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A recurring theme in a number of recent Newsletters has been adverse effects of modern drugs. It would seem that this is an inevitable consequence of the modern paradigm where drugs are designed to rectify a situation where some biochemical is either low or high compared to what is judged normal or ideal. The biochemistry and microbiology are then modified. Receptors are blocked, enzyme reactions inhibited, pathways interrupted, etc. The end result may be benefit, sometimes barely measurable, sometimes quite large; however, the drug which inhibits, blocks or interferes in some way to increase or decrease the level of some biochemical almost always does not confine its activity to the targeted process, but rather can alter some or many other processes, or even the same process in a number of organs or locations. When statins inhibit the mevalonate pathway and thus ultimately inhibit the production of cholesterol, at the same time a large number of other pathways downstream are inhibited with concomitant disturbance in the natural balance of a large number of biochemicals. When glucose-lowering drugs increase insulin sensitivity by interacting with a particular receptor, there are also consequences wherever the receptor is expressed. Gastric reflux is painful because of the irritation due to the acidic stomach fluid so let's eliminate stomach acid even though humans evolved over eons to have high stomach acidity which in turn is critical for the control of numerous biochemical and microbiological processes. Ads on TV for drugs frequently enumerate an amazing array of side effects for a single drug ranging from acute hypotension to adverse changes in hearing and eyesight. The modern paradigm appears simplistic and ignores the incredible complexity of human biochemistry which prevents the drug developers from predicting what will happen when they introduce their inhibitors, activators and blockers.

Long forgotten is the era when deficiency diseases such as rickets, pellagra, goiter, anemia, scurvy and certain mental problems were cured or prevented simply by addressing the deficiency in a single mineral or vitamin. But cancer, atherosclerosis, diabetes and mental degeneration represent a much bigger challenge and the barrier presented by the incredible complexity of human biochemistry has never really been overcome. Cancer mortality has not changed in three decades. Some scientists do not believe the modern models for the development of atherosclerosis. There is neither a cure nor successful treatment for Alzheimer's disease. Models for Alzheimer's pathophysiology and etiology are frequently questioned. The new paradigm is not working very well, and is probably hindering progress toward the ultimate goals of true primary prevention or cures for chronic diseases.

Examples appear constantly in the literature of failed therapy based on correcting too much or too little serotonin, blood glucose, various blood lipids, homocysteine, beta amyloid, etc. The goal is modifying chronic, high prevalence diseases. These diseases develop over long periods and when observational and epidemiological studies find a risk factor, preventive therapy or treatment of the symptomatic disease will frequently be late in the disease's natural history. Sorting markers from causal agents has proved challenging and failures in this area lead to failed therapy. Clinical studies involving primary prevention based on hypotheses generated by observation of epidemiological studies need to involve young individuals and extend over 10-30 years. But the event rates are too low, the number of required subjects too high, length of the required study too long, and the cost astronomical. Interventions may be too late even if the hypothesis-generating study points in the right direction. This issue of the Newsletter, as well as those that have preceded it, contains a number of examples.

Finally, this issue also contains a review of the role of iodine deficiency in a number of diseases.

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

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ALZHEIMER’S DISEASE. WHERE DO WE STAND REGARDING TREATMENT AND PREVENTION?

This question has recently been addressed in two reviews by researchers at Mount Sinai School of Medicine in New York.^{1,2} This institution is very active in Alzheimer’s disease (AD) clinical studies with seven trials currently underway. FDA approved treatments with either prescription or over-the-counter drugs were reviewed. The following interventions were discussed: Cholinesterase inhibitors, memantine, anti-inflammatory agents, antioxidants, cholesterol lowering, estrogen therapy, ginkgo biloba, and homocysteine lowering with B vitamins.

Treatments listed provide only limited (6-18 months) or negligible benefits or impact on the progression. The short-term benefits must be measured against the natural history where progression from the onset of memory impairment to total functional dependency and death in untreated persons with AD takes approximately 8-10 years. There is currently no recognized cure for AD. As Geldmacher *et al*³ discuss, it is important that patients and caregivers be advised such that they have realistic expectations when conventional treatments are recommended. It is commonly believed that by the time a patient presents

with frank dementia, it is too late to make a substantive change in the disease outcome.²

The treatment dilemma is further highlighted by the announcement on August 17 by Eli Lilly and Company that it was halting two placebo controlled clinical trials (phase III) of a new Alzheimer’s drug called semagacestat, because those on the drug worsened to a greater degree than those on the placebo, and there was an increased risk of skin cancer (see Medscape Medical News, August 17). Over 2600 patients with mild-to-moderate disease were involved. This is a perfect example of the drug discovery paradigm failure discussed in the editorial at the start of this Newsletter. The motivation was the long standing amyloid hypothesis which holds that the disease occurs when beta amyloid accumulates in the brain. The Lilly drug inhibited an enzyme needed to make beta amyloid, and the drug was shown to decrease the amyloid production in the brain. But the clinical trial failed dramatically, causing renewed questioning of the hypothesis that is central to programs involving the development of over 100 Alzheimer’s drugs. Are they all doomed to failure?

Non-pharmacologic interventions have also been investigated for both primary and secondary prevention. Both physical activity and cognitive training have been found to offer modest benefits. Cognitive training trials, however, did not include evaluation of function outcomes or dementia risk.² In the context of primary prevention regular mid-life physical activity has been shown to reduce the risk of dementia and AD in later life and the Mediterranean diet has also been found protective. Other evidence of lifestyle benefits came from the “nun” study where most nuns that surpassed age 100 showed no evidence of functional AD and no signs of AD at autopsy. In this case the lifestyle was low-stress, satisfying, and involved a diet high in

fruits and vegetables and regular mental and physical exercise.⁴ Among phytochemicals, curcumin, resveratrol and green tea catechins have all be suggested as having the potential to prevent AD or slow its progression,⁵ but at this point any solid evidence appears lacking.

Recent studies and a remarkable case history suggest that the rather dismal picture presented above as regards the treatment of AD may not present the complete story. There is a “pharmacologic” approach not mentioned in the above reviews that may have considerable promise. This treatment evolved logically from early work on the metabolism of glucose in the brain which is different than in other tissues in the body in that the brain does not efficiently metabolize fats to generate energy. Glucose is the principal source. In periods of starvation or a very low carbohydrate diet (ketogenic diet), some of the energy for brain metabolism is supplied not by glucose but by ketones. In AD, it is well established that there is a decline in the cerebral rate of glucose metabolism, and low cerebral glucose metabolism correlates with a decline in cognitive function. It is interesting that persons with Parkinson’s disease, Huntington’s disease, multiple sclerosis and ALS have a similar defect in utilizing glucose for brain metabolism but the area of the brain affected is disease specific. This hypometabolism in the brain has been reviewed by Henderson.⁶

