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William R. Ware, PhD - Editor

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"Science advances one funeral at a time."
(Max Planck, famous theoretical physicist)

In 2013 there were approximately 20,000 new students enrolled in medical school in the US. Among young individuals, there appears to be a growing tendency to question the status quo, the conventional wisdom, and the honesty and integrity of leaders in all fields from government to industry. Currently we see this in presidential politics. Thus there arises an interesting question. Will there be a significant number of medical students with the courage to question and challenge what they are taught because they have encountered contrary views or strong criticism in the peer-reviewed medical literature? Will this impact what is taught? Will the widespread pharmaceutical company influence in all areas of medicine be understood by some students leading them to openly question and challenge the validity of the guidelines and evidence-based medicine? Will some students come to understand and become concerned about the constraints placed on the practice of medicine by insurance companies and administrators? Will they rebel at the possibility of heavy-handed monitoring of their clinical judgements which may prevent them from practicing medicine in a manner they regard as correct and ethical once they have finished training? Will they elect upon completing training not to treat patients? There is some evidence this is an increasing trend.

It is easy to say that any sort of revolt against the medical education establishment is hard to imagine simply due to the potential disastrous impact on career prospects, a career in which students are investing large sums of money and long hours of effort and taking on huge debt. They dream of a rewarding and fulfilling career. The motivation will be intense to simply keep ones opinions to oneself and never question standard practice on rounds. Will they dismiss the critics even though their credentials are impeccable, and ignore the devastating commentary and papers critical of the current system that appear in such high impact publications as the *British Medical Journal?* Will they choose to ignore the fact that a significant fraction of experts writing guidelines that will control how they practice medicine have strong conflicts of interest associated with Big Pharma and ignore the signs that evidence based medicine is in fact based on studies which may be fraudulent, biased, and merely part of the grand scheme of the beautiful business plan of Big Pharma, the success of which has been so phenomenal that it has laid out

the essentials of a game plan transferable to other businesses? Or will the even know about these issues?

It can be argued that only an incurable and unrealistic optimist would look to each new generation of medical students to lead the revolution necessary to precipitate real change. Their careers are in the hands of those who by and large resist change and are dedicated to the conventional wisdom and current practice. The sources of power in the academic superstructure and the current evolution and philosophy of medical education are too strong. However, those putting career prospects ahead of concerns about what they perceive as wrong, unethical and contrary to even the oath they will take on graduation may find themselves experiencing significant stress and disillusionment. However, the ever-expanding social media may serve to acquaint medical students even early in their studies with critical literature they otherwise might never have encountered.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

PREVENTION OF CANCER—ONE OF THE BIGGEST CHALLENGES WE FACE

It is well-known that cancer is a leading cause of what professionals' term morbidity and mortality. Morbidity refers to the pain, suffering, loss of organ and system functions and the associated profound psychological damage. There can be a long time interval between the start of cancer and its symptomatic manifestation and this depends of the cell type and the environment in which is growing. The number of cancer cells necessary to cause symptoms is also variable, but with solid tumors is thought to be roughly in the range of a billion cells.[1] Prognosis depends partly on how well localized the tumor is and how quickly it starts to spread. But the window of best opportunity to eliminate the cancer is probably in the period from initiation to symptoms or tell-tale biomarkers. The use of markers involves so-called screening to look for evidence of tumors and biomarkers. Screening however is opposed for a large fraction of the population because, among other things, the harm of false positives outweighs the benefits of early detection except for high-risk individuals. This view is continuously debated.

The search for cures has motivated several US "wars on cancer." Critics claim that this approach has been a dismal failure. A contrary and highly authoritative view has recently been presented by Vincent DeVita, and Elizabeth Devita-Raeburn in a book titled *The Death of Cancer. Why the War on Cancer is Winnable—and How WE Can Get There.* Dr. Vincent DeVita is highly qualified to present this view given his life-long work at the frontier. The message is that much more progress has been made than generally appreciated, but there is a long way to go. The achievement of total and permanent remission has mostly been in the so-called blood cancers like leukemia and myeloma. When solid tumors are treated initially with surgery or radiation followed by chemotherapy or radiation if not used as the primary treatment, the standard therapies are frequently not successful in the long term and cancers described as gone eventually recur either at the primary site or as metastatic disease.

