

INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 192

NOVEMBER 2008

17th YEAR



In this issue we update the subject of homocysteine and cardiovascular risk. Several recent studies, which incidentally support older studies, all suggest that while circulating levels of homocysteine, if high, present a risk for cardiovascular disease, when an intervention which modifies the homocysteine biochemistry is tried and lowers the levels significantly, there is no decrease in risk. This is yet another example where randomized, placebo controlled studies fail to confirm epidemiologic studies. The reason these results are important is that the intervention generally includes very high doses of folic acid, and there is growing concern that these high doses, which end up principally as unmetabolized folic acid, may present a health risk. This unmetabolized folic acid is in fact a synthetic chemical foreign to human biochemistry. The combination of a therapeutic dose combined with what is in a multivitamin and what is in fortified food can yield an intake of this synthetic chemical that is very high.

In this issue we also deal with a number of topics of general interest such as the primary prevention of stroke, second-hand smoke risks and the critical nature of the omega-3 fatty acids and in particular docosahexaenoic acid (DHA) in child development. Considering modern dietary practices and preferences, this last item is potentially an area of considerable concern.

Finally, this issue contains a review that questions the risk of cancer associated with exposure to levels of x-ray radiation encountered in modern diagnostic procedures. The review acquaints the reader with scientific literature which is largely ignored in North America. While the issues addressed are far from settled, what is known to date should provide grounds for skepticism regarding the conventional wisdom and motivate the reader to question fears of exposure both from diagnostic procedures and from other sources. The evidence that low-dose radiation may in fact be protective will no doubt come as a surprise to most readers.

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Wishing you good health,

William R. Ware, PhD, Editor

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HOMOCYSTEINE, B-VITAMINS AND CARDIOVASCULAR DISEASE

In the past year several large randomized trials have reported concerning the impact of lowering homocysteine levels with vitamin B intervention on the risk of cardiovascular events. Thus it seems appropriate to update this subject.

In 1969 Kilmer McCully proposed that circulating homocysteine causes cardiovascular disease. Some Newsletter readers may have read one or both of McCully's books which popularized homocysteine. This theory was based on the observation that children with extreme elevations of homocysteine due to metabolic anomalies had premature atherothrombotic disease. This prompted epidemiological studies which looked for an association in adults. Studies that measured homocysteine levels after the diagnosis of cardiovascular disease (retrospective and cross-sectional studies) found that plasma levels of 3 to 4 micromol/L may increase the risk by about 33%. Subsequent large follow-up studies supported these findings but found a much smaller magnitude of risk. In a meta-analysis of prospective follow-up studies, after accounting for known CVD risks, a 25% lower homocysteine level was associated with an 11% lower risk of CHD and a 19% lower risk of stroke. It was also found that there was a risk dependence on level extending to mild elevations of homocysteine which are associated with dietary vitamin B deficiencies.

These encouraging results prompted a number of intervention trials with folic acid, vitamin B12 and in most studies, vitamin B6. These studies were complicated by the large number of participants needed to provide statistical significant results, the length of the trials required, and the advent of fortification of the North American food supply with folic acid which started in 1998. Three large trials that reported between 2004 and 2006 concluded that moderate doses of folic acid and vitamins B6 and B12 had little or no effect on the risk of recurrent heart attack or stroke. But all of the participants in these trials had advanced disease that had been progressing for several decades, and the intervention lasted only 2-5 years. While these results did not contradict the notion that homocysteine was somehow involved in the risk of CVD, it appeared that lowering plasma levels had no beneficial effect in this context.¹

The latest randomized intervention trials reported in 2007 and 2008. The first (HOST) involved 2056 patients with advanced chronic or end-stage kidney disease, a group with both elevated homocysteine levels higher than in other intervention trials and also extensive vascular disease with estimates of annual mortality as high as 20%. Daily intake of 40 mg of folic acid, 100 mg of vitamin B6 and 2 mg of vitamin B12 resulted in a 26% drop in mean homocysteine levels. However, over a 3.2-year follow-up, this intervention did not improve survival

(the primary endpoint) or reduced the incidence of vascular disease. The secondary endpoints included fatal and non-fatal heart attack, stroke, amputation and the need for dialysis, all of which exhibited null results.²

The second trial (WAFACS) was from Harvard and examined the effect of folic acid and B-vitamin intervention of the risk of cardiovascular events and total mortality among women at high risk. This was a much-needed study since women had been under-represented in earlier studies. A total of 5445 women were given 2.5 mg of folic acid, 50 mg of B6 and 1 mg of B12 daily or a placebo for 7.3 years. The participants either had prior cardiovascular disease or 3 or more coronary heart disease risk factors. Thus this was a both a primary and second prevention trial, although all the participants were judged to be at high risk of adverse events. A composite outcome was heart attack, stroke, coronary revascularization (bypass, stent or angioplasty) and CVD mortality. The intervention resulted in lowering homocysteine levels by over 18%, but while no adverse effects were observed, no beneficial effects were found either.³

The third study (WENBIT) from Norway was randomized and involved 3096 patients who had undergone angiography which identified coronary artery disease or aortic valve stenosis. The intervention involved (a) 0.8 mg of folic acid, 0.4 mg of B12 and 40 mg of B6, (b) folic acid plus B12, (c) B6 alone, or a placebo. Follow-up was for 38 months. The primary endpoint was all-cause mortality, non-fatal heart attack, hospitalization for unstable angina or a non-fatal stroke (excluding strokes involving haemorrhage). No beneficial effect for any of the treatment options was found. For the groups receiving folic acid and B12, mean homocysteine levels decreased by 30% from baseline. This trial was halted early due to concern regarding reports of adverse effects from another ongoing Norwegian trial.⁴

Thus, consistent with earlier intervention studies, these three recent trials involving over 10,000 participants failed to support the use of folic acid, vitamin B6 and B12 to prevent adverse cardiovascular events or increase survival in individuals with heart disease, kidney disease, or simply at high risk of coronary heart disease in spite of the significant homocysteine lowering that occurred. This again illustrates the importance in some situations of randomized, placebo-controlled trials to validate expectations based on epidemiologic studies. In fact, McCully's first book

had on the paperback cover the statement “Lower homocysteine and cut your risk of heart disease with a proven 6 week program.” One theory for this failure is that the intervention causes both positive and negative effects in the context of the endpoints involved.⁵ Attention is directed primarily at folic acid since large doses result in unmetabolized, circulating folic acid, which incidentally is a synthetic chemical foreign to humans.^{6,7} Another theory is that homocysteine is merely a marker and not a cause of artery disease, but this is just now receiving some attention and might lead to an intervention sometime in the future. It is of interest that homocysteine lowering does not affect inflammatory markers of atherosclerosis in patients with stable coronary artery disease. The failure to reverse inflammatory processes may partly explain the failure of intervention trials.⁸ Also, in a study of factors influencing coronary artery calcification in type 2 diabetics, homocysteine was not independently associated with the calcium score.⁹