The ketones present during periods of starvation or fasting are produced in the liver from fatty acids and are called *ketone bodies*. This process is tightly regulated. But among the fatty acids, a unique group called medium chain triglycerides (MCTs) with saturated carbon chains between 5 and 12 atoms are not subject to this regulation and the ingestion of MCTs produces ketone bodies regardless of the other macronutrients consumed. While one might consider a ketogenic diet to enhance the production of ketone bodies, MCT ingestion is simpler and easier to implement. This leads to a potential therapeutic approach to AD where the reduced glucose metabolism in the AD brain is compensated by an increase in circulating ketone bodies provided by the metabolism of MCTs which then provide an alternative energy source. In 2009 the results of a randomized, double blind, placebo-controlled,

multicenter clinical trial were reported by Henderson *et al* where the impact of an oral MCT intervention was tested in subjects with probable AD to examine the potential for improving cognitive performance.⁷ This intervention produced a rapid elevation in serum ketone bodies and resulted in significant improvement of cognitive test scores. This benefit was most notable in those who did not carry the APOE4 allele. The action of MCT oil to produce ketone bodies for brain energy was also confirmed by a study where 40 g were ingested in a controlled intervention during the induction of hypoglycaemia. In the controls, cognitive function dropped strongly as expected, but in those supplemented with MCT oil the baseline cognitive function was maintained.⁸

These two clinical studies strongly relate to a case history presented online by Dr. Mary Newport.⁹ Dr Newport is a pediatrician and medical director of the newborn ICU at the Spring Hill Regional Hospital in Spring Hill, FL. At the time this case history begins, Dr. Newport’s husband Steve, an accountant, had moderate AD, could not cook for himself, or even use a calculator to perform the simplest addition. He had already tried the standard drug therapy, but his condition continued to deteriorate with a grim future. While researching trials of new treatments he might enter, Dr. Newport accidentally came across the one by Henderson *et al* described above which was then recruiting. She found that the intervention was simply MCT oil, the principal component of what was designated AC-1202, and it was in coconut oil which was readily available. Guided by the above study in which the proposed daily dose was 20 g of MCT oil, she proceeded to try 70 mL of coconut oil, first in oatmeal, at double the MCT dose in the trial just for “good luck.” This was first done early in a day when Steve was to undergo an assessment for entry into a trial. That afternoon when the tests were done there was a remarkable improvement compared to previous performances. He was able to supply information she had given him prior to the test such as the month, day, where he was and the name of the institute doing the screening, something he previously could not do. At 60 days into the coconut oil intervention, there was a dramatic improvement in his overall condition. The web link to the case history⁹ shows a diagram illustrating the improvement

in the famous clock test at 14 and 37 days and provides many details of other beneficial changes.

Dr. Newport updated Steve's status as of April 2009, one year after the start of the MCT treatment.¹⁰ He was then taking a mixture of coconut oil and MCT oil (both available at health food stores. MCT 4 teaspoons + coconut oil 3 teaspoons at each meal). Ten areas of significant improvement are listed in this update. He retained all of his improvements and continued to improve. This is in sharp contrast to the treatments described in the review cited above where at best there was a slowing in the relentless decline and the benefits quickly disappeared as treatment continued. Dr. Newport's story was published in the St. Petersburg Times (October 29, 2008) and since then she has received reports from some people who, like Steve, have had dramatic improvements using coconut or MTC oil, and many more that have had more subtle improvements. A curious aspect of this case history is that Steve is APOE4 positive, and that according to the study of Henderson *et al* this was the group exhibiting the smallest response the MCT intervention. Perhaps the higher doses used by Dr. Newport are partly responsible. In addition, he was taking mixed coconut oil and purified MCT oil since Dr. Newport had observed that the mixture provided a more constant level of ketone bodies over 24 hours. This was based on actual serum ketone level measurements.

A new update has just appeared.¹¹ Examination of 3 serial MRIs indicated that Steve had a normal scan in 2004, significant brain atrophy in 2008 at the start of the MCT

intervention, and no change since, a stabilization which is uncommon for AD patients. He is now able to use a riding lawnmower with somewhat complex controls and is doing better by many measures than two or even three years ago. Dr. Newport comments "I don't know if we will beat it, but we have at least gotten a reprieve from this disease." This appears to be an understatement.

It is understood that one case history is just that, one example of a success, but in AD, where dramatic reversals appear to be rare indeed, the biologically plausible MCT intervention using readily available edible oils seems to be of considerable interest. Coconut oil is a common nutrient in some cultures and MCT oil has been extensively studied as an aid to weight loss. Older studies used up to 80 g/day which is comparable to that used in the updated dose Steve used, about twice that used in hypoglycaemic study and considerably higher than used in the Henderson *et al* study. In the latest update, Dr. Newport also describes ongoing research from the laboratory of R. L. Veech at the NIH on the therapeutic use of one specific ketone body rather than a mixture of MCTs. This may increase the effectiveness of the treatment. A preliminary positive rodent study from this laboratory has just appeared.¹² Incidentally, there does not appear to be convincing evidence that consumption of MCT fat is atherogenic, although no studies appear to have directly examined coronary atherosclerosis. But we are talking about a potentially powerful treatment for a widespread, dreadful, incurable and fatal disease.

VITAMIN D AND AUTISM—AN UPDATE

Dr. John Cannell has recently updated his 2005 paper connecting vitamin D deficiency with autism.¹³ He makes the following points:

- If the hypothesis is correct, there should be an association between rickets, the classic vitamin D deficiency disorder, and autism. While no modern studies appear to have been done, two papers which appeared before autism was described in
- 1943 identify autism symptoms common to children with rickets, and these mental conditions improved with vitamin D therapy.
- There is an increased prevalence of autism among children of richer college-educated parents, especially women, and attempts to show that this is due to ascertainment bias have not been convincing. The simple explanation is that

this group is more likely to practice sun avoidance and use sunscreen preparations.

- The prevalence of autism is higher among black children. Dark skin is associated with higher risk of vitamin D deficiency.
- Somali immigrants to Sweden call autism the “Swedish disease” and Somali immigrants in Minnesota call it the “American disease” but in equatorial Somalia, autism has no name.
- The hypothesis that autism is caused by environmental toxins is inconsistent with the increase in autism in the face of a decrease in these toxins due to the US clean air and water acts passed and implemented since the 1960s.
- Autistic boys have an unexplained bone defect which presents as a decreased metacarpal bone thickness. But this would be an expected result from childhood or even intrauterine vitamin D deficiency.
- There continue to be reports of a correlation between climatic controlled UV exposure and the prevalence of autism in the US.
- While it is commonly believed that mercury is associated with autism, high maternal seafood consumption of fish known to be contaminated with mercury is

associated with lower autistic markers in offspring.

- The urban/rural difference in the incidence of rickets is well known and was one of the factors leading to the connection between this disorder and sunlight. There is a two fold urban/rural gradient for autism.
- Autism is more common in the offspring of women on antiepileptic drugs, which are known to interfere with vitamin D metabolism.