Most studies directed at the problem of primary prevention are of the so-called reductionist nature and deal with only one type of cancer and explore modifying one or more risk factors. Given the large number of cancers, this information is interesting, but is too specific to be of general applicability. The mainstream recommendation for prevention is to eat plenty of fruits and vegetables or adopt the Mediterranean diet, avoid obesity, drink in moderation, limit processed meats, exercise, and avoid smoking. The danger of toxic substances is rarely mentioned but is very important. The reader is referred to the review concerning the prevention of chronic disease at the end of the September 2015 IHN and to the section on environmental and dietary toxins and detoxification and as well the What *Not To Eat* discussion and the additional discussion in the October issue. Meat and cancer was discussed in the December 2015 issue.

There is another approach to prevention which remains somewhat theoretical but with compelling biological plausibility. It involves a targeted approach, but targeted not just on one type of cancer, but rather is aimed at almost or perhaps all cancers. The active agent here is the group of chemicals common to fruit called Salvestrols. This topic has been discussed and updated in IHN over several years. To review briefly the biological plausibility, the following points are important.

- There is an enzyme present in almost all if not all cancer cells called CYP1B1 which is present only in trace amounts in normal cells. The presence in cancer cells has been known for over a decade and a large number of different cancer types have been studied and the results reported in peer reviewed journals.[2]
- This is an important enzyme because it metabolizes certain natural products found in fruit with the production of cytotoxic substances which kill the cells.
- Studies using one of the most extensive collections of cancer cell lines in the world allowed researchers to identify extracts from certain common fruits that yielded the greatest cytotoxicity in cell-culture survival experiments. These were named Salvestrols, a term derived from the hypothesis that this enzyme is an integral part of the human defense mechanisms against cancer.[2, 3]
- Sophisticated methods of isolation and concentration resulted in formulations containing several Salvestrols that optimized the cytotoxicity.[2]

- Techniques were developed that enabled researchers to detect not only blood levels of Salvestrols but also levels of the toxic metabolite. Compelling evidence was found that the larger the tumor, the greater the decrease in circulating Salvestrols which was accompanied by an increase in the levels of cytotoxin.[4] This allows the assessment of the success of therapy.
- Highly sensitive techniques have been developed to detect the presence of CYP1B1 in the blood as a marker for the presence of cancer and this obviously offers significant diagnostic potential.[4] The fact that the type of cancer is not identified is compensated for by the existence of Salvestrols.
- The success of cancer treatment with Salvestrols can also be quantified by measuring the disappearance of CYP1B1.[4]

The application to prevention seems obvious. Presumably for many if not all individuals, cancer cells are being produced continuously through cosmic and environmental radiation, and toxins in food, water, air, and consumer products. When the immune system is unable to cope, Salvestrols should be able to deal with the residual cells. ***Thus Salvestrols have the unique potential to stop cancer development at a very early stage and even before a tumor has started to form.*** If one has a localized tumor which is starting to spread, Salvestrols should mop up these cell at the same time it is attacking the tumor. The prevention of metastatic spread is of course a key aspect of reducing cancer morbidity and mortality. In the initial stages of the development of cancer, Salvestrols should eliminate cancer cells and thus arrest the development of the cancer. Since it is probably unrealistic to expect that all cancer cells would be eliminated, maintenance doses of Salvestrol are indicated once there is no evidence of the presence of a tumor after Salvestrol therapy.

It can be hypothesized that just eating fruit should provide protection during the early development of cancer. However, research has also revealed that hybridization to reduce the bitterness of fruits and modern pesticide-based agriculture have over the last century reduced the concentration of Salvestrols.[2] This is consistent with the results of searching for the best fruit to use in isolating Salvestrols. Organic grown heritage varieties proved best and these are used to obtain the commercial product. Thus low doses of Salvestrols may have merit over fruit consumption in early cancer prevention.

The above is not merely hypothetical or theoretical. The success of Salvestrols in putting a number of different cancer types into remission has been documented although only through case histories, which while of limited number and are based on medical records and scans.[5-7] Salvestrols work both for patients who have not received conventional treatment and after surgery, chemotherapy and radiation. The greatest success in maintaining remission involves continued use of Salvestrols, general at a lower dose than was used therapeutically.

The need for an alternative to the mainstream approach to cancer prevention and treatment is clear from the widespread failure of conventional approaches although there are notable exceptions, especially in blood-related cancers. Targeted therapies for

specific cancers are a hot area of research and the resultant approved drugs generally exceedingly if not outrageously expensive. Also, the cancer type must be known. On the other hand, use of Salvestrols prevention does not require the identification of the cancer type and the same formulation of Salvestrols is used for all types of diagnosed cancer.