Finally, it is important to point out that the merits of homocysteine lowering for individuals without cardiovascular disease or high risk of CHD remain unknown. Studies to examine this question would require huge numbers of participants and a long follow-up because the event rate is very low. Such studies would be very expensive and may never be done, especially since the intervention involves vitamins that can be obtained at health food stores,

pharmacies and even grocery stores, and the cost is minimal as is interest from the pharmaceutical industry. While knowledge of a high homocysteine level might prompt some to “try this at home,” the use of high doses of folic acid may carry risks of decreased natural killer cell activity and increased risk of cancer. Folic acid appears to have a dual effect on cancer of protecting against initiation but facilitating progression of subclinical cancers.^{6,7} In fact, North Americans may already be at risk of excessive folic acid intake due to food and beverage fortification combined with the use of multivitamins or even B-complex products which can contain large amounts of folic acid.

Measuring homocysteine levels is probably not part of most routine physical exams. Many individuals are unaware of elevated levels. For those with identified high homocysteine, what approach should be taken? If one is otherwise healthy, there is no evidence one way or the other regarding B-vitamin therapy. The above discussion makes it clear that for those at high risk of CVD or for secondary prevention, B-vitamin therapy does not seem to work. Thus what is the answer? Until other methods of lowering homocysteine are studied, it seems that directing attention to other modifiable risk factors is appropriate. This was discussed at length in Part II of the last Research Review and in the context of stroke, will now be discussed.

PRIMARY PREVENTION OF STROKE

Non-fatal stroke is a leading cause of permanent disability and the third leading cause of death in the U.S. Most adults fail to make a complete functional recovery. One needs to be acquainted with stroke victims to fully appreciate the potential devastation of quality of life and the tremendous effort required to achieve partial recovery of functionality. Thus steps that can lead to prevention are of great interest. A recent prospective study from Harvard based on cohorts drawn from the Nurses' Health Study (71243 women) and the Health Professionals Follow-up Study (43,685 men) addresses this issue. Data was collected periodically from 1986 to 2002. A low risk lifestyle was defined as not smoking, a body mass index < 25 kg/m², moderate activity ≥ 30 min/day, modest alcohol consumption (men 5-30 g/day, women, 5-15 g/day, i.e. men ≤ 2 drinks/day, women ≤ 1 drink/day), and scoring within the top 40% on a healthy diet score. The principal diet score used was based on higher intakes of

vegetables, fruit, nuts, soy, and cereal fiber, a high ratio of chicken plus fish to red meat, and a high ratio of polyunsaturated to saturated fat, low intake of *trans* fat, and multivitamin use for ≥ 5 years. Relative risks were calculated for the incidence of both ischemic (occlusive) strokes and hemorrhagic (bleed) strokes.

Women with all 5 low-risk factors had a 79% risk reduction for total stroke and 81% risk reduction for ischemic stroke when compared to women who had none of these factors. For men the comparable figures were 69% and 80% for the same comparison. In general, the relative risk dropped from 1 (reference) to about 0.5 when one low-risk lifestyle factor was present, and then for women decreased in almost a straight line to about 0.2 for both types of stroke as more factors were added. For men the decline was not as regular but for total stroke still ended up at 0.2 with ischemic stroke at

0.31. No one can deny that these are dramatic declines in risk. Within these study populations, approximately half of ischemic strokes could be attributed to unhealthy lifestyle factors. The authors comment that these factors likely influence the risk of stroke partly through clinical risk factors including hypertension and diabetes. They also point out that midlife BMI was a stronger predictor of stroke than current BMI, as seen with other diseases as well. Also, the low-risk lifestyle was not significantly associated with hemorrhagic stroke. Finally, the authors make the important point that greater benefit is likely to be gained by adherence to the healthy lifestyle choices they identified in populations with a less healthy lifestyle than in the populations of health professionals involved in this study.⁶

Prevention of stroke is part of a larger challenge—healthy aging. By this is meant reaching old age without any of the major chronic diseases such as coronary heart disease, stroke, cancer (excluding non-melanoma skin cancer) and diabetes. Chronic diseases account for 75% of health care

expenditures and yet society invests only 1% to 3% of health care expenditures in primary prevention. Funding for prevention research is scarce.¹⁰ Modern medicine focuses for the most part on treating both causes and symptoms once patients present with disease, mainly drawing on the armament provided by the pharmaceutical industry. This recent stroke prevention study from Harvard highlights what can be accomplished in one area just with lifestyle changes targeted on primary prevention. Similar dramatic results from essentially the same lifestyle modifications have been repeatedly reported for coronary heart disease and diabetes. There are no pharmaceutical interventions that come even close to the approximately 80% risk reduction associated with the healthy lifestyle defined in this or other studies. Yet, only 2% of the men and women were at low risk for all 5 factors, a result which indicates the magnitude of the problem of healthy aging. It may be that knowledge of healthy lifestyle factors is fairly widespread, but that the problem is simply that many individuals are not motivated or lack the fortitude to adopt them.

SECONDHAND SMOKE AND BREAST CANCER—EVIDENCE STRONGER THAN FOR LUNG CANCER

In 2005, the California Environmental Protection Agency issued a report which provided an extensive examination of the question of the connection between breast cancer risk and exposure to secondhand tobacco smoke. For breast cancer for younger, primarily premenopausal women, pooled relative risk estimate were 1.68 for all exposed women and 2.19 for the studies with better exposure assessment. It was concluded that there was a causal relationship. For postmenopausal women, the evidence was considered inconclusive. This conclusion was not accepted by the American Cancer Society or by the U.S. Department of Health and Human Services, i.e. the Surgeon General.

In a study from the Centre for Chronic Disease Prevention and Control in Ottawa, Canada, Johnson and Glantz have compared the pooled risk estimates for suggesting that secondhand smoke causes breast cancer with data available from 1986 from the U.S. concerning the same question but with regard to lung cancer from spousal exposure. The results suggesting that secondhand smoke caused lung cancer were a statistically significant with relative risk estimates between 1.53 and 1.88

for high exposure. Subsequent studies have continued to find significant increases in risk.