This is obviously circumstantial evidence, but it can hardly be ignored, especially when added to the case presented in the 2005 paper. Cannell concludes with a comment that if the vitamin D hypothesis is true, part of the cause is the promotion of warnings about sun exposure for pregnant women and young children by governments, organizations, committees, newspapers and physicians “without any understanding of the tragedy they have engendered.” The frequently cited figure of a prevalence in the US of about 1 per 100 children born with or developing autism should be viewed as a national crisis.

RISK VS. BENEFIT FOR STATIN THERAPY

During the six weeks leading up to the writing of this issue, there were a number of significant papers published which address the merits or lack thereof of statin therapy in the context of primary prevention. This is a very serious matter since in the developed world huge numbers of individuals free of clinical manifestations of cardiovascular disease (CVD) are on lifetime regimes of statin therapy. Some medical scientists are deeply concerned about the risk-benefit problem. Others staunchly defend what appears to have all the characteristics of a dogma.

The first attack, which appeared in the high profile *Archives of Internal Medicine*, was launched by a multinational group led by Michel de Lorgeril, a very well known physician and researcher in the field of cardiovascular disease.¹⁴ They re-evaluated some of the results of the famous JUPITER

statin trial which, with the FDA’s blessing, is about to vastly increase the number of individuals being encouraged to pop statin pills (the reader is referred to the Newsletter archives. See the Perspective in the February 2009 issue, for a discussion of the JUPITER trial.) Using only the numbers presented in the original JUPITER paper, they demonstrate that the cardiovascular mortality rate was identical in the treatment and placebo groups, that the percentage of heart attacks that were fatal was remarkably low in both treatment and placebo groups based on expectations from a number of studies, and that in fact treatment tripled rather than reduced this percentage. Furthermore, there were a remarkably large and difficult to explain number of cardiovascular deaths that were not due to a heart attack or stroke. These latter two results were interpreted as an indication of serious bias in the study. The authors then point out

that 9 of the 14 authors of the JUPITER article had financial ties to the drug company sponsor, the principal investigator is a co-holder of a patent on the C-reactive protein test, and that the methods section of the JUPITER paper made it clear that the sponsor collected the trial data and monitored the study sites. While they did not directly accuse the company of bias, they point out three recent instances where in major studies; this situation was responsible for “misrepresentation of data.” The final conclusion is that the results of the JUPITER trial were clinically inconsistent and therefore should not alter medical practice or clinical guidelines, which of course is exactly what is happening. The authors also point out that the problems they identified carry over to the several sub-group analyses recently published.

The second paper, which also appeared in the *Archives of Internal Medicine*, involved a meta-analysis of 11 randomized mostly primary prevention trials involving over 65,000

high risk patients.¹⁵ This meta-analysis failed to find any evidence for benefit of statin therapy on all-cause mortality in this group where benefit according to the conventional wisdom is widely regarded as an established fact. The majority of individuals on statins are taking them for primary prevention. This result is very important for those who evaluate the benefit of long-term therapy in terms of life extension.

To examine the other side of the risk-benefit equation, it is timely that a very large study has just appeared in the *British Medical Journal* that addresses this question.¹⁶ This cohort follow-up study involved over 2 million patients aged 30-84 roughly equally divided between men and women. So-called unintended effects of various statins were examined, both beneficial and adverse. An informative way to look at the adverse effects is with the number needed to treat to create one harmful event (NNH). The following results were reported for the NNH over a five-year period.

	<u>Men</u>	<u>Women</u>
Renal failure	346	434
Moderate to severe myopathy	91	259
Moderate to severe liver problems	142	136
Cataract	52	33

The study did not collect cardiovascular risk reduction data but found a protective effect for esophageal cancer. The small NNH found for myopathy in men and for liver dysfunction and cataract in both men and women should prompt considerable concern, given that the above studies suggest serious concerns regarding benefit. The small NNH for cataract is especially alarming. While dementia was included in the adverse effects studied (null result), the researchers did not appear to include transitory total amnesia which has been discussed in this newsletter and in Dr.

Duane Graveline’s books which are available at www.spacedoc.net.

Guidelines call for aggressive statin therapy with the statin used in JUPITER for individuals at high risk for CVD or individuals with elevated C-reactive protein and one other risk factor. Considering the above papers and the absence of any benefit from statin therapy on mortality or the prevalence or progression of coronary plaque,¹⁷ it would appear that this aggressive therapy benefits mainly the manufacturers of the statin drugs while placing the patient at increased risk of morbidity.

NON-STEROIDAL ANTI-INFLAMMATORIES, A “CAN’T WIN” SITUATION

The common non-steroidal anti-inflammatory drugs (NSAIDs) are diclofenac (Voltren plus a number of other trade names), rofecoxib (Vioxx—recently pulled from the market),

naproxen (Aleve), Ibuprofen (Advil) and celecoxib (Celebrex). Ibuprofen, diclofenac and naproxen are termed non-selective in that they inhibit both the COX-1 and COX-2

pathways; whereas, rofecoxib and celecoxib are called selective in that they more strongly inhibit the COX-2 pathway. The issues with the COX inhibitor class of pain medications involve increased cardiovascular death, coronary death or non-fatal heart attack, and fatal and non-fatal stroke. There is also the very important issue of enhanced risk of gastric bleeding and perforation, the latter representing an acute medical emergency. It was thought that there would be less risk of gastric irritation with the selective anti-inflammatories. The physician has the problem of which to prescribe or recommend, and the patient which one to select from the drug store shelf. While there have been a number of studies, a recent study from Denmark is particularly interesting because it involved a nationwide cohort of over 4.6 million healthy individuals over the age of 10 and took into account as endpoints the above vascular issues as well as dose dependence and risk of fatal and non-fatal gastric bleeding.¹⁸

Ignoring rofecoxib, diclofenac turned out to carry a high risk for the cardiovascular endpoints studied and was clearly more dangerous than the other drugs examined. Its use at any dose increased the risk of CV death by 91%, coronary death or non-fatal heart attack by 82% and stroke by 71%, although different statistical strategies produced somewhat different numbers. The authors state that diclofenac should be used with caution for most individuals.

In short there was no real winner. Rofecoxib is no longer an issue since its withdrawal. In fact, there are a large number of lawsuits concerning its CV risks. For the three endpoints, CV mortality, coronary death and non-fatal heart attack, and fatal and non-fatal stroke, the drug with the least risk was naproxen, although ibuprofen was a close second. When the statistical analysis held up as the least subject to confounding was used, only an enhanced risk for stroke was found at any dose of naproxen, but the stroke risk became non-significant when dose stratification was done. For CV mortality naproxen actually appeared significantly protective at doses below 500 mg/day.

