cause mortality. Secondary endpoints were PSA progression, local progression, distant progression and event-free survival. Event-free survival was defined in terms of the time to first PSA or clinical progression, secondary therapeutic intervention or death. The study protocol did not mandate the type of secondary therapeutic intervention administered upon progression, but recommended that such interventions should be delayed until clinical progression occurred. This last aspect of course is an unavoidable complication to an otherwise nicely designed study.

The results for the primary and secondary endpoints given below provide evidence for the long term enhanced benefit of 6-month vs. 3-month neoadjuvant ADT. Given are the percentage decreases in risk taken from the hazard ratios obtained by multivariable analysis (NS= not significant statistically).

	Ten-Year Decrease in Endpoint Risk	
Endpoint	3-month NADT	6-month NADT
All-cause mortality	16%	37%
PC-specific mortality	14% (NS)	51%
Event-free survival	37%	49%
PSA progression	28%	43%
Local progression	51%	55%
Distant progression	11% (NS)	51%

In an accompanying editorial, Cris Parker from the Royal Marsden Hospital in the UK commented that the magnitude of the observed benefit for 6-month NADT compared to RT alone is truly remarkable.[6] He raises the question of the potential benefit for some adjuvant ADT which one study showed benefit from 4 months of NADT combined with 2 years of adjuvant treatment, but this new study raises the possibility that much of the benefit might be achieved just from 6 months of NADT. He also points out that RT protocols and techniques have changed since TROG study was designed but that the 10 year results suggest that 6 months of NADT produce far greater benefits as compared to RT

dose escalation and dose escalation can be accompanied by permanent adverse effects, something that appears absent in the 6-month NADT protocol.

The authors of the TROG study conclude that 6 months of neoadjuvant androgen deprivation combined with radiotherapy is an effective treatment option for men with locally advanced prostate cancer, and in particular, for men without nodal metastases or pre-existing metabolic comorbidities that could be exacerbated by prolonged androgen deprivation. The considerably increased benefits associated with 6 vs. 3 months of NADT will probably influence future practice. The effect of RT dose escalation in this context is now an important issue.

TREATMENT OF HORMONE-REFRACTORY METASTATIC PROSTATE CANCER

A recent multicenter study has reported results in connection with hormone-refractory metastatic prostate cancer. The study compared a bisphosphonate (zoledronic acid) with a human monoclonal antibody which inhibits osteoclast-mediated bone destruction.[7] Zoledronic acid received regulatory approval on the basis of a phase 3 trial published in 2002.[8] This trial randomized 643 men to either a low or high dose of zoledronic acid (214 and 221 subjects) or a placebo (208 subjects). However, during the trial the dose in the high-dose group was reduced to the low dose because of concerns over kidney safety. If one examines this study closely, one finds a very large percentage of discontinuations which left only 81, 62 and 65 in the low, high and placebo groups, respectively. The authors list five categories of reasons for discontinuation, including death, which accounted for 12-15% of the randomized groups. The list of reasons obscures the real motivation. When the various skeletal-related events were examined at 15 months, the percentages and benefit were based on the total numbers at randomization, not those that completed the trial even though 62 to 73% of subjects dropped out of the study. Thus the results are difficult to evaluate, but the authors admit there were no differences in disease progression, performance status or quality of life scores observed. Only a small extension of the median time to first skeletal event was found (365 vs. 321days). The study was industry sponsored and a number of the authors of the paper had financial ties with the sponsor. This short history provides some insight into the approval process to generate what is now termed the established therapy, the standard of care and a treatment superior to a placebo.[7]

The monoclonal antibody study used denosumab, a product of the company that provided funding. In a previous trial of men receiving androgen-deprivation therapy for nonmetastatic prostate cancer, denosumab was shown to be superior to a placebo in increasing bone mineral density and reducing the incidence of fractures. As with the above study, many of the authors of this new study report financial ties with the sponsor. This was a randomized head-to head trial with 952 in the zoledronic acid group and 951 in the denosumab group. Again, the dropout rate was high (76% and 78%) and the death rate was 28-31% during the 41 months of the study. The list of reasons for withdrawal again obscures the real motivation. The median time to first on-study skeletal-related event was 17.7 months in the zoledronic group and 20.7 months in the denosumab group. In an accompanying editorial, the clinical significance of this difference was questioned.[9] Safety was judged by adverse events. For the zoledronic group compared to the denosumab group, serious adverse events were almost identical, totalling 60% and 63%, with fatal adverse events at 29% and 30%. Fatigue, bone pain, weakness and debility were similar in the two intervention groups, results that suggest little if any differential impact on quality of life.

It was concluded that denosumab was better than zoledronic acid for preventing skeletal related events and potentially represents a novel treatment option in men with metastases from hormone resistant prostate cancer.

The magnitude and significance of the therapeutic advance represented by this particular monoclonal antibody is left to the judgement of the reader, but it is difficult to avoid the discouraging conclusion that in the past decade there has been little progress in dealing with the skeletal-related aspects of metastatic prostate cancer.

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