Johnson and Glantz discuss some of the reasons for the rejection of the breast cancer data as indicating a causal relationship.¹¹ One objection involves the possibility of confounding, but almost all the studies in question controlled for most or all known confounders. A more serious objection involves the belief that active smoking does not cause breast cancer and therefore how could passive exposure. With regard to active smoking, this was the consensus in 2004. Subsequent meta-analyses however found risk comparable to secondhand smoke. However, even if this inconsistency is resolved in favour of risk, there is still the large difference in exposure yielding roughly the same risk which requires an explanation. Johnson and Glantz discuss several theories, one is that active smoking damages ovaries and depresses estrogen levels and thus lowers the risk. This is clearly an area requiring more research. The authors point out that it took a decade between the observation of the increased risk of heart disease and passive smoking and a reasonably complete

understanding of why active and passive smoking carried similar risk.¹¹

Thus, while this is an area of considerable controversy and uncertainty, there appears to be sufficient justification for the position that avoiding secondhand smoke is prudent in the context of breast cancer risk for premenopausal women. There is in fact evidence that for young women

between puberty and first full-term pregnancy, the risk associated with smoke is particularly strong. This is rapidly becoming only a spousal issue since the movement to ban smoking in public places is gathering momentum daily. Even restaurants and bars in France are banning smoking starting in December, an action some would consider extraordinary.

OMEGA-3 FATTY ACIDS AND CHILD DEVELOPMENT

Fetal life and early infancy are recognized as critical periods for brain development and growing evidence suggests that early nutrition plays a role in neurodevelopment. Furthermore, the long-chain omega-3 fatty acid docosahexaenoic acid (DHA) is an essential structural component of the brain. Humans must get DHA from food (or the health food store) and the primary dietary source is fish and other seafood. DHA is present in breast milk but only recently has it been added to infant formulas. This is a particularly important issue since a dislike of fish is not uncommon nor are fears of fish consumption due to the presence of mercury and other contaminants. Furthermore, the culture of mainstream medicine works against the physician suggesting supplementation, although folic acid supplementation is an exception due to its success in reducing a common birth defect. A recent study published in the *American Journal of Clinical Nutrition* by Oken *et al* has addressed this issue by examining the association between maternal fish or DHA intake during pregnancy and the duration of infant breastfeeding with the attainment of so-called child development milestones.¹²

Oken *et al* studied over 25,000 children of mothers participating in the Danish National Birth Cohort, a prospective population based study that enrolled pregnant women between 1997 and 2002. Data was collected on maternal fish intake, the duration of breastfeeding and measures of child development milestones. The primary outcome was total development at 18 months ascertained by an interview. Mothers were questioned about whether the child could climb stairs, remove socks and shoes, drink from a cup, be occupied for 15 minutes with adult participation, fetch an object when requested, write or draw, orient a book correctly, use word-like sounds, and put two words together. Ages at which the child could first sit unsupported and could walk unassisted and the total number of words the child could correctly say were recorded.

Data was also collected at 6 months with an appropriate set of questions. From this data scales were constructed and scores derived. Other data collected included birth weight and evidence of early or late delivery (gestational age), maternal smoking and alcohol use and other information which allowed correcting for confounding. It was found that higher maternal fish intake during pregnancy and the duration of breastfeeding were associated with higher child development scores at 18 months. For example, 5.7% of children with a mother in the lowest quintile of fish intake had the lowest total development score at 18 months whereas only 3.5% of children with mother in the highest quintile of fish intake had the lowest total development score. Women in the lowest quintile consumed < 1 fish serving/week whereas in the highest quintile it was about 3.5 servings/week. Fish most frequently consumed were cod, plaice, salmon, herring and mackerel. Species with high mercury content are not commonly consumed in Denmark.

Longer duration of breastfeeding was associated with better development at 18 months. After adjusting for maternal fish intake, longer breastfeeding remained associated with a greater achievement of developmental milestones with a 28% increase when ≥ 10 months was compared with ≤ 1 month. This pattern of association with fish intake and duration of breastfeeding was a robust result which persisted after a number of different corrections for potential confounding.

The authors comment that in the U.S. and Europe, expert panels have advised that pregnant women consume a minimum of 200 mg. of DHA/day. They point out that most women do not consume this much DHA from fish or other dietary sources, and thus supplements may offer a reasonable alternative. They cite studies which found improved development in children of women randomly assigned to take supplemental DHA although doses

were much higher (1-2 g/day) than the experts recommended. The authors cite evidence that in the case of the long-chain polyunsaturated fatty acids, supplementation with a single acid may be less

desirable than providing a more natural balance of these nutrients. Fish oil, for example contains both DHA and EPA.

NEWS BRIEFS

GREEN TEA AND GLUCOSE METABOLISM

Green tea appears to improve blood glucose levels. In a recent study from Japan, plasma glycosylated hemoglobin (HbA1c) was used as an indicator of circulating blood glucose in a group that were receiving supplementation with green tea extract. HbA1c provides a long-term average of blood glucose due to the approximately 3-4 month lifetime of red blood cells and is used extensively in the monitoring of glucose control in diabetics. HbA1c levels are expressed as a percentage of total hemoglobin. Values above about 6% suggest insulin resistance or diabetes whereas values below about 5% represent very good glucose control and normal glucose metabolism. In this study, participants had fasting blood glucose ≥ 6.1 mmol/L (110 mg/dL) or nonfasting values of ≥ 7.8 mmol/L (140 mg/dL). Thus this cohort had abnormal glucose metabolism and could be described as prediabetic. Two months of supplementation with green tea extract (544 mg polyphenols, 465 mg catechins) daily resulted in a significant reduction in HbA1C levels. Half of the group received supplementation for 2 months and were followed for 4 months. HbA1C dropped from 6.2% to 5.9% after 2 months and was 5.8% at 4 months. Supplementation was on top of green tea consumption in this cohort which may have decreased the magnitude of the effect. The authors comment that green tea consumption has been shown to be inversely associated with the risk of diabetes, a result consistent with their results. The decrease observed was significant in terms of cut-offs for identifying individuals with impaired glucose tolerance or insulin resistance.¹³