All the NSAIDs except celecoxib were associated with significant increased risk of fatal and non-fatal major gastrointestinal (GI)

bleeding, and the results were dose dependent. A systematic review and pooling of results published at about the same time as the above study reported on the risk for upper gastrointestinal bleeding and perforation.¹⁹ The increased risk for celecoxib, rofecoxib, ibuprofen, diclofenac and naproxen, expressed as relative risks in comparison to non-users, were 42% (not statistically significant), 112%, 123%, 261% and 360% respectively. The Danish study also found celecoxib to have a non-significant risk for bleeding and/or perforation. Thus the NSAID that offered the least risk for the three CVD endpoints carried the largest risk of GI bleeding or perforation, according to this pooled analysis, and this was consistent with an unusually high relative risk found in the Danish study for naproxen at doses > 500 mg. Using a NSAID to deal with pain is indeed a "no win" situation. Ibuprofen may offer a reasonable compromise.

The over-the-counter NSAIDs, which include diclofenac in some countries, are dosed *ad libitum*, and it would not be surprising that very large doses are used on occasion in an attempt to deal with chronic pain. Thus GI bleeds are very commonly seen in the ER. Patients who rely on NSAIDs thus appear to have a problem. There is growing interest in using proton pump inhibitors to protect against the adverse gastric effects of NSAIDs. But these come with their own set of serious problems, as discussed in detail in a recent Research Report. Also, narcotics do not provide a solution, given their addictive properties, their impact at high doses on mental activity and the common side effect of severe constipation. They are also not anti-inflammatories and for that matter, neither is acetaminophen.

Natural anti-inflammatories such as curcumin and fish oil perhaps deserve to be considered as alternatives. Note that the bioavailability of curcumin is low unless the supplement is in a form with high bioavailability. Also, there is a considerable literature regarding anti-inflammatory diets as well as other supplements. The reader is referred to *The Inflammation Syndrome* by Jack Challem and *The Anti-inflammation Zone* by Barry Sears. Also, in the Perspective on the famous JUPITER trial presented in the February 2009 Newsletter, there is a discussion of anti-

inflammatory diets which produce significant reductions in C-reactive protein. Since inflammation is implicated in a number of

serious disorders, the reduction of chronic inflammation may be an important goal even if pain suppression is not the issue.

DO SUPPLEMENTS DECREASE BREAST CANCER RISK?

What appears to be the first prospective study specifically designed to investigate the association between commonly used supplements and the risk of breast cancer has just reported.²⁰ The authors point out that a few case-control studies have found statistically significant or borderline statistically significant inverse associations between supplement intake and breast cancer risk. Supplements studied included black cohosh, soy and red clover phytoestrogens and St. John's wort. Only black cohosh achieved statistical significance in case controlled studies. A randomized trial of ginkgo biloba reported borderline significant *increased* risk of breast cancer in the intervention group. Studies that examined fish oil or omega-3 polyunsaturated fatty acids (PUFA), mostly from diet, have been inconsistent.

In this new prospective study the following supplements were examined: glucosamine, chondroitin, fish oil, grapeseed, black cohosh, dong quai, soy supplement, St. John's wort, acidophilus, coenzyme Q-10, garlic extract, ginkgo biloba, ginseng, melatonin and methylsulfonylmethane (MSM). The prospective cohort consisted of over 35,000 postmenopausal women. Information was collected at baseline regarding both current and past supplement use, as well as other information on known or suspected risk factors for breast cancer including reproductive history and alcohol and medication use. The mean follow-up was 6 years.

The only supplement to exhibit statistically significant risk reduction (32%) was fish oil, and this was only for current use. They failed to confirm the results from case-control studies of black cohosh nor did they find enhanced risk for ginkgo biloba. For fish oil, the reduced risk was restricted to women who

developed ductal but not lobular carcinoma. Stratification of the fish oil results by local vs. regional or distant disease suggested borderline risk reduction for local disease. Stratification according to hormone receptor status gave statistically significant risk reductions only for ER+ and PR+ tumors (36-37%). The authors discuss their results in the context of prior research findings and attribute the differences to poor measurement precision of self-reporting in diet studies and to the fact that the daily dose of omega-3 PUFAs in their study was much higher than most people in the U.S. consume from diet. Eighty-three percent of fish oil users took fish oil ≥ 4 times a week and 60% were daily users. The authors cite the Singapore breast cancer study where the dietary intake of omega-3 PUFAs was much higher than in the US. That study showed statistically significant risk reduction (28%) in breast cancer incidence for high dietary intake of omega-3 PUFAs from marine sources. In the present study, data on the dose levels was not collected. The authors also point out that their results for fish oil are consistent with the inverse associations found in a meta-analysis of biomarkers of fatty acids and breast cancer where risk reductions where results similar to theirs were observed.

Fish oil is commonly taken for cardiovascular protection and an elevated omega-3 status appears particularly important in connection with the risk of sudden cardiac death. This study provides women with an additional reason for being concerned about their omega-3 intake even though studies of timing and dose are absent as are the "mandatory" randomized controlled trials. It is noteworthy that the risk reduction odds ratios and their 95% confidence limits suggest clinical significance as well as statistical significance.

NEWS BRIEFS

CATARACTS AND NEWER-GENERATION ANTIDEPRESSANTS

A case-control study involving almost nineteen thousand cases and almost two hundred thousand controls has examined the association between the newer-generation antidepressants, the so-called selective serotonin reuptake inhibitors (SSRIs) and the risk of developing cataract.²¹ A positive association was found with relative risks ranging from 23 to 39% for three commonly used drugs (paroxetine, venlafaxine and fluvoxamine). The average time to diagnosis of cataract while on SSRI therapy was almost two years. Incidentally, the older generation antidepressants were also implicated in enhanced cataract incidence. As was noted above, significant increased risk for cataract was found as a class effect for statin drugs, and now it also turns up in SSRIs. Both are widely prescribed worldwide.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS, TAMOXIFEN AND BREAST CANCER

For over three decades tamoxifen has been widely used in breast cancer therapy. A new study²² suggests that one SSRI antidepressant, paroxetine (Paxil) significantly increases the risk of death from breast cancer when used with Tamoxifen. This is an important issue since up to 25% of patients with breast cancer experience a depressive disorder. Tamoxifen is a so-called prodrug that is converted by enzyme action to an active agent. The problem is that the enzyme responsible is inhibited in varying degrees by antidepressants and paroxetine is a particularly potent inhibitor. This recent study examined the risk of breast cancer mortality based on the overlap in the use of tamoxifen and paroxetine. For overlaps of 25, 50 and 75% in the proportion of the time on tamoxifen along with paroxetine, the statistically significant increase in breast cancer mortality was 24%, 54% and 91% respectively. It was estimated that if paroxetine use overlapped with tamoxifen 41% of the time (the mean in this study) one additional cancer death would result from treating about 20 patients. This study provides a clear warning regarding mixing these two drugs, and it is clear that a large number of women may be at increased and unnecessary risk. Of the six SSRIs studied, only paroxetine was found to produce significant increased disease-related mortality, consistent with its potent enzyme inhibitory power.