Critics would be quick to point out that neither case histories nor the hypothesis regarding primary prevention or the prevention of metastasis are in any way evidence-based by their standards and therefore until the appropriate clinical studies are performed, it is wise to ignore this approach to cancer. After all, fruit extracts from common berries and citrus may prove to be dangerous, although there do not appear to be reports where individuals who eat large amounts of fruit experienced adverse consequences. The same applies to those who consume large doses of Salvestrols. However, today heavy fruit consumption might in fact cause one to accumulate a dangerous burden of toxins that are present in non-organic fruits. Nevertheless, being faced with the arguments of proponents of strict adherence to evidence-based medicine is not new. Evidence-based medicine presents a huge barrier to the use of alternative therapies. Difficulties of obtaining financial support for studies on therapies that do not involve patented agents are the norm. However, in this context there is now a patented synthetic chemical that acts as metabolite for CYP1B1 and generates a cytotoxin. This may ultimately achieve regulatory approval.

Readers wishing to acquire more information about Salvestrols are referred to two books by Dr. Brian Schaefer, *Salvestrols, Nature's Defense Against Cancer*[2] and *Salvestrols, Journeys to Wellness.*[5] The latter contains a detailed account and summary of case histories and is also available in German (S*alvestrole. Die Antwort der Natur auf Krebs).*

BOTTOM LINE

It seems sufficient simply to quote Professor Dan Burke. "Salvestrols are the most significant breakthrough in nutrition since the discovery of vitamins." Professor Burke and colleagues at the University of Leicester, UK, are responsible for the basic research and development of Salvestrols. Your editor agrees with this opinion, and incidentally has no financial interests in this product. It is available online from Victoria, BC (Salvestrols.ca). The company can advise concerning distributors of authentic Salvestrols outside North America.

WHY DO SO MANY INDIVIDUALS HAVE ZERO CORONARY ARTERY CALCIFICATION?

IHN readers will recall that over the years we have reviewed either books or studies that attempted to characterize extraordinarily healthy or long-lived populations. Included were the Okinawa studies, the Blue Zone research, and recently the work of Weston Price done in the early 1930s. A subpopulation that needs to be studied in the same manner in search of characteristic lifestyle and dietary factors is the large group of

individuals that have zero coronary calcium as measured by a CT scan (CAC = 0). In the Multi-Ethnic Atherosclerosis Study they constituted about 50% of the entire cohort of nearly 9000 individuals and they had a very low risk of coronary heart disease. What are they doing right? Is it genetics, lifestyle, absence of certain disorders or diseases, or absence of traditional coronary heart disease risk factors? Unfortunately, no one appears to have examined this question retrospectively in a comprehensive fashion. The next best source of guidance involves studies that looked at the factors associated with progression of CAC from an initial CAC = 0. This information can inform as to what might be the indicated actions in order to remain in the CAC = 0 state. The following studies appear relevant.

- Valenti *et al* examined the long-term prognosis of asymptomatic individuals with CAC =0 and what they termed a 15-year "warranty" period associated with zero CAC.[8] Unfortunately they looked just at mortality. Almost 10,000 individuals age 52 ± 10 years, 58% male, were followed for almost 15 years. For those with CAC = 0, only treated hypertension, diabetes and smoking were significantly associated with all-cause mortality. Factors which failed to achieve significance included dyslipidemia (high triglycerides, low HDL) and family history of coronary heart disease.
- A study based on data from the Multi-Ethnic Atherosclerosis Study (MESA) looked at the impact of CAC on coronary heart disease (CHD) events over a range of traditional risk factors.[9] These factors were smoking, elevated LDL or low HDL, hypertension and diabetes. Hard CHD events per 100 persons over 10 years (heart attack, resuscitated cardiac arrest and CHD death were 0.6 (i.e. 0.6%!) for zero risk factors and 1.4 for ≥ 3 risk factors when CAC = 0. Both are very low rates. For comparison a CAC > 300 and ≥ 3 risk factors has a rate of 14.1 per 100 persons over 10 years vs. 1.8 for zero risk factors. However, this study did not stratify by individual risk factors.
- A study by Min *et al* examined the significant factors in the conversion from CAC = 0 to having any coronary calcium.[10] A 5-year follow-up involved 422 individuals with zero calcium score. Only hypertension, diabetes and smoking were found to significantly impact this conversion. Dyslipidemia was not important.
- Another study also looked at factors associated with incident CAC among those initially free of CAC.[11] The study involved 6800 participants age 45 to 84. Repeated CAC scans were done at an average of 1.6 and 3.2 years after the participant's first examination. Significant factors for the development of CAC were high blood pressure, elevated triglycerides, smoking and diabetes.
- Diabetes was also significant in a study of almost 3000 individuals with CAC = 0 at baseline. Not only was diabetes a significant risk factor for the development of CAC but so was the presence of the metabolic syndrome. Furthermore, the increase of CAC associated with metabolic syndrome increased with the number of risk factors (high blood sugar, hypertension, high cholesterol, elevated triglycerides and increased waist circumference) involved in a patient's diagnosis of the metabolic syndrome.[12]