A CASE OF MISTAKEN IDENTITY—A BREAST CANCER CELL LINE

The shocking news is out. Some, maybe even most breast cancer researchers have probably been studying the wrong type of cancer. An investigation that has been ongoing for over 8 years appears to be reaching a conclusion. A cancer cell line that has been the cornerstone of metastatic breast cancer research for over 25 years now appears to be derived from melanoma cells. This cell line has been used in more than 650 published breast

cancer studies which are now in doubt and will probably require reinterpretation. While not all agree that the evidence is definitive, two major cell line repositories have reclassified the line as melanoma and a leading cell line vendor has stopped selling it. In a paper in the September 16 journal *The Scientist*, the author quotes an oncologist as saying that at a recent conference on metastasis, 40% of the presentations used this cell line and nobody even questioned that they were not breast cancer cells. This is in spite of the fact that the key papers offering proof was published in 2005 and 2006. It would appear that now journal editors and granting agencies have a real problem. But some researchers suggest that there is an upside—a suddenly born literature on melanoma which can now be reinterpreted.¹⁴

We are constantly told that we live in the new era of evidence-based medicine. But as Ralph Moss points out in his recent newsletter *Cancer Decisions* (September 21, 2008), now that it appears that the cells used in breast cancer research are really not breast cancer cells at all, how valid is the evidence on which current breast cancer treatment is based?

MORE NEGATIVE RESULTS FROM THE WOMAN'S HEALTH INITIATIVE TRIALS

The Woman's Health Initiative Dietary Modification trial included a study of the impact of decreasing fat and increasing vegetable and fruit intake on the risk of what is called benign proliferative breast disease; a condition associated with increased risk of, and considered to be a pathway to invasive breast cancer. Almost 50,000 postmenopausal women were involved. In this study, participants randomized to the intervention arm were told to reduce their fat intake to 20% of total energy and increase fruit and vegetables intake to ≥ 5 servings per day and grain products to ≥ 6 servings per day. The dietary changes that actually occurred were smaller but were still, in the view of the researchers, significant. The end result was that the intervention has no impact on the risk of benign proliferative breast diseases. While if there has been good adherence to the study guidelines some effect might have been seen, it can be argued that the fruit,

vegetable and grain intakes were perhaps a bit unrealistic. But fat intake did decrease and this evidently had no effect. This is not surprising considering the inconsistent results that have been obtained when studies attempt to link fat and cancer.¹⁵

PSYCHOLOGICAL FACTORS AND BREAST CANCER RISK

A recent case-control study from Israel has examined two hypotheses: (a) psychological distress and severe life events are risk factors for breast cancer among young women and (b) there is a cumulative effect of life events on the initiation of the disease. The cases (255) were women aged 25-45 who had been diagnosed with breast cancer. The controls (367) were recruited from women visiting outpatient clinics in the same region who were free of breast cancer or other malignant disease. Data were collected through a set of questionnaires. Included was a life event questionnaire which listed the following events: loss of a close relative, loss of a spouse, parent's divorce before 20, loss of parent before 20, spouse separation, job loss, economic crisis, severe illness, severe illness of close relative, other severe event. Anxiety, depression and the combination of happiness and optimism were also assessed. While the data was collected for the cases about a year after diagnosis, participants were asked to report their feelings prior to diagnosis but they had no way of estimating the impact on the study of the accuracy of recollection. A significant difference was found comparing cases and controls according to the cumulative number of life events. Exposure to more than one life event was positively associated with breast cancer risk (62% increase) and a general feeling of happiness and optimism had a protective effect (25% risk reduction). Both of these results were statistically significant.

The authors cite a number of studies that provide evidence of biological plausible pathways through which psychological stress could contribute to the increase in cancer risk.¹⁶

ARTHROSCOPIC KNEE SURGERY FOR ARTHRITIS

A study from Canada (University of Western Ontario) has just appeared in *The New England Journal of Medicine* which compared arthroscopic knee surgery for osteoarthritis with a group that just received physical and medical therapy.¹⁷ While this study was widely covered by the media, just in case some readers missed it, brief mention will be made of the results. This type of surgery allows for lavage, a procedure that removes particulate material such as cartilage fragments and calcium crystals. It also allows for the smoothing of various surfaces. The goal is to reduce synovitis (inflammation of a membrane associated with the joint) and eliminate mechanical interference with joint motion. The minimally invasive procedure is widely used. There were 86 patients in each group and the follow-up was for 2 years. It was found that surgery provided no additional benefit as compared to optimized physical and medical therapy. The nonsurgical treatment involved physical therapy (one session per week for 12 weeks followed by an unsupervised program at home), patient education, and the stepwise use of acetaminophen, nonsteroidal anti-inflammatory drugs, glucosamine, and the injection of hyaluronic acid. In an editorial accompanying the research report, Marx comments that this study does not imply that arthroscopic surgery has no role for patients who may have both osteoarthritis and another knee condition where surgery is appropriate, but that the selection of patient who are likely to benefit is difficult.¹⁸

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REVIEW

LOW-DOSE RADIATION EXPOSURE AND RISK OF CANCER: IS THE CONVENTIONAL WISDOM WRONG?

William R. Ware, Ph.D.

The right dose differentiates a poison from a remedy. Paracelsus (1493-1541)

INTRODUCTION

The conventional wisdom holds that there is no threshold associated with the dangers of radiation. Any radiation above the ambient or background levels is considered to increase the risk of cancer and the relationship is regarded as linear. The risk is in direct proportion to the dose, starting at zero excess exposure. Thus this view involves the belief that there is no level below which exposure is safe. This is in fact called the *Linear-No-Threshold Model* or LNT model, a model of great utility since it allows extrapolation from data collected for high dose exposure way down to modern levels of diagnostic radiation. The high dose data is primarily derived from extensive studies of the survivors of the atomic bomb exposure in Japan with doses estimated according to the

distance from the epicenters of the explosions. The bomb radiation was primarily from, x-ray and much higher energy gamma-rays. Both are so-called electromagnetic radiation which includes microwave and infrared radiation and visible and ultraviolet light. Gamma rays and x-rays also described as *ionizing radiation*.

Why is this important? Modern medicine makes ever increasing use of imaging with x-rays and radiation from infused radioactive isotopes, both for primary diagnosis, whole-body CT screening and for guiding invasive procedures such as angiograms, stent placement, etc. In addition, there are concerns regarding radiation associated with several aspects of the nuclear power industry and even worry about terrorists using so-called dirty bombs. If it is indeed true that any level of exposure exceeding natural background radiation increases the risk of cancer, then there is reason to limit all exposure no matter what the source. If the LNT model is in fact not correct and there is a threshold, then the conventional wisdom may be creating unnecessary concern and unjustified avoidance of diagnostic and screening procedures. It may also cause unjustified anxiety among patients who have had or are facing radiologic diagnostic procedures. If the LNT model is incorrect, then studies which use this model to predict future cancer incidence due to, for example, CT scans, are providing misleading guidance. While we have all been led to believe in the LNT model and its implications (although we may not have realized what the model was called), as will be discussed in this review the conventional wisdom has been repeatedly challenged. In fact, there are growing indications regarding the lack of evidence for and validity of the LNT model and the predicted dangers of low-dose radiation.