VITAMIN D, PARKINSON'S DISEASE AND COGNITIVE DECLINE

Two studies just appeared which address these two issues. In the first study, comparison of older individuals with 25-hydroxyvitamin D (25(OH)D) deficient levels (< 25 nmol/L) with those with sufficient levels (\geq 75 nmol/L) revealed a 60% increase in the risk of substantial cognitive decline over 8 years.²³ In the second follow-up study of men and women 50 to 79 years and initially free of Parkinson's disease, the relative risk between the highest and lowest quartile of 25(OH)D was 0.33, i.e. a 66 % risk reduction (95% confidence interval 0.14-0.8) for developing the disease. This was after adjustments for gender, age, marital status, education, alcohol consumption, leisure-time physical activity, smoking, body mass index and month of the blood draw.²⁴ These studies obviously suggest that vitamin D sufficiency may provide protection from both of these serious disorders.

THE ADVERSE EFFECTS OF SPIN

In the March 2010 issue of the Newsletter a radical view of two cardiologists from the University of California, Los Angeles was discussed which promoted very high standards for judging the clinical significance of trials. At issue was clinical vs. statistical significance. A paper which just appeared in the *Journal of the American Medical Association (JAMA)* looks at the other side of the coin, i.e. the practice of distorting the presentation of clinical trials that result in statistically non-significant results or in other words introducing spin into the reporting to suggest a treatment is beneficial when in fact there is no generally acceptable evidence.²⁵ This, it turns out, is an important problem given the manner in which trial results are disseminated to those potentially interested or likely to be influenced in their clinical practices.

Over 600 randomized controlled clinical trials published in December 2006 were examined. Only 72 met the criteria for inclusion which included those which had a clearly identified primary outcome and statistically non-significant results. Spin was defined as using specific reporting strategies to highlight that the experimental treatment was beneficial despite a statistically non-significant difference for the primary outcome, or to distract the reader from statistically non-significant results. Spin was found in 18% of titles, 38% of the abstract results sections, and 58% in the abstract conclusions sections. In the main text the results, discussion and conclusions sections had 29%, 43% and 50% spin. This does not inspire confidence in the process of disseminating the evidence of evidence-based medicine. Also for many concerned individuals, only the abstract is available free for most papers. For drug trials, the industry of course widely distributes full-text reprints as the reps make their rounds of doctor's offices.

TWO INVESTIGATIVE REPORTS AVAILABLE ONLINE

The following investigative reports are recommended to readers. Both are free online. The first appeared in the *New York Times*, July 19, 2010 titled Prone to Error—Earliest Steps to Find Cancer. The article explores the problem of errors in early detection of cancer and breast cancer in particular. The author is Stephanie Saul. The second is from the January 29, 2010 issue of *Newsweek* and with the title *The Depressing News about Antidepressants* by Sharon Begley. Both contain well-researched discussions of the issues and fascinating quotes from high profile physicians familiar with the subject and provide insights not fully available in the peer-reviewed literature. Retrieve the NYT article by the author name at the search feature on their website. Retrieve the Newsweek article by Googling “Sharon Begley antidepressants.”

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RESEARCH REVIEW

IODINE AND CANCER

William R. Ware, Ph.D.

BREAST CANCER

INTRODUCTION

Iodine is an essential trace element. Obviously, the body is capable of making an immense number of chemical compounds using numerous pathways, but it cannot make elements! Trace elements must be derived from food, beverages and from drinking water. The primary sources are soil, lakes or the ocean, and for iodine, the ocean is the largest source. Lands far removed from the oceans typically have low iodine levels, a classical example being the U.S. Midwest which is also called the goiter belt because of the high incidence of this thyroid disorder caused by iodine deficiency. This problem was addressed a long time ago by adding iodine to table salt. It was also added to bread as a dough conditioner but the additive was later changed to a bromine-containing compound which in fact increases the chances of iodine deficiency.

Iodine is necessary for the production of thyroid hormones but is also found in every cell in the body. It is involved in the production of other hormones and enzymes and is involved in numerous biochemical pathways.¹ Insufficient iodine intake can cause abnormal neuronal development, mental retardation, congenital abnormalities, spontaneous abortion, miscarriage, congenital hypothyroidism, infertility, goiter, and as well appears to increase the risk of thyroid, breast, prostate, and gastric cancer. For example, after the Chernobyl disaster, the risk of thyroid cancer was inversely associated with urinary iodine excretion levels, suggesting a strong link with iodine status. Also, thyroid uptake of radioactive iodine is enhanced by an iodine deficiency and large doses of potassium iodide are considered the best protection for the thyroid in the event of exposure to radioactive iodine. Some individuals living downwind from nuclear power stations actually keep a bottle of high-dose potassium iodide on hand in case there is an accident. As early as 1976 it was postulated that iodine deficiency was associated with the risk of prostate, endometrial, ovarian and breast cancer. This was based on geographical associations of the prevalence of goiter and the incidence of reproductive cancers.²

According to the World Health Organization, nearly 2 billion individuals have insufficient intake of iodine.³ Furthermore, studies based on the National Health and Nutrition Examination Survey I and III which compared the period 1971-1974 with 2000 in the US, found that iodine levels dropped 50%. This drop was seen over all demographic categories including ethnicity, region, economic status, race and population density. Also, the percentage of pregnant women with low iodine levels increased almost 700 %.

In his book *Iodine. Why You Need It. Why You Can't Live Without It*,¹ Dr. David Brownstein describes his own experience with the prevalence of iodine deficiency. Over a number of years he has tested 5000 patients and approximately 96% test low for iodine. Laboratories which conduct iodine testing report similar prevalence of deficiency in over 30,000 individuals. However, this is based on an iodine load test described below, and defining deficient is somewhat arbitrary.

How many readers of this Newsletter have ever had an iodine status test ordered as part of a physical? There is almost no literature on the subject of iodine status testing, and what exists is in a very obscure journal called *The Original Internist*. Identifying deficiency of course depends on how one defines sufficiency and when sampling world populations one must have a simple test which may not be ideal. This simple test involves determining the iodine level in a casual urine sample. Iodine status is not really on the preventive medicine radar screen. However, there is a good discussion of an interesting approach to a more sophisticated iodine status test in Dr. Brownstein's book.¹ This is called the *Iodine Loading Test* and involves taking 50 mg of iodine/iodate and then collecting a 24-hour urine sample. This sample measures how much of the 50 mg of iodine is eliminated. According to the threshold developed over a number of years, anything less than 90% recovery of the iodine is considered a manifestation of deficiency. This is because according to this view, the iodine body stores should be near saturation for optimum health, and if this is not true, then one excretes less than 90% of the load. Numbers can range all the way to near zero. A low excretion takes on real meaning when it is correlated with clinical symptoms which then show dramatic beneficial changes upon iodine supplementation. As will be discussed later in this review, Brownstein and colleagues have seen this especially in thyroid diseases, and cancers of the thyroid, breast and ovary. The iodine loading test is reminiscent of the glucose tolerance test where glucose metabolism is assessed by challenging the system with 75 g of glucose and then watching over several hours the changes in blood glucose. In the iodine test, it is also like seeing how full a glass is by not looking but trying to fill it. The overflow provides the answer.