- A study just published found that asymptomatic individuals with CAC = 0 had a favorable 5-year survival, but beyond that, out to 15 years, the risk of death was higher in individuals with diabetes compared to those without even while CAC = 0 was maintained. From survival plots, one can calculate that diabetes conferred a decrease in absolute survival of about 7%, i.e. 90% survived vs. 97%. When CAC was ≥ 400, the 15-year survival was 76% for non-diabetics vs. 54% for diabetics.[13]
- In a study also based on MESA data, the issue of lifestyle in the context of CAC incidence for individuals initially having CAC = 0 was investigated.[14] Cardiovascular events and mortality were also examined. 6200 participants ranged in age from 44 to 84 years. Four lifestyle-related factors were used to form a scoring system: Mediterranean diet vs. unhealthy diet, optimal body mass index vs. suboptimal, never smoker vs. ever smoker, and regular physical activity vs. sedentary lifestyle. A Score of 1 was given for each healthy behavior and calcium scans were performed annually. For CHD event probability over 7 years, those with the healthiest lifestyle had 3.6% vs. 5.5% for the least healthy. For survival probability, the two extremes in lifestyle had a 5% absolute difference. The odds of CAC incidence was about 0.4 for 3-4 healthy factors compared to zero factors as a reference.

Taken together, these results suggest that individuals who have CAC = 0 have managed to avoid diabetes and the metabolic syndrome, hypertension, and smoking and as well maintained a normal weight, ate a healthy diet, a model of which is the Mediterranean diet, and exercised. A more quantitative picture does not seem possible at this point in time, but considering the large number of individuals with CAC = 0 in these studies suggests that following the guidance provided by some of these preventive factors or actions may have been sufficient since it is unlikely that 50% of the MESA study population were characterized by the total spectrum of beneficial factors. But this appears not to apply to diabetes. However, if one has a scan and gets a CAC = 0 results, the above provides a check list that may help in maintaining this fortunate status. Anyone with a CAC = 0 or equal to a very low score who notes a metabolic change indicating prediabetes should consider the strong associations reported above with diabetes and take action to return to normal glycemia. This suggests the importance of annual blood tests to detect prediabetes or diabetes. Note that a significant number of diabetics are undiagnosed. Anyone with CAC = 0 and diabetes should considerer trying to becoming a non-diabetic using the Newcastle Diet (INH October 2014). For prediabetes, the same severely calorie restricted diet for a month or two should reverse prediabetes.

Arresting or reversing atherosclerosis as quantified by coronary calcium is another matter since one cannot automatically conclude that correcting a risk factor will produce plaque regression nor extrapolate from what is learned by studying those with CAC = 0. Once one has coronary plaque, the burden tends to relentlessly increase each year with the associated increase in CHD morbidity and mortality. The following is a list, mostly of

evidence-based actions, that may either slow or arrest CAC progression or may even reduce the plaque burden.