Radiation doses are generally expressed in the units of the Sievert (Sv) or the Gray (Gy). While the details of these units need not concern us, it is necessary to refer to dose levels and both are used in the context of diagnostic exposure. To keep this discussion simple, the millisievert (mSv, one thousandth of a Sievert) will be used and the Gy will be taken as equivalent to the Sv for x-ray and gamma ray radiation. To provide perspective, the following are the typical modern exposures per procedure for medical diagnostic application, given in units of mSv. Chest x-ray: 0.02-0.04; thoracic spine x-ray: 0.4; barium swallow x-ray: 1.5; barium enema x-ray: 7; mammography x-ray: 0.7; dental examination x-ray: 0.02-0.09; abdominal x-ray: 1.2; CT head scan: 2; CT chest or abdominal scan: 8-10; angioplasty procedures: 8-57; coronary angiogram: 5-16; technetium-99 nuclear medicine scan: 2-7 (Source--Health Physics Society Website, www.hps.org, fact sheets). Incidentally, so-called electron beam tomography used for coronary calcium scans does not irradiate the patient with high-energy electrons but is an x-ray based CT procedure. The name is derived from the manipulation of the electron beam inside the x-ray tube in order to create a scan.

The above are approximate values and are dependent on the equipment used. But the general range is what is important for understanding the subsequent discussion. Radiation therapy involves much higher doses, generally well above 1 Sv and frequently above 10 Sv with multiple exposures. These numbers can be put in perspective by recognizing that in the U.S. people are exposed on average to background radiation level of about 3 mSv annually. However, most of this natural exposure comes from radon gas which deposits radioactive decay products in the lungs which then emit alpha-particles and gamma rays. Alpha particles have a somewhat different mechanism for inflicting radiation damage than ionizing radiation. Dose rates or accumulated doses associated with radiation therapy, in particular for cancer, are in a range where there is evidence of radiation carcinogenesis. This review is concerned with much lower doses.

Two recent reports from respected sources relate to the issues raised above. One originated as a joint effort of the French Academy of Medicine and the French Academy of Sciences and was published in 2005. A summary is available.¹ The other report, also published in 2005, was from the U.S. National Academy of Sciences and is referred to as the BEIR VII report. Both address the question of the cancer risks associated with low dose ionizing radiation. The authors of the French report conclude that epidemiological studies have been unable to detect a significant increase in cancer incidence in humans for doses below about 100 mSv. This dose level is clearly above all common diagnostic, screening, and intervention associated radiation exposure. The French also addressed the question of the validity of the LNT model. The report points out that the studies used to justify the LNT model involved A-bomb survivors and individuals exposed to radiation in the workplace and that the levels of exposure were in the range of 125 to 500 mSv. If the studies are restricted to those receiving less than 100 mSv, they maintain that the excess cancer rates can not be determined, either because of the problems in statistical significance associated with the fact that the number of individuals included is too small, or because there is a lack of a carcinogenic effect at low doses. In taking this position they reject as not significant several

studies that are frequently quoted in support of the LNT model in investigations attempting to estimate risk of developing cancer from medical diagnostic exposure to radiation.²

The conclusions of the French Report were challenged by Brenner and Sachs.³ They present essentially two arguments. One is based on studies of the cancer in offspring associated with *in-utero* exposure. The French Report considers the evidence of *in-utero* carcinogenesis produced by low doses to be doubtful. It is interesting in this context that an increased risk of leukemia was not found in the offspring of Japanese women pregnant at the time of exposure to the bomb radiation. Also, the principal concern is with adult radiation exposure and most critics of the conventional wisdom are willing to concede that there are potential risks for unborn and young children. Their second argument is based on what they regard as the absence of extensive understanding of the mechanisms whereby low-dose radiation could offer protection. This effect is called *hormesis* or the *hormetic effect*. Do we dismiss epidemiologic evidence where radiation hormesis seems indicated simply because the protective mechanisms are not fully understood? This second objection also ignored considerable evidence already in the literature regarding hormesis,^{4,5} especially cell culture and animal studies, and the fact that hormesis is a widespread phenomenon in biology and pharmacology. In fact, the French report devotes considerable space to a discussion of potential mechanisms for the hormetic effect and its impact on low-dose risks.

The position taken in the joint report of the two French Academies is echoed in position statements from the Australasian Radiation Protection Society⁶ and by seven participants of the 15th Pacific Basin Nuclear Conference which was held in Sydney, Australia in October 2006.⁷

The BEIR VII report does not agree with the French view. Rather, the investigators believe that a comprehensive review of the available biological and biophysical data supports the LNT model as the best representation of risk at low doses although they also appear to agree that there are no data demonstrating a carcinogenic effect below 100 mSv.⁸ Both groups had access to the same literature and such disagreements generally arise from differences in interpretation of results, different views of statistical significance and data quality or simply differences in opinion. It is well beyond the scope of this review to compare in detail these two reports and their differences, but there are studies that relate to the issues involved that post-date these reports that are of interest, and in addition, there has been growing criticism of the LNT model. Also, some studies that predate the French Report seem sufficiently relevant to merit review.

Finally, in the summary of the French Report,¹ they urge great caution when considering studies that use the LNT model for risk prediction and cite a paper in the *Lancet*⁹ as an example. This same cautionary advice would no doubt apply to a recent paper by Brenner and Hall in the *New England Journal of Medicine*, where it was argued on the basis of the LNT model and data not accepted as adequate by the French investigators that in a few decades about 1.5 to 2% of all cancers may be the result of CT scan usage.¹⁰ However, the French Report admits that a significant although small risk associated with low-dose radiation may exist for pregnant women, infants and young children, and that caution should influence practice for these groups.