There is considerable evidence that there is a problem worldwide regarding iodine deficiency, but to assess the iodine status involves a test which is not simple, and in fact appears to be available only in four laboratories in the U.S. But kits can be ordered and the samples mailed, and thus anyone wishing to know where they stand can get this test. The two labs with the longest track record appear to be

FPP Laboratory, <http://www.optimox.com/pics/iodine/loadTest.htm>
Hakala Laboratory, <http://www.hakalalabs.com/resources.html>

The iodine added to salt can be sodium or potassium iodide or sodium or potassium iodate. The amounts are rather variable and some individuals do not purchase iodized salt or salt naturally containing iodine and thus eliminate what may be their only source of this element. The food sources high in iodine include seafood, seaweed, and kelp. The black nori used to wrap the rice and filling in sushi is also very high in iodine. The current high profile recommendations to reduce salt consumption should also have a deleterious impact on iodine status, although the major salt source is in prepared food, and this may not be fortified.

WHY IS IODINE DEFICIENCY INCREASING?

To understand the forces at work here one must appreciate that iodine is a member of the halide family, familiar to chemistry students as occupying a column on the periodic chart. Other members important in our discussion are fluorine, chlorine and bromine. Of these, bromine compounds play the most important role in inducing iodine deficiency by direct competition. In his book, Brownstein discusses a number of cases where iodine loading dramatically increase bromine excretion and enhanced bromine levels are characteristic of those deficient in iodine.

The seriousness of the problem presented by bromine can be appreciated by the fact that it is widely encountered in the environment. Examples include fire retardants found in numerous consumer products, bromates used as an additive in bread and bun dough, the use of bromine compounds in swimming pools, and their presence in medicines. The increased use of bromine-containing chemicals over the past several decades may be the simplest explanation for the decrease in iodine status worldwide.

Intake of perchlorates also decreases iodine status. Perchlorates from industrial, rocket and weapons sources are also a problem in connection with iodine status and there is considerable ground water and river contamination. This in turn results in perchlorate-containing produce, especially from the Southwest US.

Fluorine also interferes with iodine and exposure to fluoride is hard to avoid. It is added to drinking water in many cities and as well it is almost impossible to find fluoride-free toothpaste except in health food stores. All of this is in spite of the absence of convincing evidence that fluoride decreases the risk of dental cavities and in fact, there is considerable evidence falsifying this hypothesis. Avoiding bromine and fluorine and chlorine containing compounds in drinking water can be achieved by using a reverse osmosis system just for drinking and cooking water, a relatively inexpensive approach to pure drinking water which also removes numerous other impurities and toxins. However, in the process, healthy minerals obtained in part from drinking water are lost and must be replaced by supplementation or diet.

Finally, if a hypothyroid condition is treated with a thyroid hormone preparation and there is also an iodine deficiency present, this therapy will exacerbate the iodine deficiency. In other words, the treatment increases the body's need for iodine but there is no additional iodine being supplied.

With this background in mind, we will now discuss the evidence connecting iodine deficiency with breast cancer.

IODINE DEFICIENCY AND BREAST CANCER RISK

There is considerable circumstantial evidence linking iodine deficiency to the prevalence of breast cancer. In addition, there are case histories suggesting that iodine supplementation can slow the progression or even eliminate breast tumors. This evidence is as follows:

- In the developed world Japan has one of the lowest age-adjusted rates of breast cancer mortality with 6.6 per 100,000 as compared to 27.7 and 22.0 for the UK and the US respectively.⁴ The daily intake of iodine in Japan has been estimated to range from 5 to 13 mg, mostly obtained from seaweed products such as nori, wakame and kombu. Other seafoods are also important sources of iodine in Japan. By comparison, in the UK and US, the average iodine intake is approximately

0.17 and 0.21 mg/day. When Japanese women migrate and adopt the Western lifestyle, the risk of breast cancer increases toward that of women in this new environment. This tends to rule out a genetic factor for the huge disparity in Japanese vs. Western rates of breast cancer mortality.

- During pregnancy and lactation, hormonal stimulation of the mammary gland leads to glandular differentiation and a dramatic enhancement of both iodide absorption and local generation of free iodine. This generation occurs in the same regions of the breast anatomy where the majority of breast cancers arise. It is well known that pregnancy and lactation reduce the risk of breast cancer.⁵
- Molecular iodine (I₂) is effective in diminishing mammary dysplasia and atypia secondary to iodine deficiency.⁵
- Breast cancer patients are much more likely to exhibit thyroid disease manifest by goiter.⁶
- Studies with cultured breast cancer cell lines find that an uptake of molecular iodine has an anti-proliferative effect⁷ and can induce apoptosis (programmed cell death).^{7,8} Molecular iodine also inhibits the growth of human breast cancer cells.⁹
- Five case histories presented in Brownstein's book¹ illustrate the potential for iodine supplementation to correct iodine deficiency in breast cancer cases and individuals presenting with fibrocystic breast disease. The positive results in the context of these breast diseases will be discussed below.

TOXIC HALOGENS FLUORINE AND BROMINE AND THE BREAST CANCER EPIDEMIC

In his book on iodine, Brownstein asks the question, "Are the toxic halogens fluoride and bromine responsible for the epidemic rise in breast cancer?" This question follows naturally from the information presented above. If one turns to the literature for an answer, it does not appear to be there, which is not surprising. Brownstein describes a study he undertook among his own breast cancer patients. Comparison was with patients who did not have breast cancer. Urinary levels of bromide and fluoride were measured at baseline, one day after taking 50 mg of Iodoral, a commonly used supplement, and 30 days after taking this dose daily. Iodine levels from loading tests were low for all the women tested. As described above, iodine loading displaces bromine and fluoride. What he found was that bromide and fluoride levels were significantly elevated in breast cancer vs. non-breast cancer patients, suggesting that the cancer patients were absorbing and retaining larger amounts of the toxic halides as compared to the controls. This observation clearly deserves to be followed up but even in the absence of a more detailed study, it adds to the importance of achieving and maintaining an iodine sufficient state and this may require ingesting more iodine when the potential for bromide and fluoride intake is high. It also highlights the importance of avoiding these two halogens.

IODINE IN BREAST CANCER THERAPY

There appear to be no organized clinical trials, much less randomized placebo controlled trials. Iodine supplements can not be patented. One of the best preparations was "invented" in 1829 by a French physician named Jean Lugol and is still very popular! Your editor obtains his Lugol's solution from a compounding pharmacy. There is absolutely zero incentive for pharmaceutical companies to conduct studies and in fact cynics wonder if they really want to "cure" cancer. This leaves foundations and government. But iodine deficiency and its role in cancer is totally off the radar screen of mainstream medicine, and thus one is left with little hope of definitive trials and case histories thus are the only source of information regarding efficacy. The safety issue is better researched. Here are five case histories from David Brownstein's book.¹

Case History #1. The patient, age 60 was diagnosed with breast cancer in 1989. A holistic doctor put her on 2 mg/day of an iodine supplement. She felt fine for over 10 years, but developed metastatic disease in 2005. She was started on 50 mg/days of a supplement (Iodoral, the tablet form of Lugol's solution). A PET scan 6 weeks later showed her tumors disintegrating. Brownstein commented that he has seen similar results with nodules, cysts and tumors in the thyroid, ovary and uterus. Unfortunately, there was no additional follow-up reported.