- Achieve and then maintain a 25-hydroxyvitamin D3 level above 50 ng/mL (125 nmol/L) [15-17] In other words, know your vitamin D status and act accordingly. This is especially important for those who live in northern latitudes, even the northern half of the US, and for anyone limiting their sun exposure.
- Achieve and maintain a low blood ferritin level, ideally probably below 100 microg/L through blood donation, iron chelation (milk thistle, or phlebotomy (blood-letting).[18] (CAC used). Also see IHN OCT 2012. Iron is a vastly underappreciated risk factor for many health problems.
- Eat a Mediterranean diet with lots of olive oil and nuts, and if not contraindicated, moderate red wine with the largest meal.[19, 20] (Carotid artery atherosclerosis measured)
- Never drink diet soda sweetened with aspartame and never use this sweetener.[21] See IHN June 2012)
- Detoxify with an oral program and saunas. See IHN March 2014, May 2014.
- Supplementation with resveratrol may be beneficial.[22, 23] (indirect evidence)
- Supplement with N-acetyl cysteine for arterial foam cell suppression.[24] (indirect evidence)
- Reduce psychosocial stress if at all possible, perhaps even with professional help. [25, 26] (Coronary artery angiography)
- There is some evidence that taking a calcium channel blocker at the lowest dose used for mild hypertension may be beneficial. If on hypertension medication, consult with physician regarding adding this drug if not already used. If not hypertensive, monitor blood pressure initially to make sure hypotension does not occur.[27, 28] (CAC and coronary angiography)
- Avoid second hand smoke and of course don't smoke.[29] (CAC used)
- For postmenopausal women with low fat intake, increasing saturated fat decreases progression of coronary atherosclerosis.[30] (coronary angiography)
- Low HDL, elevated triglycerides and small dense LDL particles are important risk factors but total and LDL are not, except perhaps for the very obese. Elevated triglycerides are particularly important, as is elevated homocysteine.[31, 32] These two lipid abnormalities are commonly associated with low-fat high-carbohydrate diets, especially where the carbohydrates are highly glycemic. Now very recently considered part of an unhealthy diet. Originally made hugely popular by the fat-is-bad hypothesis and later transformation to dogma. A low-carbohydrate diet rich in low-glycemic foods, aggressive weight reduction, and a diet or supplementation with long-chain omega-3 fatty acids such as found in oily fish may address these risk factors.[33, 34] (CAC used)
- Quercetin and curcumin may prevent or cause regression in atherosclerosis.[35, 36] (experimental evidence)

- Consider examining in detail the subject of nutraceuticals and the prevention of atherosclerosis. Google “Marika Massaro nutraceuticals” which will bring up a review in *Cardiovascular Therapeutics* published in 2010.[34] The full text is free and provides a detailed discussion of a number of possibilities for supplementation. One can also access the free PDF paper another way. Google PubMed and put the PMID number 20633019 in the inquiry box at the top of the home page. Use the journal buttons at the top right when the abstract comes up.[34]

BOTTOM LINE

Ideally, avoiding or significantly reducing the risk of heart disease involves avoiding coronary atherosclerosis or if it is present, arresting progression or reducing the burden. Statins are well known for having no significant effect but most will be told that is a one of the best things they can do. Mainstream medicine does not routinely measure coronary calcium burden. They are focused on cholesterol, blood pressure and some no doubt still believe in the now discredited fat hypothesis. The potential interventions and actions discussed above considerably expand on what little recommended by mainstream medicine appears to have merit. Diabetics should consider the Newcastle Diet to eliminate type 2 diabetes or prediabetes (See IHN October 2014). The above are only suggestions offered for reader consideration, not medical advice.

THE PAXIL SAGA – NOTORIOUS STUDY CASTS SHADOW OVER ALL CLINICAL TRIALS

In the last issue the editorial discussed a proposal from major journal editors to demand as a condition for a clinical study being considered for publication that the company agrees to make the patient-level trial data available so that it could be independently analyzed. The story of the antidepressant Paxil where the study data has been reexamined serves to emphasize the importance of this new condition for publication. The following is mostly derived from the Study 329 website.

Paxil was developed by SmithKlineBeecham (which then became GlaxoSmithKline—GSK) and was tested against a placebo for treatment of major depression in adolescents.[37] This was Study 329 and was published in 2001 with the claim that the drug was effective and had no significant side effects. Almost immediately the study came under criticism, mostly because the data in the paper did not support the conclusion. Calls were made for the paper to be retracted and this continues today. It was also discovered that the paper was ghost written by a commercial firm under the guidance of GSK and the lead author merely examined the final manuscript and gave his OK. The trial was reviewed by an FDA administration officer who concluded that it should be regarded on balance as a failed trial since the data in the study drug showed no significant benefit over the placebo. Thus the aggressive marketing for adolescents was “off label,” i.e. for an unapproved indication, depression in young individuals. In 2002 already over 2 million prescriptions had been written for children and adolescents

in the US based on the pitch to doctors that Study 329 demonstrated “remarkable efficacy and safety.”