TOXICOLOGY MODELS

Toxicology mainly uses two models for exposure or dose dependence. One has a threshold followed by an increase in risk or incidence (the threshold model) whereas the other has no threshold and views the risk or incidence as increasing from a zero dose level. When the increase is assumed linear with dose, one has the Linear-No-Threshold model (LNT). The risks associated with non-carcinogens are generally described by the threshold model whereas for carcinogens it is assumed that there is no threshold. Neither model includes the possibility of a U- or J-shaped curve where there is a dose range that confers benefit (the risk ratio falls below 1.00, the reference for no exposure) followed by adverse effects at higher doses. Calabrese and Baldwin in 2003 stated that in their view the toxicological community made an error of historic proportions in its formative years (the 1930-1940s) by buying into only these two models, which once accepted, became dogma and provided the basis for subsequent progress as well as confusion.¹¹ This was in spite of individuals such as radiation biologists, pharmacologists and even some toxicologists who pointed out unmistakable exceptions.

The U- or J-shaped dose response curve represents *hormesis* or a *hormetic effect*. Hormesis appears to be very commonly encountered in pharmacology. Calabrese and Baldwin list more than 30 receptor systems that show

hormesis.¹² Closer to everyday life, readers of this Newsletter have repeatedly encountered the J-shaped dose–risk relationship when reading about studies of alcohol consumption and heart disease. Parsons¹³ as well as Tubina *et al*⁸ have in fact described the hormesis model as an evolutionary imperative reflecting adaptation to environmental levels of toxins and other hazards such as radiation. As Caroline Hadley puts it in a commentary in the journal *European Molecular Biology Organization Reports*, “what doesn’t kill you makes you stronger.”¹⁴

The principal issue with the LNT model is its use in estimating risk at low doses by assuming a linear dose relationship. This application of the LNT model continues to be widely employed in studies aimed at assessing cancer risks associated with medical diagnostic procedures. The literature used to justify this procedure predates the French Report and was presumably considered when the French investigators took the position that the evidence was inadequate. Many scientists and even economists regard extrapolations as fraught with danger because the procedure assumes a regularity such as linearity or exponentially which has not been observed and may not actually exist.

RADIATION AND BREAST CANCER RISKS

As the French Report indicates, studies that attempt to address the question of risk of radiation-induced cancer at low doses, taken as a whole, in their opinion either yields statistically insignificant indications or no evidence of risk at all. But some actually show evidence of hormesis and in some cases the odds ratios indicating a protective effect are statistically significant as judged by whether or not the 95% confidence interval includes the null result, i.e. 1.00. Studies that examine the association of breast cancer and radiation exposure are interesting in this context, especially since breast tissue is regarded by some as being particularly susceptible to this risk. There are also studies that predate 2005 where it is hard to ignore the fact that the results appear to falsify the LNT model.

The use of fluoroscopic x-ray monitoring during the treatment of tuberculosis was common between 1920 and 1960 and has provided some interesting data on cumulative exposures that are both above and below the 100 mSv “threshold of uncertainty.” Most of the data are derived from patients treated during the second quarter of the 20th century. Follow-up studies for breast cancer incidence and mortality after treatment for tuberculosis are thus interesting for what they reveal at the low end of the exposure range and as well, relate to the question of hormesis. Typically, each dose was in the range of 10 to 100 mSv and exposure occurred as frequently as every 2-3 weeks for 3-5 years. Studies have looked at the relationship between cumulative dose and breast cancer. One study by Howe *et al*¹⁵ which examined the association between breast cancer mortality and radiation exposure is of particular interest because it provided good dose stratification and also compared the results with an atom bomb survivor cohort. When a comparison among tuberculosis patients was made between those with doses < 10 mSv and those with cumulative doses between 10 and 490 mSv, the latter had a relative risk of 1.09 which statistically was indistinguishable from 1.00, i.e. not statistically significant. For the atom bomb survivors, the same comparison yielded a relative risk of 1.05 which again was not statistically significant. This dose range starts below 100 mSv and then exceeds it by a factor of 5, although it is unlikely that many patients received doses as low as 10 or 20 mSv. Thus, if x-ray radiation is dangerous for diagnostic x-rays that are either well below the reference of < 10 mSv or even at most twice this figure, why were not these patients found to be at enhanced breast cancer mortality risk? Furthermore, for the tuberculosis patients, even the dose range of 500 mSv to 1 Sv still failed to reveal a statistically significant risk, although it did appear in the atom bomb survivor cohort.

The results reported by Howe *et al* are consistent with those found by Boice *et al*¹⁶ where, compared to untreated patients, those tuberculosis patients exposed to 10 to 1000 mSv had a relative risk of 1.2 which was found to be not statistically different from 1.00. In this study, the observed to expected ratio for breast cancer incidence ranged from 0.59 to 0.75 for doses in the range of 470 to 700 mSv for women of age > 25. This suggests a hormetic effect below 700 mSv. In both of these studies, significant risk appeared above 1000 mSv and appeared dose dependent which is consistent with high dose studies and not in dispute.

Today, multiple and frequent exposures to x-rays at single doses from 10 to 100 mSv for the purposes of imaging would be unusual, although occasional exposure during some interventions would fall in this range. But in the above studies even when the accumulated dose ranged from 500 to 1000 mSv, no evidence was found of enhanced breast cancer risk. It would seem that these results, which involved a large number of individuals and

a follow-up of 30 or more years, would suggest at least a threshold model for breast cancer below which the risk becomes insignificant. This is contrary to the LNT model.

Since the French and BEIR VII reports there have been several studies reported concerning diagnostic x-rays and breast cancer. The most recent by Ma *et al*¹⁷ involved a case-control study of 1742 cases and 411 controls resident in Los Angeles County. They found an elevated risk for chest x-rays which showed a trend for frequencies of 1-2 to ≥ 9 exams as compared to those who never had such an x-ray. For mammography the association failed to achieve statistical significance even though the doses were higher. Also, most of the results for dental x-rays provided results that were not statistically significant. All risk factors were adjusted for confounding. Recall that these procedures employ doses below 1 mSv. The authors point out that the median age at first exposure was 15 years for chest x-rays and 35 years for mammography exposure and that early exposure to chest x-rays might enhance the effect of radiation in spite of the lower dose. The chest x-ray results of Ma *et al* are inconsistent with the results for exposure associated with tuberculosis treatment as discussed above, where the exposure was frequent and at much higher. The results of Ma *et al* are also inconsistent with a recent study by Lie *et al* who found no clear association between ionizing radiation and cancer of the breast for a large cohort of Norwegian nurses who experienced work-related exposure.¹⁸