Case History #2. The patient, 73 years of age, was diagnosed with breast cancer in 2003. Refused conventional therapy on the grounds that those promoting it could not provide statistics acceptable to her concerning the impact on mortality. She was then treated by Dr. Brownstein. He found her

severely iodine deficient. She was treated with 50 mg of Iodoral. Her bromine excretion increased as expected and was still elevated after 30 days but now her iodine excretion was up from a very low amount to 30% of the 50 mg dose. After 3 months on iodine with an additional holistic regimen she felt significantly improved with vastly enhanced energy levels. An ultrasound at 18 months found the malignancy considerably diminished as compared to a baseline scan. After two years on the program, mammography indicated no cancer present which was consistent with an ultrasound done at the same time. This is not an isolated case. Dr. Brownstein states that these results have been repeated over and over in his practice.

Case History #3. This 52-year-old patient was diagnosed with breast cancer two years prior to the writing of this history. She refused chemotherapy and radiation therapy. She had a long history of fibrocystic breast disease which appears to put one at enhanced risk of developing breast cancer. She also had a goiter. Brownstein's tests indicated a poorly functioning immune system and severe iodine deficiency (12% excretion of the load dose whereas the normal is 90%). After 3 months on 50 mg/day of Iodoral her iodine deficiency had resolved and along with this came an improvement in energy and overall feeling of good health. The symptoms of her fibrocystic disease decreased significantly. After 3 years of maintaining iodine sufficiency, she continues to feel well and there have been no signs that the cancer is progressing. In fact, the lesions seen on radiological examination have gotten slightly smaller.

Case History # 4. A 45 year old nurse had suffered from fibrocystic disease for over 15 years. The condition caused her significant pain and made exercising difficult. Frequent drainage of breast cysts was necessary. She was even considering the mastectomy option. She was found to be severely iodine deficient and was treated with 50 mg/day of Iodoral. It took only one month to dramatically reverse her condition, which seemed like a miracle.

Case History #5. This is another case of fibrocystic disease, this time in a 39 year old woman. Again there was a big issue with pain, her iodine loading test revealed a deficiency with only 50% of the load excreted. It took just 2 weeks of Iodoral to significantly eliminate this painful condition and increase her energy and mood levels.

While the two case histories involving fibrocystic disease are not examples of cancer treatment, this condition is regarded as potentially precancerous, and thus these cases are closely related to the main theme of this review.

BIOLOGICAL PLAUSIBILITY OF IODINE DEFICIENCY IN BREAST CARCINOGENESIS

Both the thyroid and the breast are major locations where iodine concentrates. The salivary glands and gastric mucosa also have the ability to concentrate iodine. Thus breast health would be expected to depend on having iodine levels consistent with the demands set by human genetics. As discussed above, there is considerable circumstantial and anecdotal evidence that iodine status is involved in the prevalence of cancer and fibrocystic breast disease and correcting deficiencies can reverse fibrocystic changes and impact breast cancer progression and may even affect regression or a complete cure. Given this, it is surprising that there is so little work reported on potential mechanisms that might account for these observations, observations that go all the way back to before 1990. Today, iodine deficiency seems to be where vitamin D deficiency was in the 1980s. The recommended intake was set to prevent rickets for vitamin D and for Iodine, the focus is still on the minute amounts required to prevent goiter but totally inadequate to provide sufficiency or counteract the onslaught of interfering chemicals. Mainstream medicine does not appear to think iodine deficiency is significant, and there appears little incentive and probably little money for research into the details to the biochemistry associated with the observations and results presented above.

Information concerning potential biochemical mechanisms whereby iodine exerts its influence in breast cancer comes mostly from cell culture studies of breast cancers cells. The general observation is that molecular iodine but not the iodide ion (as from potassium iodide) exhibit potent anti-proliferative effects and impact apoptosis (programmed cell death, a critical aspect of normal cell biology), and that these effects are consistent with animal experiments where mammary cancer is

induced chemically. In breast cancer cells, treatment with iodine activates an apoptotic pathway which has been shown to be mitochondrial mediated.¹⁰ The search for active derivatives generated by the reaction with iodine has found that a potent compound involved in the inhibition of cancer cell growth is the result of the reaction of iodine with the long-chain omega-6 fatty acid familiar to readers of this Newsletter, arachidonic acid, which is a major fatty acid in cell walls.^{8,9,11} It is called 6-iodolactone.¹¹

Animal and cell culture studies do not however, shed much light on how iodine might function to prevent the formation of cancer cells in the first place. It is well known that reproductive history has a consistent effect on increasing or decreasing the risk of developing breast cancer. Early age at menarche, late age at menopause, and not having any pregnancies increase the risk, as does the failure to breastfeed over an extended period. However, as was pointed out some time ago, the majority of women who develop breast cancer do not have any of these risk factors.¹² During pregnancy and lactation, hormonal stimulation of the mammary gland leads to glandular differentiation that dramatically enhances both iodide absorption and local generation of free molecular iodine.⁵ It has been suggested that a high iodine concentration in breast tissue also explains the reduction in breast density often observed following pregnancy and lactation, and that this plays a role in decreasing the risk of developing breast cancer.⁵

There is also some evidence that iodine can function as an antioxidant and that maintaining a high iodine status as seen in for example Japanese women, affords protection that is in part antioxidant mediated.¹³

SUPPLEMENTATION

In simple terms, the thyroid uses mostly the iodide ion (I⁻) and the breast tissue molecular iodine. In iodine replacement therapy in the rat model, the iodide ion is found to restore normal morphology and physiology in the thyroid gland, whereas molecular iodine results in a decrease of breast hyperplasia and fibrosis. Thus supplementation should provide both. There are several choices:

- Lugol's solution, a mixture of 5% iodine and 10% potassium iodide in water. This mixture allows the preparation of a solution with a high concentration of iodine because the potassium iodide and iodine react to form the triiodide ion which provides the high solubility. One drop contains about 5 mg of iodine and 7.5 mg of iodide. This 12.5 mg amount provides what Brownstein terms a physiologic dose. The intake is similar to the average in Japan.
- Iodoral is essentially a tablet formulation of Lugol's solution and is sold in doses of 12.5 and 50 mg per tablet.
- Iosol is also a mixture of iodine and iodide, but ammonium iodide is used instead of potassium iodide. It is sold as a liquid and one drop contains 1.8 mg of iodine total.
- SSKI is simply a saturated solution of potassium iodide, and thus only a source of the iodide ion. Brownstein does not consider this a satisfactory supplement.