According to the Study 329 website, in 2004 the New York Attorney General filed a criminal consumer fraud action against GSK over the disconnect between the marketing claims for Paxil and the supporting data. The suit was settled for $2.5 million and the company, while admitting no guilt, agreed to grant access to the trial data. The company however, delayed using arguments based on different interpretations of “access” and ‘data.” Over the next few years, there were many civil lawsuits involving violence and suicidality attributed to Paxil that were settled. There was never any admission of guilt or responsibility. The FDA recognized violence and suicidality as established side effects of the class of drug (selective serotonin reuptake inhibitors—SSRIs) to which Paxil belonged and required a black box warning for all ages. Black boxes around text in the drug information material required by the FDA represent their strongest warning. In November 2012 GSK was charged again and agreed to pay a fine of $3 billion in settlement of an action brought by the US Department of Justice on the basis of the false claims act. This was a criminal suit, not a civil one.

After much wrangling, independent researchers finally obtained access to the clinical trial data, although via a GSK remote access portal, but the website claims that they could neither print or download and the information which was also organized in a way that made analysis difficult. After reviewing 77,000 pages of patient records, they determined that suicide attempts were significantly higher than the original study reported, that there were many other unreported serious adverse events in the Paxil group, and that the drug was no more effective than a placebo in alleviating major depression in young people. The new study has just been published in the *British Medical Journal*.[38] The results directly contradict the original study of 2001 with its claims that Paxil was well tolerated, had few adverse events including suicide ideation or attempts and was effective for the age group in question. And still no retraction, no apology, and this study raises serious issues about academic institutional responsibility associated in general with the ghost-writing of papers “authored” by academics and the 2001 paper in particular.[39]

BOTTOM LINE

The above makes one wonder how many other studies out there, many influencing guidelines of practice, that have results at variance with the actual patient data on which the studies are allegedly based. In other words, evidence-based medicine is to some extent a joke, even a marketing slogan. In fact, critics of Big Pharma would probably point out that what we are looking at is the norm, not the exception. This is the message of Professor Peter Gøtzsche’s book *Deadly Medicine and Organized Crime* and Dr. Ben Goldacre’s book *Bad Pharma,* and Professor Gøtzsche’s just published book *Deadly Psychiatry and Organized Denial* with the cover showing a tombstone on which is written *500,000 Americans and Europeans in 2014* (at this writing only available as a paperback from Amazon.uk) Incidentally, Peter Gøtzsche is a specialist in internal medicine. He co-founded the Nordic Cochrane Center (part of a highly respected worldwide organization which does independent meta-analyses and systematic

reviews). He is a professor in Clinical Research Design and Analysis at the University of Copenhagen and a world leader in his field.

VERY LOW BLOOD PRESSURE TARGETS. MAJOR OR MINOR BENEFIT?

In the December 2015 issue of IHN the SPRINT study was discussed and while the results were met by mainstream medicine with great enthusiasm it turned out that medicating systolic blood pressure from 140 to 120 had only a small absolute benefit on the cardiovascular endpoints in question (1.6% with 98.4% no benefit) and even a smaller benefit for all-cause mortality (1.1% with 98.9% no benefit). While the subject of the importance of absolute results has come up frequently in IHN, it is encouraging that this criticism of SPRINT also just appeared in an editorial in *Annals of Internal Medicine* in an editorial. To quote, and this appeared in a major high impact mainstream journal:

"Patients may believe that it is worthwhile to aim for lower BPs if they hear that receiving 3 drugs every day for more than three years might reduce their risk for cardiovascular events by 25%. However, after learning that their likelihood of absolute benefit is only 1.6% with a greater likelihood of serious harm, their enthusiasm for more medications may diminish."[40]

It is interesting to examine the consistency of SPRINT with what would be predicted by the Multi-Ethnic Study of Atherosclerosis (MESA) which also gives absolute values. Predictions from this large, modern study of a US population can be obtained from the free MESA online calculator. As a test case, consider a male and female with total cholesterol of 180 (near the top of the desirable range), a HDL of 50 (also a good value), no diabetes or family history of heart disease, no smoking and no lipid lowering drugs. The table gives the **absolute risk difference** over 10 years in major cardiovascular events when either an untreated or treated blood pressure of 140 is compared to 120.