In 2006 Redpath reviewed work in his laboratory at the University of California, Irvine (Department of Radiation Oncology, School of Medicine) which demonstrated J-shaped dose-response curves for radiation-induced neoplastic (potentially malignant cellular transformations) *in vitro* (cell culture studies) for a variety of radiations including those used in low energy imaging. He then made a comparison with the variation of the incidence of breast cancer for doses from about 20 to over 700 mSv based on calculations involving data of Preston *et al*.¹⁹ Below approximately 200 mSv, for Preston's epidemiologic data (human studies) the relative risk dropped below 1.00 and over the dose range of 20 to 140 the relative risk ranged from about 0.75 to 0.9, i.e. protective. This behaviour mirrored quite well the relative risk of neoplastic transformation observed in the *in vitro* studies which also showed a dose response curve with a minimum at around 20 mSv. But the point is that relative to patients exposed only to natural background radiation, the relative risk Redpath derived from the data of Preston *et al* suggested the presence of hormesis and yielded a J-shaped curve, actually a sort of "lazy J" in the parlance of ranchers and their cattle brands. Even if one ignores the hormetic effect, no excess incidence was found over the dose range below about 200 mSv.

DATA FROM THE WORK-RELATED RADIATION EXPOSURE

Here the literature is extensive and consistently exhibits protection from cancer associated with low-dose radiation exposure. An excellent review is to be found in a very recent paper in the journal *Dose-Response* (full-text articles are free) by Sanders and Scott.²⁰ They examine a large number of studies which have addressed this issue, which have found either no effect or a protective effect from radiation exposure. Nineteen studies are listed showing radiation hormesis where the percentage of lung cancer cases or mortality avoided ranges from 7% to 100% with typical results in the range of 25-50%. For all cancers, 13 studies showed evidence of avoided cases or mortality ranging from 7% to 49%.²⁰ Exposures involved both ionizing radiation and alpha particle radiation from the decay products of radon.

Work-related epidemiology is confounded by what is called *The Healthy Worker Effect* (HWE). When examining the question of expected cases in unexposed individuals, it is common to use large population databases. The HWE arises when workers are potentially healthier or less susceptible due to selection at employment, company health benefits, early detection by company medical personnel, etc. Some of the studies discussed by Sanders and Scott avoided this source of confounding by using unexposed but otherwise more or less identical company employees as controls. For example, in a study of workers in the nuclear industry, the protocol compared workers required to wear film badges (radiation monitors) vs. those who were not considered at risk (unbadged workers). It was found for women working in 12 U.S. nuclear weapons facilities there were 25% fewer deaths from all causes and 17% fewer deaths from cancer among the badged workers compared to the unbadged workers. The relative risk for lung cancer mortality in badged workers was 49% lower than unbadged workers.²¹

Another study of interest in this context involved examining 100 years of data from British radiologists. It was found that for those professionally registered after 1920, there was no indication of enhanced risk. Expected mortality rates were calculated based on three different data sets: all men in England and Wales, all males of a

social class equal to physicians, and all male practitioners. The results for the relative risk of cancer mortality were 0.63, 0.82 and 1.04 for comparisons with these three control groups, respectively. The first two numbers were highly statistically significant and suggest hormesis, whereas the comparison with male practitioners (RR = 1.04) was not statistically significant.²² Also there was no statistical evidence of decreased longevity compared to the control groups. Cameron has suggested that radiation provided protection by stimulated their immune systems.²³

Thus some studies of work-related exposure may be confounded by the HWE but others are not. The majority of these studies consistently exhibit no enhanced mortality or enhanced incidence of either specific cancers or cancer in general, and the levels of exposure are high compared to modern diagnostic radiation. Indeed, hormesis appears to be the rule rather than the exception. This is exactly the opposite of what we have all been led to believe. As long as the dose is not too high, workplace radiation exposure appears to present no enhanced risk and may even be protective in terms of cancer incidence and mortality. These results appear to falsify the LNT model, and in addition the doses where no enhanced risk was found were well above those normally encountered in diagnostic procedures.

RADON AND LUNG CANCER

The notion that exposure to the radioactive emissions associated with radon and its decay products increase the risk of lung cancer is part of the conventional wisdom. As mentioned above, radon is a major source of natural background radiation. In 1995 Cohen²⁴ found a highly significant *negative* correlation between radon exposure and lung cancer mortality in the U.S., even after adjusting for smoking and other socioeconomic factors. The study involved about 300,000 radon measurements in over 1600 counties in the U.S. This result held up under extensive adjustment (over 500 factors) for confounding. The author concluded that there was no evidence from this study that low-level radiation causes lung cancer, that there is at least some evidence that it may be protective, and the LNT model failed completely. In addition, Colorado which has the highest residential radon concentrations in the U.S., the average rate of lung cancer is well below that for the U.S. overall. Also, there are villages in Japan that have radon levels 3 times the national average, but have half the cancer death rates compared to the country as a whole. Radon is involved in therapy in Europe at a number of spas and other locations, has a long history, and is being actively studied as a therapeutic agent.²⁵

However, the Biological Effects of Ionizing Radiation (BEIR) committee of the U.S. National Research Council took a totally different view. Luckey and Lawrence²⁶ point out that this position is actually contradicted by the data in the BEIR reports which showed conclusively that for 68,000 miners and 2,700 cases of lung cancer, there was no statistical significant association with the extent of exposure to radon. Luckey and Lawrence conclude that carcinogenic particulates and/or noxious gases, not radon and its decay products, must be the cause of lung cancer in miners. In addition, the data presented by the BEIR VII committee on lung cancer from radon in homes showed that the relative risk did not rise significantly with increased radon exposure.

OTHER EVIDENCE OF HORMESIS OR PROBLEMS WITH THE LNT MODEL

There are areas around the world where the background radiation is very high compared to the normal levels in the US.²⁷ Extreme levels of background radiation are found for example in Guarapari (Brazil), southwest France, Ramsar (Iran), parts of China, and the Kerala coast (India). Black sand beaches in Brazil have radiation levels 400 times normal. In India, the 570-km coastline of Kerala has very high natural radiation similar to the beaches in Brazil. In some locations in the city of Ramsar in Iran, the radiation levels are 55 to 200 times higher than normal background levels. What is interesting about these areas is that the individuals continually exposed to high background radiation do not appear to suffer any adverse health effects and in fact, in some cases, they appear healthier and live longer than those living in areas used for control.²⁸ But these are anecdotal observations and must be treated with caution.