The approach to correcting chronic iodine deficiency described above for the treatment of clinical indications such as breast cancer or fibrocystic breast disease involves doses vastly greater than the recommended daily allowance which is about 0.15 mg/day. The conventional reaction to this is to worry about adverse effects, i.e. are high doses safe and what is the evidence. In general terms the high intake in Japan suggests that doses averaging about 13-14 mg/day are completely safe since there is no evidence from Japan that the iodine-rich diet carries enhanced risk for any disorder. Brownstein and his colleagues have been using 50 mg/day over long periods as a therapeutic dose with no problems, and he reports in his book that other physicians who also use this dose level therapeutically have the same observation. Nevertheless, critics are quick to make a list of potential safety issues. They are allergy, autoimmune thyroid diseases, detoxification reactions, iodine-induced hypothyroidism and goiter, iodine-induced hyperthyroidism, iodism (a metallic taste and associated headache) and thyroid cancer. Brownstein finds these to all be very rare. As regards thyroid cancer, if increasing iodine levels increased the risk, then it is hard to explain why declining levels over a number of years have been accompanied by an increase in thyroid cancer. It is only common sense that the use of therapeutic doses should be done under the supervision of someone knowledgeable in

the symptoms of these side effects. But this of course presents a serious problem since there are only a very limited number of physicians who are even aware of the material in this review or Brownstein's book. However, if one lived in Japan and ate the traditional diet, would one worry about the potential intake of 10-15 mg/day of iodine? If not, then perhaps one should not worry about a drop or two a day of Lugol's solution.

There is also the question of how much iodine supplementation to take simply for prevention and promoting overall health. From what has been discussed above, it should be clear that this is not a simple question and is only answered satisfactorily after an iodine loading test and this is not a test that can be routinely ordered to be done at the local clinical laboratory. Also, the amounts needed depend on the bromide-fluoride status of the individual. One can order a test kit, supplement on the basis of the result with Iodoral or Lugol's solution, and then repeat the test, eventually arriving at a dose that maintains one above 95% excretion. In other words, not a simple matter and most easily done with the help of a doctor experienced in this problem.

THYROID CANCER

Thyroid cancer is relatively uncommon, accounting for 0.5 to 1.5% of all cancer worldwide. However, it is the most common endocrine malignancy. There is much less information available from the literature and anecdotal sources concerning the association between iodine status and thyroid cancer. Part of the problem concerns estimating prevalence changes and their correlation with the addition of iodine to salt. Also a major issue is that over the past two to three decades there has been a significant increase in the use of carotid artery ultrasound to screen for and study atherosclerosis. Since the thyroid gland is also imaged during this procedure, thyroid nodules are found that otherwise would have remained unnoticed. This can prompt a biopsy, the discovery of cancer, and thus an increase in prevalence associated with what amounts to unintentional screening. This presents a problem when one attempts to correlate estimated changes in iodine intake and the incidence of thyroid cancer over this time period. Furthermore, the iodine intake in many countries is very low compared to some Asian countries and while salt fortification impacts goiter prevalence, comparing cancer incidence in areas of high goiter incidence with that where the goiter incidence is low still involves comparing populations where the iodine intake can be quite low. Furthermore, there may be a considerable variation in the intake of bromates, perchlorates and fluorides, and as discussed above, iodine intake studies would need to be corrected for this when examining the association between iodine and cancer rates.

The three general types of thyroid cancers are anaplastic, follicular and papillary. The latter is considered much less dangerous. It appears that the overall incidence of all types is not influenced by iodine intake in a population, but iodine intake can shift the distribution in favor of papillary carcinomas. Brownstein points out that thyroid cancer incidence have increased along with iodine deficiency, which is inconsistent with the view of some that increased iodine intake increases the risk. In addition, the incidence of thyroid cancer in Japan¹⁴ is much lower than found in the data from the US SEER registries. Thus, while the question of increased risk associated with high intakes of iodine and thyroid cancer has received little study, there is little indication that there is a risk. Also, comparison between areas with adequate or high iodine intakes, iodine deficient regions have a higher proportion of aggressive follicular and anaplastic carcinomas.¹⁵

As regards the use of high-dose iodine for the treatment of thyroid cancer, there does not appear to be either studies or anecdotal evidence.

PROSTATE CANCER

Just like breast cancer, prostate cancer prevalence in Japan is much lower than in the US and Japanese men who move to the US have higher incidence than mainland Japanese, the same phenomenon as seen for breast cancer in Japanese women. In fact, Japan has one of the lowest

age-adjusted prostate cancer rates in the developed world (13/100,000 vs. 125/100,000 in the US).¹⁶ Iodine status as measured by a casual urine sample in Japanese men ranges from 800 to 3400 microg/L whereas for US men a typical value would be 50 microg/L.¹⁶ In a Japanese case-control study, a 53% reduction in relative prostate cancer risk was found in men who had a high consumption of seaweed, a significant source of iodine in the Japanese diet.¹⁷ Similar results have been reported in other studies, but exhibited only trends rather than a clear-cut benefit.

A recently reported prospective study of iodine status, thyroid function and prostate cancer based on the National Health and Nutrition Examination (NHNES) database found that a history of thyroid disease and a > 10 year period since its diagnosis were significant predictors of prostate cancer. For thyroid disease, the enhanced risk of prostate cancer was 134%.¹⁸ There also appears to be a connection between thyroid cancer and prostate cancer. An increase risk of prostate cancer follows the diagnosis of thyroid cancer and conversely, an increase in thyroid cancer follows a diagnosis of prostate cancer.

Thus there is only circumstantial evidence that iodine deficiency is a risk factor for prostate cancer but no studies appear to have been done on the treatment of prostate cancer using therapeutic doses of iodine nor is there anecdotal evidence of therapeutic benefit.

CONCLUSIONS

Mainstream medicine views prevention as involving measuring cholesterol, blood pressure, markers of kidney and liver function, and fasting glucose (which incidentally is not the best way to examine how well glucose metabolism is functioning). Aside from this, it is mostly a wait-for-symptoms game. Screening for such disorders as prostate or breast cancer is plagued by false positives and the resultant over-diagnosis and treatment. It has taken several years, hundreds of papers and the efforts of a handful of experts for us to have reached the point where vitamin D status is on the radar. It is doubtful that recognition of the role of iodine in health will come as quickly. Ask your family physician for an iodine load test. The reaction should be fascinating.

This review raises the obvious question, is breast cancer in part an iodine deficiency disease? The circumstantial evidence seems quite strong and the hypothesis certainly deserves critical examination. If true, then the indicated therapy is both trivial, safe and inexpensive and of course of no interest to Big Pharma or probably even to conventional oncologists who think in terms of chemotherapy, surgery and radiation, the complete solution. An interesting situation. The same question can be raised for thyroid and prostate cancer, but unfortunately there is much less information available. However, enough is known regarding the connection of iodine with all three of these cancers so that there should be strong motivation for additional experimental and clinical studies.

In general, all one can do is attempt to maintain an adequate iodine status, but this is made difficult by the absence of easy and convenient testing, especially since bromine should be included.

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