		No BP Meds	**BP Meds**
SEX	**AGE**	**10-YEAR RISK 140 vs. 120 (%)**	**10-YEAR RISK 140 vs. 120 (%)**
M	50	0.5	0.7
	60	0.8	1.0
	70	1.1	1.6
F	50	0.2	0.3
	60	0.4	0.6
	70	0.5	0.8

Differences in absolute risk associated with population values of systolic blood pressure of either 140 or 120 are not only very small but also smaller than observed in the SPRINT study which provided 3-year risk decreases related to treatment. The above

table does not directly reflect the results of intervention, but suggests that the difference between 140 and 120 in systolic BP is not very important. Small absolute risk differences imply almost no one benefits, the same point raised in the above quotation. Note the ***increase*** in risk if BP meds were in use and as well the considerably lower risk levels and changes for women. The conventional (hypothetical) explanation for the increase in risk with medication is that it implies untreated high blood pressure in the past which has had small but lasting adverse effect not addressed by drug treatment. It would be very interesting if this turned out not to be the case (see IHN November 2015).

In the MESA calculation and the SPRINT study, stroke was included in the composite endpoints. A recent study has examined the impact of pharmacological treatment of BP on just the incidence of stroke.[41] The study examined the incidence of stroke in a large group of individuals age ≥ 45 who either had normal blood pressure or fell into three systolic blood pressure categories, prehypertension (120-139), Stage 1 (140-159) and Stage 2 (≥ 160). These four groups were stratified at baseline into either no BP meds, or 1, 2 or 3 meds. Follow-up was for about 6 years. Absolute results were not given except for crude event rates which tend to give deceptive absolute results, but for this type of follow-up study, realistic values can be estimated from the adjusted hazard ratios (similar to risk ratios or odds ratios) and the stroke incidence rate over 6 years of those who were both non-medicated and had normal systolic blood pressure (normotensive as compared to hypertensive). It was found that when the non-medicated normotensive group was used as a reference, the absolute risk difference between this group and the group taking 3 meds was for the four blood pressure group given above, 0.5%, 0.4% 1.4% and 1.5% respectively. That is, there was an increase in treated risk associated with treatment even when is resulted in a systolic blood pressure < 120. This is exactly what was seen in the MESA calculation and would have been seen if other risk calculators were used, although for MESA stroke was only one of the events in the composite endpoint.

The authors comment that maintaining normotensive status solely through drugs intervention failed to return stroke risk levels to untreated normotensive levels. They term this a lost opportunity and pointed to non-drug interventions that should also be considered, including physical activity, maintaining normal body weight, limiting alcohol consumption, reducing sodium intake, maintaining adequate potassium levels and consuming a diet rich in fruit, vegetables, low-fat dairy and reduced saturated and total fat. These recommendations were based on guidelines which may be somewhat out of date with regard to the issue of fat.

BOTTOM LINE

As we have seen repeatedly in studies discussed in IHN, dealing with patient problems needs to go beyond the prescription pad and involve a much more comprehensive approach. The non-drug interventions mentioned above all are backed by randomized trial data. This study also supports the general criticism offered in a perspective by Dr. M. A. Hyman in 2010 which seems even more appropriate today. The title is self-explanatory: *The Failure of Risk Factor Treatment for Primary Prevention of Chronic Disease.*[42] We constantly see this in approved therapies directed at reducing risk

factors where the percentage treated that actually benefit is very small leaving 95 to 99.9% without benefit. However, in most cases, the reader of the paper is forced to do the absolute risk calculation, having been given only deceptive relative risk reductions or the equivalent. In some cases, research reports are written such that it is impossible to even estimate absolute results, no doubt in some cases intentionally. Critics of guidelines are now becoming more vocal in the peer-reviewed literature about the absence of absolute results for both benefits and risks of adverse effects which renders guidelines to some extent useless. In fact, if absolute results were required in all study reports, including the abstract which is all many read, it would be a disaster for the industry and leave the medical profession with few treatments they could describe as convincingly effective, and this would not only be for chronic diseases. For example see IHN February 2013 for an example derived from a published meta-analysis of controlled trials of flu vaccination where vaccinated laboratory-verified viral influenza cases were compared with unvaccinated cases rather than the way the CDC does it. This piece also includes a sample calculation for those interested in the details of how one can get a large relative risk reduction of 20% or 30% or 40% and still reach the conclusion that almost no one benefits from the treatment or intervention.