There is also the interesting case of the radioactive apartment houses in Taiwan.²⁹ Accidental exposure allows a unique opportunity to examine the validity of the LNT model since obviously, given the views regarding the danger of any radiation, no one is going to volunteer to participate in meaningful studies. Such an exposure occurred in Taiwan where about 20 years ago, steel contaminated with cobalt-60, a radioactive isotope emitting penetrating gamma rays, was used in the construction of a number of apartment houses which were then

occupied by about 10,000 persons for from 9 to 20 years. These residents unknowingly received doses that ranged from a high of over 500 mSv to a low of 18 mSv with an average of around 50 mSv. The half-life of cobalt-60 is 5.3 years. Subsequent to the discovery of this situation, the occupants were followed-up to ascertain the incidence of cancer. The predicted cancer deaths were based on two models, the natural rate expected in this population and the predicted rate from the LNT model, and were 238 and 302 respectively. The observed number of cancer deaths was 7. When residents younger than 20 were excluded, the predicted cancers were 186 and 242 according to the two models. Only 5 cancers cases were actually found. It was estimated that when the buildings were completed, the maximum annual dose rate was as high as 500 mSv in some apartments.

A second study regarding the radioactive apartment houses in Taiwan was published in 2006.³⁰ This study criticized the earlier study for underestimating the cancer mortality rate. Also, they looked at the incidence of cancer rather than mortality. For all cancers except leukemia and for solid cancers, the standardized incidence ratios were 0.8 and 0.7, respectively with both results statistically significant. This lower rate of observed vs. expected cases again suggests a protective effect.

While the Taiwan apartment houses offered a unique opportunity to examine the carcinogenic effects of low-dose radiation, data analysis was complicated by a very wide range of exposures, both with regard to level and duration, given variable residency times, the differences in levels in various apartments and rooms, and the natural decay of intensity due to the 5.3 year half-life of cobalt-60. However, independent of the possibility of a protective effect, it seems hard to argue against the point that no statistically significant increase in mortality or incidence over that expected from unexposed individuals was found, even though the exposure was relatively high.

HYPOTHESES CONCERNING THE PROTECTIVE MECHANISM

Mechanistic investigations of the protective effect of low-dose radiation have involved both animal and cell-culture studies. This subject has been discussed by Scott⁴ and by Scott *et al.*⁵ Low doses and low dose-rates of gamma rays and x-rays appear to stimulate the body's natural defenses, an effect that has been called radiation activated natural protection (ANP). This protective mechanism involves selective removal of aberrant cells such as those that are precancerous via apoptosis (cell death). The selective removal of precancerous cells via apoptosis it thought to involve intercellular signaling involving reactive oxygen and nitrogen species and certain cytokines. In addition, there is considerable evidence supporting the action of low-dose radiation in connection with stimulating immunity against cancer cells. These protective effects would operate for both sporadic and hereditary cancers. As mentioned above, there are evolutionary arguments suggesting that such protective mechanisms may have been essential to survival.

CONCLUSION

The thesis developed in this mini-review is summarized by the warning: *Beware of the conventional wisdom*. A more comprehensive review would have provided more extensive support for the lack of carcinogenic effects and the possible protective effects of low-dose radiation. Some of the papers cited provide this additional information along with documentation. The question of the validity of the LNT hypothesis, especially in connection with radiation exposure, is very important since the LNT model has been the basis of environmental and public health policy for several decades. It is responsible for the fear of any radiation common among the general public, the reluctance seen among some individuals regarding diagnostic or screening procedures involving exposure to radiation, the fear of contamination from nuclear plant accidents or negligence and concerns about dirty bombs employed for terrorism. While there is no doubt regarding the risks of exposure starting somewhere between 100 and 1000 mSV, the result discussed above suggest at the very least the existence of a threshold and probably beneficial effects below this threshold such that many of the concerns enumerated are unjustified. Those who believe in the LNT model regard such statements as heresy, reckless and dangerous. But it appears that scientific research is chipping away at the foundations of the LNT theory and its use in extrapolating to low doses. The growing evidence of biologically plausible mechanisms for hormesis, its widespread presence in many biological systems, animal models and response to pharmacological interventions suggests that in the context of the interaction of radiation with human cells, it must now be taken seriously.

The two alternatives to the LNT model are a threshold model and hormesis. It would be surprising if the latter two models were not common since in order to survive organisms had to evolve defence mechanisms, but these mechanisms presumably could always be overwhelmed, thus providing a threshold for morbidity and mortality. Likewise, defence mechanisms, once activated, could provide a mechanism for a hormetic effect.

Articles such as the one mentioned above by Brenner and Hall in the *New England Journal of Medicine*,¹⁰ which predicted that in a few decades up to 2% of all cancers may be attributable to CT scans, have a profound impact on opinion and medical practice and yet the study in question was based on a model which more and more is being questioned and considered by some experts as invalid. But it is highly unlikely that readers of that paper will take the time to inform themselves regarding the pros and cons of the model even though the whole thesis of the paper critically hinges on its validity. In addition, the journal in question has a high profile and is highly respected world-wide. While the study no doubt correctly applied the model and within that framework obtained a significant result, if the model is wrong, then so is the result, and the readers and the media that track papers in these journals and duly report the results are misled into believing in risks that may not exist.

The issues raised in this review will probably not be resolved any time soon. The conventional wisdom generally blocks alternative views, discourages research and limits research funding, and makes publication of contrary results in major journals difficult. A substantial amount of the recent literature in this field is reported in journals that are not even covered by Medline (PubMed), the National Library of Medicine search engine. The purpose of this review has been to acquaint the reader with an alternative view which does not appear to be well known, not only among the general public but also among many medical professionals. Readers must recognize the uncertainties associated with this subject. However, when two distinguished Academies in France, one concerned with medicine and one with basic science, jointly tell us that there is no evidence of risk and possible indications of benefit for exposures to ionizing radiation below 100 mSv, the risk vs. benefit for medical diagnostic procedures appears to be shifting strongly in the direction of benefit. But their report is a monograph in French, and the summary, while in English, is in a specialized journal with a limited audience. Also, the absence of evidence of risk does not prove it is not there, but given the amount of research that has already been done and what it suggests, it is not unreasonable to have justified concerns regarding the conventional wisdom.

The editor is indebted to a reader of the Newsletter for calling this subject to his attention.

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Editor: William R. Ware, PhD

INTERNATIONAL HEALTH NEWS is published 10 times a year by
Hans R. Larsen MSc ChE, 1320 Point Street, Victoria, BC, Canada, V8S 1A5
E-mail: editor@yourhealthbase.com World Wide Web: <http://www.yourhealthbase.com>

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