In the context of prevention, it is time to focus on the huge majority who fail to benefit. We need much more research on alternative and non-drug therapy and the poor compliance generally found in non-drug interventions. However, it is hard to be optimistic.

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BOOKS – FICTIONAL THERAPY

This newsletter frequently mentions books of interest in the context of issues being discussed. Occasionally book reviews have been presented and are indexed in the archives. However, books also have therapeutic value in their own right. For example, the author of the book *Death of Cancer* mentioned in this issue describes his ordeal with cancer and its profound psychological impact, especially before treatment—waiting for news on diagnosis and staging and problems with finding a surgeon who would tackle his difficult and risky presentation. Being a doctor, in fact an expert in the field of cancer, he fully appreciated the total picture of what his future might hold. He had taken leave of absence and had all day and half the night to devote to worry. His way of dealing with these psychological issues was reading mysteries by the dozen. This enabled him to lose other worlds. They were in a sense like antidepressants or even narcotics, but without the side effects. Prozac packaged in hard or soft covers. Thus appropriate fiction consistent with an individual's preferences may have significant therapeutic value. Obviously not a new notion. Here are some suggestions inspired by Dr. DeVita's choice of genre.

The mystery literature is of course huge and highly variable. This short note will mention mostly one class that may have special appeal to readers who desire mild intellectual stimulation and major distraction to take their minds off disturbing aspects of life. These are the classical English mysteries introduced a long time ago by Wilkie Collins and followed up by Arthur Conan Doyle. Readers are no doubt familiar with the immense and unique contribution of Agatha Christie and a number of other English mystery writers of lesser note. There are modern authors who have maintained the tradition and offer charming entertainment and potentially powerful distraction from day-to-day worries, be they problems having their origin in serious health issues, domestic troubles, job problems, stock market volatility or the decline of portfolio values, fear of running out of pension money or being unable to pay medical bills, or concern about the current problems facing North America and the European Union, accentuated by the current US political circus that seems unparalleled in recent times. It is however doubtful that this approach would be effective for someone faced with the choice of a drug that might be lifesaving or provide life extension for a rare disorder when the price is personal bankruptcy and the loss of almost everything associated with their lifestyle. A new and unpresented scenario in medicine we will be following.

The following is a list of a few authors that your editor considers worth sampling based on availability and on having read most of their works. The motivation is that some of these mystery writers may be unknown to readers who may find their discovery rewarding. These authors are still active and produce new books at the rate one or two per year while carefully maintaining the styles that make them popular. They range from Edwardian to modern but more or less follow the classical English model. The Beaton mysteries are a bit lighter reading than those of the other three.

- David Dickinson—the Lord Francis Powerscourt series
- M.C. Beaton—the Hamish Macbeth series, the Agatha Raisin series and a small set of novels (really mysteries) concerning the trials and tribulations of young Lady Rose in Edwardian England.
- Jacqueline Winspear—the Maise Dobbs series
- Dorothy Simpson—the Luke Thanet series

Finally, for variety it seems worth mentioning the great French writer Georges Simenon (1903-1989) and his unique creation, Chief Inspector Maigret of the Paris Police Judiciary. During his lifetime he produced a very large number of mysteries as well deep, dark psychological novels. Many of his books are available in translation. Some may find biographies of Georges Simenon fascinating. There is even a Madam Maigret cookbook giving recipes of dishes mentioned in the books. Maigret took on a life of his own. There were TV series, tour operators drive past the house tourists are told Maigret was imagined to have reside in on Boulevard Richard Lenoir, although the exact spot if any Simenon had in mind is actually unclear, or past the Palais de Justice on the île de la Cité, then generally simply called the Quai des Orfèvres, out of which the police judiciary operated. Maigret fans make pilgrimages to these places when in Paris. Anyone who fancies mysteries should sample a "Maigret."

Familiarity with Paris and London, as your editor has found, considerably enhances the pleasure of reading these mysteries. These authors have produced a sufficient number of books to provide distractions enabling some to get through trying times or merely derive beneficial pleasure and diversion. Amazon worldwide is of course the obvious source but Powell Books in Portland Oregon also frequently can supply many titles in used paperback or even hard cover format in one online order shipped anywhere in North America, i.e. one-stop shopping once one is hooked on an author.

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